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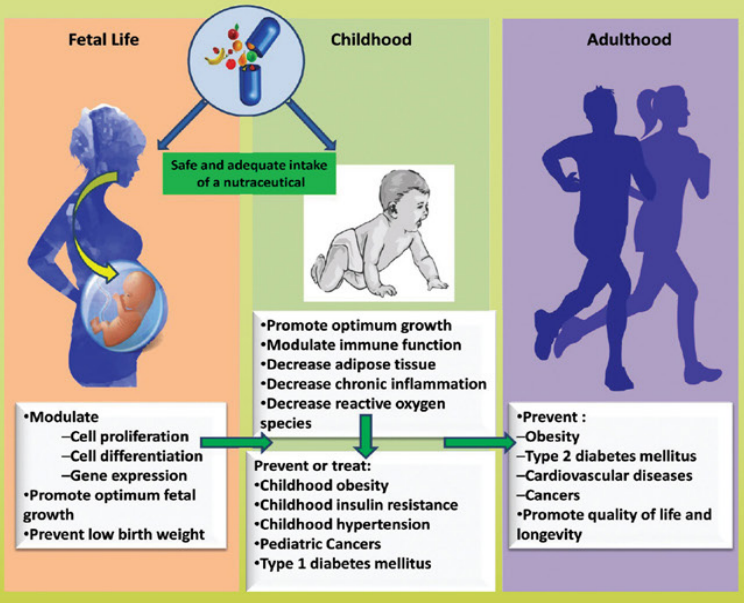

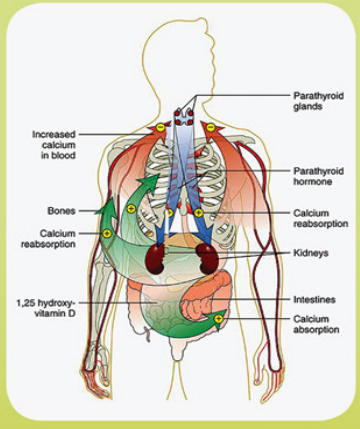

Edited by
Priyanka Bhatt • Maryam Sadat Miraghajani
Sarvadaman Pathak • Yashwant Pathak

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Nutraceuticals for Prenatal, Maternal and Offspring's Nutritional Health

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Dedicated to my mother who always taught me the medicinal importance of each spice we add to food. Also, to my whole family for their unconditional support and love.

Priyanka Bhatt

To my family members for always standing by me and to all those who taught me love. And to my beloved, Mehrsa. Their love has been the major spiritual support in my life.

Maryam Miraghajani

To all mothers across the globe, we appreciate all you have done for all of us, without you we would not be here. I am fortunate to have many mothers everywhere, who have helped me to grow personally and professionally, and have fed me. I would like to dedicate this book to all my mothers, and my mother's mothers: Seema Pathak, Sushma Deshpande, Kokila Shah, Daksha Shah, Seema Zuberi, Madhulika Patel, Linda Stanley, Joann Hattey, Sindhu Deo, Shalini Pathak, Smita Khandekar, Alexandra Schyns-van den Berg, Shashi Pampanwar, Sara Hand, Mary McKay, Patti Perez-Smith, and Lihua Zhong. Without your love, guidance, support, and food, life would be incompatible.

Sarvadaman Pathak

Dedicated to all the Rushies, sages, Shamans, medicine men and women, and people of ancient traditions and cultures who contributed to the development of drugs and nutraceuticals worldwide and kept the science of health alive for the past several millennia.

Yashwant V Pathak

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Foreword

Adequate nutrition is a crucial component in normal fetal development. Taken together, maternal body mass index (BMI), nutritional stores, and diet, coupled with the integrity of utero-placental-fetal circulation determine nutrient availability for the fetus. During pregnancy, preconceptional maternal weight and BMI, as well as gestational weight gain, have a direct effect on fetal growth, birth weight, and perinatal outcome. Maternal obesity and excess weight gain are associated with gestational diabetes, fetal macrosomia, shoulder dystocia, and the development of preeclampsia, while underweight mothers and inadequate gestational weight gain are associated with an increased risk of low birth weight and growth-restricted infants as well as spontaneous preterm birth. Deficiencies in maternal intake of vitamins and minerals are linked to birth defects and adverse pregnancy outcomes – e.g., folate deficiency and neural tube defects, selenium and preterm birth) while excess maternal consumption of vitamin A can cause pleiotropic malformations in offspring. Thus, an appreciation of the impact of maternal nutritional status on fetal development is crucial to optimizing pregnancy outcomes.

There is also growing evidence that maternal nutrition can induce epigenetic modifications of the fetal genome. Epidemiological studies have suggested that metabolic programming is a critical factor contributing to the etiology of obesity as well as the concurrent increase in related chronic diseases (e.g., type 2 diabetes, hypertension, and cardiovascular disease). Fetal metabolic programming is the phenomenon whereby a nutritional stress/stimulus applied during critical periods of early development permanently alters an organism's physiology and metabolism, leading to unfavorable outcomes and adverse consequences later in life. The fetal origins of adult disease hypothesis, first proposed by Barker, suggests that adequate nutrition during fetal development is critical to

long-term health. Therefore, it is also crucial to gain an understanding of the molecular mechanisms underlying the relationship between alterations in intra-uterine environments and their long-term effects on the health of an individual.

It is from this perceptive that the authors of this text address the role of nutraceuticals in pregnancy outcomes and offspring nutritional health. The role of nutraceuticals in promoting successful pregnancy outcomes is particularly vital in developing nations where deficiencies in vitamins, minerals, and overall caloric intake are most common and, paradoxically, susceptibility to the harmful effects of over-nutrition are the greatest. This book addresses this important issue affecting global health. **Priyanka Bhatt, Maryam Sadat Miraghajani, Sarvadaman Pathak, and Yashwant Pathak** have collected a wonderful team of experts to address these issues and provide up-to-date clinical evidence to inform recommendations for nutraceuticals use in pregnancy. Topics include the role of nutraceuticals in preconceptional health, miscarriage, and fetal development, as well as their impacts on maternal health including the occurrence of preeclampsia, gestational diabetes, depression, bone and dental health, and pregnancy and puerperal anemia. I congratulate the four editors for proffering this important text, and I am sure it will help scientists and clinicians working in this field around the globe and serve as an excellent reference on this topic.

Charles J. Lockwood, MD, MHCM
Senior Vice President, USF Health
Dean, Morsani College of Medicine
Professor of Obstetrics & Gynecology, and Public Health
University of South Florida
Tampa, Florida

Preface

Nutraceuticals are important products based on natural bioactive compounds that cross the frontier between drugs and food. The definition of a nutraceutical is "a food or part of a food that provides benefits for health in addition to its nutritional content." Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure and function of the body.

Globally the growing demand for value-added nutraceuticals for the prevention and treatment of human diseases have rendered nutraceuticals a multibillion-dollar market. As well as the increasing numbers of people attaching importance to health in the nutraceuticals area, pregnant women also affect the nutraceuticals market because of the potential health benefits for both mothers and their offspring.

The book focuses on the role of nutraceuticals for the health of mothers and their offspring before, during, and after pregnancy and birth.

Although there is an increasing number of pregnant individuals taking nutraceuticals to maintain good health and get possible health benefits for their babies, many gaps exist in the knowledge base. The question of whether an adequate nutraceutical intake in pregnant women is safe is always raised. These nutraceuticals might be involved a wide variety of biological processes, including activation of signal transduction pathways, antioxidant defenses, gene expression, cell proliferation, differentiation, and the preservation of mitochondrial integrity. So, the biological and epidemiological findings of relevant studies of nutraceuticals intake effects on the health of mothers and their offspring need to be addressed.

Also, a growing body of literature suggests that nutraceuticals have a favorable impact on mothers and their offspring. It should be mentioned that the role of these products could be confounded by dietary patterns, genetic variability, the effects of gut microbiota, different ages, race, ethnicity, and socioeconomic factors, all of which should be assessed in order to support the potential nutraceutical effects on the health of mothers and their offspring.

Importantly, the timing and duration of exposure to utraceuticals should be considered when assessing the health of mothers and their offspring, due to the establishment of epigenetic programs in utero and during the early stages of life.

In recent years new trends have been established in this area of prenatal nutrition, based on the consideration of appropriate nutrition and the effect it has on the health of mothers and their offspring during pre-pregnancy, pregnancy, and after pregnancy.

Nutraceuticals and natural products have been used by many cultures and societies around the world, such as Indian (in Ayurveda), Chinese (Chinese medicine), traditional African medicines, and aboriginal and indigenous medicines. Every country has interesting and specific recommendations in this area, and while some have been widely used in recent years there is proven clinical evidence, that many of these have been used for centuries.

This book addresses the nutraceuticals used for prenatal health and the health of mother and child, and the focus is mainly on recent trends and possible clinical evaluations of such nutraceuticals and natural products.

Several chapters have been written by established leaders in this field. Chapter 1 provides a detailed account of nutraceuticals and their application. Chapters 2 and 3 address nutraceuticals used before pregnancy.

Chapters 4 to 13 discuss the nutraceuticals used during pregnancy. They cover the role of nutraceuticals in placental development, nutraceuticals for gestational weight gain and postpartum obesity, the role of nutraceuticals in the risks of miscarriage and related outcomes, still birth, and maternal mortality, as well as many other aspects.

Chapters 14 to 19 discuss nutraceuticals used for the offspring's health. This group of chapters covers nutraceuticals impacting uterine growth, gestational age and mortality rate, nutraceuticals for the dental health of the offspring, nutraceuticals and chronic disease (including blood pressure, obesity, insulin resistance, and certain pediatric cancers), and many more.

We believe this to be the first published book examining the role of nutraceuticals and their impact on the health of mothers and their offspring with a focus on human population-based research. This is very important because many of the health claims about nutraceuticals have not been validated in humans. It is quite possible that many of these health claims, mostly emerging from animal studies and cell culture models, have been exaggerated.

This book addresses very important findings of the latest scientific research regarding the role of nutraceuticals intake before pregnancy and during the pregnancy on the health of mothers and their offspring.

We are extremely thankful to all the chapter authors for their contributions. We believe that this book will be an indispensable reference in libraries, and will be a valuable resource for pharmaceutical companies, pharmacists, nutritionists, dietitians, and scientists, as well as for those in the allied health sciences such as nursing and medical students. Also it may be a great help in planning the health services for mothers and their offspring.

We are extremely thankful to our families and their support getting this book out in the market.

We also would like to express our sincere thanks to CRC Press and all those concerned in bringing this book to publication.

Editors:

Dr Priyanka Bhatt, PhD

Dr Maryam Miraghajani, PhD

Dr Sarvadaman Pathak, MD and

Dr Yashwant Pathak, PhD

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Contributors

Ofosua Adi-Dako
Department of Pharmaceutics & Microbiology
School of Pharmacy
University of Ghana
Accra, Greater Accra Region, GA, Ghana

Amanda Rodrigues Amorim Adegboye
Department of Psychology
Social Work and Counselling
Faculty of Education and Health
University of Greenwich
Old Royal Naval College
London, UK

Parth Amin
College of Pharmacy
University of South Florida Health
Tampa, Florida

Reza Amani
Professor of Nutrition Science
Food Security Research Center
Department of Clinical Nutrition
School of Nutrition and Food Science
Isfahan University of Medical Sciences
Isfahan, Iran

Shirin Amini
Department of Nutrition
Ahvaz Jundishapur University of Medical Sciences
Ahvaz, Iran
Biotechnology and Management of Bioresources Division
The Energy and Resources Institute Darbari Seth Block
India Habitat Centre
Lodhi Road New Delhi, India

Akansha Atulkar
Taneja College of Pharmacy
University of South Florida
Tampa, Florida

Yasmin Azad
College of Pharmacy
University of South Florida Health
Tampa, Florida

Priyanka Bhatt
College of Pharmacy
University of South Florida Health
Tampa, Florida

Kunal Dhankhar
Department of Pharmaceutics
Delhi Pharmaceutical Sciences and Research University (DPSRU)
New Delhi, India

Reza Ghiasvand
Department of community nutrition
School of Nutrition and Food science
Isfahan University of Medical Science
Isfahan, Iran

Deepti Kaushalkumar Jani
Associate Professor
Babaria Institute of Pharmacy
Varnama, Vadodara, India

Keerti Jain
Department of Pharmaceutics
Delhi Pharmaceutical Sciences and Research University (DPSRU)
New Delhi, India

Vineet Jain
Department of Pharmaceutics
Delhi Pharmaceutical Sciences and Research University (DPSRU)
New Delhi, India

Rupal Jani
Parul Institute of Pharmacy and Research
Parul University
Vadodara, Gujarat, India

Kavita Joshi
Department of Pharmaceutics
Delhi Pharmaceutical Sciences and Research University (DPSRU)
New Delhi, India

Anastasia Victoria Lazaridi
The Early Life Research Unit
Division of Child Health
Obstetrics and Gynaecology
University of Nottingham
Nottingham, UK

Maryam Miraghajani
Cancer Research Center
Shahid Beheshti University of Medical Sciences
Tehran, Iran
and
The Early Life Research Unit
Division of Child Health, Obstetrics and Gynaecology
University of Nottingham
Nottingham, UK

Nafiseh Shokri Mashhadi
Department of Clinical Nutrition
School of Nutrition and Food science
Isfahan University of Medical Science

Michaela McMahon
Morsani College of Medicine
Tampa, Florida

Natalia Mercado
College of Pharmacy
University of South Florida Health
Tampa, Florida

Hamed Mohammadi
Students' Research Committee
Department of Clinical Nutrition
School of Nutrition and Food Science
Isfahan University of Medical Sciences
Isfahan, Iran

Ashley Oake
Morsani College of Medicine
Tampa, Florida

Sarvadaman Pathak
Faculty, East West College of Natural Sciences
Sarasota, Florida

Yashwant Pathak
College of Pharmacy
University of South Florida Health
Tampa, Florida
Faculty of Pharmacy
Airlangga University
Surabaya, Indonesia.

Param Patel
College of Pharmacy
University of South Florida Health
Tampa, Florida

Sujan Patel
College of Pharmacy
University of South Florida Health
Tampa, Florida

Vasudha Prithipaul
College of Pharmacy
University of South Florida Health
Tampa, Florida

Arti Patel
Taneja College of Pharmacy
University of South Florida
Tampa, Florida

Shrushti Patil
College of Pharmacy
University of South Florida Health
Tampa, Florida, USA

Harvinder Popli
Department of Pharmaceutics
Delhi Pharmaceutical Sciences and Research University (DPSRU)
New Delhi, India

Meera Ratani
College of Arts and Science
University of South Florida
Tampa, Florida

Neda Roshanravan
Cardiovascular Research Center
Tabriz University of Medical Sciences
Tabriz, Iran

Asra Sami
College of Art and Science
University of South Florida Health
Tampa, Florida

Michael E Symonds
The Early Life Research Unit
Division of Child Health, Obstetrics and Gynaecology
University of Nottingham
Nottingham, UK

Nasrin Sharifi
Assistant Professor of Nutrition Science
Research Center for Biochemistry and Nutrition in Metabolic Diseases
Kashan University of Medical Sciences
Kashan, Iran

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Introduction

Maryam Miraghajani, Anastasia Victoria Lazaridi, Sarvadaman Pathak, Priyanka Bhatt, and Yashwant Pathak

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What Are Nutraceuticals?

About 2000 years ago, Hippocrates correctly stated: "Let food be your medicine and medicine be your food" (1). Currently, there is increased global interest due to the recognition that "nutraceuticals" play a major role in health enhancement. The term "nutraceutical" was coined by combining the terms "nutrition" and "pharmaceutical" and was originally defined by Dr. Stephen L. De Felice, founder and chairperson of the Foundation of Innovation Medicine (2). Nutraceuticals have potential nutritional and therapeutic effects, and are easily accessed, cost-effective, and tolerable, with a wide margin of safety (3).

Nutraceuticals, which have also been called medical foods, designer foods, phytochemicals, functional foods, and nutritional supplements, include such everyday products as "bio" yogurts and fortified breakfast cereals, as well as vitamins, herbal remedies, and even genetically modified foods and supplements (4). There is also a lot of confusion regarding the terminology, which differs between countries, but the usual definition is a product isolated from foods that is generally sold in medicinal forms not usually associated with food (5). Both in Canada and in Great Britain, a functional food is essentially a food, but a nutraceutical is an isolated or concentrated form of a nutrient (6, 7). In the United States, "medical foods" and "dietary supplements" are regulatory terms; however "nutraceuticals", "functional foods", and related terms are determined by consultants and marketers, based on consumer trends (8).

There also seems to be a "thin dividing line" between the definitions of "pharmaceuticals" and "nutraceuticals". "Pharmaceuticals" may be considered as medication used to treat and improve outcomes of interventions provided to patients, while "nutraceuticals" are those that are intended to prevent diseases (9, 10). However, a nutraceutical for one consumer can act as a pharmaceutical for another (9). Examples of nutraceuticals include fortified dairy products (milk as such is a nutrient and its product, casein, is a pharmaceutical) and citrus fruits (orange juice is a nutrient and its constituent, ascorbic acid, is a pharmaceutical). So, in another definition, both pharmaceutical and nutraceutical compounds might be used to cure or prevent diseases, but only pharmaceutical compounds have governmental approval. Also, nutraceuticals, in contrast to pharmaceuticals, are substances that usually have no patent protection (9).

Overall, nutraceuticals should provide a health benefit to the consumer that is greater than that of a general food item. Indeed, they are non-specific biological therapies used to promote wellness, prevent malignant processes, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body (5). However, nutraceuticals are claimed to provide protection against some chronic disorders including obesity, diabetes, degenerative and inflammatory diseases, cancer, and cardiovascular diseases (5). These conditions involve many physiological and metabolic changes, including increased oxidative stress and an imbalance between the oxidative and antioxidative systems leading to cellular dysfunction. This can cause compromised cell signaling and cell cycle control, cellular transport and overall decreased biological activity, immune activation, and inflammation. Most nutraceuticals have antioxidant, anti-inflammatory, anticarcinogenic, and neuroprotective effects with the ability to counteract these adverse conditions (5, 11, 12). Hence, they are considered as optimal sources of health promotion, especially for the prevention of life-threatening diseases.

Presently over 470 nutraceutical products are available with documented health benefits. Some popular nutraceuticals include polyphenols and vitamins (for dermatologic benefits), glucosamine (for arthritis), lutein (for macular degeneration), ginseng (for colds), echinacea (anti-immune properties), folic acid, minerals, essential fatty acids, amino acids, etc. (9, 13). Knowing the safety concerns related to nutraceuticals, it is necessary to ensure maximum potential benefits without adverse effects. From a large number of nutraceutical-related studies, they appear to be safe, although this can be compromised by contamination with toxic plants, metals, mycotoxins, pesticides, fertilizers, drugs, etc. (3). The assessment of claimed toxicity and the safety of nutraceuticals need appropriate pharmacokinetic/toxicokinetic studies.

Scope and Future Development of the Nutraceuticals

Currently, nutraceuticals, which provide various health benefits in the treatment and prevention of diseases, are receiving more attention. Many "Western" diseases derived from metabolic syndrome, which is a result of

chronic inflammation, have been studied for years to identify their causes as well as prevention and treatment. These include:

- cardiovascular diseases (CVDs) including coronary artery diseases, stroke, and heart failure;
- cancer of any type, such as colorectal, brain, and breast cancers;
- Type II diabetes; and
- neurodegenerative diseases (such as Alzheimer's and Parkinson's diseases).

This list is extensive. For this reason, companies have produced drugs to treat and regulate most of these diseases as well as tablets containing food substances that can prevent or regulate certain conditions. However, there are many challenges to overcome when developing nutraceuticals in a laboratory. One challenge is that, as nutraceuticals are made from food products, their formulation is limited. Another challenge is to determine the stability of the formula, because factors such as pH, temperature, and pressure might affect the desired effectiveness of the product (14). Additionally, complete tests of active uptake, the metabolic response, and the biological variability should be considered before introducing the final product onto the market (15).

Our current way of life includes high levels of stress, anxiety and bad eating habits, which add a significant burden to people's health. Because nutraceuticals can potentially minimize factors that contribute to health deterioration, research on nutraceuticals should be emphasized. Thus, laboratories at nutraceutical companies are not restricted to the development of new "superfoods" to address human needs. The aim is to link nutrition and health and to create pioneering products that could significantly decrease the effects of some non-communicable diseases (NCDs), such as diabetes, cardiovascular disease, and cancer. Thus, the population's mortality rate, and consequently the public sector's health expenditures, could potentially be reduced. With this objective, both food and pharmaceutical companies have to combine their product strategies, technology, marketing, and supply chain management to obtain a competitive advantage for their products, which are based on innovation and creativity.

Recently, many people have developed the habit of taking nutraceuticals regularly to boost their health because, for example, they might not be able to eat a food product because of its smell, taste, and/or appearance, or it because it does not fit with their eating patterns. All nutraceuticals can be found on the market at a low cost or available to the public without any prescription, so they can be purchased with just a click of the mouse, without any further information or explanation about them from a pharmacist. Thus, regulatory models need to be expanded to performed research, examine emerging issues and hazards, and contribute to improvements in legislation. In the United States, dietary supplements are regulated by the Dietary Supplement Health and Education Act (DSHEA), and food additives are regulated by the Federal

Drug and Cosmetic Act. In China, the State Food and Drug Administration (SFDA) handles the regulation of dietary supplements and the Ministry of Health manages all the approvals. In Europe, there is the European Food Safety Authority (EFSA), and in India there is the Food Safety and Standards Act (FSSA). The role of all these regulatory agencies is to protect the public from harm caused by food products, increase awareness, and explain scientific work to the public.

Thus, even if there are many researchers who have shown the benefits of food ingredients, people have to take into consideration the issues that have not been explored. A particular example is green tea. Green tea can protect humans from various types of cancer resulting from environmental causes, because it has antioxidant, anticarcinogenic, and antimutagenic effects (16, 17). It has been also associated with most of the NCDs, such as CVD and diabetes, as well as neurodegenerative diseases (16, 18). Despite its extensive benefits, the EFSA scrutinized the safety of green tea catechins from all dietary sources in a 2018 report. Even though it is believed to be safe for daily use, cases of liver injury, increased serum transaminase levels (which is a marker of liver damage), and hepatotoxicity have been noted. Thus, the EFSA recommends that further research is conducted on adverse events related to pyrrolizidine alkaloids, which can contribute to the hepatotoxicity, are required, and that the labeling system should be improved (19).

Importance of Nutraceuticals in Healthy Living

The value of longevity and life prosperity has been known since the fifth century BC. Hippocrates, the father of Western medicine, noted: "Let food be thy medicine and the medicine be thy food" (20). There is evidence that, in ancient civilizations, herbs and food were used for treatment purposes, for example in Egypt (21), China (22), and India (23). Food was used to heal the body, give it strength, and satisfy the feeling of hunger. Unfortunately, food is now used differently. The boom in the industrial era and the technological progress of the past century have inevitably led to many changes in the way that people live. Nowadays, people have forgotten the real purpose of eating and now they are satisfying their cravings. Currently, hunger is not satisfied after a meal with many artificial flavors, coloring agents, sugars, and other harmful ingredients that destroy our bodies (24).

We live in a century where our eating behavior has changed from being influenced by biological to psychological and socioeconomic factors. These modifications to the food pattern led to the necessity of nutritional advisory expertise, which was implemented in 1980. During the 1980s, a series of clinical studies revealed a successful nutritional intervention to prevent diseases by following a specific diet (25–27). The probability for both sexes of dying between the ages of 30 and 70 years from CVDs, cancer, diabetes, and chronic respiratory diseases was reduced by 4.1% between 2000 and 2016 (28).

However, in most regions, the rate of obesity has increased and the Organization for Economic Co-operation and Development (OECD) has projected that levels of obesity will increase to 47%, 39%, and 35% in the United States, Mexico, and England, respectively (29). Thus, each country has its own regulatory system for food-based dietary guidelines, which constantly change over time as well as with regard to the needs of each country's population. In Europe, almost every country has different guidelines for the products eaten, relating to the population's eating pattern. For example, Greece has a food pyramid based on the Mediterranean diet (30) and the United Kingdom uses the Eat Well Guide (31), which both show the food patterns that are required for a well-balanced and healthy diet. Across Asian countries, such as China (32), food pyramids have also been established.

The amount of a specific ingredient that is ingested during our daily food consumption is not enough to help our bodies defend against some diseases. Thus, companies have developed nutraceuticals to fill the gap between the healthy diet we should follow and the one that we actually do. There are both established and potential products because sufficient research should be done before a product is placed on the market (33). Potential products include a supplement that could fight obesity, such as capsaicin (34), which is well known to activate brown adipose tissue, a tissue in our body that, once triggered, will produce heat in the form of energy, meaning that it burns stored fat from our body. There are also traditional products, which are foods that have not undergone any manual changes, so they are natural and can have some health benefits. An example is oranges, which are rich in vitamin C, which helps the immune system (35).

One of the categories of nutraceuticals is probiotics. These are food or supplements that contain live microorganisms that can help maintain good bacteria in the gut. Many supplements include micronutrients and minerals that have various health benefits. Vitamin E and selenium are antioxidants that can help to protect our immune function (36), and iron helps with energy production, proper growth and development, and cell formation (37). These are some examples of the function of macronutrients. They contribute to good intestinal health, immune function, decreases in cholesterol levels, and reduce the risk of cancer (38). Fortified foods, herbs, and dietary supplements are also included in the category of nutraceuticals that boost our health because we have forgotten to maintain healthy patterns in our lives.

References

1. Oszkiel H, Wilczak J, Jank M. Biologically active substances: Enriched diet regulates gonadotrope cell activation pathway in liver of adult and old rats. *Genes & Nutrition*. 2014 Sep;9(5):427. PubMed PMID: 25156242. Pubmed Central PMCID: PMC4172640. Epub 2014/08/27. eng.
2. Ratnaparkhi PK, Karode NP, Patil KB, Gohel SN, Prajapati VD, Jani GK. Nutraceuticals: Its current scenario and challenges in dietary supplements. *World Journal of Pharmaceutical Sciences*. 2015;4(07):460–74.

3. Gupta RC, Srivastava A, Lall R. Toxicity potential of nutraceuticals. *Methods in Molecular Biology (Clifton, NJ)*. 2018;1800:367–94. PubMed PMID: 29934903. Epub 2018/06/24. eng.
4. Gupta S, Chauhan D, Mehla K, Sood P, Nair A. An overview of nutraceuticals: Current scenario. *Journal of Basic and Clinical Pharmacy*. 2010;1(2):55.
5. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New concepts in nutraceuticals as alternative for pharmaceuticals. *International Journal of Preventive Medicine*. 2014 Dec;5(12):1487–99. PubMed PMID: 25709784. Pubmed Central PMCID: PMC4336979. Epub 2015/02/25. eng.
6. Guzmán-Maldonado SH, Paredes-López O. Functional products of plant indigenous to Latin America: Amaranth, quinoa, common beans and botanicals. In *Functional Foods: Biochemical and Processing Aspects*, edited by Giuseppe Mazza. CRC Press; 1998:308–11.
7. Cockbill C. Food law and functional foods. *British Food Journal*. 1994;96(3):3–4.
8. Aarts TD. How long will the "Medical Food" window of opportunity remain open? *Journal of Nutraceuticals, Functional & Medical Foods*. 1998;1(3):45–57.
9. Rajasekaran A, Sivagnanam G, Xavier R. Nutraceuticals as therapeutic agents: A Review. *Research Journal of Pharmacy and Technology*. 2008;1(4):328–40.
10. Swieczkowski D, Mogielnicki M, Merks P, Gruchala M, Jaguszewski M. Pharmaceutical services as a tool to improve outcomes in patients with cardiovascular diseases. *International Journal of Cardiology*. 2016 Nov 1;222:238–41. PubMed PMID: 27497101. Epub 2016/08/09. eng.
11. Rani V, Deep G, Singh RK, Palle K, Yadav UC. Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. *Life Sciences*. 2016;148:183–93.
12. Moore P, Ginwala R, Revuri N, Kranz VA, Houle JD, Khan ZK, et al. Nutraceutical Apigenin: Mechanism of action associated with its anti-inflammatory activity and regulation of dendritic cell metabolism. *The American Association of Immunologist*. 2017 May 1;198(1).
13. Souyoul SA, Saussy KP, Lupo MP. Nutraceuticals: A review. *Dermatology and Therapy (Heidelb)*. 2018 Mar;8(1):5–16. PubMed PMID: 29411317. Pubmed Central PMCID: PMC5825326. Epub 2018/02/08. eng.
14. Ruchi S. Role of nutraceuticals in health care: A review. *International Journal of Green Pharmacy (IJGP)*. 2017;11(03):385–94.
15. Dev R, Kumar S, Singh J, Chauhan B. Potential role of nutraceuticals in present scenerio: A review. *Journal of Applied Pharmaceutical Science* 2011;1:26–8.
16. McKay DL, Blumberg JB. The role of tea in human health: An update. *Journal of the American College of Nutrition*. 2002;21(1):1–13.
17. Mukhtar H, Wang ZY, Katiyar SK, Agarwal R. Tea components: Antimutagenic and anticarcinogenic effects. *Preventive Medicine*. 1992;21(3):351–60.
18. Jamieson M, McKinley H. *Handbook of Green Tea and Health Research*. Nova Science Publishers; 2009.
19. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, Filipič M, Frutos MJ, Galtier P, Gott D and Gundert-Remy U. Scientific opinion on the safety of green tea catechins. *European Food Safety Authority Journal*. 2018;16(4):05239.
20. Schiefsky MJ. *Hippocrates on ancient medicine: translated with introduction and commentary*. Leiden: Brill. 2005;361–74.
21. Aboelsoud N. Herbal medicine in ancient Egypt. *Journal of Medicinal Plants Research*. 2010;18(4(2)):082–6.
22. Cheng JT. Drug therapy in Chinese traditional medicine. *The Journal of Clinical Pharmacology*. 2000;40(5):445–50.
23. Saini A. Physicians of ancient India. *Journal of Family Medicine and Primary Care*. 2016;5(2):254.
24. Higgs S. Social norms and their influence on eating behaviours. *Appetite*. 2015;86:38–44.

25. Arky RA. Nutrition therapy for the child and adolescent with type I diabetes mellitus. *Pediatric Clinics of North America*. 1984;31(3):711–9.
26. Puska P, Vartiainen E, Pallonen U, Salonen JT, Pöyhiä P, Koskela K, et al. The North Karelia youth project: Evaluation of two years of intervention on health behavior and CVD risk factors among 13- to 15-year old children. *Preventive Medicine*. 1982;11(5):550–70.
27. American Cancer Society. Nutrition and cancer: Cause and prevention: An American Cancer Society special report. *A Cancer Journal for Clinicians*. 1984;34(2):121–6.
28. World Health Organization. Noncommunicable diseases and mental health. Data tables 2018. Available from: http://apps.who.int/gho/data/view.sdg.3-4-data-reg?lang=en.
29. Organisation for Economic Co-operation and Development. Obesity Update 2017 2017. Available from: https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf.
30. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: A cultural model for healthy eating. *The American Journal of Clinical Nutrition*. 1995;61(6 Suppl):1402S–6S.
31. Buttriss J. The Eatwell guide refreshed. *Nutrition Bulletin*. 2016;41(2):135–41.
32. SOCIETY TCN. Dietary Guidelines and the Food Guide Pagoda. *Journal of the American Dietetic Association*. 2000;100(8):886–7.
33. Pandey M, Verma RK, Saraf SA. Nutraceuticals: New era of medicine and health. *Asian Journal of Pharmaceutical and Clinical Research*. 2010;3(1):11–5.
34. Saito M. Capsaicin and related food ingredients reducing body fat through the activation of TRP and brown fat thermogenesis. *Advances in Food and Nutrition Research*. 2015;76:1–28.
35. National Health System. Vitamin C. 2017. Available from: https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-c/.
36. Bendich A. Antioxidant micronutrients and immune responses. *Annals of the New York Academy of Sciences*. 1990;587(1):168–80.
37. Lieu PT, Heiskala M, Peterson PA, Yang Y. The roles of iron in health and disease. *Molecular Aspects of Medicine*. 2001;22(12):1–87.
38. Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, et al. Health benefits of probiotics: A review. *International Scholarly Research Notices*. 2013;1–7.

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Preconceptional Nutraceuticals during Gestation and Promotion of Women's Health

Akansha Atulkar and Yashwant Pathak

Contents

Introduction

Malnutrition is a major factor for global reproductive diseases and maternal death. Maternal undernutrition and premature introduction of low-energy nutrient density lead to low birth weight, impaired growth, intellectual development, and mortality.

Good nutrition is needed to meet the added demands on a woman's body, as well as for the growing baby. The old saying that you are eating for two during pregnancy is still true but it doesn't mean that you can eat twice as much. A pregnant woman who is of normal weight before pregnancy needs only about 300 extra calories a day, so a balance between getting enough nutrients while maintaining a healthy weight is important for both mother's and baby's future health. Healthy eating during pregnancy may take a little effort.

Nutraceuticals can be helpful in getting that balance. They are easy to introduce into the diet, as they are in a pharmaceutical form, for example pills, powders, capsules, vials, etc., which contain bioactive compounds in food as active principal components. Second, they can also be added in functional food; for example, foods can be fortified or enriched during processing. Nutraceuticals may range from isolated nutrients, dietary supplements, and diets to genetically engineered food, herbal products, and processed products such as cereals, soups, and beverages.

The term "optimal nutrition" during pregnancy and lactation means food additives that are additionally recommended based on their dietary values.

There exist some recommendations regarding the maternal intake of a limited number of nutrients, such as iron, iodine, and folic acid during pregnancy and the lactation period. Dietary reference intakes are the recommended amounts an individual should consume daily of certain nutrients, vitamins, and minerals during pregnancy (Table 2.1). They are used for good nutrition and are the basis of the nutrition guidelines issued by the US Department of Agriculture.

Table 2.1 Dietary Reference Intakes for Women

	14–18 years	19–30 years	31–50 years
Protein (gm)	71	71	71
Calcium (mg)	1000	1000	1,000
Phosphorus (mg)	1250	700	700
Magnesium (mg)	400	350	360
Iron (mg)	27	27	27
Zinc (mg)	12	11	11
Iodine (μg)	220	220	220
Selenium (μg)	60	60	60
Vitamin A (μg)	750	770	770
Vitamin C (mg)	80	85	85
Vitamin D (μg)	5	5	5
Vitamin E (mg)	15	15	15
Vitamin K (μg)	75	90	90
Thiamin (mg)	1.4	1.4	1.4
Riboflavin (mg)	1.4	1.4	1.4
Niacin (mg)	18	18	18
Vitamin B6 (mg)	1.9	1.9	1.9
Folic acid (μg)	600	600	600
Vitamin B12 (mg)	2.6	2.6	2.6

Getting Started

At the time of pregnancy, nutrient requirements increase to support fetal growth and development. A diet should include protein, carbohydrates, vitamins, minerals, and fats. These nutrients fuel the body and help the baby grow. The best source of nutrients is food. The role of nutraceuticals in pregnant females is of crucial importance.

Nutraceutical types:

*Antioxidants
*Dairy-based ingredients
*Enzymes
*Fatty acids
*Fibers and carbohydrates
*Green foods
*Herbs and botanicals
*Minerals
*Omega-3 fatty acids
*Probiotics and prebiotics
*Protein peptides, amino acids
*Sweeteners
*Vitamins

Nutraceuticals in Pregnancy

Probiotics

Probiotics are live bacteria and yeast that are good for the digestive system. Probiotics are often called good and helpful bacteria because they help to keep the digestive system healthy.

Types of Probiotics

Many types of bacteria are classified as probiotics. But most come from two groups.
Lactobacillus—this is the most common probiotic
Source: yogurt and other fermented foods
Bifidobacterium
Source: dairy products

Functions of Probiotics

- Probiotics can help replace good bacteria that might be lost, for example after taking a dose of antibiotics.
- Probiotics help to provide a balance between good and bad bacteria.

Some common conditions they help with are:

*Irritable bowel syndrome
*Inflammatory bowel disease (IBD)
*Infectious diarrhea
*Diarrhea caused by antibiotics

Apart from helping the digestive system, they are also useful for other diseases.

Probiotics Use

1) Prevention of *gestational diabetes* in overweight and obese women
   Overweight pregnant women are at risk of gestational diabetes affecting both mother and child for the long term. Gestational diabetes is associated with higher rates of Caesarean section for the mother and increased risks of macrosomia, higher body fat mass, respiratory distress, and hypoglycemia for the infant. A study showed that ingestion of specific probiotics altered the composition of the gut microbiome and thereby the metabolism from early gestation and decreased rates of gestational diabetes in normal weight women. In The Study of Probiotics in the Prevention of Gestational Diabetes (SPRING), the effectiveness of probiotics ingestion for the prevention of gestational diabetes will be assessed in overweight and obese women.
2) Preventing GBS in pregnancy
   Many women experienced a reversal from a positive to a negative culture of group B streptococcus (GBS) after the following methods:
   - Boosting healthy and competitive bacteria in order to compete against group B streptococcus, therefore weakening and killing GBS. Taking probiotic supplements such as acidophilus and basophilus orally, eating fermented foods such as yogurt, tempeh, and aged cheese, and inserting plain yogurt or an unopened probiotic capsule into the vagina.

     The use of oral probiotics raises the numbers of good bacteria in systemic circulation, specifically targeting the intestine. The vaginal insertion of probiotics specifically increases good bacteria in the vagina. Lactobacillus is one of the main good bacteria. The application of unsweetened yogurt into the vagina just before going to bed two or three weeks before testing for GBS is also advised.
   - Avoiding sugars and carbohydrates in the diet and increasing vitamins C and D intake, preferably through food sources. The diet should be rich in protein and vegetables.

Long-Chain Fatty Acids

The use of long-chain polyunsaturated fatty acids (LC-PUFAs) such as docosahexaenoic acid (DHA) and arachidonic acid (AA) during pregnancy, especially

during the last semester and lactation, have many benefits for the growth and development of fetus and infants.

Health Benefits for the Fetus

1) Preterm labor
   Preterm babies are born in between 22 and 36 weeks of gestation. DHA intake reduces the risk of preterm labor and birth. A study showed that omega-3 fatty acids, including eicosapentaenoic acid (EPA) and DHA, were effective in preventing preterm delivery.
2) Bronchopulmonary dysplasia
   Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity, occurring in around 30% of low birth weight infants.

   BPD is highly susceptible to preterm injury during resuscitation, mechanical ventilation, and pro-inflammatory substance injury. The dietary intake of omega-3 fatty acids during pregnancy and the perinatal period has potential benefits. The effect of docosahexaenoic acid may prevent BPD injuries induced by hyperoxia in a model of newborn rats and postnatal neural development. Long-chain omega-3 fatty acids have important physiological properties during pregnancy, both for the pregnant woman and for the unborn child, and studies have shown that the placenta plays an important role in modulating its own fatty acid supply depending on fetal demands and is capable of preferentially transporting LC-PUFA to the fetal site.
3) Building blocks for the brains and retinas of children
   Omega-3 fatty acids, including EPA and DHA, are very rapidly utilized by the fetal retina and brain. LC-PUFAs, including arachidonic acid, omega-3 fatty acids, and omega-6 fatty acids, are essential for fetal brain growth. Approximately 70% of the brain of a baby develops during pregnancy, and the absorption of omega fatty acids starts from second trimester of pregnancy continuing into the first two years of a baby's life. So omega fatty acids in the diet of pregnant and lactating mothers play an essential role for the retinal and brain development of babies.
4) Impact on the body mass index (BMI) of children
   According to a study in 2018 published in the *American Journal of Clinical Nutrition*, the intake of DHA in pregnant women has an impact on the lean body mass of children.

   It was found that women who took 600 mg of DHA during pregnancy had children with more fat-free body mass at the age of 5 years when compared with a placebo group.
5) Sustained attention
   Sustained attention is the ability to concentrate until a task is finished.

   According to a study in the *American Journal of Clinical Nutrition*, a mother who takes 400 mg of DHA during her pregnancy will have children with better sustained attention.

6) Improvement in infant response to stress
An infant whose mother took DHA during pregnancy will have a better one-minute Apgar score compared with an infant whose mother did not take DHA during pregnancy.
7) Necrotizing enterocolitis
The role of maternal administration of fatty acid and its effect on the prevention of incidence of infants' necrotizing enterocolitis (NEC) is controversial.

Health Benefits for the Mother

Lower plasma omega-3 fatty acids and higher omega-6:omega-3 fatty-acid ratios were associated with higher antenatal anxiety, but not postpartum anxiety. In order to alleviate antenatal anxiety, it is recommended that mother should eat seafood containing omega-3 fatty acid, DHA, and EPA.

Other Essential Nutraceuticals Benefits

Iron

Iron makes hemoglobin and carries oxygen to the organs of mother and child. When a woman becomes pregnant she does not have enough iron stored in the body to make extra blood for the baby as well as herself. Eating food rich in iron and taking a daily supplement of extra iron is highly recommended.

Folic Acid

1) Neural tube defects
This vitamin is crucial before and during pregnancy to reduce the risk of neural tube defects in infants. The lack of folic acid may increase the risk of certain other birth defects too.

Folic acid can be added as a supplement to certain foods, such as breads, cereal, pasta, rice, and flour. Some foods, such as green leafy vegetables, fruits, and beans, have folic acid naturally. However, it is difficult to get all the folic acid needed for the body, so it is recommended that all child-bearing-age women should take a multivitamin supplement containing 0.4 mg of folic acid a day.

Women who are pregnant with twins, have certain medical conditions, or are taking certain medications may have increased folic acid needs. If a woman has already had a child with neural tube or other birth defects, she will need 4 mg daily—which is ten times the amount recommended for most women.
2) Congenital heart defects
According to a study, folic acid supplementation before pregnancy is associated with a reduced risk of heart defects in newborns. The

observed associations varied by congenital heart defect (CHD) subtypes. A synergistic effect of dietary folate intake and folic acid supplementation was also observed.

3) Autism spectrum disorder
   Preconceptional folic acid supplementation may reduce the risk of autism spectrum disorder (ASD) in those with inefficient folate metabolism.

Calcium

Calcium is used in the body to build and maintain bones and teeth in pregnant women as well as in the baby.

Pregnant women should get approximately 1000 mg of calcium each day. If there is not enough calcium available for the baby, it will take what is needed from the bones of the mother. Calcium deficiency can lead to osteoporosis and can cause the loss of teeth.

Foods such as milk and dairy products are rich in calcium. Other sources of calcium are fortified orange juice, nuts and seeds, sardines, salmon with bones, spinach, etc.

However, calcium can block iron absorption, so pregnant women taking both calcium and iron supplements are advised to take one type in the morning and the other in the evening in order to avoid them clashing.

Vitamin D

Vitamin D in a pregnant woman's diet will help to build the baby's bones and teeth, and it also helps calcium to be absorbed by the bones. It is often added to calcium-rich food such as milk. Vitamin D can be manufactured on its own in the presence of sunlight. Despite these natural sources, as many as half of American women are deficient in vitamin D. Among women of child-bearing age, those with vitamin D deficiencies are obese women, women who spend little time outdoors, and women with digestive disorders, such as Crohn's disease or celiac disease, that prevent them from absorbing nutrients well.

Vitamin C

Vitamin C helps the body to absorb iron from food. It is recommended to take vitamin C together with the iron supplement.

Maternal smoking during pregnancy adversely affects the offspring's lung development, with lifelong decreases in pulmonary function and increased asthma risk. It was found that supplemental vitamin C taken by pregnant women who smoked improved newborn pulmonary function test (PFT) results and decreased wheezing through year 1 in their offspring. The use of

vitamin C for pregnant women who smoke may be an inexpensive and simple way to decrease the effects of smoking in pregnancy on newborn pulmonary function and respiratory morbidities.

Zinc

Maternal zinc restriction during pregnancy can affect fetal growth. Insufficient quantities of zinc during embryogenesis may influence phenotype of all organisms.

Magnesium

For both fetal skeleton and enamel formation magnesium, alongside calcium, is also needed in high quantities. Magnesium is important for energy metabolism, nerve conduction, muscle activity, immune function, and DNA synthesis and degradation.

Ginger

Taking ginger during pregnancy is found to reduce nausea and vomiting in some pregnant women. However, it could raise the risk of miscarriage, especially in high doses. Less than 1500 mg/day is considered safe in pregnancy. It is used in tea.

The following teas can be used during pregnancy:

1) Ginger tea: There's strong evidence that ginger may ease osteoarthritis pain. It may also help with:
   *Rheumatoid arthritis
   *Muscle and joint pain
   *Headache
2) Nettle tea: Nettle tea provides high levels of magnesium and calcium.
3) Raspberry tea: This tea prepares the uterus for labor and prevents postpartum hemorrhage.
4) Dandelion leaf tea: This tea is a wonderful support in late pregnancy when fluid retention is an issue. It is high in potassium and has a gentle but effective diuretic effect.
5) Peppermint tea: This very good for relaxing stomach muscles and helping to settle an upset stomach.
6) Rooibos tea: It contains calcium, magnesium, and other antioxidants.

Conclusion

The requirements of nutraceuticals with regard to macronutrients and micronutrients vary between developed and developing countries on maternal and fetal outcome. There are many contradictory studies that have been conducted

in many different countries—see for example the study of the advantages of folic acid and iron supplements in Asia and Africa under the umbrella of United Nations Multiple Micronutrients Preparation (UNIMMAP).

It is essential to take suitable amounts of vitamins and other minerals, whether contained in foods or as supplements, in the preconception and pregnancy period in order to reduce the incidence of adverse maternal and fetal outcomes.

Nutraceuticals are available without a prescription.

An increasing number of women are turning to natural supplements and functional foods during pregnancy despite warnings from obstetricians about the risks to maternal and fetal outcomes.

In spite of nutraceutical side effects they can exert drug-like action and so nutraceuticals should be regulated in the same way as prescription drugs, and so should not be available as over-the-counter drugs, especially for pregnant women.

Quality control of the active constituents in nutraceuticals for safety and efficacy is essential. Nutraceutical products in most countries are launched on the market without proper scientific evaluation and mandatory safety.

Bibliography

Agrawal S, Fledderjohann J, Vellakkal S, Stuckler D. Adequately diversified dietary intake and iron and folic acid supplementation during pregnancy is associated with reduced occurrence of symptoms suggestive of pre-eclampsia or eclampsia in Indian women. *PLoS One*. 2015;10(3):e0119120. doi: 10.1371/journal.pone.0119120.

Al-Dughaishi T, Nikolic D, Zadjali F, Al-Hashmi K, Al-Waili K, Rizzo M, Al-Rasadi K. Nutraceuticals as lipid-lowering treatment in pregnancy and their effects on the metabolic syndrome. *Curr Pharm Biotechnol.* 2016;17(7):614–23. Review. PMID:27033506.

Al-Dughaishi T, Nikolic D, Zadjali F, Al-Hashmi K, Al-Waili K, Rizzo M, Al-Rasadi, K. Nutraceuticals as lipid-lowering treatment in pregnancy and their effects on the metabolic syndrome. Curr Pharm Biotechnol. 2016;17(7):614–23

Allen LH. Pregnancy and lactation. In Bowman BA, Russell RM, editors. *Present Knowledge in Nutrition*. 9th ed Vol 2. Washington, DC: International Life Sciences Institute, 2006, 529–43.

Alokail MS, Sabico S, Al-Saleh Y, Al-Daghri NM, Alkharfy KM, Vanhoutte PM, McTernan PG. Effects of probiotics in patients with diabetes mellitus type 2: study protocol for a randomized, double-blind, placebo-controlled trial. *Trials*. 2013 Jul 4;14:195. doi: 10.1186/1745-6215-14-195. PMID:23822518.

Bodnar LM, Tang G, Ness RB, Harger G, Roberts JM. Periconceptional multivitamin use reduces the risk of preeclampsia. Am J Epidemiol. 2006;164:470–7. [PubMed].

Botto LD, Khoury MJ, Mulinare J, Erickson JD. Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. *Pediatrics*. 1996;98:911–7. [PubMed].

Carlson SE. Docosahexaenoic acid supplementation in pregnancy and lactation. Am J Clin Nutr. 2009;89(suppl):678S–84S. [PMC free article] [PubMed].

Center for Food Safety and Applied Nutrition. *Overview of Dietary Supplements*. Washington, DC: US Food and Drug Administration, 2001. Available from: http://www.cfsan.fda.gov/~dms/ds-oview.html#what (cited 23 April 2007).

Correa A, Botto L, Liu Y, Mulinare J, Erickson JD. Do multivitamin supplements attenuate the risk for diabetes-associated birth defects? *Pediatrics*. 2003;111:1146–51 [PubMed].
Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med*. 1992;327:1832–5. [PubMed].
Czeizel AE, Metneki J, Dudas I. The effect of preconceptional multivitamin supplementation on fertility. Int J Vitam Nutr Res. 1996;66:55–8. [PubMed].
Czeizel AE, Metneki J, Dudas I. The higher rates of multiple births after periconceptional multivitamin supplementation: an analysis of causes. *Acta Genet Med Gemellol (Roma)*. 1994;43:175–84. [PubMed].
Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. Am J Med Genet. 1996;62:179–83. [PubMed].
Gupta R.C. *Nutraceuticals: Efficacy, Safety and Toxicity*. Elsevier, 2016.
Institute of Medicine (US), Subcommittee on Nutrition during Lactation. *Nutrition During Lactation*. Washington, DC: National Academy Press, 1991.
Jasti S, Siega-Riz AM, Cogswell ME, Hartzema AG, Bentley ME. Pill count adherence to prenatal multivitamin/mineral supplement use among low-income women. *J Nutr*. 2005;135:1093–101. [PubMed].
Kaiser LL, Allen L. American Dietetic Association. Position of the American Dietetic Association: nutrition and lifestyle for a healthy pregnancy outcome. J Am Diet Assoc. 2002;102:1479–90. [PubMed].
Lammer EJ, Shaw GM, Iovannisci DM, Finnell RH. Periconceptional multivitamin intake during early pregnancy, genetic variation of acetyl-N- transferase 1 (NAT1), and risk for orofacial clefts. *Birth Defects Res A Clin Mol Teratol*. 2004;70:846–52 [PubMed].
Mahabir S., Pathak Y. *Nutraceuticals and Health: Review of Human Evidence*. CRC Press, 2016.
Mao B, Qiu J, Zhao N, Shao Y, Dai W, He X, … Zhang Y. Maternal folic acid supplementation and dietary folate intake and congenital heart defects. *PloS One* 2017;12(11):e0187996. doi: 10.1371/journal.pone.0187996.
McEvoy CT, Schilling D, Clay N, Jackson K, Go MD, Spitale P, Bunten C, Leiva M, Gonzales D, Hollister-Smith J, Durand M, Frei B, Buist AS, Peters D, Morris CD, Spindel ER. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. *JAMA*. 2014 May;311(20):2074–82. doi: 10.1001/jama.2014.5217. PMID: 24838476.
National Healthy Mothers Healthy Babies Coalition. Folic acid position statement. Available from: http://www.hmhb.org/ps_folicacid.html (cited 23 April 2008).
Nitert MD, Barrett HL, Foxcroft K, Tremellen A, Wilkinson S, Lingwood B, Tobin JM, McSweeney C, O'Rourke P, McIntyre HD, Callaway LK. SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women. *BMC Pregnancy Childbirth*. 2013 Feb 25;13:50. doi: 10.1186/1471-2393-13-50. PMID: 23442391.
Pathak Y. *Handbook of Nutraceuticals Volume 2*. CRC Press, 2011.
Picciano MF, McGuire MK. Efficacy and safety of dietary supplements during pregnancy. In Lammi-Keefe CJ, Couch SC, Philipson E, editors. *Nutrition and Health: Handbook of Nutrition in Pregnancy*. Totowa, NJ: Humana Press, 2008:191–214.
Picciano MF. Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. *J Nutr*. 2003;133(suppl):1997S–2002S [PubMed].
Picciano MF., McGuire MK. Use of dietary supplements by pregnant and lactating women in North America. *Am J Clin Nutr*. 2009 Feb;89(2):663S–7S. doi: 10.3945/ajcn.2008.26811B. Epub 2008 Dec 10. Review. PMID: 19073789.
Stolzfus RJ, Dreyfuss ML. *Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia*. Washington, DC: International Life Sciences Institute Press, 1998. Available from: http://inacg.ilsi.org/file/b2_vuhuq8ak.pdf (cited 23 April 2008).
Terrin G, Berni Canani R, Di Chiara M, Pietravalle A, Aleandri V, Conte F, De Curtis M. Zinc in early life: a key element in the fetus and preterm neonate. *Nutrients*. 2015 Dec 11;7(12):10427–46. doi: 10.3390/nu7125542. Review. PMID: 26690476.

Terrin G, Berni Canani R, Passariello A, Messina F, Conti MG, Caoci S, Smaldore A, Bertino E, De Curtis M. Zinc supplementation reduces morbidity and mortality in very-low-birth-weight preterm neonates: a hospital-based randomized, placebo-controlled trial in an industrialized country. *Am J Clin Nutr.* 2013 Dec;98(6):1468–74. doi: 10.3945/ajcn.112.054478. Epub 2013 Sep 11. PMID: 24025633.

Vahratian A, Siega-Riz AM, Savitz DA, Thorp JM., Jr. Multivitamin use and the risk of preterm birth. Am J Epidemiol. 2004;160:886–92. [PubMed].

Williamson C, Wyness L. Nutritional requirements in pregnancy and use of dietary supplements. Community Pract. 2013 Aug;86(8):44–7. PMID: 2398699.

World Health Organization Iron and folate supplementation. Available from: http://www.who.int/making_pregnancy_safer/publications/standards1.8N.pdf (cited 23 April 2008).

Zeisel SH. Is maternal diet supplementation beneficial? Optimal development of infant depends on mother's diet. Am J Clin Nutr. 2009;89(suppl):685S–7S. [PMC free article]. [PubMed].

Zeisel SH. Is maternal Supplementation diet beneficial? Optimal development of infant depends on mother's diet. *Am J Clin Nutr.* 2009 Feb;89(2):685S–7S. doi: 10.3945/ajcn.2008.26811F. Epub 2008 Dec 30. Review. PMID:19116319.

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The Effects of Preconceptional Nutraceuticals Intake on Foetus Development and Health

Ofosua Adi-Dako

Contents

1 Introduction

1.1 The Concept of Preconceptional Health

The nutritional status of pregnant women together with a healthy lifestyle is essential for both mother and baby. An insufficient dietary intake of appropriate nutrients could lead to the disruption of crucial biological functions and processes such as the reprogramming of foetal development. Children born in such conditions have the likelihood of being susceptible to chronic diseases as they grow up.

In many instances, interventions are made for infants with such health challenges after birth. Currently it seems that more attention has been paid to reversing the foetal developmental disorders than on the prevention and maintenance of foetal health (Shaw and Yager, 2019). Consequently in the prevention of such adverse pregnancy outcomes, preconceptional health is critical for both mother and unborn child if optimal birth outcomes are to be achieved. Some women believe in making health changes when a pregnancy is confirmed. However, this realisation could come too late when the woman is unaware of her pregnancy for the first few weeks.

During conception, embryonic and foetal growth are dependent on the mother's nutritional status, especially during perimplantation and placental development. This stage is crucial as it occurs mostly very early in the pregnancy, when the mother may be unaware that she is pregnant. Moreover foetal organs form between the third and seventh week after the mother's last menstrual period, when the foetus is vulnerable to teratogenic effects. As such, crucial steps. such as adequate preconceptional nutrient intake in women of child-bearing age and health changes critical for the prevention of chronic diseases in unborn children, should be taken. In some instances both paternal and maternal nutrition play a role in fertility, conception and ultimately the long-term health of their offspring (Singh, 2016; Toivonen et al., 2017).

2 The Role of Nutraceuticals in Maternal Preconceptional Health and Foetal Development and Health

Women of reproductive age are therefore encouraged to engage in a healthy lifestyle and ensure the consumption of healthy foods, together with appropriate vitamin and mineral supplementation, which all play a major role in preconception, foetal health and child health outcomes (Procter et al., 2014).

Subsequently adherence to such goals would lead to a reduction in adverse pregnancy outcomes such as foetal growth restriction and preterm delivery. Nutraceuticals, a term from "nutrition" and "pharmaceuticals", are food components, or components isolated from food, with preventive and curative health benefits. They could be derived from plants, animals or microbes, and include vitamins, dietary fibres, flavonoids, antioxidants, polyphenols, polyunsaturated fatty acids, spices, prebiotics and probiotics (Sharif and Khalid, 2018).

In contrast to pharmaceuticals that have a specific disease target, nutraceuticals have a wide spectrum of therapeutic benefit in the prevention and progression of chronic disease and provide a holistic approach in preconceptional health (Barnes et al., 2018; Singh et al., 2018) Even though nutraceuticals are used in the prevention and treatment of disease, there has been a growing interest in the benefits of nutraceuticals in preconception, especially in the prevention of birth defects and the improvement of reproductive function and infertility in males and females. Adequate nutrition affects the conception rate. Moreover, nutraceuticals are able to reverse oxidative damage in reproductive processes caused by free radicals (Singh, 2016).

3 Animal and Human Studies on the Influence of Types of Nutraceuticals in Preconception and the Effects on Foetal Development and Health

3.1 Herbal Nutraceuticals

It appears that some women in their reproductive years are already making use of complementary and alternative medicine for health care in pregnancy (Steel et al., 2017). In developing countries, such as the Philippines, the high cost of healthcare treatments and supplements could be a burden for most of the populace, including women of child-bearing age, leading to the use of alternative herbal remedies. Nettle is consumed as a vegetable and is high in nutraceuticals such as iron, manganese and calcium. Potassium and vitamins A, C, D and E. Other phytochemicals present are essential amino acids, minerals, phenolics and flavonoids which have antioxidant properties There are other species of nettle such as *Urtica dioica* and *Urtica urens*, however, *L. interrupta and B. nivea* are usually the species found in the Philippines. In China, the traditional use of *B. nivea* includes treatment of excessive menstrual flow, miscarriages and abnormal placental and foetal movements.

A study of *L. interrupta* (also known as stinging nettle) in mice by Guzman et al. supported its nutraceutical potential in preconception. The study suggests that the antioxidants from stinging nettles are able to cross the placenta and counteract oxidative stress. Oxidative stress occurs when the production of free radicals is in excess of the antioxidant capacity, creating an imbalance between the free radicals and antioxidant capacity (Gagné, 2014).

Reproductive processes involving cell division during pregnancy could give rise to free radicals and products of oxidative stress that exceed the protective antioxidant capacity of the mother and foetus. Consequently, there is cell damage, malformation of the placenta and chromosomes, and sometimes abortion. Oxidative stress negatively affects growing blood vessels and causes cell death. The preconceptional intake of stinging nettle leaf decoction supports the normal function of placental growth and development of new blood vessels. This occurs through enhanced antioxidant capacity and the normal functioning of oxidative pathways and nutritional status, which greatly impacts foetal growth and maternal health and has implications for human preconceptional health (de Guzman et al., 2015).

4 Nutraceuticals as Dietary Supplements, Vitamins, Minerals and Trace Elements in Preconception

A dietary supplement could contain dietary components, such as minerals, vitamins, amino acids, botanicals or any other dietary ingredient, as a supplement to diet alone or in combination with these components (Nasri et al., 2014).

4.1 The Effects of Nutraceuticals as Vitamins

4.1.1 The Effects of Vitamin D Intake in Preconception

Gestational diabetes mellitus is a metabolic disorder diagnosed in pregnancy (Farrar et al., 2017) that causes glucose intolerance as well as various other complications, adverse birth outcomes and the risk of chronic disease for the mother and child. Foetal abdominal circumference measured during gestation, associated with maternal glucose intolerance was predictive of higher than average birth weight in the new-born (Lee et al., 2014) as a result of changes in foetal growth (Macaulay et al., 2018). With reports of vitamin D deficiency in many non- pregnant women of child bearing age and pregnant women in some regions in the first trimester, there is a high likelihood of inadequate levels of vitamin D in women during preconception. Maternal vitamin D-deficient states in early pregnancy present a risk of gestational diabetes mellitus. Vitamin D is essential for the regulation of insulin secretion and sensitivity. A foetus exposed to gestational diabetes mellitus is susceptible to foetal growth changes with the risk of a higher than average birth weight. There are associated sex differences in foetal growth affecting male foetuses compared with female foetuses (Lee et al., 2014; Macaulay et al., 2018). Vitamin D supplementation in vitamin D

deficiency states regulates fasting blood sugar and improves insulin resistance. Although there seems to be conflicting reports on the role of vitamin D in the prevention of gestational diabetes mellitus (GDM) pregnant women deficient in vitamin D had a higher risk of suffering from GDM (Al-Ajlan et al., 2018). Previous studies indicate a combination of calcium and vitamin D has the potential to prevent GDM (Karamali et al., 2016), and that the preconceptional intake of vitamin D has the potential to lower the risk of gestational diabetes mellitus in women of child-bearing age (Bao et al., 2018).

Earlier reports suggest that the susceptibility to larger than average weight in foetal development begins in pre-pregnancy and is linked to poor maternal intake of appropriate nutrients. Subsequent insulin resistance and hyperglycaemia in early pregnancy induces changes in placental morphological and normal function of the placenta. Such changes have a negative influence on the foetal supply of nutrients and foetal fat accrued. Hence interventions that start during an established pregnancy are unable to provide optimal solutions and can only partially affect foetal development and health. Established micronutrient interventions such as vitamin D supplementation give better prospects of enhancing foetal and maternal health (Godfrey et al., 2017).

A few kinds of foods, such as fatty fish, oils, liver, eggs and dairy products will usually contain vitamin D. Sufficient dietary intake of vitamin D or supplementation before pregnancy has also been associated with decreased risks of low birth weight, poor bone health and respiratory disorders, such as wheezing and asthma in the offspring, which have implications for foetal development and health (Looman et al., 2018).

4.1.2 Vitamin A and Betacarotene

There is a prevalence of low serum levels of vitamin A in about 19.1 million pregnant women in the world. About 10 million of these pregnant women experience gestational night blindness. Previous reports from Malawi indicate a threefold probability of mortality for the offspring of vitamin A-deficient mothers. Vitamin A plays a prominent role in normal functioning of the immune system. A deficiency of this vitamin could have severe implications for developing the foetal immune system and for maternal health. Nutrient deficiencies affect the production of white blood cells and render the immune system development highly vulnerable to damage and reprogramming in foetal life, leading to chronic diseases triggered by inflammation.

Vitamin A is responsible for foetal red blood cell production (Cañete et al., 2017), development of the foetal and neonatal B1a cells, and together with its derivative retinoic acid, is essential for early production of lymphocytes, one of the types of white blood cells. The B1a lymphocytes also produce most natural antibodies.

This is supported in animal studies where a deficiency of vitamin A, disrupts the physiological function of B1a cells.

Palmer et al. studied the effects of vitamin A and betacarotene (a provitamin A carotenoid) supplementation in preconception and lactation on the levels of production of natural antibodies in the offspring. The findings suggest that the supplementation produced a greater percentage of B1 precursors in the foetus and a sustained increment in natural antibody-secreting B1a cells. There were also enhanced natural antibodies from adequate retinol levels in the offspring that were born after supplementation as compared to the control (Palmer et al., 2015).

A reduction in the B1a lymphocytes and natural antibodies has the capacity to inflict immune-related chronic disease, e.g. asthma and cardiovascular disease later on in life. Low concentrations of antibody IgM, which offers protection against Streptococcus pneumonia, could result in fatalities, especially in developing countries. Production of these antibodies does not depend on age or a response to disease, and they are critical defensive agents in foetal life prior to infancy. Maternal preconceptional exposure to vitamin A has long-term effects on foetal health.

4.1.3 The Effects of Vitamin B6, B12, and Trace Elements Intake in Preconception

Maternal and foetal health are dependent on nutritional intake. La Vecchia et al. measured the concentrations of homocysteine, folate and vitamin B12, which are essential for fertility in women of reproductive age. Aside the role folate plays in fertility, foetal neural-tube defects could be prevented by adequate levels in preconception (La Vecchia et al., 2017).

A woman's nutritional status before conception and early pregnancy is critical for placental development, the epigenetic processes involving foetal genes, and, ultimately, the growth and development of the foetus. Vitamins B6 and B12 are essential for the production of gametes, fertilisation and embryo development before implantation. Deficiencies in the levels of copper, zinc, manganese and selenium, essential for antioxidant enzymes such as glutathione peroxidase, could adversely affect blood flow to the foetus and cause pre-eclampsia and reduced foetal growth. A study in four districts in north-east Vietnam investigating the long-term impact of preconception supplementation of iron and folic acid, and multiple micronutrients, showed there was improved linear growth and motor development (Nguyen et al., 2017).

4.1.4 The Effects of Folic Acid Intake in Preconception

Folic acid, a methyl donor, is critical for DNA methylation, production and repair. Stress, environmental factors and the maternal food intake could adversely alter epigenetic patterns. However, folic acid supplement intake and the consumption of folate-rich foods are recommended in women pre-pregnancy and during pregnancy for the prevention of birth defects, such as spinal

bifida, and for protection from neural-tube defects. The maternal intake of folic acid is associated with significant epigenetic changes that prevent foetal growth restriction associated with long-term effects on childhood health. In addition, the preconceptional use of folic acid prevents folic acid-related congenital abnormalities in the foetus (De-Regil et al., 2010; Pauwels et al., 2017; Qian et al., 2016; Stephenson et al., 2018; Stevens et al., 2018; Wilson et al., 2015; Wu and Yang, 2017). A deficiency in folic acid and vitamin B12 could affect reproduction, fertility and the development of the foetus, with associated foetal defects.

5 The Effects of Nutraceuticals as Omega-3 Fatty Acids such as Mono- and Polyunsaturated Fatty Acids

5.1 The Effects of Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA) and Folate Supplementation

5.1.1 Polyunsaturated Fatty Acids (PUFA)

Omega-3 fatty acids, e.g. linolenic acid and eicosapentaenoic acid, are found in soybean and canola oils, fish oils, mackerel, sardines, salmon, swordfish, trout, flaxseed and walnuts. However, omega-6 fatty acids, e.g. linoleic and arachidonic acid, are found in sunflower, corn and soybean oils. Both fatty acids prevent the conversion of arachidonic acid to the eicosanoids, prostaglandin E2, leukotriene B4 and thromboxane A2, which promote inflammation. As such these fatty acids play a significant role in the prevention and progression of arteriosclerosis, cardiovascular disease, chronic inflammatory disease, such as ulcerative colitis, and asthma (Hernández and Gil, 2016).

Docosahexaenoic acid is an essential (n-3) polyunsaturated fatty acid found in the brain. The source of the DHA in the brain is obtained from dietary sources, as the conversion of alpha-linoleic acid to DHA is inadequate. Fatty acids such as DHA and EPA are recommended nutrients for retina and foetal brain development in preconception. Previous studies support dietary supplementation of DHA for anti-inflammatory action and neuroprotection in the brain. The concentrations of DHA are involved in long-term effects resulting in schizophrenia, depression, autism and Alzheimer's disease.

Animal studies show the potential benefits of DHA in improving behavioural deficits. More such studies are recommended to derive further information about the dose, duration and mode of administration of DHA in animals (Brawerman and Dolinsky, 2018; Nasri et al., 2014; Sun et al., 2018).

A study conducted by Chiu et al. (2017) evaluated the effect of a maternal fatty-acid diet on pregnancy and in vitro fertilisation was done. A high intake of dietary omega-3 fatty acids, such as docosahexaenoic acid (DHA) and α-linoleic acid (ALA), enhanced embryo morphology in assisted

reproduction. On the other hand, a higher saturated fat to polyunsaturated fat ratio in follicular fluid produced a decreased quantity of matured oocytes. These reports have implications for inflammation and insulin resistance that adversely affects fecundity outcomes. There were enhanced implantation, fertility and pregnancy rates associated with an increased ratio of omega-6 to omega-3 fatty acids after assisted reproduction treatment. There were also better pregnancy rates in obese women after polyunsaturated fatty acid intake during maternal preconception. These findings suggest improved fertility can result from preconception polyunsaturated fatty acid intake (Chiu et al., 2017; Moran et al., 2016).

Earlier reports have indicated an improved incidence of live births after an increased intake of omega-3 fatty acids even though other reports have failed to show this correlation with respect to live births. In addition, omega-3 fatty acid intake has been shown to reduce the incidence of anovulation (Mumford et al., 2016) and endometriosis in women and to have had a positive influence on time-to-conception fecundity. However, the positive effects of the consumption of fish oil containing omega-3 fatty acids could be hampered by the presence of toxicants such as organochlorine compounds which affect fertility in humans. A deficiency of DHA also affects sperm quality in reproduction (Gaskins et al., 2018; Lass and Belluzzi, 2019; Scaioli et al., 2018; Wise et al., 2017) Preconceptional dietary intake of polyunsaturated fatty acids, e.g. DHA and alpha-linoleic acid, improves embryo morphology (Braga et al., 2015; Genuis and Genuis, 2016).

5.1.2 Foods Containing Monosaturated Fatty Acids such as Avocados

Maternal nutrition during preconception, pregnancy and lactation is critical for conception, the maintenance and support of a pregnancy, the normal functioning of foetal placenta, and foetal development. Avocados contain monounsaturated fats, folate, potassium, antioxidants such as vitamin E and C, and phytosterols, which are critical for foetal development and health (Comerford et al., 2016).

Antioxidant vitamins such as carotenoids and vitamins C and E exert their protective effects by preventing cell damage from oxidative reactions and free radicals. Vitamin C is found in rosehips, black currants and citrus fruits. Edible plant oils contain vitamin E, which protects low-density cholesterol from oxidation. Carotenoids also reduce the risk of disease. Carotenoids such as lycopene, lutein, zeaxanthin and carotene offer protection against macular degeneration, night blindness and cataracts (Hernández and Gil, 2016).

The administration of vitamin C to female diabetic Sprague-Dawley rats before mating reduced the risk of stillbirths and foetal abnormalities. Vitamin C levels were detected in the placenta and foetal liver, which prevented the production of free radicals and enhanced antioxidant protection (Brawerman and Dolinsky, 2018).

6 Nutraceuticals as Polyphenols

Polyphenols are usually found in vegetables, fruits, cereals, tea and wine. Plant polyphenols such as phenolic acids and flavonoids are essential for their antioxidant activity. Flavonols, flavones, catechins, flavonones, anthocyanidins and isoflavonoids are all characterised as flavonoids. Resveratrol is found in red wine, epigalocatechin-3-gallate in green tea, and isoflavones, genistein and daidzein are in soybean. Such antioxidants have anti-inflammatory, antioxidant, antimicrobial, anticancer, antiatherogenic and cardioprotective properties (Hernández and Gil, 2016).

6.1 Resveratrol in combination with Vitamins

Resveratrol is a polyphenol found in red wine, grapes, berries and vegetables. Its action is similar to reduced calorie intake and exercise as therapy in gestational diabetes mellitus. An amount of 10 mg/kg of resveratrol was given to Db/+ mice before and during pregnancy. Resveratrol increased offspring survival, with a lower body weight, reduced glucose-6-phosphatase and glucose secretion, and increased expression of 5′ adenosine monophosphate protein kinase (AMPK) in the offspring. C57bL/6 obese mice were supplemented with vitamin D, folic acid or multivitamins before and during pregnancy. The administration of vitamin D and folate had no effect on foetal glucose tolerance and foetal insulin sensitivity (Brawerman and Dolinsky, 2018; Huang et al., 2015).

6.1.1 The Effects of Resveratrol

Resveratrol is able to inhibit activity in a way similar to interventions such as reduction of calorie intake and exercising in metabolic disorders such as GDM. Resveratrol has elicited anti-hyperglycaemic activity, anti-inflammatory, antioxidant and antiproliferative activity in diabetic rats and other animal models. It activates the enzyme AMPK, which regulates glucose balance and fatty acid oxidation in the cells. Animal studies involving resveratrol intake in pregnancy report reduced obesity, decreased triglycerides, decreased fat deposits in the liver, a better insulin sensitivity and decreased glucose-6-phosphate production both maternally and in the offspring. This probably suggests an associated foetal metabolic health improvement with the administration of resveratrol. However, there have been some contradictory reports on resveratrol in preconception.

In another study, Japanese macques were given supplements of 0.37% resveratrol, 3 months before mating and during pregnancy. In the offspring, there was a 42% increase in pancreatic weight, increased glucagon, Ki-67 and Bcl-2 gene expression, and decreased alpha cell mass. The foetal islet mass, beta cell mass and insulin gene expression remained the same. This suggests that the enlargement of the foetal pancreas was due to an increase in the proliferation marker Ki67 and anti-apoptotic marker in the pancreas. It is expected

that many more studies would be conducted to clarify previous data obtained in research and the effects of resveratrol on alpha and beta cells (Brawerman and Dolinsky, 2018).

6.2 Nutraceuticals as the Flavonoids, Quercetin and Genistein

Flavonoids that are nutraceuticals are found mostly in apples, cherries, grapes, cruciferous vegetables and berries. They have a profound effect on the reversal of oxidative stress during developmental programming. In a prior study conducted by Morais et al. (2015), the administration of preconceptional quercetin and genistein in mice resulted in reduced foetal DNA liver damage caused by oxidative stress in mice.

6.2.1 Quercetin

Doxorubicin and cyclophosphamide, which are very effective anticancer agents, were administered to female Wistar rats in doses of 1.8 mg/kg and 2.7 mg/kg respectively, every third week for 10 weeks. Also, 10 mg/kg of quercetin in combination with these anticancer agents was administered to two other groups of rats separately. The female rats were then moved to cages with male rats for mating to take place. The foetal brains were subsequently removed from foetuses and examined. The study showed an increase in superoxide dismutase and malondialdehyde, accompanied by a decrease in carnitine acylcarnitine translocase and glutathione indicative of oxidative damage in both cyclophosphamide and doxorubicin treatment groups. Treatment with quercetin improved the antioxidant capacity of foetal brain tissue with a reduction of free radical damage caused by oxidative stress. Women of child-bearing age on anticancer treatment with doxorubicin and cyclophosphamide could be treated with nutraceuticals such as quercetin, if they became pregnant, to reduce the risk of foetal damage of brain tissue (Doğan et al., 2015).

Quercetin is also an iron chelator and can oxidise haeme iron in haemoglobin from iron II to iron III. Quercetin is able to cross the placenta into the foetus. Maternal exposure in mice to quercetin before conception and during pregnancy, and its effect on the production of red blood cells and the maintenance of iron balance, was investigated. Findings on foetal development showed no negative effects on erythroid lineage switch nor concomitant globin switch. There was, however, increased iron storage in the liver of the adult mice, increased expression of inflammation cytokines and reduction in DNA damage from oxidative stress (Tang et al., 2014; Xiao et al., 2018).

7 Nutraceuticals as Minerals

7.1 The Effects of Preconception Iodine Intake

A sufficient dietary intake of foods containing iodine and iodine supplementation or both are critical for attaining optimal pregnancy outcomes. Iodine

deficiency in pregnancy has been associated with miscarriage. Even low levels of iodine in pregnant women during the foetal neurodevelopment stages could adversely affect cognitive and psychomotor functions, behaviour and brain development with low non-verbal and verbal intelligence quotients in children.

Even though iodine supplementation is encouraged in Australia by fortifying foods with iodised salt, pregnant women and lactating mothers were still deficient. A study conducted by Hynes et al. reported that the intake of iodine, both preconceptionally and throughout pregnancy, was effective in maintaining adequate maternal iodine levels and providing a reversal of the negative effects on foetal neurocognitive development. However, iodine supplementation after pregnancy in some of the study participants could not achieve sufficient levels of iodine. There is the probability that the amount taken was not enough to replace and maintain sufficient iodine levels during pregnancy. Since quite a number of pregnancies could be unplanned it is vital that women of child-bearing age are encouraged to have sufficient iodine intake in the preconception period (Hynes et al., 2019).

8 Nutraceuticals as Probiotics

Probiotics consist of live microbial cultures such as *lactobacilli*, *bifidobacteria* and Gram-positive bacteria, which create an intestinal microbiota balance by promoting a healthy balance between the non-pathogenic and pathogenic bacteria. In addition probiotics can be used to treat lactose intolerance, diarrhoea and antibiotic-associated intestinal disease, and to reduce the risk of ear and urinary tract infections, allergies, asthma and cancer (Hernández and Gil, 2016; Nasri et al., 2014).

An optimal microbial balance in the female reproductive tract is essential for the new-born offspring to acquire beneficial microbiota for its health. A healthy intake of probiotics before and throughout pregnancy is beneficial for a full-term, healthy pregnancy and for the prevention of infections and inflammation in the new-born (Reid et al., 2016).

Berti et al. studied the role of nutrition, with regards to probiotics and vitamin D intake, in pregnancy outcomes and breastfeeding. The findings of this study underlines the importance of such nutritional exposures from preconception, pregnancy and after the birth in ensuring foetal and offspring health (Berti et al., 2017).

Disorders in the maintenance of normal glucose levels during the preconception period and early pregnancy could lead to certain biological changes in the placenta and foetus which predisposes the offspring to unhealthy weight gain and adiposity. There is therefore growing evidence for more intervention studies during preconception where probiotics, myo-inositol, vitamins B6, B12 and D, and zinc are administered to optimise maternal blood glucose and glucose levels in the placenta and foetus to prevent adiposity and ensure healthy offspring (Godfrey et al., 2017).

9 Metallonutraceuticals

9.1 Dietary Copper

A deficiency of physiological amounts of the trace elements copper, manganese and zinc could lead to infertility, gestational hypertension, recurrent miscarriages, low birth weight in offspring and pregnancy complications resulting in preterm birth. The production of reactive oxygen species coupled with inadequate antioxidant capacity to counteract this results in negative effects on placental and foetal development and the formation of foetal organs and renders the foetus susceptible to oxidative stress and chronic disease later on in life (Al-Gubory, 2017).

Dietary copper is essential for biochemical and physiological processes (Bost et al., 2016; Catalani et al., 2018). Trace elements such as copper, manganese, zinc and selenium play a role in physiological functions and regulate oxidative reactions with enhanced antioxidant capacity in animals as well (Cazarotto et al., 2019).

Hawk et al. investigated the effects of copper deficiency during preconception and early pregnancy. A deficiency in copper resulted in an increased incidence of foetal death in utero, with subsequent partial or full reabsorption, as well as increased brain and heart developmental disorders in the mouse model (Al-Gubory, 2017).

9.2 Dietary Zinc

Micronutrients such as zinc are critical in cell division in reproductive processes, ovulation, embryo development and foetal health. A diet deficient in zinc was fed to female CD1 mice 3–5 days before ovulation, in preconception. There was a dramatic disruption of oocyte development and impairment of epigenetic programming. It is interesting to note that even temporal insufficiency in zinc has implications in fertility (Beaver et al., 2017; Hester et al., 2017; Jeon et al., 2015; Tian and Diaz, 2013).

9.3 Dietary Iron

Dietary iron is useful in red blood cell and haemoglobin production. A low dietary intake of iron during preconception coupled with diseases such as helminthiasis, in low- and-middle income countries poses as a maternal health risk. Low haemoglobin levels also result in impaired foetal growth and low birth weight. Iron supplements alone or in combination with folic acid can prevent anaemia in pregnancy (Dean et al., 2014).

10 The Way Forward

Substantial evidence shows that susceptibility to genetic modifications and progression to chronic disease later in offspring begins in the vulnerable

period of foetal development. Several determinants leading to disease have the potential to be prevented in the preconceptional period. The awareness of the immense benefits of preconceptional maternal health, which ultimately influences foetal development and health, is crucial for the health of future generations. The focus therefore should be on the nutritional status of women of child-bearing age (Genuis and Genuis, 2016). Moreover, the failure of micronutrient interventions in pregnancy is imperative for considerable attention to be given to the implementation of interventions in preconception (Stephenson et al., 2018). Women of child-bearing age, regardless of whether they are from low-, middle- or high-income countries, may not have adequate nutritional status to support a pregnancy. Hence the preconception period presents as an opportune time to initiate critical nutritional interventions (Stephenson et al., 2018).

Nutraceuticals are bioactive compounds, e.g. dietary supplements, vitamins, minerals and probiotics, with unique health benefits beyond their nutritional value that ameliorate physiological disorders (Mukherjee et al., 2017).

There is growing evidence of the role of nutraceuticals in improving preconceptional nutritional status which affects the growth, development and health of the foetus (Genuis and Genuis, 2016).

Maternal deficiency in nutraceuticals like dietary supplements, vitamins and minerals, irrespective of socioeconomic background, is a public health concern indicating the need for maternal health literacy in making informed choices. An important aspect is the awareness and education of professional health providers about the benefits of nutraceuticals, to be able to provide necessary information for women in preconceptional health care (Genuis and Genuis, 2016).

The male partners of women of child-bearing age could benefit from preconceptional care counselling as nutraceutical intake can improve male fertility as well (Singh, 2016).

Some women of child-bearing age are already exposed to the use of complementary medicine in their reproductive years to assist in fertility. Additionally, depending on their background, they may prefer herbal remedies, which may be more accessible than conventional health care. Such herbal remedies could be consumed as food and also be utilised to assist in fertility, female hormonal imbalance, miscarriage and abnormal placental/foetal movements, and to support maternal and foetal health. In effect such women are already making use of herbal nutraceuticals for health care (de Guzman et al., 2015).

Even though the body of scientific evidence on the benefits of preconception diets that include nutraceuticals is growing, there is still the need for more education in this area (Comerford et al., 2016).

Policymakers should provide access for the activities of health professionals who are not otherwise included in the structure of conventional healthcare

systems for the regulation of health literacy in order to enhance their contribution to preconceptional health care (Barnes et al., 2018). A holistic approach in the integration of maternal literacy in preconceptional healthcare is encouraged, to enable informed decisions on nutritional status associated with vital nutraceutical intake (Barnes et al., 2018; Steel, Adams and Sibbritt, 2017).

Earlier reports indicate the safety of nutraceuticals in physiological doses and highlight the need for more studies to establish the therapeutic or pharmacological doses and their effects (Hernández and Gil, 2016).

There are also several studies that indicate the remarkable anti-toxic effects of nutraceuticals in reversing the effects of synthetic/conventional drug and toxicant exposure (Akinmoladun et al., 2017; Mokni et al., 2015; Ouyang et al., 2014; Supic et al., 2018; Tabeshpour et al., 2018; Yan et al., 2016). It is postulated that this could be applicable where the effects of maternal and foetal exposure to environmental toxicants could be ameliorated in maternal preconceptional health care and foetal health. Other reports indicate conflicting or inconclusive results about the use of nutraceuticals such as vitamin D in preconception (Al-Ajlan et al., 2018).

With this emerging field of interest it is envisaged that further randomised controlled trials should be conducted on the use of nutraceuticals in preconception and the related effects on the foetus, in order to assess the consistency of the experimental data with clinical data and to provide further scientific evidence to support the use of nutraceuticals as an intervention in preconceptional health (Mokni et al., 2015; Pirro et al., 2016; Singh, 2016; Tabeshpour et al., 2018).

Public preconceptional health awareness involving knowledge of the significant role nutraceuticals play and levels of intake in nutritional status, supported by vigorous research, would enhance the informative use of nutraceuticals in preconception (Garcia et al., 2018). The introduction of preconception nutraceutical intake in family planning and extensive fortified food programmes would have long-term benefits (Stevens et al., 2018). The education of women of reproductive age would also be effective in the event of unplanned pregnancies (Dean et al., 2014). Nutraceuticals have a unique ability to reverse the adverse effects of oxidative stress and to reprogramme foetal development in its vulnerable period, which has long-term effects in ensuring the health of the next generation.

References

Akinmoladun, A. C., Oguntunde, K. O., Owolabi, L. O., Ilesanmi, O. B., Ogundele, J. O., Olaleye, M. T. & Akindahunsi, A. A. 2017. Reversal of acetaminophen-generated oxidative stress and concomitant hepatotoxicity by a phytopharmaceutical product. *Food Science and Human Wellness*, 6, 20–27.

Al-Ajlan, A., Al-Musharaf, S., Fouda, M. A., Krishnaswamy, S., Wani, K., Aljohani, N. J., Al-Serehi, A., Sheshah, E., Alshingetti, N. M., Turkistani, I. Z. & Alharbi, A. A. 2018.

Lower vitamin D levels in Saudi pregnant women are associated with higher risk of developing GDM. *BMC Pregnancy and Childbirth*, 18, 86.

Al-Gubory, K. H. 2017. Plant antioxidants in the prevention of early life programming diseases. *In*: Al-Gubory, K. & Laher, I. (eds.) *Nutritional Antioxidant Therapies: Treatments and Perspectives*. Springer.

Bao, W., Song, Y., Bertrand, K. A., Tobias, D. K., Olsen, S. F., Chavarro, J. E., Mills, J. L., Hu, F. B. & Zhang, C. 2018. Prepregnancy habitual intake of vitamin D from diet and supplements in relation to risk of gestational diabetes mellitus: A prospective cohort study: 孕前习惯从饮食以及补充剂中摄入的维生素 D 剂量与妊娠糖尿病风险的关系: 一项前瞻性队列研究. *Journal of Diabetes*, 10, 373–379.

Barnes, L. A. J., Barclay, L., McCaffery, K. & Aslani, P. 2018. Complementary medicine products: Information sources, perceived benefits and maternal health literacy. *Women and Birth*. https://doi.org/10.1016/j.wombi.2018.11.015

Beaver, L. M., Nkrumah-Elie, Y. M., Truong, L., Barton, C. L., Knecht, A. L., Gonnerman, G. D., Wong, C. P., Tanguay, R. L. & Ho, E. 2017. Adverse effects of parental zinc deficiency on metal homeostasis and embryonic development in a zebrafish model. *The Journal of Nutritional Biochemistry*, 43, 78–87.

Berti, C., Agostoni, C., Davanzo, R., Hyppönen, E., Isolauri, E., Meltzer, H. M., Steegers-Theunissen, R. P. & Cetin, I. 2017. Early-life nutritional exposures and lifelong health: Immediate and long-lasting impacts of probiotics, vitamin D, and breastfeeding. *Nutrition Reviews*, 75, 83–97.

Bost, M., Houdart, S., Oberli, M., Kalonji, E., Huneau, J.-F. & Margaritis, I. 2016. Dietary copper and human health: Current evidence and unresolved issues. *Journal of Trace Elements in Medicine and Biology*, 35, 107–115.

Braga, D. P. A. F., Halpern, G., Setti, A. S., Figueira, R. C. S., Iaconelli, A. & Borges, E. 2015. The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation. *Reproductive BioMedicine Online*, 31, 30–38.

Brawerman, G. M. & Dolinsky, V. W. 2018. Therapies for gestational diabetes and their implications for maternal and offspring health: Evidence from human and animal studies. *Pharmacological Research*, 130, 52–73.

Cañete, A., Cano, E., Muñoz-Chápuli, R. & Carmona, R. 2017. Role of vitamin A/retinoic acid in regulation of embryonic and adult hematopoiesis. *Nutrients*, 9, 159.

Catalani, S., Paganelli, M., Gilberti, M. E., Rozzini, L., Lanfranchi, F., Padovani, A. & Apostoli, P. 2018. Free copper in serum: An analytical challenge and its possible applications. *Journal of Trace Elements in Medicine and Biology*, 45, 176–180.

Cazarotto, C. J., Boito, J. P., Glombowsky, P., Baggio, R. A., Galli, G. M., Machado, G., Bottari, N. B., Leal, M. L. R., Kessler, J. D., Baldissera, M. D. & Da Silva, A. S. 2019. Nutraceutical effect of trace elements as additional injectable doses to modulate oxidant and antioxidant status, and improves the quality of lamb meat. *Biological Trace Element Research*, 191, 115.

Chiu, Y. H., Karmon, A. E., Gaskins, A. J., Arvizu, M., Williams, P. L., Souter, I., Rueda, B. R., Hauser, R., Chavarro, J. E. & For The, E. S. T. 2017. Serum omega-3 fatty acids and treatment outcomes among women undergoing assisted reproduction. *Human Reproduction*, 33, 156–165.

Comerford, K. B., Ayoob, K. T., Murray, R. D. & Atkinson, S. A. 2016. The role of avocados in maternal diets during the periconceptional period, pregnancy, and lactation. *Nutrients*, 8, 313.

De Guzman, J. A. S., Beltran, R. J. L., Rubio, R. & Ramos, G. B. 2015. Potential of pre–gestational intake of *Laportea interrupta* L. (stinging nettle) leaf decoction as an aid for fetal–maternal health. *Asian Pacific Journal of Reproduction*, 4, 85–90.

De-Regil, L. M., Fernández-Gaxiola, A. C., Dowswell, T. & Peña-Rosas, J. P. 2010. Effects and safety of periconceptional folate supplementation for preventing birth defects. *The Cochrane Database of Systematic Reviews*, (10), CD007950–CD007950.

Dean, S. V., Lassi, Z. S., Imam, A. M. & Bhutta, Z. A. 2014. Preconception care: Nutritional risks and interventions. *Reproductive Health*, 11, S3.

Doğan, Z., Kocahan, S., Erdemli, E., Köse, E., Yilmaz, I., Ekincioğlu, Z., Ekinci, N. & Turkoz, Y. 2015. Effect of chemotherapy exposure prior to pregnancy on fetal brain tissue and the potential protective role of quercetin. *Cytotechnology*, 67, 1031–1038.

Farrar, D., Duley, L., Dowswell, T. & Lawlor, D. A. 2017. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. *Cochrane Database of Systematic Reviews*, (8)

Gagné, F. 2014. Chapter 6 - Oxidative stress. *In*: Gagné, F. (ed.) *Biochemical Ecotoxicology*. Oxford: Academic Press.

Garcia, R., Ali, N., Griffiths, M. & Randhawa, G. 2018. Understanding the consumption of folic acid during preconception, among Pakistani, Bangladeshi and white British mothers in Luton, UK: A qualitative study. *BMC Pregnancy and Childbirth*, 18, 234–234.

Gaskins, A. J., & Chavarro, J. E. 2018. Diet and fertility: A review. *American Journal of Obstetrics and Gynecology*, 218, 379–389.

Genuis, S. J. & Genuis, R. A. 2016. Preconception care: A new standard of care within maternal health services. *BioMed Research International*, 2016, 6150976.

Godfrey, K. M., Cutfield, W., Chan, S.-Y., Baker, P. N. & Chong, Y.-S. 2017. Nutritional intervention preconception and during pregnancy to maintain healthy glucose metabolism and offspring health ("NiPPeR"): Study protocol for a randomised controlled trial. *Trials*, 18, 131.

Hernández, A. F. & Gil, F. 2016. Chapter 59 - Nutraceuticals and adverse outcome pathways. *In*: Gupta, R. C. (ed.) *Nutraceuticals*. Boston: Academic Press.

Hester, J., Hanna-Rose, W. & Diaz, F. 2017. Zinc deficiency reduces fertility in *C. elegans* hermaphrodites and disrupts oogenesis and meiotic progression. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, 191, 203–209.

Huang, Y., Liu, T. & Sun, C. 2015. Little beneficial effect of maternal vitamin supplement on metabolic disturbances in the offspring from the obese mother mice. *The Journal of Maternal-Fetal & Neonatal Medicine*, 28, 272–275.

Hynes, K. L., Seal, J. A., Otahal, P., Oddy, W. H. & Burgess, J. R. 2019. Women remain at risk of iodine deficiency during pregnancy: The importance of iodine supplementation before conception and throughout gestation. *Nutrients*, 11, 172.

Jeon, Y., Yoon, J. D., Cai, L., Hwang, S.-U., Kim, E., Lee, E., Jeung, E. B. & Hyun, S.-H. 2015. Effect of zinc on in vitro development of porcine embryos. *Theriogenology*, 84, 531–537.

Karamali, M., Asemi, Z., Ahmadi-Dastjerdi, M. & Esmaillzadeh, A. J. P. H. N. 2016. Calcium plus vitamin D supplementation affects pregnancy outcomes in gestational diabetes: Randomized, double-blind, placebo-controlled trial. 19, 156–163.

La Vecchia, I., Paffoni, A., Castiglioni, M., Ferrari, S., Bortolus, R., Ferraris Fusarini, C., Bettinardi, N., Somigliana, E. & Parazzini, F. 2017. Folate, homocysteine and selected vitamins and minerals status in infertile women. *The European Journal of Contraception & Reproductive Health Care*, 22, 70–75.

Lass, A. & Belluzzi, A. 2019. Omega-3 polyunsaturated fatty acids and IVF treatment. *Reproductive BioMedicine Online*, 38, 95–99.

Lee, B. H., Park, T. C. & Lee, H. J. 2014. Association between fetal abdominal circumference and birthweight in maternal hyperglycemia. *Acta Obstetrica et Gynecologica Scandinavica*, 93, 786–793.

Looman, M., Van Den Berg, C., Geelen, A., Samlal, R., Heijligenberg, R., Klein Gunnewiek, J., Balvers, M., Leendertz-Eggen, C., Wijnberger, L., Feskens, E. & Brouwer-Brolsma, E. 2018. Supplement use and dietary sources of folate, vitamin D, and n-3 fatty acids during preconception: The GLIMP2 study. *Nutrients*, 10, 96.

Macaulay, S., Munthali, R., Dunger, D. B. & Norris, S. A. 2018. The effects of gestational diabetes mellitus on fetal growth and neonatal birth measures in an African cohort. *Diabetic Medicine*, 35, 1425–1433.

Mokni, M., Hamlaoui, S., Kadri, S., Limam, F., Amri, M., Marzouki, L. & Aouani, E. 2015. Efficacy of grape seed and skin extract against doxorubicin-induced oxidative stress in rat liver. *Pakistan Journal of Pharmaceutical Sciences*, 28.

Morais, C. A., Oyama, L. M., De Moura Conrado, R., De Rosso, V. V., Do Nascimento, C. O. & Pisani, L. P. 2015. Polyphenols-rich fruit in maternal diet modulates inflammatory markers and the gut microbiota and improves colonic expression of ZO-1 in offspring. *Food Research International*, 77, 186–193.

Moran, J. L., Tsagareli, V., Noakes, M. & Norman, R. 2016. Altered preconception fatty acid intake is associated with improved pregnancy rates in overweight and obese women undertaking in vitro fertilisation. *Nutrients*, 8, 10.

Mukherjee, P. K., Harwansh, R. K., Bahadur, S., Duraipandiyan, V. & Al-Dhabi, N. A. 2017. Chapter 34 - factors to consider in development of nutraceutical and dietary supplements. *In*: Badal, S. & Delgoda, R. (eds.) *Pharmacognosy*. Boston: Academic Press.

Mumford, S. L., Chavarro, J. E., Zhang, C., Perkins, N. J., Sjaarda, L. A., Pollack, A. Z., Schliep, K. C., Michels, K. A., Zarek, S. M., Plowden, T. C., Radin, R. G., Messer, L. C., Frankel, R. A. & Wactawski-Wende, J. 2016. Dietary fat intake and reproductive hormone concentrations and ovulation in regularly menstruating women. *The American Journal of Clinical Nutrition*, 103, 868–877.

Nasri, H., Baradaran, A., Shirzad, H. & Rafieian-Kopaei, M. 2014. New concepts in nutraceuticals as alternative for pharmaceuticals. *International Journal of Preventive Medicine*, 5, 1487.

Nguyen, P. H., Gonzalez-Casanova, I., Young, M. F., Truong, T. V., Hoang, H., Nguyen, H., Nguyen, S., DiGirolamo, A. M., Martorell, R. & Ramakrishnan, U. 2017. Preconception micronutrient supplementation with iron and folic acid compared with folic acid alone affects linear growth and fine motor development at 2 years of age: A randomized controlled trial in Vietnam. *The Journal of Nutrition*, 147, 1593–1601.

Ouyang, F., Longnecker, M. P., Venners, S. A., Johnson, S., Korrick, S., Zhang, J., Xu, X., Christian, P., Wang, M.-C. & Wang, X. 2014. Preconception serum 1,1,1-trichloro-2,2, bis(p-chlorophenyl)ethane and B-vitamin status: Independent and joint effects on women's reproductive outcomes. *The American Journal of Clinical Nutrition*, 100, 1470–1478.

Palmer, A. C., Schulze, K. J., Khatry, S. K., De Luca, L. M. & West, K. P. 2015. Maternal vitamin A supplementation increases natural antibody concentrations of preadolescent offspring in rural Nepal. *Nutrition*, 31, 813–819.

Pauwels, S., Ghosh, M., Duca, R. C., Bekaert, B., Freson, K., Huybrechts, I., As Langie, S., Koppen, G., Devlieger, R. & Godderis, L. 2017. Dietary and supplemental maternal methyl-group donor intake and cord blood DNA methylation. *Epigenetics*, 12, 1–10.

Pirro, M., Mannarino, M. R., Bianconi, V., Simental-Mendía, L. E., Bagaglia, F., Mannarino, E. & Sahebkar, A. 2016. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. *Pharmacological Research*, 110, 76–88.

Procter, S. B., Campbell, C. G. 2014. Position of the Academy of Nutrition and Dietetics: Nutrition and lifestyle for a healthy pregnancy outcome. *Journal of the Academy of Nutrition and Dietetics*, 114, 1099–1103.

Qian, Y. Y., Huang, X. L., Liang, H., Zhang, Z. F., Xu, J. H., Chen, J. P., Yuan, W., He, L., Wang, L., Miao, M. H. & Du, J. 2016. Effects of maternal folic acid supplementation on gene methylation and being small for gestational age. *Journal of Human Nutrition and Dietetics*, 29, 643–651.

Reid, G., Kumar, H., Khan, A., Rautava, S., Tobin, J. & Salminen, S. 2016. The case in favour of probiotics before, during and after pregnancy: Insights from the first 1,500 days. *Beneficial Microbes*, 7, 353–362.

Scaioli, E., Sartini, A., Bellanova, M., Campieri, M., Festi, D., Bazzoli, F. & Belluzzi, A. 2018. Eicosapentaenoic acid reduces fecal levels of calprotectin and prevents relapse in patients with ulcerative colitis. *Clinical Gastroenterology and Hepatology*, 16, 1268–1275. e2.

Sharif, M. K. & Khalid, R. 2018. Nutraceuticals: Myths versus realities. *In*: Holban, A. M. & Grumezescu, A. M. (eds.) *Therapeutic Foods* (pp. 3–21). Academic Press.

Shaw, O. E. & Yager, J. Y. 2019. Preventing childhood and lifelong disability: Maternal dietary supplementation for perinatal brain injury. *Pharmacological Research*, 139, 228–242.
Singh, R. K. 2016. Nutraceuticals in reproductive and developmental disorders. *In*: Gupta, R. C. (ed.) *Nutraceuticals* (pp. 123–134). Boston: Academic Press.
Singh, S., Razak, M. A., Sangam, S. R., Viswanath, B., Begum, P. S. & Rajagopal, S. 2018. The impact of functional food and nutraceuticals in health. *In*: *Therapeutic Foods*. Elsevier.
Steel, A., Adams, J. & Sibbritt, D. 2017. The characteristics of women who use complementary medicine while attempting to conceive: Results from a nationally representative sample of 13,224 Australian women. *Women's Health Issues*, 27, 67–74.
Stephenson, J., Heslehurst, N., Hall, J., Schoenaker, D. A. J. M., Hutchinson, J., Cade, J. E., Poston, L., Barrett, G., Crozier, S. R., Barker, M., Kumaran, K., Yajnik, C. S., Baird, J. & Mishra, G. D. 2018. Before the beginning: Nutrition and lifestyle in the preconception period and its importance for future health. *The Lancet*, 391, 1830–1841.
Stevens, A., Gilder, M. E., Moo, P., Hashmi, A., Toe, S. E. T., Doh, B. B., Nosten, S., Chotivanich, K., Somerset, S. & Mcgready, R. 2018. Folate supplementation to prevent birth abnormalities: Evaluating a community-based participatory action plan for refugees and migrant workers on the Thailand-Myanmar border. *Public Health*, 161, 83–89.
Sun, G. Y., Simonyi, A., Fritsche, K. L., Chuang, D. Y., Hannink, M., Gu, Z., Greenlief, C. M., Yao, J. K., Lee, J. C. & Beversdorf, D. Q. 2018. Docosahexaenoic acid (DHA): An essential nutrient and a nutraceutical for brain health and diseases. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 136, 3–13.
Supic, G., Zeljic, K. & Magic, Z. 2018. Chapter 15 - Epigenetic nutraceuticals in cancer treatment. *In*: Holban, A. M. & Grumezescu, A. M. (eds.) *Therapeutic Foods*. Academic Press.
Tabeshpour, J., Mehri, S., Shaebani Behbahani, F. & Hosseinzadeh, H. 2018. Protective effects of Vitis vinifera (grapes) and one of its biologically active constituents, resveratrol, against natural and chemical toxicities: A comprehensive review. *Phytotherapy Research*, 32, 2164–2190.
Tang, Y., Li, Y., Yu, H., Gao, C., Liu, L., Chen, S., Xing, M., Liu, L. & Yao, P. 2014. Quercetin prevents ethanol-induced iron overload by regulating hepcidin through the BMP6/SMAD4 signaling pathway. *The Journal of Nutritional Biochemistry*, 25, 675–682.
Tian, X. & Diaz, F. J. 2013. Acute dietary zinc deficiency before conception compromises oocyte epigenetic programming and disrupts embryonic development. *Developmental Biology*, 376, 51–61.
Toivonen, K. I., Oinonen, K. A. & Duchene, K. M. 2017. Preconception health behaviours: A scoping review. *Preventive Medicine*, 96, 1–15.
Wilson, R. D., Audibert, F., Brock, J.-A., Carroll, J., Cartier, L., Gagnon, A., Johnson, J.-A., Langlois, S., Murphy-Kaulbeck, L., Okun, N. & Pastuck, M. 2015. Pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies. *Journal of Obstetrics and Gynaecology Canada*, 37, 534–549.
Wise, L. A., Wesselink, A. K., Tucker, K. L., Saklani, S., Mikkelsen, E. M., Cueto, H., Riis, A. H., Trolle, E., McKinnon, C. J., Hahn, K. A. & Rothman, K. J. 2017. Dietary fat intake and fecundability in 2 preconception cohort studies. *American Journal of Epidemiology*, 187, 60–74.
Wu, M. & Yang, F. 2017. Research advances in the association between maternal intake of methyl donor nutrients during pregnancy and DNA methylation in offspring. *Chinese Journal of Contemporary Paediatrics*, 19, 601–606.
Xiao, L., Luo, G., Tang, Y. & Yao, P. 2018. Quercetin and iron metabolism: What we know and what we need to know. *Food and Chemical Toxicology*, 114, 190–203.
Yan, S.-L., Wang, Z.-H., Yen, H.-F., Lee, Y.-J. & Yin, M.-C. 2016. Reversal of ethanol-induced hepatotoxicity by cinnamic and syringic acids in mice. *Food and Chemical Toxicology*, 98, 119–126.

4

The Role of Nutraceuticals in the Placental Growth, Development and Function

Maryam Miraghajani and Michael E. Symonds

Contents

4.1 Introduction

4.1.1 What Are Nutraceuticals?

About 2,000 years ago, Hippocrates correctly stated "Let food be your medicine and medicine be your food" (1). Currently there is an increased global interest due to the recognition that "nutraceuticals" play a major role in health enhancement (2).

Nutraceuticals, which have also been called medical foods, designer foods, phytochemicals, functional foods and nutritional supplements, include such everyday products as "bio" yogurts and fortified breakfast cereals, as well as vitamins, herbal remedies and even genetically modified foods and supplements (3). Overall, nutraceuticals should provide a health benefit to the consumer that is greater than that of a general food item. Indeed, they

are non-specific biological therapies used to promote wellness and prevent chronic diseases (4).

4.1.2 The Developmental Origins of Health And Disease

Many animal studies and human epidemiological findings have shown that impaired growth in utero is associated with physiological abnormalities in later life and have linked this to tissue programming during suboptimal intrauterine conditions at critical periods of development (5, 6). As the importance of foods and nutrients on in utero growth has been established, the field of "developmental origins of health and disease" has emerged. It considers that programming during critical periods of early development following fetal nutrition exposure in pregnancy permanently alters certain aspects of the metabolic status and an organism's physiology, which consequences are often observed much later in adulthood (7–9).

Among the potential mechanisms proposed to regulate early-life programming, that of epigenetics is one candidate, explaining gene expression adaptations that persist in the long term. Epigenetic marks can be remodeled during development. Consequently, exposure to adverse environments during critical developmental windows can trigger long-lasting influences on the epigenome of the differentiating cell. The resulting changes in epigenetic marks may alter cell fate and the growth and development of tissues and organs, and may subsequently be responsible for adverse responses to later challenges, such as an obesogenic environment (10, 11).

Placental growth, development and function is an important feature of the "developmental origins of health and disease" phenomenon. As the interface between mother and fetus, the placenta plays a primary role in fetal growth and development (12, 13). Also as fetal life is characterized by a great plasticity and ability to respond to various environmental factors (14), changes in nutrition can influence epigenetic enzymes and placental development, leading to greater susceptibility to adult disease (12, 14, 15).

4.1.3 The Placenta and its Role in Fetal Programming

The placenta is one of the most important mammalian organs, not only for the health of the fetus and the mother during pregnancy but also for the lifelong health of both. Placental structure and function affect the health of the mother, as seen in the impaired development with preeclampsia, gestational hypertension and diabetes (16). It is a regulator of nutrient supply, respiratory gases exchange and waste product removal, and it controls fetal growth and development. Hormonal signals, which affect maternal and fetal metabolism (17–19) also arise from the placenta. Indeed, during its transient existence, the placenta performs actions that are later taken on by a diverse range of organs, including the lungs, liver, gut, kidneys and endocrine glands. Alterations in the placental growth, development and function can contribute

to fetal programming (17–19). Adverse maternal conditions can affect placental morphology, blood flow, feto-maternal nutrient exchanges and endocrine function, which modify placental efficiency (17–19). The effects on placental development and function are linked to the type of insult, stage of development and sex of the conceptus (20, 21).

Early placental angiogenesis is critical for the establishment of the placental vasculogenesis and thus for normal fetal programming, growth and development (22–24). The health of future generations may be damaged, and the incidence of some diseases can increase as a consequence of disturbed placental vasculogenesis development (25). Such maladaptations can be dependent on various factors including over- or undernutrition, maternal age or parity, body mass index and genetic background (22–24). For example, altered one carbon metabolism such as folate and vitamin B12 contribute to disturbed angiogenesis and placental apoptosis in women with preeclampsia (26). Docosahexaenoic acid (DHA) 22:6 n-3 as well as some other fatty acids including conjugated linoleic acid (CLA), can stimulate angiogenesis in placental first trimester cells. These dietary fatty acids stimulated the expression of not only major angiogenic factors such as vascular endothelial growth factor (VEGF) and angiopoietin-like 4 (ANGPTL4), but also fatty acid-binding proteins (FABP-4 and FABP-3), which directly modulate angiogenesis (27). Placental circulation through uterine and umbilical blood flow also contributes to a successful pregnancy and normal fetal growth (28, 29). Impaired fetal or placental growth, or both, are associated with reduced utero-placental blood flow (30). Abnormal blood flow can cause reduced placental area and weight resulting in abnormal fetal growth (28).

As mentioned previously, the placenta facilitates substrate exchange for the fetus between maternal and fetal circulations. Substances have to cross several cellular placental layers, which are characterized by the processes of simple or facilitated diffusion or active transport, that depend on the type of components (31, 32). Inappropriate placental nutrient transfer capacity has the potential to cause fetal programming effects through its impact on nutrient supply. It is responsive to a wide range of environmental factors including foods and nutrients. Placental size directly affects the capacity for nutrient transfer through changes in the surface area for transport and, when measured as a proportion of placental weight, is positively correlated to body weight at term in a wide range of species (20, 33). Also, the abundance of transporters, the concentration gradient between maternal and fetal compartments, and placental metabolism are all sensitive to foods and nutrients as environmental stimuli (20, 33).

The placenta is also an endocrine organ, which secretes hormones in both maternal and fetal circulations and controls fetal growth and maternal metabolism. These hormones are important for the establishment and maintenance of pregnancy, exerting autocrine and paracrine effects that regulate placental development, angiogenesis, endometrial receptivity, embryo implantation,

immunotolerance and fetal development. Placental hormones also have profound effects modulating maternal energy reserves that are then released to support fetal growth in later pregnancy and lactation (34, 35). They include progesterone, placental lactogen and the placental variant of the growth hormone and facilitate glucose delivery to the fetus. Insulin-like growth factor (IGF) II can modulate nutrient exchange between maternal and fetal circulations specifically for simple and facilitated diffusion. Prostaglandins and corticotropin-releasing hormone (CRH) also control fetal nutrient and oxygen supply by effecting blood flow and myometrial contractility. These examples illustrate that dysregulation of placental hormones could adversely impact maternal and fetal metabolism, fetal growth and postnatal metabolic function (20). Promoting optimal nutrition can ensure effective placental growth and development including angiogenesis, circulation, nutrient transfer capacity and placental hormone production (36).

It should be mentioned that although the placenta has long been considered a 'sexless' organ, due to its fetal origin (37), the long-term effects of the same environmental insult, such as unbalanced maternal nutrition, can have different phenotypic effects on male and female offspring. In many species, the placentas of male fetuses are bigger than those of female fetuses and can have a different shape. This is linked to the sexually dimorphic placental response to changes in maternal nutrition. For example, the Dutch famine at the end of the Second World War caused a decrease in placental size and area, with the long-term effect of reduced placental area being more severe for males (38). Furthermore, the health outcomes differed, and it was only in males that changes in placental shape were associated with the onset of hypertension later in life (39). Male fetuses appeared to be less adaptive, leading to an increased risk of neonatal complications and death, and thereby contributing to sex-specific differences. However, the mechanisms underlying these sex-specific outcomes remain to be fully elucidated (40, 41).

4.2 Nutraceutical Supplements and Placental Growth, Development and Function

Maternal nutraceutical intake in humans and animals can interfere with normal placental growth and development as reflected by changes in placental weight, size, peripheral villous mass, villous surface and deoxyribonucleic acid (DNA) content (42). They have several roles in regulating placental growth, development and function. These include providing nutrients for the placenta, controlling vascularization, metabolic function, modifying gene expression and DNA methylation, and the prevention of oxidative stress and inflammation (43). So one of the intervention strategies for targeting the placenta in order to optimize fetal growth could include modifying maternal nutraceutical intake. The most popular nutraceuticals supplements include folic acid, vitamin B12, omega-3, vitamin D

and antioxidants, which are all known to contribute to placental growth, development and function (44–48).

4.2.1 Folic Acid

Genome-wide epigenetic regulations such as DNA methylation participate in many aspects of placenta development, including trophoblast cell adhesion and invasion, angiogenesis and placental imprinted gene expression. In mammals, DNA methylation occurs predominantly at cytosines in CpG dinucleotides, which depend upon the availability of methyl groups, and can impact on the placenta (49).

Genomic imprinting as an epigenetic process is responsible for the monoallelic expression of a subset of genes. Indeed, it results in the expression of those genes from only one of the two parental chromosomes. This process has an important role in feto-placental development and function. Adverse imprinting disrupts development and is the cause of various disease syndromes (49–51). For example, *IGF2/H19* imprinted genes are associated with fetal growth. In contrast to the paternal expressed of the IGF2, the maternal allele of the mentioned gene is silenced through DNA methylation. The maternally expressed H19 is located downstream of IGF2 encoding a noncoding RNA, which regulates cellular growth. Loss of imprinting leads to reactivation of the silent allele, resulting in biallelic expression and several disorders, such as Angelman syndrome (25) and Prader-Willi syndrome (49).

Some nutraceuticals, such as folic acid, contribute to placental growth and development by modulating global DNA methylation and imprinted gene expression. This nutrient acts as a single carbon methyl donor, which generates methyl groups for DNA methylation(49–51), but there have been relatively few human studies. Although, some findings suggest that maternal folate concentrations during weeks 24–28 of gestation affect DNA methylation in the placenta (44), others do not (52). Tserga et al. investigated the association between folic acid supplementation during pregnancy and loss of imprinting of *IGF2* and *H19* genes in placenta and cord blood of 90 mother–child dyads. Pyrosequencing data showed no significant associations between self-reported supplement use before pregnancy and imprinting control of H19 in the placenta (52).

As well as the important role of folic acid in DNA methylation, this nutrient is essential for the synthesis of DNA, cellular division and proliferation, and development of the placenta including extravillous trophoblast invasion, angiogenesis and secretion of the matrix metalloproteinases (53). Low folate concentrations in early pregnancy can adversely influence placentation, increase the risk for preterm birth and lead to fetal growth retardation (53). When cultured with folic acid, placental explants at 7 weeks gestation increases extravillous trophoblast invasion, proliferation and vascular density, and decreased apoptosis (54). Also, a population-based prospective cohort study including 5,993 pregnant women showed self-reported low-dose

periconception folic acid supplementation was associated with a significant reduction in uteroplacental vascular resistance (55). However, a meta-analysis in 2012 investigating the effect of folic acid supplementation on placental weight did not find any beneficial effect (50).

With regard to increased folic acid requirements in pregnancy to meet fetal demands (56), a direct link between maternal folic acid intake and complications in pregnancy the World Health Organization (WHO), recommends at least 400 μg/d of folic acid intake periconceptually to prevent developmental defects (57). Other guidance for healthy women is 400–800 μg/d preconceptually and throughout the first trimester. In many countries folic acid supplementation is recommended for all women at reproductive age as many pregnancies are unplanned (56). Folic acid supplementation may have adverse effects in individuals with a low vitamin B12 level and has been associated with increased incidence of small for gestational age (SGA) births (56). In vitro, high folic acid alone had a detrimental effect on placental health and functions through decreased viability, epidermal growth factor receptor (EGFr) expression and increased tumor necrosis factor alpha (TNFα) expression, homocysteine and malondialdehyde (MDA) levels (58). Furthermore, additional supplementation with folate during pregnancy, coupled with a low intakes of vitamin B12, could increase the ratio of folate/vitamin B12 which can alter DNA methylation, by hyper- or hypomethylation of specific genes, by inhibiting (protective genes) or by increasing (disease-related genes) respectively. The subsequent changes in gene expression of those genes lead to long-term effects, so the possible consequences of an elevated folate maternal intake on the offspring should be considered (59).

On the other hand, folic acid metabolism enzymes such as methylenetetrahydrofolate reductase (MTHFR) have important roles in the maintenance of normal placenta and fetal development. Not only does folic acid intake affect serum folate but single-nucleotide polymorphisms (SNPs) in MTHFR influence folate metabolism. For example, individuals with the MTHFR 677TT genotype have significantly lower serum folate compared to other genotypes. Moreover, interventions based on genotype may be more effective for motivating individuals to change their lifestyle and improve their nutrition (60). So, folic acid supplementation based on personalized nutrition by considering their genotype could be more effective.

4.2.2 Vitamin B12

Similar to folic acid, vitamin B12 is involved in one carbon metabolism, which generates purines and thymidylate for DNA synthesis and repair, while S-adenosylmethionine (SAM), the donor for cellular methylation reactions, remethylates cytotoxic homocysteine to methionine. Also, the close metabolic interrelationship between vitamin B12 and folate is best explained by the methyl trap hypothesis stating that vitamin B12 deficiency lowers methionine synthetase, which results in a functional folate deficiency by trapping an

increased proportion of folate as the 5-methyl derivative (61). Although vitamin B12 deficiency is common among vegetarians due to suboptimal intake, the fetus and the pregnant woman are more likely to suffer from a deficiency of this vitamin due to their greater requirements (56). Both folic acid and vitamin B12 are present at higher concentrations in fetal than maternal circulation because of the fetal capacity for absorption, transport and intracellular storage, which are all tightly controlled (56). However, there are relatively few human studies in this area. In the human placenta, methylated CpG sites in the methionine synthase (MTR) gene, a gene encoded methionine synthase, were negatively associated with maternal plasma vitamin B12 (46); and in another study, pregnant women with low serum vitamin B12 concentrations (<200 pmol/L) who received balanced protein-energy supplementation of 500 mL milk/d plus a 10-μg vitamin B12 tablet/d did not have any significant difference in placental mRNA expression of genes involved in methionine pathways, and placental long interspersed nuclear elements-1 (LINE-1) (62).

Many molecular and cellular mechanisms associated with methyl donor deficiency including folic acid and vitamin B12 during pregnancy lead to restricted placental growth and development. Mounting evidence in studies of both animals and humans indicates that oxidative stress induces injury on the developing embryo, which is extremely sensitive to oxygen tension and oxygen free radical species. The consequences of oxidative stress in embryonic tissues appear to be modifications in differentiation and development. Similar to the fetus, the placenta is susceptible to oxygen free radical generation, so detoxification must occur in order to avoid placenta damage (63).

Recently evidence for a critical role of folic acid in protection against oxidative stress, through the generation of nicotinamide adenine dinucleotide phosphate (NADPH) has emerged (56). Also, folic acid and vitamin B12, through restitution in the one-carbon metabolic pathway and cellular methyl pool, exert antioxidative actions against high homocysteine (26, 64, 65). Homocysteine is involved in the formation of free radicals leading to increased oxidative stress, thereby stimulating apoptotic markers in the placenta (26). High homocysteine following folic acid or vitamin B12 deficiency also down-regulates peroxisome proliferator-activated receptor (PPAR) expression. PPARs are nuclear transcription factors that mediate the effects of folic acid and B12 on gene expression responses during placental development. Interestingly, all nuclear transcription factor isotypes are expressed in the placenta and play key roles during placentation. A recent review suggested that deficiency of folic acid and vitamin B12 reduced the expression of PPARs, thereby restricting placental growth (66). Elevated homocysteine has also been implicated in placental vascular changes and endothelial dysfunction-related complications of pregnancy and adverse neonatal outcomes. The placental chorionic plate artery distensibility index of vessel stiffness, has been inversely related to cord arterial maternal and fetal total homocysteine levels. This potential interaction between homocysteine and placental artery distensibility emphasizes the clinical relevance of vitamin B12 in the mother and fetus, with the

maintenance of low vascular resistance needed to facilitate nutrient exchange (67). Placental epigenetic programming is another possible mechanism for affecting the availability of methyl group donors and placental growth and development. An imbalance in maternal intake of folate and vitamin B12 alters the methyl group transfer to DNA. This leads to changes in the placental epigenetic profiles leading to change the expression of various vital genes that are important for fetal programming and also for the onset of chronic diseases in later life (68).

4.2.3 Omega-3

The fetus not only requires the maternal dietary intake of essential fatty acids, but also their subsequent transfer from the placenta to support rapid cellular growth and activity (69). Essential fatty acid intake can modify placental function. Suboptimal intake can lead to placenta-related disorders, including intrauterine growth restriction (IUGR), preeclampsia, gestational diabetes mellitus and spontaneous miscarriage. Maternal dietary supplementation with omega-3 as an essential fatty acid during pregnancy reduces the risk of these disorders and enhances fetal growth (70).

Its supplementation to overweight and obese women during mid- to late-pregnancy inhibits the placenta's ability to esterify lipids and lipid accumulation leading to reduced lipotoxicity and inflammation (45, 71). The placenta of women treated with DHA plus EPA (2g/d) from weeks 10–16 to term exhibited lower, toll-like receptor 4 (TLR4) placental gene expression as a central target of the anti-inflammatory treatments (71), although not found in all studies (72).

Interestingly, transcriptome data sets suggest that human placenta show sexually dimorphic gene expression and responsiveness to maternal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation with more pronounced effects in female fetuses (73). Fetal growth and birth weight (74) can also be affected, and maybe male fetus are better able to maintain their growth independently of environmental stimuli. For example, in female placenta from the intervention group, the adipogenesis pathway was up-regulated, through several pathways, such as adipogenesis, cell cycling and Wnt signaling (73).

Pregnancy represents a state of oxidative stress and inflammation that can lead to complications, however, these may be prevented with omega-3 LCPUFA supplementation (75), as summarized in a review from 2014. Despite the differing pathologies of placental dysfunction, inflammatory and oxidative stress are potential risk factors. n-3 polyunsaturated fatty acids (PUFAs) appear to promote vascular development, and angiogenesis, which can enhance placental growth (70). They contain phospholipids, one of the major methyl group acceptors in the one-carbon metabolism pathway. Therefore, inadequacy of n-3 PUFA may disrupt methyl groups, resulting in aberrant DNA methylation. These changes can lead to alterations in the genes expression affecting

placental development and giving rise to a risk of chronic disease in later life through dysregulation of angiogenesis/vasculogenesis (68).

Some conflicting results in clinical trials regarding the impact of n-3 PUFAs supplementation on placenta might be due to the timing of supplementation (gestational age) (75). Furthermore, the effects of these fatty acids are dose-dependent, and, when excessive, they have the capacity to increase oxidative damage (75). However, variability in placenta responses to omega-3 LCPUFA supplementation can be explained by the inter- or intra-individual variation, fatty acid transfer capacity and maternal genome (75). It should be noted that, despite the potential benefits of n-3 PUFA intake during pregnancy, the World Health Organization states that evidence is as yet insufficient to support routine supplementation with fish oil during pregnancy and further research is needed before specific recommendations (70).

4.2.4 Vitamin D

At no other time during the lifespan is vitamin D status more important than during pregnancy, affecting not only the mother but her growing fetus, and, later, her offspring's long-term health (43, 47).

Over the last three decades, it has become clear that the role of vitamin D goes beyond maintaining calcium homeostasis and bone health. A significant role for vitamin D in modulating antimicrobial and anti-inflammatory responses within the placenta has been suggested (43, 76). Vitamin D can also stimulate the synthesis of hormones involved in pregnancy, such as estradiol, progesterone and human chorionic gonadotropin (hCG), which are important in maintaining placental blood flow and neovascularization (77). As the human placenta expresses all components for vitamin D signaling, including the vitamin D Receptor (VDR), retinoid X receptor (RXR), cytochrome p450 27B1 (CYP27B1) and cytochrome p450 24A1 (CYP24A1), recent researches emphasize the importance of vitamin D in the placental growth, development and function. The components mentioned facilitate response to vitamin D as a modulator of implantation, cytokine production and immune response to infection (76). However, there have been relatively few human studies to address this. In a prospective cohort study including 1,768 well-characterized low-risk, nulliparous pregnant women, the association of a 25(OH) D concentration and the risk of placental dysfunction at 15 weeks of gestation was assessed. It showed a protective association with a 25(OH) D concentration >75 nmol/L and placental dysfunction as indicated by a composite outcome of SGA and preeclampsia (47). Another link between low vitamin D_3 and impaired placental cytochrome P450scc activity inducing oxidative stress and pregnancy complications was reported in a randomized prospective study performed on a small group of 74 pregnant women (78). In addition, a significant association between maternal vitamin D and down-regulated gene expression of soluble FMS-like tyrosine kinase 1 (sFlt-1 or sVEGFR-1) and vascular endothelial growth factor in the placenta was reported. It might potentially

decrease antiangiogenic factors contributing to vascular pregnancy complications. The analysis of placental mRNA expression related to angiogenesis, pregnancy maintenance and vitamin D metabolism was conducted in placenta from 43 subjects enrolled in a randomized controlled trial supplementing 400 IU or 4,400 IU of vitamin D_3 per day during pregnancy (79).

Due to the importance of vitamin D level during pregnancy, it was suggested that all pregnant women maintain a circulating 25(OH) D concentration at least 40 ng/mL to achieve both better outcomes and the maximum protection from pregnancy complications. Based on randomized clinical trials and epidemiological data, daily intakes of at least 4,000 IU/d vitamin D_3 will be required because of individual variable abilities to convert vitamin D to its active form (25(OH) D). Furthermore this amount of supplementation is safe without any single adverse events in thousands of patients over the past 15 years (80).

4.2.5 Antioxidants

Oxidative stress is referred to as an imbalance between the generation of reactive oxygen species (ROS) or reactive nitrogen species (RNS) and their clearance by defensive antioxidants. Oxidative stress is generated during normal placental development and promotes replication, differentiation and maturation of cells. However, when the supply of antioxidant micronutrients is limited, exaggerated oxidative stress occurs that seems to be linked with pregnancy-related disorders through pathways such as an imbalance in the autophagy and apoptosis (81, 82). Antioxidants such as vitamins C and E are often investigated as promising therapies to reduce oxidative stress during pregnancy and in the placental level, and their beneficial effects have been shown in some but not all trials. Administration of these vitamins can mediate oxidative stress in human placenta through many pathways, including blocked activation of the p38 and stress-activated mitogen-activated protein kinase (MAPK) and nuclear factor-κB (48) Also they reduce cyclooxygenase-2 expression, tumor necrosis factor-α and interleukin-1β secretion, and apoptosis (48). As well as the well-known antioxidant function of vitamin C in the placenta, it serves as an essential cofactor to numerous monooxygenases and dioxygenases, including the ten-eleven translocation (TET) enzyme family. This catalyzes the hydroxylation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) in the active process of DNA demethylation (83, 84). However, there is a lack of human studies in this field.

Vitamin C supplementation (500 mg/d) in pregnant smokers has an effect on the placental genomic DNA libraries. It was associated with a reduction or reversal in smoking-related changes across the genome and across tissues at both hypo- and hypermethylated loci (85). Cigarette smoking reduces circulating vitamin C, a response linked to adverse effects on the fetus associated with modified DNA demethylation (83, 84). Further evidence suggests that taking vitamin C (1,000 mg/d) and vitamin E (400 IU/d) supplements in women at risk of preeclampsia was associated with an improvement in indices

of placental dysfunction and oxidative stress, including ascorbic acid, 8-epi-prostaglandin $F_{2\alpha}$, leptin and plasminogen activator inhibitor-1/-2 (86). In contrast, other clinical trials investigating the impact of vitamin C and E supplementation on antioxidant enzyme activity and lipid peroxidation in Type 1 diabetic placenta reported no significant effects of maternal supplementation on placental content of these vitamins, nor on placental antioxidant enzyme activity or lipid peroxidation indices (87). Another randomized placebo-controlled trial showed that daily maternal supplementation with vitamin C [1,000 mg] and vitamin E [400 IU], between 8 and 22 weeks' gestation until delivery, could not modulate placental p38-Mitogen-Activated Protein Kinase α (p38-MAPKα), as a oxidative stress response kinase, along with other members of the placental MAP kinase pathways including Extra Cellular-Signal Regulated Kinase (ERK) and c-Jun NH2-Terminal Kinase (JNK) activity (88). Other studies on oral administration of antioxidants including vitamin C and vitamin E in pregnant women who had hypertension decreased Bax, a pro-apoptotic protein, expression in placenta with no effect on Bcl-2 as an anti-apoptotic protein (89). The influence of maternal antioxidant supplements in the first trimester on placenta-related obstetric morbidity (composite analysis of preterm, premature rupture of membranes, preterm delivery, placental abruption, intrauterine growth restriction or pregnancy loss) has also been investigated by Parrish et al. Supplements of a blended fruit and vegetable juice powder concentrate derived from acerola cherry, apple, beet, broccoli, cabbage, carrot, cranberry, kale, orange, peach, papaya, parsley, pineapple, spinach and tomato, with each capsule providing B7.5 mg beta-carotene, 234 mg vitamin C, 30 mg vitamin E, 420 mg folate and 60 mg calcium. Although, the results revealed a decreased mean incidence in the antioxidant group compared with the placebo, they were not statistically significant (63).

4.3 Conclusion

The use of nutraceuticals has become increasingly popular in pregnancy due to their wide range of health benefits, easy access, cost-effectiveness and tolerability. However, human studies investigating the effects of maternal nutraceuticals supplementation on placental growth, development and function are scarce, and those available are inconsistent. In future, more longitudinal and well-designed studies are needed to decipher the impact of nutraceuticals on the placenta, fetus and long-lasting programming of chronic disease. They will help us to understand the possible link between alterations of placenta and its role in health and disease. It should be noted that the role of maternal nutraceutical intake during pregnancy on placental growth, development and function could be confounded by demographic, lifestyle and psychological characteristics. Furthermore, between and within individual variability, genetic factors and gene–environment interactions for placental growth, development and function should be considered in interpreting these results. So, a personalized nutraceutical intervention that not only accounts

for the nutritional needs but also includes each woman's genotype is needed to ensure any benefits for the health of their children.

References

1. Oszkiel H, Wilczak J, Jank M. Biologically active substances-enriched diet regulates gonadotrope cell activation pathway in liver of adult and old rats. *Genes & Nutrition*. 2014 Sep;9(Pubmed):427. PubMed PMID: 25156242. Central PMCID: PMC4172640. Epub 2014/08/27. eng.
2. Gupta RC, Srivastava A, Lall R. Toxicity potential of nutraceuticals. *Methods in Molecular Biology (Clifton, NJ)*. 2018;1800:367–94. PubMed PMID: 29934903. Epub 2018/06/24. eng.
3. Gupta S, Chauhan D, Mehla K, Sood P, Nair A. An overview of nutraceuticals: current scenario. *Journal of Basic and Clinical Pharmacy*. 2010;1(2):55.
4. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New concepts in nutraceuticals as alternative for pharmaceuticals. *International Journal of Preventive Medicine*. 2014 Dec;5(12):1487–99. PubMed PMID: 25709784. Pubmed Central PMCID: PMC4336979. Epub 2015/02/25. eng.
5. Dyer JS, Rosenfeld CR. Metabolic imprinting by prenatal, perinatal, and postnatal overnutrition: a review. *Seminars in Reproductive Medicine*. 2011 May;29(3):266–76. PubMed PMID: 21769766. Epub 2011/07/20. eng.
6. Symonds ME, Sebert SP, Budge H. The impact of diet during early life and its contribution to later disease: critical checkpoints in development and their long-term consequences for metabolic health: symposium on 'Early nutrition and later disease: current concepts, research and implications'. *Proceedings of the Nutrition Society*. 2009;68(4):416–21.
7. Ojha S, Fainberg HP, Sebert S, Budge H, Symonds ME. Maternal health and eating habits: metabolic consequences and impact on child health. *Trends in Molecular Medicine*. 2015;21(2):126–33.
8. Symonds ME, Sebert SP, Hyatt MA, Budge H. Nutritional programming of the metabolic syndrome. *Nature Reviews Endocrinology*. 2009;5(11):604.
9. Symonds ME, Stephenson T, Gardner DS, Budge H. Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. *Reproduction, Fertility and Development*. 2006;19(1):53–63.
10. Vickers MH. Early life nutrition, epigenetics and programming of later life disease. *Nutrients*. 2014 Jun;6(6):2165–78. PubMed PMID: 24892374. Pubmed Central PMCID: 4073141. Epub 2014/06/04. eng.
11. Gali Ramamoorthy T, Begum G, Harno E, White A. Developmental programming of hypothalamic neuronal circuits: impact on energy balance control. *Frontiers in Neuroscience*. 2015;9:126. PubMed PMID: 25954145. Pubmed Central PMCID: 4404811. Epub 2015/05/09. eng.
12. Miraghajani M, Salehi R, Hajianfar H. Prenatal nutrition exposure leading to adult obesity, diabetes, and hypertension. *Nutrigenomics and Nutraceuticals: Clinical Relevance and Disease Prevention*. 2017:377–404.
13. Symonds ME, Budge H, Perkins AC, Lomax MA. Adipose tissue development–impact of the early life environment. *Progress in Biophysics and Molecular Biology*. 2011;106(1):300–6.
14. Chango A, Pogribny IP. Considering maternal dietary modulators for epigenetic regulation and programming of the fetal epigenome. *Nutrients*. 2015 Apr;7(4):2748–70. PubMed PMID: 25875118. Pubmed Central PMCID: 4425171. Epub 2015/04/16. eng.
15. Canani RB, Costanzo MD, Leone L, Bedogni G, Brambilla P, Cianfarani S, et al. Epigenetic mechanisms elicited by nutrition in early life. *Nutrition Research Reviews*. 2011 Dec;24(2):198–205. PubMed PMID: 22008232. Epub 2011/10/20. eng.

16. Guttmacher AE, Maddox YT, Spong CY. The human placenta project: placental structure, development, and function in real time. *Placenta*. 2014;35(5):303–4.
17. Myatt L. Placental adaptive responses and fetal programming. *The Journal of Physiology*. 2006;572(1):25–30.
18. Jansson T, Powell TL. Role of the placenta in fetal programming: underlying mechanisms and potential interventional approaches. *Clinical Science*. 2007;113(1):1–13.
19. Godfrey KM. The role of the placenta in fetal programming—a review. *Placenta*. 2002;23:S20–S7.
20. Tarrade A, Panchenko P, Junien C, Gabory A. Placental contribution to nutritional programming of health and diseases: epigenetics and sexual dimorphism. *Journal of Experimental Biology*. 2015;218(1):50–8.
21. Aiken CE, Ozanne SE. Sex differences in developmental programming models. *Reproduction (Cambridge, England)*. 2013;145(1):R1–R13.
22. Charnock-Jones DS, Kaufmann P, Mayhew TM. Aspects of human fetoplacental vasculogenesis and angiogenesis. I. Molecular regulation. *Placenta*. 2004 FebMar;25(23):103–13. PubMed PMID: 14972443. Epub 2004/02/20. eng.
23. Kaufmann P, Mayhew TM, Charnock-Jones DS. Aspects of human fetoplacental vasculogenesis and angiogenesis. II. Changes during normal pregnancy. *Placenta*. 2004 FebMar;25(23):114–26. PubMed PMID: 14972444. Epub 2004/02/20. eng.
24. Bairagi S, Quinn KE, Crane AR, Ashley RL, Borowicz PP, Caton JS, et al. Maternal environment and placental vascularization in small ruminants. *Theriogenology*. 2016 Jul 1;86(1):288–305. PubMed PMID: 27173956. Epub 2016/05/14. eng.
25. Escudero C, Roberts JM, Myatt L, Feoktistov I. Impaired adenosine-mediated angiogenesis in preeclampsia: potential implications for fetal programming. *Frontiers in Pharmacology*. 2014;5:134. PubMed PMID: 24926270. Pubmed Central PMCID: PMC4046493. Epub 2014/06/14. eng.
26. Kasture VV, Sundrani DP, Joshi SR. Maternal one carbon metabolism through increased oxidative stress and disturbed angiogenesis can influence placental apoptosis in preeclampsia. *Life Sciences*. 2018 Aug 1;206:61–9. PubMed PMID: 29772225. Epub 2018/05/18. eng.
27. Basak S, Das MK, Duttaroy AK. Fatty acid-induced angiogenesis in first trimester placental trophoblast cells: possible roles of cellular fatty acid-binding proteins. *Life Sciences*. 2013 Nov 13;93(21):755–62. PubMed PMID: 24095946. Epub 2013/10/08. eng.
28. Salavati N, Sovio U, Mayo RP, Charnock-Jones DS, Smith GC. The relationship between human placental morphometry and ultrasonic measurements of uteroplacental blood flow and fetal growth. *Placenta*. 2016 Feb;38:41–8. PubMed PMID: 26907381. Epub 2016/02/26. eng.
29. Jansson T, Powell TL. Role of placental nutrient sensing in developmental programming. *Clinical Obstetrics and Gynecology*. 2013 Sep;56(3):591–601. PubMed PMID: 23703224. Pubmed Central PMCID: PMC3732521. Epub 2013/05/25. eng.
30. Reynolds LP, Caton JS, Redmer DA, Grazul-Bilska AT, Vonnahme KA, Borowicz PP, et al. Evidence for altered placental blood flow and vascularity in compromised pregnancies. *The Journal of Physiology*. 2006;572(1):51–8.
31. Desforges M, Greenwood SL, Glazier JD, Westwood M, Sibley CP. The contribution of SNAT1 to system A amino acid transporter activity in human placental trophoblast. *Biochemical and Biophysical Research Communications*. 2010 Jul 16;398(1):130–4. PubMed PMID: 20599747. Pubmed Central PMCID: PMC2941036. Epub 2010/07/06. eng.
32. Wloch S, Palasz A, Kaminski M. Active and passive transport of drugs in the human placenta. *Ginekologia Polska*. 2009 Oct;80(10):772–7. PubMed PMID: 19943543. Epub 2009/12/01. eng.
33. Fowden AL, Ward JW, Wooding F, Forhead AJ, Constancia M. Programming placental nutrient transport capacity. *The Journal of Physiology*. 2006;572(1):5–15.

34. Burton GJ, Fowden AL. The placenta: a multifaceted, transient organ. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences*. 2015 Mar 5;370(1663):20140066. PubMed PMID: 25602070. Pubmed Central PMCID: PMC4305167. Epub 2015/01/21. eng.
35. Costa MA. The endocrine function of human placenta: an overview. *Reproductive Biomedicine Online*. 2016 Jan;32(1):14–43. PubMed PMID: 26615903. Epub 2015/12/01. eng.
36. Guan Z, Li H-f, Guo L-l, Yang X. Effects of vitamin C, vitamin E, and molecular hydrogen on the placental function in trophoblast cells. *Archives of Gynecology and Obstetrics*. 2015;292(2):337–42.
37. Gabory A, Roseboom TJ, Moore T, Moore LG, Junien C. Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics. *Biology of Sex Differences*. 2013 Mar 21;4(1):5. PubMed PMID: 23514128. Pubmed Central PMCID: PMC3618244. Epub 2013/03/22. eng.
38. Roseboom T, Painter R, De Rooij S, Van Abeelen A, Veenendaal M, Osmond C, et al. Effects of famine on placental size and efficiency. *Placenta*. 2011;32(5):395–9.
39. van Abeelen AF, de Rooij SR, Osmond C, Painter RC, Veenendaal MV, Bossuyt PM, et al. The sex-specific effects of famine on the association between placental size and later hypertension. *Placenta*. 2011;32(9):694–8.
40. Gifford RM, Reynolds RM. Sex differences in early-life programming of the hypothalamic-pituitary-adrenal axis in humans. *Early Human Development*. 2017 Nov;114:7–10. PubMed PMID: 28927573. Epub 2017/09/21. eng.
41. Sundrani DP, Roy SS, Jadhav AT, Joshi SR. Sex-specific differences and developmental programming for diseases in later life. *Reproduction, Fertility, and Development*. 2017 Oct;29(11):2085–99. PubMed PMID: 28380326. Epub 2017/04/06. eng.
42. Rosso P, editor Placental growth, development, and function in relation to maternal nutrition. Federation Proceedings. 1980;39(2):250–4.
43. Richard K, Holland O, Landers K, Vanderlelie JJ, Hofstee P, Cuffe JSM, et al. Review: effects of maternal micronutrient supplementation on placental function. *Placenta*. 2017 Jun;54:38–44. PubMed PMID: 28031147. Epub 2016/12/30. eng.
44. Park BH, Kim YJ, Park JS, Lee HY, Ha EH, Min JW, et al. [Folate and homocysteine levels during pregnancy affect DNA methylation in human placenta]. *Journal of Preventive Medicine and Public Health = Yebang Uihakhoe chi*. 2005 Nov;38(4):437–42. PubMed PMID: 16358830. Epub 2005/12/20. kor.
45. Calabuig-Navarro V, Puchowicz M, Glazebrook P, Haghiac M, Minium J, Catalano P, et al. Effect of omega-3 supplementation on placental lipid metabolism in overweight and obese women. *The American Journal of Clinical Nutrition*. 2016 Apr;103(4):1064–72. PubMed PMID: 26961929. Pubmed Central PMCID: PMC4807706. Epub 2016/03/11. eng.
46. Khot VV, Yadav DK, Shrestha S, Kaur L, Sundrani DP, Chavan-Gautam PM, et al. Hypermethylated CpG sites in the MTR gene promoter in preterm placenta. *Epigenomics*. 2017 Jul;9(7):985–96. PubMed PMID: 28617183. Epub 2017/06/16. eng.
47. Kiely ME, Zhang JY, Kinsella M, Khashan AS, Kenny LC. Vitamin D status is associated with uteroplacental dysfunction indicated by pre-eclampsia and small-for-gestational-age birth in a large prospective pregnancy cohort in Ireland with low vitamin D status. *The American Journal of Clinical Nutrition*. 2016 Aug;104(2):354–61. PubMed PMID: 27357092. Epub 2016/07/01. eng.
48. Cindrova-Davies T, Spasic-Boskovic O, Jauniaux E, Charnock-Jones DS, Burton GJ. Nuclear factor-κB, p38, and stress-activated protein kinase mitogen-activated protein kinase signaling pathways regulate proinflammatory cytokines and apoptosis in human placental explants in response to oxidative stress: effects of antioxidant vitamins. *The American Journal of Pathology*. 2007;170(5):1511–20.
49. Kwan STC, King JH, Grenier JK, Yan J, Jiang X, Roberson MS, et al. Maternal choline supplementation during normal murine pregnancy alters the placental epigenome: results of an exploratory study. *Nutrients*. 2018;10(4):417.

50. Fowden A, Sibley C, Reik W, Constancia M. Imprinted genes, placental development and fetal growth. *Hormone Research in Paediatrics*. 2006;65(Suppl. 3):50–8.
51. Fekete K, Berti C, Trovato M, Lohner S, Dullemeijer C, Souverein OW, et al. Effect of folate intake on health outcomes in pregnancy: a systematic review and meta-analysis on birth weight, placental weight and length of gestation. *Nutrition Journal*. 2012;11(1):75.
52. Tserga A, Binder AM, Michels KB. Impact of folic acid intake during pregnancy on genomic imprinting of IGF2/H19 and 1-carbon metabolism. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*. 2017 Dec;31(12):5149–58. PubMed PMID: 28778973. Pubmed Central PMCID: PMC5690385. Epub 2017/08/06. eng.
53. Dhobale M. Neurotrophic factors and maternal nutrition during pregnancy. *Vitamins and Hormones*. 2017;104:343–66. PubMed PMID: 28215301. Epub 2017/02/22. eng.
54. Williams PJ, Bulmer JN, Innes BA, Broughton Pipkin F. Possible roles for folic acid in the regulation of trophoblast invasion and placental development in normal early human pregnancy. *Biology of Reproduction*. 2011 Jun;84(6):1148–53. PubMed PMID: 21349824. Epub 2011/02/26. eng.
55. Timmermans S, Jaddoe VW, Silva LM, Hofman A, Raat H, Steegers-Theunissen RP, et al. Folic acid is positively associated with uteroplacental vascular resistance: the Generation R study. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD*. 2011 Jan;21(1):54–61. PubMed PMID: 19819678. Epub 2009/10/13. eng.
56. Baker BC, Hayes DJ, Jones RL. Effects of micronutrients on placental function: evidence from clinical studies to animal models. *Reproduction (Cambridge, England)*. 2018 Sep;156(3):R69–R82. PubMed PMID: 29844225. Epub 2018/05/31. eng.
57. Green BB, Marsit CJ. Select prenatal environmental exposures and subsequent alterations of gene-specific and repetitive element DNA methylation in fetal tissues. *Current Environmental Health Reports*. 2015 Jun;2(2):126–36. PubMed PMID: 26231362. Pubmed Central PMCID: PMC4522706. Epub 2015/08/02. eng.
58. Shah T, Joshi K, Mishra S, Otiv S, Kumbar V. Molecular and cellular effects of vitamin B12 forms on human trophoblast cells in presence of excessive folate. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*. 2016 Dec;84:526–34. PubMed PMID: 27693961. Epub 2016/10/04. eng.
59. Castano E, Pinunuri R, Hirsch S, Ronco AM. [Folate and Pregnancy, current concepts: it is required folic acid supplementation?]. *Revista chilena de pediatria*. 2017 Apr;88(2):199–206. PubMed PMID: 28542653. Epub 2017/05/26. Folatos y Embarazo, conceptos actuales: inverted question markEs necesaria una suplementacion con Acido Folico? spa.
60. Hiraoka M, Kagawa Y. Genetic polymorphisms and folate status. *Congenital Anomalies*. 2017;57(5):142–9.
61. Shane B, Stokstad ER. Vitamin B12-folate interrelationships. *Annual Review of Nutrition*. 1985;5(1):115–41.
62. Devi S, Mukhopadhyay A, Dwarkanath P, Thomas T, Crasta J, Thomas A, et al. Combined vitamin B-12 and balanced protein-energy supplementation affect homocysteine remethylation in the methionine cycle in pregnant South Indian women of low vitamin B-12 dtatus. *The Journal of Nutrition*. 2017 Jun;147(6):1094–103. PubMed PMID: 28446631. Epub 2017/04/28. eng.
63. Parrish MR, Martin JN, Jr., Lamarca BB, Ellis B, Parrish SA, Owens MY, et al. Randomized, placebo controlled, double blind trial evaluating early pregnancy phytonutrient supplementation in the prevention of preeclampsia. *Journal of Perinatology: Official Journal of the California Perinatal Association*. 2013 Aug;33(8):593–9. PubMed PMID: 23448939. Epub 2013/03/02. eng.
64. Acharyya N, Deb B, Chattopadhyay S, Maiti S. Arsenic-induced antioxidant depletion, oxidative DNA breakage, and tissue damages are prevented by the combined action of folate and vitamin B12. *Biological Trace Element Research*. 2015 Nov;168(1):122–32. PubMed PMID: 25850544. Epub 2015/04/09. eng.

65. Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. *Jama*. 2002;288(8):973–9.
66. Meher A, Sundrani D, Joshi S. Maternal nutrition influences angiogenesis in the placenta through peroxisome proliferator activated receptors: a novel hypothesis. *Molecular Reproduction and Development*. 2015 Oct;82(10):726–34. PubMed PMID: 26099847. Epub 2015/06/24. eng.
67. D'Souza SW, Solanky N, Guarino J, Moat S, Sibley CP, Taggart M, et al. Human placental arterial distensibility, birth weight, and body size are positively related to fetal homocysteine concentration. *Reproductive Sciences (Thousand Oaks, Calif)*. 2017 Jul;24(7):1070–8. PubMed PMID: 27879450. Epub 2016/11/24. eng.
68. Khot V, Chavan-Gautam P, Joshi S. Proposing interactions between maternal phospholipids and the one carbon cycle: a novel mechanism influencing the risk for cardiovascular diseases in the offspring in later life. *Life Sciences*. 2015 May 15;129:16–21. PubMed PMID: 25283080. Epub 2014/10/07. eng.
69. Duttaroy AK. Transport of fatty acids across the human placenta: a review. *Progress in Lipid Research*. 2009 Jan;48(1):52–61. PubMed PMID: 19041341. Epub 2008/12/02. eng.
70. Jones ML, Mark PJ, Waddell BJ. Maternal dietary omega-3 fatty acids and placental function. *Reproduction (Cambridge, England)*. 2014 May;147(5):R143–52. PubMed PMID: 24451224. Epub 2014/01/24. eng.
71. Haghiac M, Yang XH, Presley L, Smith S, Dettelback S, Minium J, et al. Dietary omega-3 fatty acid supplementation reduces inflammation in obese pregnant women: a randomized double-blind controlled clinical trial. *PloS One*. 2015;10(9):e0137309. PubMed PMID: 26340264. Pubmed Central PMCID: PMC4560373. Epub 2015/09/05. eng.
72. Keelan JA, Mas E, D'Vaz N, Dunstan JA, Li S, Barden AE, et al. Effects of maternal n-3 fatty acid supplementation on placental cytokines, pro-resolving lipid mediators and their precursors. *Reproduction (Cambridge, England)*. 2015 Feb;149(2):171–8. PubMed PMID: 25504868. Epub 2014/12/17. eng.
73. Sedlmeier EM, Brunner S, Much D, Pagel P, Ulbrich SE, Meyer HH, et al. Human placental transcriptome shows sexually dimorphic gene expression and responsiveness to maternal dietary n-3 long-chain polyunsaturated fatty acid intervention during pregnancy. *BMC Genomics*. 2014 Oct 27;15:941. PubMed PMID: 25348288. Pubmed Central PMCID: PMC4232618. Epub 2014/10/29. eng.
74. Gonzalez TL, Sun T, Koeppel AF, Lee B, Wang ET, Farber CR, et al. Sex differences in the late first trimester human placenta transcriptome. *Biology of Sex Differences*. 2018 Jan 15;9(1):4. PubMed PMID: 29335024. Pubmed Central PMCID: PMC5769539. Epub 2018/01/18. eng.
75. Leghi GE, Muhlhausler BS. The effect of n-3 LCPUFA supplementation on oxidative stress and inflammation in the placenta and maternal plasma during pregnancy. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. 2016 Oct;113:33–9. PubMed PMID: 27720038. Epub 2016/10/11. eng.
76. Shin JS, Choi MY, Longtine MS, Nelson DM. Vitamin D effects on pregnancy and the placenta. *Placenta*. 2010 Dec;31(12):1027–34. PubMed PMID: 20863562. Pubmed Central PMCID: PMC2993775. Epub 2010/09/25. eng.
77. Richard K, Holland O, Landers K, Vanderlelie JJ, Hofstee P, Cuffe JS, et al. Effects of maternal micronutrient supplementation on placental function. *Placenta*. 2017;54:38–44.
78. Zabul P, Wozniak M, Slominski AT, Preis K, Gorska M, Korozan M, et al. A proposed molecular mechanism of high-dose vitamin D3 supplementation in prevention and treatment of preeclampsia. *International Journal of Molecular Sciences*. 2015 Jun 9;16(6):13043–64. PubMed PMID: 26068234. Pubmed Central PMCID: PMC4490485. Epub 2015/06/13. eng.

79. Schulz EV, Cruze L, Wei W, Gehris J, Wagner CL. Maternal vitamin D sufficiency and reduced placental gene expression in angiogenic biomarkers related to comorbidities of pregnancy. *The Journal of Steroid Biochemistry and Molecular Biology*. 2017 Oct;173:273–9. PubMed PMID: 28216083. Epub 2017/02/22. eng.
80. Hollis BW, Wagner CL. Vitamin D supplementation during pregnancy: improvements in birth outcomes and complications through direct genomic alteration. *Molecular and Cellular Endocrinology*. 2017;453:113–30.
81. Mistry HD, Williams PJ. The importance of antioxidant micronutrients in pregnancy. *Oxidative Medicine and Cellular Longevity*. 2011;2011:841749. PubMed PMID: 21918714. Pubmed Central PMCID: Pmc3171895. Epub 2011/09/16. eng.
82. Wu F, Tian FJ, Lin Y. Oxidative stress in placenta: health and diseases. *BioMed Research International*. 2015;2015:293271. PubMed PMID: 26693479. Pubmed Central PMCID: PMC4676991. Epub 2015/12/23. eng.
83. Oliveira d, RondódC, BarrosdM. Concentrations of ascorbic acid in the plasma of pregnant smokers and nonsmokers and their newborns. *International Journal for Vitamin and Nutrition Research*. 2004;74(3):193–8.
84. Camarena V, Wang G. The epigenetic role of vitamin C in health and disease. *Cellular and Molecular Life Sciences*. 2016;73(8):1645–58.
85. Shorey-Kendrick LE, McEvoy CT, Ferguson B, Burchard J, Park BS, Gao L, et al. Vitamin C prevents offspring DNA methylation changes associated with maternal smoking in pregnancy. *American Journal of Respiratory and Critical Care Medicine*. 2017;196(6):745–55.
86. Chappell LC, Seed PT, Kelly FJ, Briley A, Hunt BJ, Charnock-Jones DS, et al. Vitamin C and E supplementation in women at risk of preeclampsia is associated with changes in indices of oxidative stress and placental function. *American Journal of Obstetrics and Gynecology*. 2002;187(3):777–84.
87. Johnston PC, McCance DR, Holmes VA, Young IS, McGinty A. Placental antioxidant enzyme status and lipid peroxidation in pregnant women with type 1 diabetes: the effect of vitamin C and E supplementation. *Journal of Diabetes and its Complications*. 2016 JanFeb;30(1):109–14. PubMed PMID: 26597598. Epub 2015/11/26. eng.
88. Johnston PC, Powell LA, McCance DR, Pogue K, McMaster C, Gilchrist S, et al. Placental protein tyrosine nitration and MAPK in type 1 diabetic pre-eclampsia: impact of antioxidant vitamin supplementation. *Journal of Diabetes and Its Complications*. 2013 JulAug;27(4):322–7. PubMed PMID: 23558107. Epub 2013/04/06. eng.
89. Karowicz-Bilinska A, Kowalska-Koprek U, Kobos J, Pasinski J. [Evaluation of the expression of selected pro- and anti-apoptotic factors in syncytiotrophoblasts of human placenta and changes observed after vitamin supplementation]. *Ginekologia Polska*. 2015 Nov;86(11):833–9. PubMed PMID: 26817315. Epub 2016/01/29. Ocena ekspresji wybranych czynnikow pro- i antyapoptotycznych w syncytiotrofoblascie lozysk ludzkich oraz ich zmian pod wplywem suplementacji witaminowej. pol.

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5

Gestational Weight Gain and Postpartum Obesity

Vasudha Prithipaul and Asra Sami

Contents

Introduction

The term nutraceutical is used to define medicinally or nutritionally functional food. Nutraceuticals can also be known as medical foods, designer foods, phytochemicals, functional foods, and nutritional supplements. They also include a wide range of common routine products such as fortified milk and cereals, vitamins, herbal remedies, and some genetically altered foods as well as supplements. [1] The term nutraceutical can have different definitions, which can lead to some ambiguity in its understanding.

This chapter, which focuses on gestational weight gain, postpartum obesity, and nutraceuticals that are beneficial during and after pregnancy, uses the above definition throughout and includes some functional foods, such as fortified milk, herbal remedies and teas, isolated chemicals probiotics, and nuts. The chapter also discusses the nutrient requirements required during gestation and its role in adequate weight gain.

Gestational Weight Gain

Gestational weight gain (GWG) can be defined as the amount of weight gained by a woman from the beginning of her pregnancy, at the first prenatal visit, until the delivery day. [2, 3] Gaining an adequate amount of weight proves to have favorable influences on maternal health as well as on the fetus during pregnancy. [4] The reason why women should increase their nutrient intake is mainly because a lot of energy is being used to maintain their basal energy expenditure (BEE) as this will increase significantly during the pregnancy. [5] GWG is comprised of several elements, such as water, proteins, and fat, in the fetus. Amniotic fluid also adds to the constituents of the weight gain as well as the increase in maternal blood volume and adipose tissue. Women gain more weight during the final months of pregnancy rather than during the beginning of the pregnancy. [6] In order to gain an adequate amount of weight, the energy requirements increase in the first, second, and third trimesters. The numbers of calories by which this should increase are 200, 300, and 400 respectively on a daily basis. However, these values vary according to the prenatal weight of the mother, the BEE of the mother, and the level of physical activity during pregnancy. [2, 5] For instance, mothers who spend a majority of the day sitting and doing little physical activity should consume 2,175 to 2,300 calories per day whereas mothers who are highly active, that is, who perform energetic tasks such as running, should consume about 2,990 to 3250 calories per day. [5]

According to the Institute of Medicine (IOM), women are required to gain weight according to their pre-pregnancy body mass index (BMI) for a healthy pregnancy and the weight gain recommendations are given in Table 5.1. The BMI is calculated by using the reported weight in kilograms divided by height in meters to the square, or as the weight in pounds multiplied by 703 divided by height in inches.

Certain situations arise where a mother might undergo multiple gestations. This involves an increase of 10% in the maternal metabolic rate in comparison with a single gestation. Therefore, the weight gain requirement also increases, and the values as recommended by the IOM are given in Table 5.2 [7].

However, a lot of conveyed data indicates that women are putting on more weight during their pregnancy than the recommended amounts. [8] This excessive weight gain increases the chances of multiple health issues, such

Table 5.1 Weight Gain Recommendations According to IOM for Pregnancy

Weight category prior to pregnancy	Body Mass Index	Recommended rate of weight gain in 2nd and 3rd trimester* (kg/wk)	Total recommended amount of weight gain (kg)
Underweight	<18.5	0.45	12.7–18.14
Normal weight	18.5–24.9	0.45	11.3–15.9
Overweight	25–29.9	0.27	6.8–11.3
Obese (Class I, II, and III)	30 and above	0.23	4.9–9.1

* This assumes that the weight gained by the mother in the first trimester is 0.5–2 kg

Table 5.2 Recommended Weight Gain for Gestation of Twins by the IOM

Weight category prior to pregnancy	Body Mass Index	Total recommended amount of weight gain (kg)
Underweight	<18.5	17–25
Normal weight	18.5–24.9	17–25
Overweight	25–29.9	14–23
Obese (Class I, II, and III)	30 and above	11–19

as gestational diabetes and high blood pressure disorders like preeclampsia and sleep apnea. Complications during childbirth can occur and the need for cesarean section may arise. The likelihood of such problems occurring arise if the mother puts on weight too quickly or very suddenly. If the weight gained within one week is half a kilogram or greater, the weight of the mother must be monitored closely. Regular check-ups including frequent blood tests and examinations are then required to ensure the healthiness and well-being of the mother and child. If the weight gain is 1 kg or higher weekly, this can be an alarming indication of a life-threatening health condition called preeclampsia with symptoms including nausea, headaches, and dizziness. However, the most concerning symptom of this illness is hypertension, which can be caused by excessive weight. Although the relationship between weight gain and hypertension is firmly established among adults and children, the mechanism by which weight gain and blood pressure increase is still under investigation. [9] Gestational diabetes is another condition that may develop due to excessive GWG during pregnancy and this entails an increase in blood sugar levels in women who were not diagnosed as diabetics before gestation.

While gaining too much weight can be detrimental to an expecting woman's health, gaining the adequate amount of weight can be tedious for certain women, especially those who fall in the underweight category according to their BMI. [10] Underprovided nutrition during gestation occurs due to poor dietary choices. The meager consumption of essential fatty acids,

micronutrients, and proteins results in an inadequate amount of GWG and low body mass. [11] Healthcare providers recommend to women at risk of not gaining sufficient gestational weight that they should avoid skipping meals. Experts recommend that frequent meals should be consumed throughout the day. Women at risk should increase their consumption of nuts, fortified dairy products, and foods high in good fats such as avocados and olive oil. Additionally, they should consume food items rich in vitamin C as well as should consider taking prenatal vitamins and supplements. [10] There are risks associated with mothers not consuming enough macronutrients as well as micronutrients with regard to the child, such as a greater risk of low birthweight and infant mortality. The child can experience a variety of childhood development disorders, one of which includes the development of cognitive abilities of the child being hindered. [12, 13] Pregorexia is a condition where a pregnant woman consumes too little food or exercises too much to gain as little weight as possible. This could lead to preterm labor, anemia, infections, and many other health concerns for the baby. [14]

Therefore, adhering to a balanced diet throughout gestation influences the mother's weight as well as the health of both the mother and the child.

Macronutrient Requirements for a Healthy GWG

Proteins

Proteins play an important role in the body and this includes structural and functional roles. Mammalian proteins consist of 20 different amino acids. The current definition of protein requirement reads as follows:

> the lowest level of dietary protein intake that will balance the losses of nitrogen from the body, and thus maintain the body protein mass, in persons at energy balance with modest levels of physical activity, plus, in children or in pregnant or lactating women, the needs associated with the deposition of tissues or secretion of milk at rates consistent with good health. [15]

Therefore the composition of the protein as well as the quantity of the protein consumed are important during pregnancy, because, during this period, there is a rapid intrauterine growth as well as maternal physiological changes. For a typical 12.5 kg gain in body weight, the amount of nitrogen increase required is 148 g which equates to 925 g of protein accretion for the mother. [16] The recommended amount of daily protein consumption for pregnant women according to the IOM is given as 0.88 g/kg. [15]

Animal protein is normally considered to be of higher quality compared to plant proteins as they comprise complete proteins, that is proteins comprising all 20 amino acids. [8, 12]

The data from most studies report conflicting results about protein intake and gestational weight gain. The consumption of the recommended amount of proteins daily can prevent the excessive weight gain during gestation in normal and overweight women according to one study. [10] A higher protein intake can lead to a higher gestational weight gain, however, certain studies have suggested the opposite, that is, a higher protein intake leads to a lower gestational weight gain. Other studies demonstrated that substituting fat and carbohydrates for proteins leads to lower gestational weight gain. [17] Further research is necessary to associate a conclusion to this subject.

Fats

Fatty acids such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and omega-3 fatty acids are important in the diet of a pregnant woman. [12] Omega-3 fatty acids and maternal serum DHA are invaluable for the development of the child's cognitive abilities and retina formation. DHA is also involved with neuronal development and plasticity, receptor-mediated signaling, membrane fluidity, and the formation of second messengers, as well as influencing inflammatory modulations by affecting toll-like receptors (TLRs) which acts as a defense mechanism against pathogens. [18]

The balance between omega-3 and omega-6 fatty acids is crucial to maintaining a healthy body. This is because omega-6 fatty acids are involved in pro-inflammatory immune functions while omega-3 fatty acids are involved in anti-inflammatory functions. Oftentimes, there is a lack of omega-3 fatty acids in the diet, which can be remedied through supplementation during pregnancy and lactation for the health of the fetus. [14]

During pregnancy, estrogen and progesterone levels increase drastically and the fat dietary intake influences these hormonal changes. [19]

The fat recommendation for pregnant women is the same as the recommendation for women who are not pregnant, 20–30% of total calories. Fat levels should only be potentially varied if the pregnant women may be impacted by malnutrition, as fat can be an excellent source of abundant calories. [14]

Some fatty acids have been associated with a higher GWG, though there is conflicting evidence and the studies often provide contradictory results. [20] Reducing saturated fat, for example, may lead to a decrease in gestational weight gain. There are some general studies and discussions exploring the possibility of unsaturated fats being less harmful to health than saturated fats. Unsaturated fats may be less likely to be stored in adipose tissues as fat, which could be beneficial in avoiding gestational weight gain. [21]

Carbohydrates

Carbohydrates are an essential component of a healthy diet during pregnancy. The recommended amount is 175 g/day. [14] However, in some cases,

carbohydrate consumption should be slightly restricted to promote the health of the baby and to reduce GWG. For example, research indicates that more sweets consumed in early pregnancy leads to a higher GWG or gestational diabetes. [22]

Because of the importance of carbohydrates in the diet during pregnancy, it is important to note a distinction between carbohydrates with a lot of empty calories, such as sweets, and complex carbohydrates that are nutrient-dense, such as fruits and vegetables. Even women with gestational diabetes are encouraged to only reduce their carbohydrate intake slightly to ensure that the fetus is still getting enough glucose to properly grow. [14]

Micronutrients

During pregnancy, micronutrient supplements are commonly recommended in order to increase vitamin and mineral intake. [23]

The connection between obesity and micronutrient intake involves the epigenetics, which is gene expression modification, of adipocyte cells. One-carbon metabolism is a DNA methylation process that involves micronutrients and can influence obesity. [24] Some vitamins that contribute to one-carbon metabolism are folate, riboflavin, choline, and vitamin B12. Folate, or vitamin B9, is a very important component of a pregnant woman's diet, due to its role in preventing birth defects, specifically in the neural tubes of the baby. [25] An adequate intake of riboflavin can decrease the risk of preeclampsia and edema. Choline is necessary to reduce chances of neural tube defects (NTDs) and support the baby's brain and liver development. Vitamin B12 also acts to prevent NTDs and preeclampsia and contributes to a healthy birthweight for the baby. [26]

It is important to note that the use of micronutrients to reduce excessive weight gain during pregnancy has had controversial results. Some studies have found a positive correlation between the overconsumption of certain vitamins, such as niacin, with obesity and diabetes. Niacin is a B vitamin containing nicotinamide, which may be responsible for increasing appetite and contributing to weight gain. More research on the influence of one-carbon metabolism and the potential negative consequences of the overconsumption of certain vitamins is necessary to form adequate conclusions. [25]

There are many other necessary vitamins that support a healthy pregnancy, including biotin, thiamin, and vitamins A, C, D, E, and K, that have not yet been extensively linked with gestational weight gain. [27]

Nutraceuticals Consumed During Pregnancy for Healthy GWG

Milk and Dairy Ingredients

Bovine milk is a liquid food which is nutrient dense with essential components such as calcium, vitamin D, vitamin B12, vitamin A, riboflavin,

potassium, and phosphorus. [28] Milk is known to be a significant source of high-quality proteins that account for nutritional, functional, and physiological activities, and such proteins are α_{s1}-caseins, β-caseins, κ-caseins, α-lactalbumin, and β-lactoglobulins. [28] These proteins are often found in weight gain supplements used by weight lifters and athletes as they help minimize muscle loss and increase muscle protein synthesis. Milk also contains all the nine essential amino acids in proportions corresponding to the recommended amino acid requirements. The presence of branched chain amino acids such as isoleucine, leucine, and valine are at higher levels than any other natural sources.

Fortified milk (milk fortified with vitamin D) contributes to this vitamin's intake worldwide. Vitamin D has not been linked to gestational weight gain and it plays an important role in bone health as it is a necessity for calcium absorption. This certainly benefits expecting mothers and aids in maintaining a healthy gestation. [29]

Milk and dairy products are considered to be the best source of calcium. The American College of Obstetricians and Gynecologists (ACOG) recommends 1,000 milligrams (mg) per day for pregnant and lactating women which can be achieved by consuming four servings of dairy products. [30] This amount of dairy consumed adds additional calories to the antenatal diet which also helps to increase weight adequately.

Probiotics

The intestinal tract, placenta, and vagina all contain an abundance of microorganisms known for their beneficial properties that can play a role in pregnancy. Acquiring probiotics from the diet has an impact on these microorganisms, enhancing or reducing their function. [31, 32]

In the intestinal tract, consuming probiotics can combat and provide protection against gastrointestinal diseases. Through the study of the microbiome of pregnant women in their third trimester, inflammation, adiposity, and insulin insensitivity can be revealed. The intestinal microbiome of pregnant women in their third trimester contains microorganisms that influence inflammation, adiposity, and a lack of sensitivity to insulin. Thus, consuming various amounts of probiotics may have an impact on these microorganisms, potentially lowering gestational weight gain. [31]

Though additional evidence is necessary to confirm the benefits of probiotics in reducing gestational weight gain, there are studies that prove the topic is worth exploring. One study indicated that the consumption of probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* reduced the risk of central adiposity of pregnant women in their first trimester. [33]

In addition to potentially reducing gestational weight gain, probiotic supplementation may also benefit pregnant women in other ways, decreasing the

risk of preeclampsia, gestational diabetes mellitus, and lowering low-density lipoproteins postpartum. [31]

Nuts

Nuts are complex foods which contain cholesterol-lowering mono- and poly-unsaturated fatty acids, arginine, soluble fibers, and several antioxidant polyphenols. [34] They are rich in calories and proteins. For instance, in a 25 g serving, peanuts contain 7.4 g of proteins, almonds contain 5.3 g and walnuts contain 3.7 g. The caloric intake of one serving (25 g) of nuts usually varies from 130 to 180 calories. [35] Nuts are also rich in folic acid, which aids in reducing the neural tubal defects in infants. [3] They contain a high fat content usually ranging between 46% to 76%, which provides 20 to 30 kJ/g of energy. [36] The addition of this component, consumed in moderation, to the pre-birth diet helps a healthy weight gain, in addition to the added calories.

Most other nutraceuticals are not primarily linked to weight gain during gestation but have several other health benefits for the mother and infant. Certain nutraceuticals aid in the reduction of the weight acquired throughout the trimesters of childbearing. Some nutraceuticals also help combat one very common and current issue which is post-pregnancy obesity.

Postpartum Obesity

Obesity is defined according to the Obesity Medicine Association as a "chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences." The Body Mass Index, as mentioned earlier in the chapter, is often used by the Centers for Disease Control and Prevention and the World Health Organization to categorize weight and, according to this measurement, obesity can be classified in three different categories: Class I, Class II, and Class III, with Class III being the most severe. Another accurate method to assess the amount of adipose tissue in the human body uses dual-energy X-ray absorptiometry (DEXA) scanning. If the percentage of body fat is greater than 25% in males and greater than 32% in females, they fall in the obese category. [37]

Over the last 20 years, the incidence of obesity has doubled and 34% of the US population is considered obese while another 34% fall in the overweight category. [38] According to data from the Centers for Disease Control and Prevention published in 2012, 36% of women aged 20–39 years old are obese and 33.9% are overweight. [39] These women are of childbearing age and, because their pre-pregnancy weight is higher than the normal range, they are more prone to retaining the weight after delivery. However, pregnancy

itself presents a risk that women may gain weight and become overweight or obese regardless of which BMI category their pre-pregnancy weight fell into. The reason is mainly because many women do not lose the gestational weight gained. Reasons why women do not lose this weight include not breastfeeding and lack of exercise after the birth of the child. Other factors that may contribute to a greater postpartum weight retention resulting in obesity are pregnancy at a younger age, being African American, and earning a low income. [39]

Other than regular fitness and the consumption of a balanced diet, the incorporation of supplements to the diet can have an impact on postpartum weight loss. Mothers should be cautious when choosing weight loss supplements, especially if they are breastfeeding, as some of them contain substances which may be unsafe to themselves or to the baby. Table 5.3 shows a list of nutraceuticals that have the potential of aiding weight loss and whether or not they are safe during nursing.

Supplements containing caffeine are generally not recommended during lactation as there have been studies demonstrating that the baby could experience jitteriness, fussiness, and poor sleep patterns. [40, 41] There have also been no published data with conclusive evidence on the usefulness of the dietary supplements as weight loss therapy. Therefore, the consumption of these supplements needs to be handled wisely and in limited amounts.

Nutraceuticals Aiding in Weight Loss Postpartum

Hibiscus Sabdariffa

Hibiscus sabdariffa tea is in extensive use across the globe both as a beverage and as a treating agent for hyperlipidemia. [42] *Hibiscus sabdariffa* L. (*Malvaceae*; common name "roselle") is a plant cultivated in Sudan and Eastern Taiwan. [43] The flower of the plant is "generally recognized as safe" (GRAS) as a food by the US Food and Drug Administration (FDA). It is highly beneficial in the sense that it contains potent antioxidant, antihyperlipidemic, antiatherosclerotic as well as hepatoprotective properties. *H. sabdariffa* are rich in anthocyanins, which are known to be effective in controlling weight gain and treating obesity. [43, 44] In a study conducted on high-fat diet-induced *Mesocricetus auratus* hamster, it was found that the floral extracts of *H. sabdariffa* could be effective in controlling body weight and adipose deposition. [43]

During pregnancy, drinking this herbal beverage is considered unsafe because of its emmenagogue effects but, in certain cultures, it is used as a galactagogue when used postpartum. [45] However, no scientifically valid clinical trials on humans support the use of *Hibiscus sabdariffa* as a galactagogue.

Table 5.3 Nutraceuticals for Weight Loss and their Eligibility for Consumption Postpartum

Nutraceuticals	Mechanism of action	Permissible or not during lactation
Psyllium	Increases satiety Lowers food intake Reduces dietary fat absorption	Acceptable [53]
Green tea	Increases fat oxidation and suppresses fatty acid synthetase	Not recommended as it contains caffeine and that the manufacturers of the product give no proof of safety and effectiveness of the supplement [40]
Caffeine	Increases fat oxidation and thermogenesis	A maternal intake limit of 300 mg daily is the safe amount. [41]
Trigonella foenum-graecum	Reduces dietary fat intake and decreases energy intake	Acceptable and is considered a galactogogue [51]
Ginseng	Reduces the incidence of fat absorption by inhibiting pancreatic lipase activities	Not recommended because of possible estrogenic activities and lack of information [54]
Capsaicin	Increases energy expenditure through thermogenesis Increases fat oxidation	Generally recognized as safe if consumed orally. Caution is required if applied topically [55]
Glucomannan	Increases satiety Lowers food intake Reduces dietary fat absorption	Acceptable as it is not absorbable in the breast milk. [56]
Guar gum	Increases satiety Lowers food intake Reduces dietary fat absorption	Not enough information available
Garcinia cambogia	Inhibits de novo lipogenesis Reduces food intake	Not enough data exist on excretion of the product in breast milk Should be avoided [57]
Ephedra sinica	Sympathomimetic agonist	Generally prescribed for postpartum difficulties. [58]
Hibiscus sabdariffa	Reduces adipose deposition	Generally recognized as safe and is considered a galactogogue. [59]
Soy protein/isoflavones	Improves satiety	Generally recognized as safe

Trigonella foenum-graecum (Fenugreek)

Trigonella foenum-graecum, commonly referred to as fenugreek, is an erect annual herb from the soy family that originated from India and North Africa. [46, 47] This has been used as a galactogogue historically, the reason being that it contains significant levels of phytoestrogens. Diosgenin is a phytoestrogen that is believed to be responsible for an increase in milk flow. [42] Habitually, fenugreek tea is prepared by brewing the seeds in boiling water

for 20 minutes and it is consumed. This ingredient is also an excellent weight loss supplement, as fenugreek seeds contain saponins and alkaloids as well as soluble dietary fibers, which help increase the feeling of satiety, reducing the wish to eat throughout the day. [46] These seeds have also demonstrated hypoglycemic and hypolipidemic effects in multiple preclinical and clinical studies, as summarized by Parveen Kumar and Uma Bhandari in the review titled "Common medicinal plants with ant obesity potential: A special emphasis on fenugreek." [48]

Soy Protein/Isoflavones

The protein that is found in soybeans is often used to replace animal protein in a vegetarian or vegan diet. It is a legume containing no cholesterol and it is rich in fibers, iron, calcium, zinc, and vitamin B. It is also low in saturated fats and contains eight essential amino acids. [49] A study conducted on postpartum mice demonstrated that the consumption of isolated soy proteins combined with adequate exercise prevents an increase in body weight and fat and augments the amount of lean muscle mass. This study concludes that a similar effect can occur in women postdelivery. [50]

Foeniculum Vulgare

Foeniculum vulgare, also known as fennel, contains a volatile oil composed largely of anethole, which is a phytoestrogen, as well as fenchone, estragole, eucalyptol, and other constituents. [51] It is a galactogogue and some claims have been made that these seeds help in weight loss. They have diuretic properties and improve metabolism. Gathered data from multiple papers indicate the efficacy of fennel in several *in vitro* and *in vivo* pharmacological properties such as antimicrobial, antiviral, anti-inflammatory, antimutagenic, antinociceptive, antipyretic, antispasmodic, antithrombotic, apoptotic, cardiovascular, chemomodulatory, antitumor, hepatoprotective, hypoglycemic, hypolipidemic, and memory-enhancing. [52] This can be consumed raw, cooked, or in the form of teas. The hypoglycemic and hypolipidemic properties of this nutraceutical has the potential to aid in weight loss although no major evidence has been reported.

Conclusion

Consuming the right number of macronutrients and micronutrients is essential prior to, during, and after pregnancy for the healthiness of the mother and child. Nutraceuticals aid in controlling the amount of weight gained during gestation in a healthy manner and also help in losing the weight postpartum. However, since not all weight loss supplements, although natural, are suitable during pregnancy and postpartum, as they can exhibit strong pharmacologic effects, and women should be cautious in choosing an option for their consumption.

References

1. Bull E, L. Rapport and B. Lockwood, Nutraceuticals: 1. What is a nutraceutical? *Pharmaceutical Journal*, 2000. **265**(7104): p. 57–58
2. Kominiarek, M.A. and A.M. Peaceman, Gestational weight gain. *American Journal of Obstetrics and Gynecology*, 2017. **217**(6): p. 642–651.
3. McStay, C.L., et al., Maternal folic acid supplementation during pregnancy and childhood allergic disease outcomes: a question of timing? *Nutrients*, 2017. **9**(2): p. 123.
4. Power, M.L., et al., A retrospective study of gestational weight gain in relation to the Institute of Medicine's recommendations by maternal body mass index in rural Pennsylvania from 2006 to 2015. *BMC Pregnancy and Childbirth*, 2018. **18**(1): p. 239–239.
5. Medicine, I.o., *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. 2005, Washington, DC: The National Academies Press. 1358.
6. *Pregnancy and birth: Weight gain in pregnancy*. Informed Health Online [Internet] 2009; Available from: https://www.ncbi.nlm.nih.gov/books/NBK279575/.
7. Kominiarek, M.A. and P. Rajan, Nutrition recommendations in pregnancy and lactation. *The Medical Clinics of North America*, 2016. **100**(6): p. 1199–1215.
8. Faucher, M.A. and M.K. Barger, Gestational weight gain in obese women by class of obesity and select maternal/newborn outcomes: a systematic review. *Women and Birth*, 2015. **28**(3): p. e70–e79.
9. Jiang, S.-Z., et al., Obesity and hypertension. *Experimental and Therapeutic Medicine*, 2016. **12**(4): p. 2395–2399.
10. Maslova, E., et al., Dietary protein-to-carbohydrate ratio and added sugar as determinants of excessive gestational weight gain: a prospective cohort study. *BMJ Open*, 2015. **5**(2): p. e005839.
11. Yang, Z. and S.L. Huffman, Review of fortified food and beverage products for pregnant and lactating women and their impact on nutritional status. *Maternal & Child Nutrition*, 2011. **7** Suppl 3: p. 19–43.
12. Danielewicz, H., et al., Diet in pregnancy-more than food. *European Journal of Pediatrics*, 2017. **176**(12): p. 1573–1579.
13. McCormick, M.C., The contribution of low birth weight to infant mortality and childhood morbidity. *The New England Journal of Medicine*, 1985. **312**(2): p. 82–90.
14. Brown, L.S., Nutrition requirements during pregnancy, in *Essentials of Life Cycle Nutrition*, J.S.S. Edelstein, Editor. 2011. Jones and Bartlett Pub. p. 1–24.
15. Joint FAO/WHO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition (2002 : Geneva, Switzerland), Food and Agriculture Organization of the United Nations, World Health Organization & United Nations University. Protein and amino acid requirements in human nutrition. *WHO Technical Report Series*, 2007. 935: p. 1–265, back cover.
16. Butte, N.F. and J.C. King, Energy requirements during pregnancy and lactation. *Public Health Nutrition*, 2005. **8**(7a): p. 1010–1027.
17. Peralta Santos, A., et al., Macronutrient composition and gestational weight gain: a systematic review. *The American Journal of Clinical Nutrition*, 2015. **103**(1): p. 83–99.
18. Walczewska, A., et al., [The role of docosahexaenoic acid in neuronal function]. *Postepy Higieny i Medycyny Doswiadczalnej* (Online), 2011. **65**: p. 314–327.
19. Lof, M., et al., Dietary fat intake and gestational weight gain in relation to estradiol and progesterone plasma levels during pregnancy: A longitudinal study in Swedish women. *BMC Women's Health*, 2009. **9**(10). doi:10.1186/1472-6874-9-10.
20. Peralta Santos, A., et al., Macronutrient composition and gestational weight gain: a systematic review. *The American Journal of Clinical Nutrition*, 2015. **103**(1): p. 83–99.

21. Piers, L.S., et al., Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *British Journal of Nutrition*, 2003. **90**(3): p. 717–727.
22. Olafsdottir, A.S., et al., Maternal diet in early and late pregnancy in relation to weight gain. *International Journal of Obesity*, 2005. **30**: p. 492.
23. Zhou, S.-S., et al., B-vitamin consumption and the prevalence of diabetes and obesity among the US adults: population based ecological study. *BMC Public Health*, 2010. **10**: p. 746–746.
24. Carboni, L. *Links Between One-Carbon Metabolism & Obesity*. 2016; Available from: https://www.nutraceuticalsworld.com/contents/view:blog/2016-02-01/links-between-one-carbon-metabolism-obesity.
25. Pannia, E., et al., Role of maternal vitamins in programming health and chronic disease. *Nutrition Reviews*, 2016. **74**(3): p. 166–180.
26. Finkelstein, J.L., A.J. Layden and P.J. Stover, Vitamin B-12 and perinatal health. *Advances in Nutrition (Bethesda, Md.)*, 2015. **6**(5): p. 552–563.
27. Gernand, A.D., et al., Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. *Nature Reviews Endocrinology*, 2016. **12**(5): p. 274–289.
28. Davoodi, S.H., et al., Health-related aspects of milk proteins. *Iranian Journal of Pharmaceutical Research*: IJPR, 2016. **15**(3): p. 573–591.
29. Steijns, J., *Milk Ingredients as Nutraceuticals*. Vol. 54. 2001. 81–88.
30. Gynecologists, T.A.C.o.O.a. *Frequently asked questions - nutrition during pregnancy*. 2018; Available from: https://www.acog.org/Patients/FAQs/Nutrition-During-Pregnancy.
31. Penner, R., R.N. Fedorak and K.L. Madsen, Probiotics and nutraceuticals: non-medicinal treatments of gastrointestinal diseases. *Current Opinion in Pharmacology*, 2005. **5**(6): p. 596–603.
32. Markowiak, P. and K. Śliżewska, Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*, 2017. **9**(9): p. 1021.
33. Baldassarre, M.E., et al., Rationale of probiotic supplementation during pregnancy and neonatal period. *Nutrients*, 2018. **10**(11): p. 1693.
34. Alissa, E. and G. Ferns, *Functional Foods and Nutraceuticals in the Primary Prevention of Cardiovascular Diseases*. Vol. 2012. 2012. 569486.
35. Cowland, D., Naturally healthy nuts in high demand, in *Nutraceuticalsworld*. 2013. Rodman Publishing.
36. Ros, E. Health benefits of nut consumption. *Nutrients*, 2010. **2**(7): p. 652–682. doi:10.3390/nu2070652.
37. *Definition of Obesity*. 2018; Available from: https://obesitymedicine.org/definition-of-obesity/.
38. Kuhlmann, A.K., et al., Weight-management interventions for pregnant or postpartum women. *American Journal of Preventive Medicine*, 2008. **34**(6): p. 523–528.
39. *Centers for Disease Control and Prevention Obesity and Overweight*. 2017; Available from: https://www.cdc.gov/nchs/data/databriefs/db288.pdf.
40. *Green Tea*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
41. *Caffeine*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
42. Mortel, M. and S.D. Mehta, Systematic review of the efficacy of herbal galactogogues. *Journal of Human Lactation*, 2013. **29**(2): p. 154–162.
43. Huang, T.-W., et al., Effect of Hibiscus sabdariffa extract on high fat diet-induced obesity and liver damage in hamsters. *Food & Nutrition Research*, 2015. **59**: p. 29018–29018.
44. Tsuda, T., et al., Dietary cyanidin 3-O-beta-D-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice. *Journal of Nutrition*, 2003. **133**(7): p. 2125–2130.

45. Scott, C.R. and H. Jacobson, A selection of international nutritional & herbal remedies for breastfeeding concerns. *Midwifery Today with International Midwife*, 2005. 75: p. 38–39.
46. Bae, J., et al., Fennel (Foeniculum vulgare) and Fenugreek (Trigonella foenum-graecum) tea drinking suppresses subjective short-term appetite in overweight women. *Clinical Nutrition Research*, 2015. **4**(3): p. 168–174.
47. Morton, J.F., Mucilaginous plants and their uses in medicine. *Journal of Ethnopharmacology*, 1990. **29**(3): p. 245–266.
48. Kumar, P. and U. Bhandari, Common medicinal plants with antiobesity potential: a special emphasis on fenugreek. *Ancient Science of Life*, 2015. **35**(1): p. 58–63.
49. Lindsay, S.H. and L.G. Claywell, Considering soy--its estrogenic effects may protect women. *AWHONN Lifelines*, 1998. **2**(1): p. 41–44.
50. Wei, L., et al., Effects of isolated soy protein and strength exercise training on exercise performance and biochemical profile in postpartum mice. *Metabolism*, 2019. **94**: p. 18–27.
51. *Fenugreek*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
52. Badgujar, S.B., V.V. Patel and A.H. Bandivdekar, Foeniculum vulgare Mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. *BioMed Research International*, 2014. **2014**: p. 842674–842674.
53. *Psyllium*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
54. *Ginseng*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
55. *Capsicum*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
56. *Glucomannan*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
57. *Garcinia*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.
58. Chu, N.-S., Chapter 46 Neurology and traditional Chinese medicine, in *Handbook of Clinical Neurology*, M.J. Aminoff, F. Boller and D.F. Swaab, Editors. 2009, Elsevier. p. 755–767.
59. *Hibiscus*, in *Drugs and Lactation Database (LactMed)*. 2006. National Library of Medicine.

6

Role of Nutraceuticals in Risk of Miscarriage and Related Outcomes

Stillbirth and Maternal Mortality

Param Patel, Parth Amin, Sujan Patel, and Yashwant Pathak

Contents

Introduction

With the World Health Organization (WHO) and the help of scientific studies, there has been a large number of comparisons made in regard to public health between different countries. Decades of studies have been done over the years that compare countries' educational levels, poverty levels, reception of public health care, and governmental policies. One of the biggest factors that affects these comparisons is the role of nutraceuticals during the development of the foetus until birth. Specific comparisons of maternal mortality, stillbirths, and miscarriage can be directly related to how developed a country is. The evolution of nutraceuticals during pregnancy plays a major role in these outcomes. Different subclasses of nutraceuticals can be identified, which vary from chemical properties of a compound to broader forms of established and potential nutraceuticals. Due to the rapidly developing food and agriculture markets, continuous studies are being done to inform the public about the effects of herbal products, probiotics, prebiotics, antioxidant vitamins, polyphenols, spices, polyunsaturated fatty acids, and dietary fibres [1]. The intake amounts of all these

subclasses play a major role in the amounts of chemical compounds being produced in the body. With different intake amounts of these nutraceuticals, the levels of proteins, acids, enzymes, hormones, etc., vary within the body. During pregnancy all these factors play a major role in the development of the foetus.

Nutraceuticals are constituents of food that have many long-lasting health benefits besides the nutritional value. *In vivo* and *in vitro* research indicates that nutraceuticals are beneficial in combating chronic illnesses. They are considered safe if taken in moderate doses. However, if they are taken at high levels then there is a higher risk of them causing unwanted changes in tissues [2]. Nutraceuticals range from botanical products, to processed and genetically engineered foods, to isolated nutrients [3]. They are obtained from natural products and can be found in nature. They are also good alternatives to many lipid-lowering drugs and are tolerated well by most people [4]. There is a growing demand for nutraceuticals across the world as they are used for the prevention and treatments of many diseases. This makes nutraceuticals part of a multi-billion-dollar market. It is difficult to extract many nutraceuticals as they need to be taken from natural sources such as animals, fungi, and plants, making the increasing demand difficult to meet [5]. Nutraceuticals are widely accepted to have a large impact on lowering both the risk of disease and cost of health care, along with the promotion of good health. When processed, nutraceuticals lose some functionality in their bioactive compounds [6].

Nutraceuticals are vital during pregnancy as they play a vital role in preventing diseases caused by nutrient deficiency. The mother's nutrition directly impacts the foetus and other pregnancy-related outcomes. Recent research suggests that nutraceuticals have the possibility of preventing many pregnancy-related issues such as preterm delivery, miscarriage, stillbirth, intrauterine growth restriction, maternal mortality, and pre-eclampsia [7].

Maternal mortality refers to the deaths of women that happen after pregnancy and this could occur within 1 to 2 months after giving birth. Women with closely spaced pregnancies are commonly at higher risk of experiencing this. One of the main reasons for maternal deaths is the lack of nutrients to be shared between the mother and foetus, therefore, the mother has a higher chance of having a preterm birth, which can negatively impact foetal growth. Due to this the mother has a high chance of maternal mortality or morbidity [8]. The three main causes of maternal mortality are induced abortions, postpartum infections, and pregnancy-induced hypertension [9]. Overall, in relation to stillbirth, miscarriages, and maternal mortality, clinical studies have shown that nutraceuticals play a vital role.

Nutraceuticals

Nutraceuticals are essential for the well-being of the human body and provide many health benefits. Many subclasses have been made in order to categorise

the different effects of nutraceuticals on the body. Of the many subclasses of nutraceuticals, antioxidative nutraceuticals are those that are responsible for the reduction of free oxygen and free radicals. They can decelerate the ageing process of cells, help replenish vital tissues, and increase the life span. Research has shown that certain antioxidant enzymes such as catalase, glutathione peroxidase, and mutase are more abundant in species that have a longer life span compared to those that do not [10] (see Tables 6.1 and 6.2).

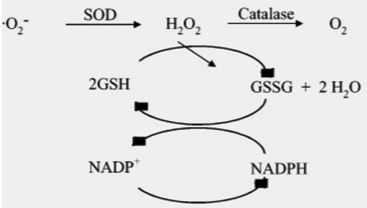
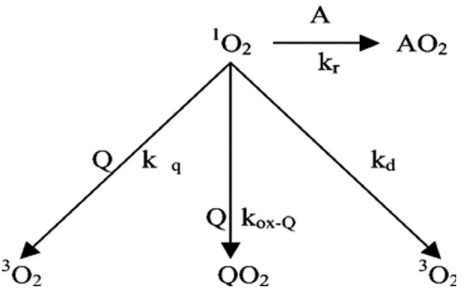
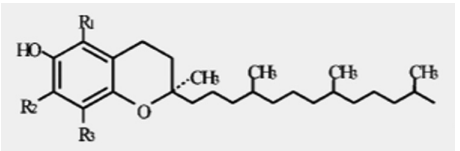
Bioavailability is the percentage of nutrients ingested and absorbed in the body that can be further used for metabolic processes. The bioavailability of antioxidative nutraceuticals is impacted by many factors, including geometric isomers, matrices around compounds, processing methodology, and nutraceutical type. Most of these factors are directly dependent on the metabolic processes in the body. When food is processed, the bioavailability is often reduced. For example, freshly picked oranges and tomatoes have a higher bioavailability than orange juice or cooked tomatoes. This is because the heat breaks down the carotenoid protein complexes of the nutraceuticals and changes the double bond structure from *cis* to *trans* which lowers bioavailability [11] (Figures 6.1 and 6.2).

There are many nutraceuticals derived from spices that play important roles in maintaining the metabolic processes of the human body. Among those is capsaicin which is derived from red chilli. Capsaicin has both resistance to insulin and helps combat obesity. It has the potential to improve inflammatory response and regulate adipokine gene expression. Gingerol from ginger is another nutraceutical that controls levels of triglycerides, insulin, and serum cholesterol. Zingerone from ginger has shown the ability to improve the inflammatory response, which has the potential to help both the mother and child. Piperine has the ability to increase curcumin bioavailability and is an antioxidant therapy for people with diabetes. Cinnamaldehyde, which is found in cinnamon, has antidiabetic effects, plus the ability to regulate protein phosphorylation and dephosphorylation. It can also increase the β levels of insulin receptors, which improves the effectiveness of adipocytes. Fenugreek seeds are able to help maintain lipid homeostasis due to the hypolipidaemic

Table 6.1 Types of Beneficial Nutraceuticals [3]

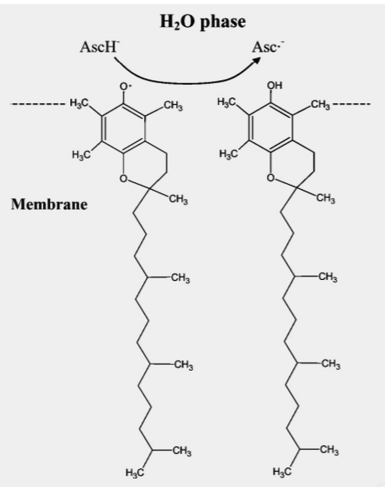
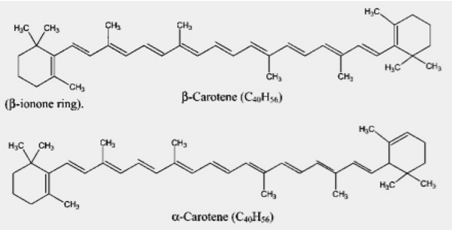
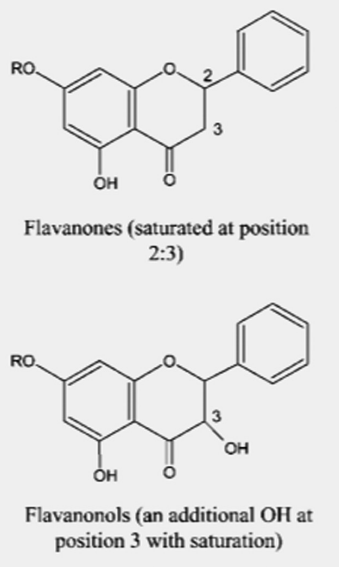
Nutraceutical subclasses	Sources
Minerals	Cashew nuts, green vegetables, chicken, eggs, liver, and sunflower seeds
Keto/amino acids, proteins, and peptides	Olive oil, meat, seafood, cheese, butter, and dark chocolate
Antioxidative vitamins	Garlic, onions, red wine, seafood, milk, and nuts
Dietary fibre	Cereals, fruits, vegetables, dried peas, lentils, nuts, whole grain bread, oats, rye, and barley
Antioxidants	Pumpkins, eggplants, spinach, mangoes, thyme, oregano, whole grain bread, sesame seeds, and grapefruits
Polyunsaturated fats	Walnuts, sunflower seeds, flax oil and seeds, safflower oil, soybean oil, corn oil, and fish (salmon, trout, herring, mackerel, and tuna)

Table 6.2 Antioxidative Nutraceuticals [10]

Nutraceuticals	Functions	Examples
Hydrogen-donating	Antioxidative nutraceuticals can donate hydrogen atoms to free radicals and can search for free radicals and prevent lipid oxidation.	$2 \cdot O_2^- + 2 H^+ \rightarrow H_2O_2 + O_2$ (Superoxide dismutase) $2 H_2O_2 \rightarrow 2 H_2O + O_2$ (Catalase) $2 GSH + H_2O_2 \rightarrow GSSG + 2 H_2O$ (Glutathione peroxidase) $GSSG + NADPH, H^+ \rightarrow 2GSH + NADP^+$ (Glutathione reductase)  GSH: Reduced glutahione, GSSG: Oxidized glutathione
Metal-chelating	Metals such as iron and copper are essential in the initiation and propagation steps of lipid oxidation. The initial step of oxygen oxidation requires the removal of a hydrogen atom.	Iron storage function includes the metal-chelating proteins of ferritin, transferrin, and lactoferrin. The haemoglobin sequestration consists of the protein haptoglobin. Copper storage proteins are ceruloplasmin and albumin. Iron transport proteins are transferrin ferro oxidase. The stabilisation of heme protein is hemopexin.
Singlet-oxygen quenching	This is highly reactive to any molecules with electrons or lone pairs of low ionisation energy. The 2 types of singlet oxygen-quenching mechanisms are physical and chemical quenching. Physical quenching changes the single oxygen into a triple oxygen by energy transfer or charge transfer without creating any other intermediates. Chemical quenching is involved with producing intermediates, such as oxidised products.	
Tocopherols and tocotrienols	These are non-polar and exist in the lipid phase. Tocopherols are natural components of biological membranes. Tocotrienols are found in palm oil, cereal grains, and kale. Tocopherols are an important antioxidant in humans.	

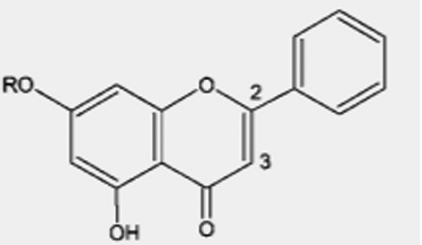
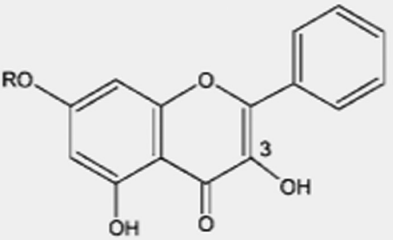
(*Continued*)

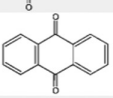
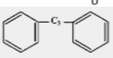
Table 6.2 (Continued) Antioxidative Nutraceuticals [10]

Nutraceuticals	Functions	Examples
Ascorbic acid	Oxidation of ascorbic acid is influenced by heat, light exposure, pH, oxygen concentration, and water activity. Ascorbic acid can prevent cancer, heart disease, and the common cold. The 3 antioxidant mechanisms of ascorbic acid are based on hydrogen atom contribution to lipid radicals, quenching of single oxygen, and removal of molecular oxygen.	
Carotenoids	These are part of a group called tetraterpenoids. They are organic pigments that are products of plants, algae, bacteria, etc. The antioxidants of carotenoids are based on the prevention of free radical diseases, including atherosclerosis, cataracts, age-related muscle degeneration, and multiple sclerosis.	
Polyphenols	Also known as phenolic compounds these are found everywhere in plants with more than 8,000 structures. Flavonoids are the most important single polyphenol group. Isoflavones do not have common flavonoid structures, but they are chemically related with flavonoids. For example soybeans contain high isoflavone levels and are a major dietary source in humans. The antioxidant process of isoflavones is suggested to be different from conventional antioxidants. The structures of genistein and daidzein are similar to naturally occurring oestrogens, suggesting that the	

(*Continued*)

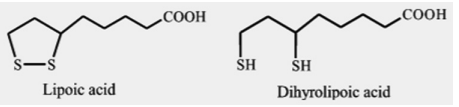
Table 6.2 (Continued) Antioxidative Nutraceuticals [10]

Nutraceuticals	Functions	Examples
	compounds can protect against hormone-dependent cancers, such prostate and mammary, by regulating the activity of oestrogen. Epidemiologic studies have shown that the consumption of the phenolic compounds reduces the risk of cardiovascular disease and certain types of cancers. Some consumption of red wine, which consists of a high content of polyphenols, reduces the risk of coronary heart disease.	 Flavones (position 2:3 unsaturated)  Flavonols (an additional OH at position 3)

Class	Basic skeleton	Basic structure
Simple phenols	C_6	
Benzoquinoes	C_6	
Phenoic acids	C_6-C_1	
Acetophenones	C_6-C_2	
Phenylacetic acids	C_6-C_2	
Hydroxycinnamic acids	C_6-C_3	
Phenylpropens	C_6-C_3	
Coumarins	C_6-C_3	
Chromones	C_6-C_3	
Anthraquinones	C_6-C_2-C_6	
Flavonoids	C_6-C_3-C_6	

(*Continued*)

Table 6.2 (Continued) Antioxidative Nutraceuticals [10]

Nutraceuticals	Functions	Examples
Lipoic acid	Lipoic acid is present in meat, liver, and heart. This can prevent oxidative damage of proteins. Antioxidant activity of lipoic acid can help reduce the risk of diabetes, which develops through oxidative stress. Lipoic acid is also important in reducing blood glucose concentration. Also it renews GSH in the liver, kidney, and lung tissue and restores vitamins C and E. A dietary study on lipoic acid was done to show a decrease in age-related decline in oxygen use and radical formation, improving mitochondrial membrane potential, and increasing ascorbic acid and GSH levels. Lipoic acid reduces age-related decline in memory and cognitive function, and brain-related diseases such as Alzheimer's and Parkinson's	

characteristics they have. They are also beneficial for treating metabolic disorders such as dyslipidaemia and the reduction of LDL cholesterol, body weight, and serum triglycerides [12] (Figure 6.3).

Nutraceuticals undoubtedly play a vital role for humans as they provide the proper nutritional components needed for survival. They also, however, impact other living things in nature such as other animals and plants. Of the many nutraceuticals, carotenoids are of particular interest as they are widely used. They help with animal behaviour changes, survival abilities, and reproduction. Along with that, carotenoids also provide plants the ability to assemble photosystems and capture light [13] (Table 6.3).

Clinical Applications of Nutraceuticals on Pregnant Women

Clinical testing plays a vital role in the understanding of our public healthcare systems. There have been many clinical tests conducted on pregnant women that have shown significant implications for the impact of nutraceuticals on the mother's body and foetus. In February of 2008, a clinical trial was published stating the effects of fish oil supplements on 311 subjects. In an effort to keep the bias at a minimum, a double-blind, placebo trial was held accordingly to acquire data. Of the 311 women subjected to the clinical trial, the ones

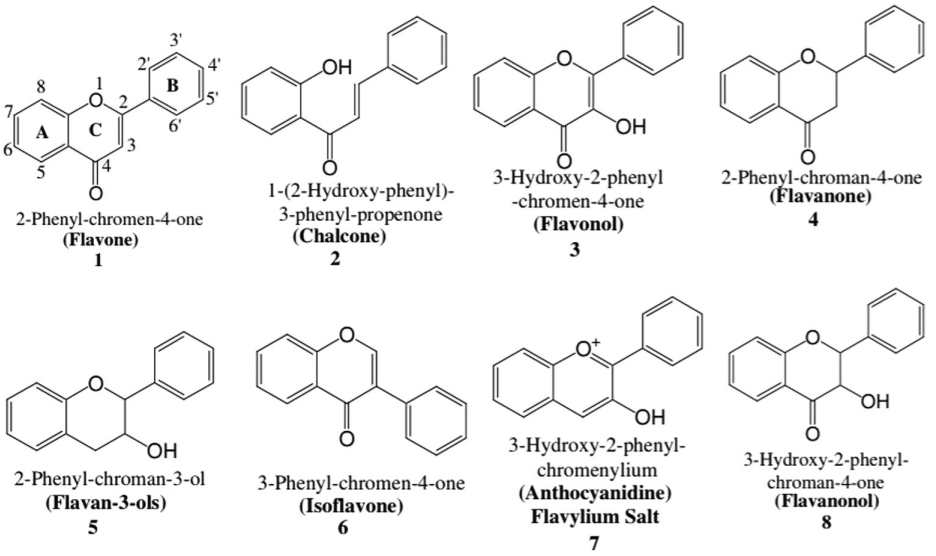


Figure 6.1 *Chemical structures of flavonoids [11].*

that were given the fish oil supplement had shown an increase in TGF-β and cord blood. On the other hand, natural killer and T-cell levels of the expecting mothers were shown to decrease. Overall, the women who did take the fish oil supplement resulted in having lower mRNA levels in the foetus and decreased maternal inflammatory cytokines. It can be speculated that this is the direct effect of lower levels of TGF-β in expecting mothers. There are several key conclusions made by this clinical trial that help in the improvement of public health. TGF-β has many pathways and mechanisms that can cause cells to do several things, such as proliferate, differentiate, or apoptosis. The deregulation of TGF-β can be detrimental to the foetus. Apoptosis is a big factor in the development of the foetus and is how the fingers and toes along with other structures are formed, however, the deregulation of TGF-β could lead to the loss of the foetus. A clinical trial was conducted to investigate the effects of supplements on pregnant women in relation to both their immunity and that of the foetus. A secondary goal of this trial was to intervene in the development of allergies while the fetus is still developing. Even though the

Figure 6.2 *General structure of flavonoids [11].*

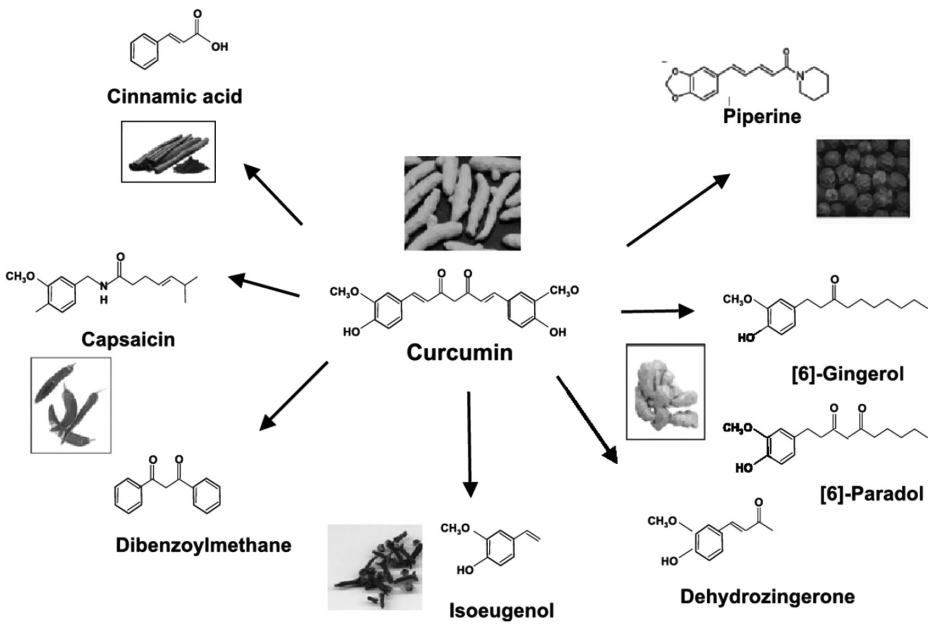


Figure 6.3 *Various flavonoids [12].*

Table 6.3 Carotenoids Found in Nature [13]

Application	Examples
Survival, behaviour, and reproduction	• Attraction • Fitness • Predation • Fitness • Pigmentation
Photosynthesis and photoprotection	• Abiotic stress • Root-mycorrhizal symbiosis • Shoot branching • Volatiles
Human health and nutrition	• Vision • Vitamins • Spices • Nutrition • Antioxidants • Feed additives
Signalling molecules and hormones	• Photoprotectants • Photosystem assembly and light capture

conclusion was inconclusive with regard to the aim of the experiment, the clinical trial showed important implications for the effects of one of countless supplements available to the public today. Since allergies are commonly "primed" during the early infancy years, it showed the effects of the supplementation of fish oil on expecting mothers [14].

Specific pathways are critical and vital to the development of the foetus. The definition of the glucose pathway is already given therefore no changes are necessary. The production of ATP helps catalyse a number of vital reactions for the development of the embryo and the homeostasis of the mother. Normal body function can be maintained through homeostasis, which is the main reason we are able to adapt to the continuous changing environment of the human body. Obesity is a growing disease that is affecting many people across the world and one of the greatest factors of obesity is poor management of the intake of glucose. A clinical study was conducted in an effort to improve glucose homeostasis among obese pregnant women and to test if probiotic supplements aid in the reduction of gastric weight gain. Improvements of such things among obese pregnant women would lead to a direct improvement of maternal mortality rates and stillbirth rates around the world. The subject pool of the clinical study consisted of 50 women who fitted the standards of the trial. Subjects were given the probiotic supplement anywhere between 14 and 20 weeks before the expected due date, with a follow-up nine months after the baby was born. In the clinical trial the blood, weight, faecal matter, urine, and vaginal tissue were all monitored. The study showed that Vivomixx (a microbiotic that helps with the homeostasis of the intestinal flora) had a good effect in the improvement of maintenance of weight gain. The cause of this effect is due to the changes in microbiota in the gut. With the help of probiotics the study was able to conclude that probiotics can be beneficial for pregnant obese women by reducing health risks for the foetus and embryo. The changes in the microbiota found in the mother's gut could lead to changes of gastric bacteria in the developing foetus [15].

The development of allergies during infancy continues to impact maternal mortality and stillbirths today across the world. Due to this profound statistic, there is an increased interest in the research in preventing allergies from developing in the early developmental stages of life. Recent research has shown that manipulating the microbiota in the gut of the mother has a direct effect on the developing embryo, which can lead to a direct effect at birth. In a particular clinical trial that was conducted on 400 pregnant women, the probiotic *Lactobacillus rhamnosus* HN001 was tested in an effort to reduce the rates of eczema and atopic sensitisation, Group B streptococcal vaginal colonisation before birth, depression stemming from bacterial vaginosis, and anxiety stemming from postpartum maternal gestational diabetes mellitus among babies who have elevated chances of developing these diseases. To minimise the amount of bias, a randomised double-blind placebo design was used to carry out the clinical trial. The women who were

Table 6.4 Concluding Results of *Lactobacillus rhamnosus* HN001 on Pregnant Women who are Prone to Autoimmune and Inflammatory Responses

Factors	Outcomes (sample sizes of 200 in each factor)
Eczema	Drop-out rate: 13% Babies with eczema: 12.3% Babies expected to have eczema: 43 Level of significance at 5%: 87%
Atopic dermatitis	Drop-out rate: 13% Level of significance at 5%: 69%
Atopic sensitisation	Drop-out rate: 13% Babies with atopic sensitisation: 120 Levels of significance at 5%: 95%
Gestational diabetes mellitus	Drop-out rate: 2.5% Percent of reduction in prevalence: 63% Level of significance in prevalence: 87%
Bacterial vaginosis	Drop-out rate: 2.5% Percentage of cure: 88% Level of significance in prevalence at 5%: >95%
Group B streptococcus	Drop-out rate: 2.5% Level of reduction: 11% Level of significance at 5%: 84%
Maternal postpartum depression and anxiety.	Drop-out rate: 13% Level of reduction: 26% Level of significance at 5%: 79%

selected to be in the trial where given the probiotics from 14 to 20 weeks' gestation and the baby was observed for six months after birth (Table 6.4).

Overall, the study showed the ability of being able to manipulate the bacteria found in the gut during pregnancy to overcome and reduce the rates of autoimmune and inflammatory responses. One of the roles of *Lactobacillus rhamnosus* HN001, which can be found in the gastrointestinal tract of healthy humans but can sometimes be detrimental to pregnant women, is to inhibit GBS (a rare condition where one's immune system harms the peripheral nerves). Even though GBS affects very few pregnancies, the effects of diseases that GBS deregulation carries are often lethal. With new knowledge of ways to inhibit GBS pathways, the endeavour to decrease the rate of stillbirths and maternal mortality increases [16].

As time has passed the discovery of many enzymes and key regulatory functions have been discovered. With the discovery of the key regulatory function of cells the ability to reduce health risk factors has greatly increased. Overproduction of harmful reactions in the human body can raise the chances of many diseases and abnormalities in the body. The intake of nutraceuticals

can help in the reduction of some of those harmful reactions, such as oxidative damage, which can lead to DNA damage and cancer. The levels of DHA (docosahexaenoic acid) are naturally increased during pregnancy. DHA is a known component for maintaining the homeostasis of oxidative damage in the body throughout pregnancy [17].

The continued interest in key regulatory factors gives benefits in the reduction of maternal mortality, miscarriage, and stillbirth rates across the world. Clearly, with the help of clinical trials, we are able to gain new information on both the harmful and the helpful effects of nutraceuticals on the body.

The Impact of Nutraceuticals on Miscarriage and Related Outcomes

Nutraceutical intake is very important for the mother as that directly impacts the foetus. The proper dietary nutraceuticals are able to provide prevention and treatment of many illnesses. Research indicates that maternal nutrition directly impacts any pregnancy-related outcomes. Due to the mother's nutritional deficiency, many new-borns have conditions such as increased mortality rates, risk of chronic illnesses, and possible mental impairment. Lack of proper nutraceuticals even increases the risk of babies being prone to continuous infections. If the mother continues to have a nutritional deficiency, the child is at risk of a reduction in mental abilities and stunted growth. This clearly indicates that malnutrition during pregnancy has implications that can last the full lifetime of the child. Proper nutraceutical intake during pregnancy and beyond is the basis for having both a healthy mother and child [18].

Research indicates that chlorophyll has important lipophilic properties that can prevent miscarriage, neonatal intracranial haemorrhage, and spontaneous abortion. Chlorophyll is also highly beneficial because it can neutralise guanidine, which is a toxin that is released into the blood from pregnancy-related trauma, burns, and muscle fatigue. Although guanidine is normally beneficial, pregnant women who have a history of abortion or miscarriage are at a higher risk of overproducing guanidine. For these women, chlorophyll is effective in controlling excess guanidine levels. Along with chlorophyll, healthy amounts of vitamin K-enriched nutraceuticals are necessary for preventing miscarriage and neonatal haemorrhaging. Nutraceuticals with vitamin K are necessary for hormonal homeostasis and to help reduce the risk of miscarriage and related outcomes. Women that have a history of miscarriage can use nutraceuticals found in herbal products and foods to reduce this risk [19] (Figure 6.4).

Folic acid, also known as vitamin B, is another critical nutraceutical that helps with the prevention of miscarriage, neural tube defects (NTDs), and low birth weight. Vitamin B is a coenzyme for purine and pyrimidine precursors that are found in nucleic acids and are vital for the proper DNA synthesis of the foetus. Pregnant women are at an increased risk of folate deficiency as it is needed in excess amounts for proper foetal growth. Mothers deficient in folic acid have an increased risk of miscarriage, IUGR (intrauterine growth

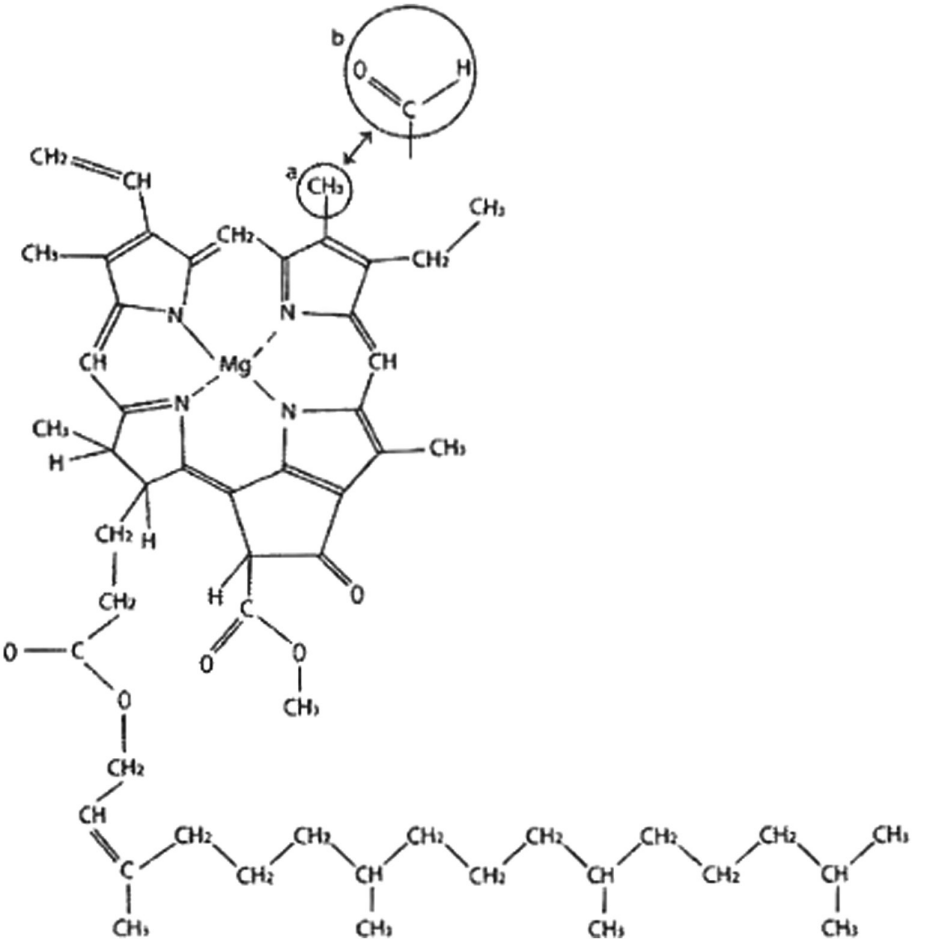


Figure 6.4 *Structure of both chlorophylls A and B [19].*

restriction, where the fetus is much smaller in size than expected), PE (pre-eclampsia, where the mother has elevated blood pressure and urine with high amount of protein), and placental abruption. Pregnant women are told to start taking vitamin B supplements, starting with their periconceptional period. These supplements are critical for the cell proliferation of the foetus during the commencement of pregnancy [20]. Multivitamins with folic acid are important nutraceuticals for maintaining a healthy lifestyle. There is a strong correlation between increased risk of miscarriage due to folate deficiency. On average, women that have a lower concentration of folate in plasma, are more likely to have a miscarriage [21] (Table 6.5) (Figure 6.5).

Pregnant women require nutraceuticals as they provide the required nutrients during the lactation period. Examples such as vitamin E, vitamin C, selenium, lycopene, and zinc are antioxidants as they inhibit PIH (pregnancy induced

Table 6.5 Effects of maternal folic acid deficiency and risk to foetal health [20]

Deficiency of folic acid	Risk Factors
Low folic acid intake	Increased birth defects Higher chance of preterm delivery
Low vitamin and protein intake	Increase in neural tube defects (NTDs) High risk of cancer Impaired neurodevelopment
Elevated folate and low vitamin intake	High chance of obesity High risk of Type 2 diabetes
Prolonged folic acid deficiency	Weakens DNA synthesis due to accumulation of levomefolic acid.
Urine and serum receptors	Folic acid is available.

hypertension, where the mother has elevated blood pressure during pregnancy). This ultimately prevents cell membrane damage, minimises oxidative stress damage from free radicals, and prevents reactive oxygen species from forming. This results in a healthy mother and child. However, not using these nutraceuticals can often lead to miscarriage and other related outcomes. L-arginine is another important nutraceutical that is crucial to the developing foetus, as it helps with maintaining normal blood pressure, proper wound healing, and helps maintain a healthy cardiovascular system. These can be found in foods such as yoghurt, cheese, milk, oats, nuts, wheat, beans, and seeds. Research has shown that doses up to 6 gm of L-arginine helps with foetal growth, increases utero placental blood circulation, reverses IUGR, lowers the chance of respiratory distress syndrome (RDS), and increases oxygen circulation to the foetus [18].

Factors such as the duration of supply and the concentrations of the nutraceuticals greatly influence the health of both the foetus and mother. Diets that are rich with nutraceuticals, together with proper exercise, are key factors during pregnancy. The reduction of stress and increased nutraceutical intake reduce the chances of miscarriage, pre-eclampsia, and other risks from pregnancy (Table 6.6).

The Role of Nutraceuticals in Stillbirths

Stillbirths today in developed countries are at an all-time low due to the help of clinical trials and studies. With the help of modern-day medicine we are able to continue to lower the number of stillbirths occurring around the world. The effects nutraceuticals have on the mother and embryo directly affect stillbirth rates and the development of the foetus. Many factors affect the embryo and the overproduction/underproduction of such proteins could lead to a number of health risks for the mother along with the embryo. Some important substances have been identified that play a direct role in the development of the foetus and help maintain the mother's homeostasis. Research has shown

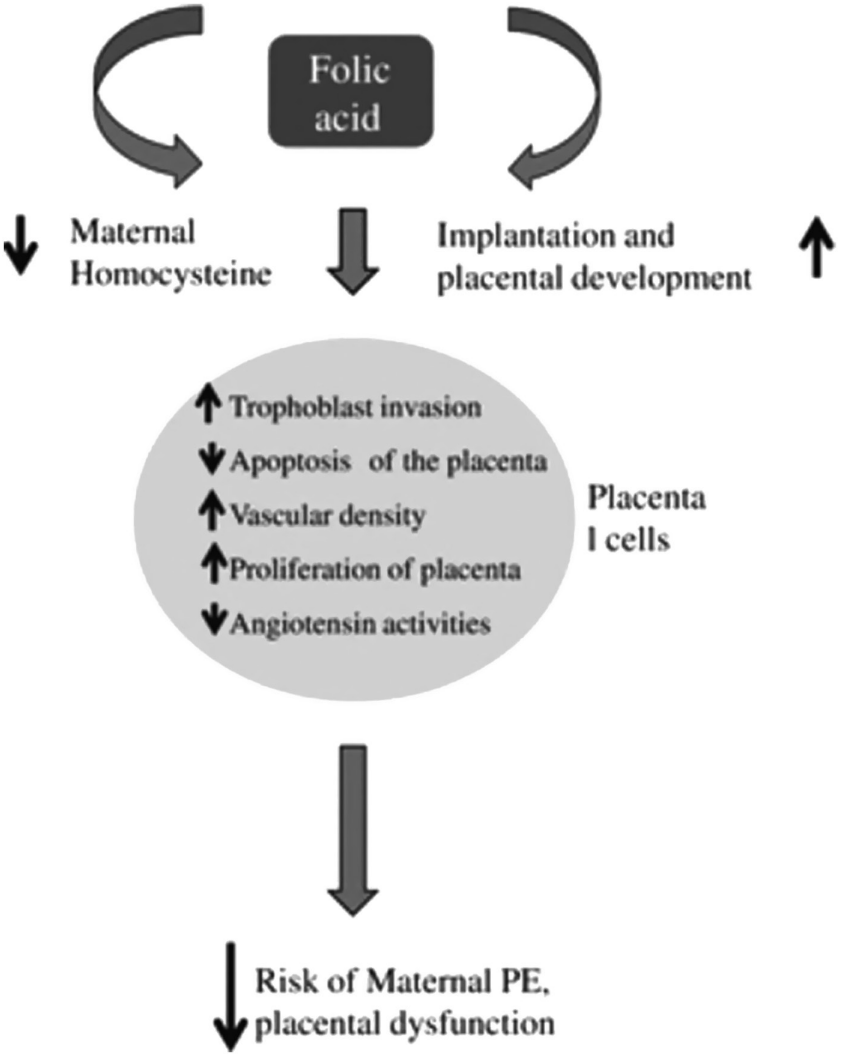


Figure 6.5 *Role of Vitamin B in reducing risk of abnormalities in the placenta [20].*

Table 6.6 Nutraceuticals and Benefits to the Developing Foetus [18]

Part of foetus	Nutraceuticals
Immunity	Vitamin C, vitamin E, zinc
Brain development	DHA, vitamin B, iodine, choline
Gastrointestinal (GI) tract improvement and digestion	Oligosaccharides, fructose
Growth and development	Vitamin D, proteins, fats, calcium

that the underproduction of folate during pregnancy has a direct relationship with vitamin B deficiencies and related diseases; and such underproduction can lead to increased health risks at later stages in life. Some of elevated health risks include cardiovascular disease, cancer, and developmental abnormalities [22]. Emerging technologies have allowed us to predict or take precautions regarding certain health aspects and have thus helped to improve the average lifespan. The development of the vascular system in the embryo is essential and happens within the first two weeks of implantation. Cardiovascular diseases are the leading causes of deaths in many countries, especially where obesity is a problem. The role of nutraceuticals has helped decrease those rates by helping to improve metabolic pathways. The rate of stillbirths is still present, and it is forever changing due to new diseases and new environmental problems. Sources besides our environment are sometimes overlooked but also contain many nutraceuticals. What we put into our bodies plays a major role in our overall health. Many nutraceuticals have been classified in order to help identify specific properties that assist in the homeostasis of certain aspects of the human body. When it comes to stillbirths the use of prebiotics and probiotics can help in the prevention of diseases that a developing foetus and infant can be susceptible to. The cataclysm of oxidative species in the body can lead to a number diseases. Through the help of trials and studies we are able to identify food groups that increase the number of oxidative reactions happening in the body. Oxidative damage is known to have DNA-damaging effects that can lead to cancer, and things like smoking and drinking alcohol can increase the oxidative damage to the body. Smoking during pregnancy is especially unhealthy due to the oxidative damage done during the developmental stages of the infant. Due to research and studies polyphenols have been identified to aid in the reduction of oxidative species in the body. The most common polyphenols are flavonoids and phenolic acid. Polyphenols are known to aid in the process of gene expression, apoptosis, intercellular signalling, and platelet aggregation [1]. With the identification of known carcinogens we are able to use nutraceuticals to help reduce the effects they have on the body.

There are many factors the affect the rate of stillbirths. The identification of the root causes of these problems brings great interest in the research aspect of the scientific community to aid in public health. Through this, nutraceuticals are able to be identified as a leading factor in the prevention of diseases detrimental to health. In areas where poverty levels are greatly elevated, the rates of stillbirths are also greatly elevated due to poor medical care. As well as poor medical care, unfortunately, with poverty comes hunger as well. Due to the lack of nutraceuticals and food, stillbirth levels are elevated in areas such as Tanzania and other underdeveloped countries. A study was done on over 7,000 pregnant women where the levels of iron and calcium were monitored during pregnancy and postpartum. Some of the factors that identified the causes of stillbirths is the lack of calcium and iron intake. The study concluded that with an improvement of diet during pregnancy could result in a great increase in the positive outcome of births [23]. Even today, the ability

to provide aid is pushed to a limit, due to monetary restrictions and, because of this, hunger and poverty continue to exist. However, with the development and production of supplements, there has been a cheap and effective way to help lower the level of stillbirths in poverty-stricken countries.

Maternal nutritional intake is essential for the proper development of the foetus. Insufficient intake of nutrition during pregnancy can have an adverse effect on the outcome of the birth and growth of the infant. Expecting mothers who lack proper nutritional intake tend to have increased chances of stillbirths, miscarriages, infant deaths, and developmental risk factors. In order to prevent these types of occurrences clinical studies are done throughout the world to aid in the improvement of public healthcare outreach. With today's expanding technologies we are able to solve these types of problems at a much faster rate. By analysing blood, urine, and faecal samples, we are able to measure the amount nutrients absorbed and lost in the body. With these types of methods we are able to prevent stillbirths at an improved rate. Along with environment, genetics plays a major role and the ability to karyotype has been a key feature in detecting and preventing a number of diseases. However, due to factors such as poverty, war, and improper health care, stillbirths still occur. Every day, efforts are being made to prevent these outcomes. In a study done in 2017, a conclusion was reached at the end of the clinical trial stating that supplementary dietary iron intake has a direct positive effect on the level of stillbirths [24].

Other factors that directly increase the rate of stillbirths are anaemia and the lack of iron storage. A direct correlation can be made with amount of iron and calcium intake to the chances of having a stillbirth and other health risk factors [25]. Since many factors have been identified that directly affect human health there are continuous efforts in trying to prevent and stop the outcome of stillbirths.

Effects of Nutraceuticals on Maternal Mortality

Maternal mortality and morbidity in developing countries are increasing each year. In developing countries, about 600,000 women die from causes arising from pregnancy and 62 million women endure morbidity and have complications during pregnancy. Maternal nutrition is important: it helps maternal health and survival. Disregarding induced abortions, the four main causes of maternal mortality are pre-eclampsia, haemorrhage, obstructed labour, and infections. Calcium has reduced the occurrence of pre-eclampsia and hypertension, though more research is required [26]. An adequate amount of nutrients is the most important environmental factor in affecting pregnancy outcomes. Nutrigerontology is the scientific discipline that studies the impact of nutrients, foods, macronutrient ratios, and diets on life span, the ageing process, and age-related diseases. Data from experimental studies in model organisms consistently show that nutrient signalling pathways are involved in longevity and affect age-related loss of function and diseases [27] (Table 6.7).

Table 6.7 Nutritional Constituents of Food Plants [28]

Category	Nutrient
Macronutrients	Energy, protein, fat
Minerals	Calcium, phosphorus, magnesium, chloride, sodium, iron, potassium
Micronutrients	Vitamins (vitamin A, vitamin B12, vitamin D, vitamin E, vitamin K), essential fatty acids, thiamine, riboflavin, nicotinic acid, pyridoxine, folate, ascorbic acid, biotin, inositol, choline, para-aminobenzoic acid
Trace elements	Copper, cobalt, chromium, zinc, molybdenum, vanadium, iodine, fluoride, silicon, vanadium
Antinutrients	Protein
– Antitrypsin	Calcium
– Oxalate	Iron, calcium
– Phytate	Iron, protein
– Polyphenols	Iodine
– Goitrogens	
Toxic factors	Lathyrism
– Oxapro	Spedenic dropsy
– Argemone	Liver injury
– Mycotoxins	

Based on studies on animals and humans, if maternal nutrients are insufficient, then the balance between maternal and foetal needs is rearranged and a state of biological competition exists. Maternal and infant health is based on energy and protein this results from short interpregnancy intervals or early pregnancies. This leads to a reduction in maternal nutritional status at conception and altered pregnancy [8]. Maternal health is crucial for the foetus to survive: a mother that is undernourished will deliver a child with low birth weight and with a higher chance of the baby dying. Anaemia is potent within women and is common in maternal mortality. And from this the risks of maternal death and damage to the foetal brain is very common [28].

Conclusion

The classifications of nutraceuticals have been critical in the ability to identify chemical pathways that aid in the prevention of numerous diseases. Nutraceuticals play a vital role in the development of the embryo and the maintenance of homeostasis of the mother. Without proper nutritional diet the chances of developmental deformities increase. The use of clinical trials has unravelled a great deal of detail about the outcomes of ingestion of fluctuating levels of chemicals in the body. The use of factors such as iron and calcium intake has shown an immense reduction in the amount of maternal mortality and stillbirth. The ability to identify problems with the development of the foetus has allowed us to solve obstacles in public health. Anaemia and other deficiencies can be solved with the help of dietary supplements. Maternal

mortality rates and stillbirths have been reduced with the aid of proper health care and health education. The metabolism of these nutraceuticals has shown an immense effect on the development of the foetus and help in the homeostasis maintenance of the mother. Without the research done and clinical trials held in the development of nutraceuticals, the rates of maternal mortality, miscarriages, stillbirths, and related outcomes would be universally higher.

References

1. Das, Lipi. et al. Role of Nutraceuticals in Pregnancy. 2014. *National Center for Biotechnology Information*, Vol. 48 (2). pp. 173–183.
2. Gonzalez-Suarez, Ignacio. et al. *Mechanistic Network Models in Safety and Toxicity Evaluation of Nutraceuticals*. 2016. Academic Press, Vol. 1. pp. 287–304.
3. Andlauer, Wilfried and Fürst, Peter. *Nutraceuticals: A Piece of History, Present Status and Outlook*. 2002. Elsevier, Vol. 35 (23). pp. 171–176.
4. Sahebkar, Amirhossein. et al. *Lipid-Modifying Effects of Nutraceuticals: An Evidence-Based Approach*. 2016. Elsevier, Vol. 32 (1112). pp. 1179–1192.
5. Wang, Jim. et al. *Microbial Production of Value-Added Nutraceuticals*. 2016. Elsevier, Vol. 37. pp. 97–104.
6. Shahidi, Fereidoon. *Nutraceuticals and Functional Foods: Whole Versus Processed Foods*. 2009. Elsevier, Vol. 20 (9). pp. 376–387.
7. Fernando, Luis. et al. *Application of Nutraceuticals in Pregnancy Complications: Does Epigenetics Play a Role?* 2017. Springer, Vol. 1. pp. 1–19.
8. King C, Janet. The Risk of Maternal Nutritional Depletion and Poor Outcomes Increases in Early or Closely Spaced Pregnancies. 2003. *The Journal of Nutrition*, Vol. 133. pp. 1732–1736.
9. Rush, David. Nutrition and Maternal Mortality in the Developing World. 2000. *The American Journal of Clinical Nutrition*, Vol. 72. pp. 212–240.
10. Lee, J. et al. *Reactive Oxygen Species, Aging, and Antioxidative Nutraceuticals*. 2004. Wiley Online Library, Vol. 3. pp. 21–33.
11. Tapas, AR. et al. Flavonoids as Nutraceuticals: A Review. 2008. *Tropical Journal of Pharmaceutical Research*, Vol. 7 (3). pp. 1089–1099.
12. Aggarwal B, Bharat. Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals. 2010. *Annual Review of Nutrition*, Vol. 30. pp. 173–199.
13. Cazzonelli I, Christopher. Carotenoids in Nature: Insights from Plants and Beyond. 2011. *Functional Plant Biology*, Vol. 28. pp. 833–847.
14. Krauss-Etschmann, Susanne. et al. Decreased Cord Blood IL-4, IL-13, and CCR4 and Increased TGF-β Levels After Fish Oil Supplementation of Pregnant Women. 2008. *The Journal of Allergy and Clinical Immunology*, Vol. 121 (12). pp. 464–470.
15. Halkjaer, S. et al. Effects of Probiotics (Vivomixx®) in Obese Pregnant Women and their Newborn: Study Protocol for a Randomised Controlled Trial. 2016. *National Center for Biotechnology Information*, Vol. 17 (1). p. 491.
16. Barthow, Christine. et al. The Probiotics in Pregnancy Study (PiP Study): Rationale and Design of a Double-Blind Randomised Controlled Trial to Improve Maternal Health During Pregnancy and Prevent Infant Eczema and Allergy. 2016. *National Center for Biotechnology Information*, Vol. 16. p. 133.
17. Shoji, Hiromichi. et al. Effect of Docosahexaenoic Acid and Eicosapentaenoic Acid Supplementation on Oxidative Stress Levels During Pregnancy. 2006. *Free Radical Research*, Vol. 40 (4). pp. 379–384.
18. Dr. Basu, S. K. et al. Role of Nutraceuticals in Pregnancy. 2014. *Association of Rural Surgeons of India*, Vol. 10. pp. 1–7.

19. Nick L, Gina. Nutraceuticals that Prevent Spontaneous Abortion and Miscarriage. 2007. *Townsend Letter*, Vol. 1. pp. 1–19.
20. Duttaroy K, Asim and Basak, Sanjay. *B Vitamins and Their Role on Trophoblast Growth and Development*. 2016. Springer, Vol. 1. pp. 51–68.
21. Bailey B, Lynn and Berry J, Robert. Folic Acid Supplementation and the Occurrence of Congenital Heart Defects, Orofacial Clefts, Multiple Births, and Miscarriage. 2005. *The American Journal of Clinical Nutrition*, Vol. 81 (5). pp. 1213–1217.
22. Patrick J. Stover. Physiology of Folate and Vitamin B12 in Health and Disease. 2004. *National Center for Biotechnology Information*, Vol. 62. pp. 3–12.
23. Mosha, Dominic. et al. Dietary Iron and Calcium Intakes During Pregnancy are Associated with Lower Risk of Prematurity, Stillbirth and Neonatal Mortality among Women in Tanzania. 2016. *National Center for Biotechnology Information*, Vol. 20 (4). pp. 678–686.
24. Ramírez-Vélez, Robinson. et al. Use of Dietary Supplements by Pregnant Women in Colombia. 2018. *National Center for Biotechnology Information*, Vol. 18. pp. 117.
25. Rosas, Peña. et al. Daily Oral Iron Supplementation During Pregnancy. 2015. *National Center for Biotechnology Information*, Vol. 7. p. CD004736.
26. Christian, Parul. Maternal Nutrition, Health, and Survival. 2002. *Maternal Nutrition, Health, and Survival*, Vol. 60. pp. 59–63.
27. Aiello, Anna. et al. Nutrigerontology: A Key for Achieving Successful Ageing and Longevity. 2016. *Immunity & Ageing*, Vol. 13. pp. 1–5.
28. Mishra, Seema. et al. Role of Edible Food Plants in Women's Nutrition and Health. 2015. *ResearchGate*, Vol. 1. pp. 1–18.

7

Nutraceuticals and Anaemia in Pregnancy

Deepti Kaushalkumar Jani

Contents

Introduction

Anaemia is one of the most common diseases worldwide. It is the leading cause of deaths during pregnancy (Rahman et al. 2016). Adverse pregnancy outcomes, including low birth weight and prematurity, are prevalent with anaemia (Balarajan et al. 2011).

According to the World Health Organization (WHO), anaemia is defined as a condition associated with a decrease in the number of red blood cells or their oxygen-carrying capacity, insufficient to satisfy physiologic needs. Factors affecting the number of red blood cells are age, sex, altitude, smoking, and pregnancy status (WHO/NMH/NHD/MNM/11.1 2011). The occurrence of anaemia in women of reproductive age (15–49 years) is common in various regions globally (Figure 7.1).

Nutritional deficiencies (iron, vitamin B12 or folate deficiency), diseases and genetic haemoglobinopathies are considered to be the most common causes of anaemia (FAO 2017; Kassebaum et al. 2016).

Globally, malaria is considered to be one of the most common causes of anaemia especially in pregnant women, with increased prevalence in women in their first-time pregnancy and with susceptibility to severe anaemia. During the first or second trimester, anaemia significantly increases the risk of premature birth and low birth weight (WHO 2017).

During pregnancy, there is an increase in maternal red blood cell production resulting in an expansion of red blood cell mass and plasma volume. Due to this expansion of red blood cell mass as well as the increased needs of the growing foetus, iron intake needs to be increased during pregnancy(Erdman,

Figure 7.1 *Prevalence of anaemia in pregnant women aged 15–49 years (WHO 2011, used with permission; Organização Mundial da Saúde 2015).*

MacDonald, and Zeisel 2012). An increase in the plasma volume is a natural process during pregnancy, starting approximately at the eighth week of pregnancy. Plasma volume expansion progresses until the 32nd to 34th week of pregnancy (Breymann et al. 2011).

Globally, the mean blood haemoglobin concentration was found to be 111 g/L (95% credibility interval [CI]: 112–116) during pregnancy (Table 7.1). It indicates that, on average, all population groups were above the threshold for mild anaemia (110 g/L for pregnant women). There are variations in the prevalence of anaemia and mean blood haemoglobin concentrations in different countries and regions. According to the WHO factsheet 2011, the lowest mean blood haemoglobin concentrations and the highest prevalence of anaemia were observed among the population groups of South-East Asia, Eastern Mediterranean, and African Regions (as designated by WHO) (Table 7.1). The prevalence of anaemia was 38.9% to 48.7% for pregnant women in these regions (Organização Mundial da Saúde 2015).

Anaemia can be classified by the cause into nutritional anaemias and haemolytic anaemias. It can also be classified according to variation in the colour, sizes, and shapes of the red blood cells. The size of the red blood cells is smaller than normal in microcytic anaemias, e.g. iron-deficiency anaemia, while the red blood cells are larger in size than normal in macrocytic anaemia, e.g. megaloblastic anaemia (Figure 7.2). In iron-deficiency anaemia, there is deficiency of iron resulting in a decreased amount of haemoglobin in each red blood cell, while in megaloblastic anaemia, there is deficiency of folate or vitamin B12 (De-Regil et al. 2014).

Anaemia has three stages according to the blood haemoglobin level, i.e. mild, moderate, and severe. There may be no effect of mild anaemia during pregnancy and labour, but due to lower stores of iron in mild anaemia, the mother will have decreased stores of iron and may have moderate to severe anaemia

Table 7.1 Global and WHO Regional Mean Blood Haemoglobin Concentration and Prevalence of Anaemia by Population Group for 2011 (WHO 2011, used with permission; Organização Mundial da Saúde 2015)

WHO region	Mean (95% CI) blood haemoglobin concentration (g/L)	Percentage (95% CI) of population with anaemia[a]	Percentage (95% CI) of population with severe anaemia[b]
African region	111 (110 to 114)	46.3 (40.6 to 51.0)	1.5 (1.0 to 2.3)
Region of the Americas	119 (116 to 122)	24.9 (19.0 to 32.5)	0.3 (0.1 to 0.6)
South-East Asia region	110 (106 to 114)	48.7 (36.1 to 58.9)	1.1 (0.5 to 2.2)
European region	118 (115 to 121)	25.8 (19.8 to 33.6)	0.3 (0.1 to 0.6)
Eastern Mediterranean region	113 (111 to 116)	38.9 (32.7 to 46.3)	1.1 (0.6 to 1.6)
Western Pacific region	119 (114 to 124)	24.3 (15.1 to 37.7)	0.4 (0.1 to 0.9)
Global	114 (112 to 116)	38.2 (33.5 to 42.6)	0.9 (0.6 to 1.3)

CI: credibility interval.

[a] Anaemia is defined as blood haemoglobin concentration <110 g/L for pregnant women.

[b] Severe anaemia is defined as blood haemoglobin concentration <70g/L for pregnant women.

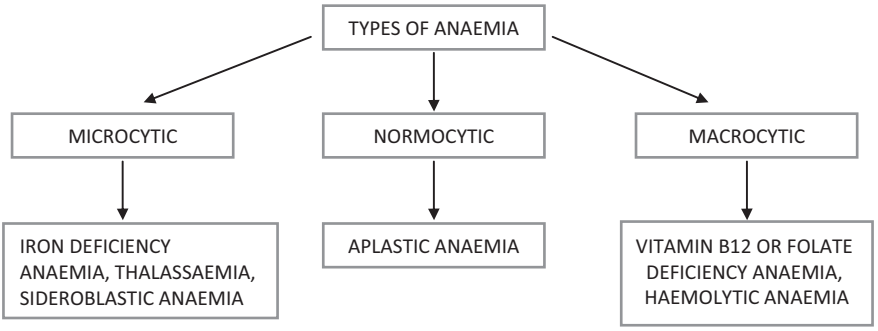


Figure 7.2 *Classification of anaemia (WHO 2017; De-Regil et al. 2014).*

in subsequent pregnancies. The symptoms of moderate anaemia are lack of energy, weakness, and reduced work performance. Severe anaemia is associated with poor consequences. Women with severe anaemia may have cardiac symptoms such as an irregular or increased heartbeat, difficulty in breathing, increased cardiac output, and cardiac failure. Severe anaemia may result in an increased incidence of preterm labour, sepsis, and pre-eclampsia in pregnant woman (Sharma and Shankar 2010; Figure 7.3).

Dietary deficiencies give rise to anaemia in pregnancy. There is increase in requirement for iron and vitamins during pregnancy and dietary deficiencies can result in an insufficient supply of iron and vitamins to meet the desired level, leading to anaemia (Van Den Broek 1996).

Nutraceuticals are emerging as a safe and effective option to prevent or treat diseases (Schütz et al. 2017). They are "natural" substances that are obtained

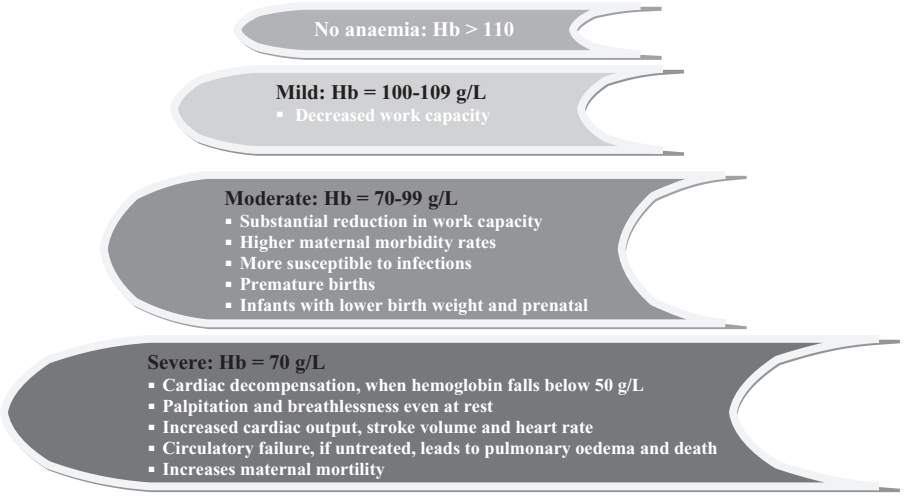


Figure 7.3 *Stages and associated maternal consequences of anaemia in pregnancy (Sharma and Shankar 2010; WHO/NMH/NHD/MNM/11.1 2011); Hb = Haemoglobin.*

from food substances and are useful for medical benefits (Trottier et al. 2010). Stephen DeFelice, chairman and founder of the Foundation for Innovation in Medicine (Cranford, New Jersey), in 1979, defined nutraceuticals as food or parts of a food that are beneficial in the treatment and prevention of disease and provide medical or health benefits (Brower 1998). Nutraceuticals are of great significance in the prevention of pregnancy-associated anaemia resulting from nutrient deficiency.

Nutraceuticals includes the use of dietary and herbal therapies for health benefits. They are natural dietary supplements with minimum side effects. Three broad categories of nutraceuticals are (Ansari et al. 2013):

- Vitamins, minerals, fatty acids, and amino acids
- Extracts of herbs
- Dietary supplements such as nutrition for sports, supplements for reducing weight, and replacements for meal

Nutraceuticals such as iron, vitamin B12 and folic acid have been the preferred treatment options to cure nutrient deficiency anaemia among pregnant women. Deficiencies of these nutrients during pregnancy result in anaemia and supplementation with these nutraceuticals is required in pregnancy to satisfy the nutritional needs of the pregnant woman as well as of the developing foetus. The concern is that the deficiency of these nutrients in a pregnant woman results in her inability to satisfy the nutrition requirement of the developing foetus. Nutritional folate deficiency before conceiving leads to an increase in the risk of neural tube defects during pregnancy. The deficiency of iron and folate in a woman can make her tired and increases the risk of infection (Peña-Rosas et al. 2015).

The occurrence of anaemia is high worldwide due to an insufficient nutrition supply from diet, with the consumption of iron at less than 20 mg/day and the intake of folic acid at less than 70 mg/day. Another cause for decreased iron levels is the intake of phytate and a fibre-rich diet resulting in the reduced bioavailability of iron, i.e. only 3–4%. In developing countries, infections such as malaria and hookworm infestations are common, resulting in chronic blood loss that can also cause anaemia in women (Kalaivani 2009).

In pregnant women, a deficiency of iron is the most common etiological factor for anaemia. Up to 56% of pregnant women may be affected by anaemia in developing countries, with a relatively high prevalence (up to ~25%) of iron deficiency-anaemia (McLean et al. 2009). In regions with endemic malaria, up to 65% of pregnant women may be affected by anaemia, e.g. in countries of sub-Saharan Africa (WHO 2008). In developed countries, approximately 16% of pregnant women suffer from iron-deficiency anaemia (McLean et al. 2009; WHO 2001).

The pregnancy of adolescent females is also an important point of concern as there is an increased risk of anaemia. In developing countries, many women enter pregnancy without sufficient iron stores. Insufficient levels of iron increase the risk of anaemia (WHO 2017).

Iron is a mineral. It is an essential component of the haemoglobin molecule. Haemoglobin transfers oxygen from the lungs to the tissues. Iron is found in many foods, is available as a dietary supplement, and can be added to some food products. The two forms of dietary iron are: heam and non-heam (Ross et al. 2012). Non-heam iron is present in plants and iron-fortified foods, whereas heam and non-heam iron are both present in meat, seafood, and poultry (Table 7.3) (Erdman, MacDonald, and Zeisel 2012).

Iron is properly absorbed in heam form. Heam form is found in animal products. Therefore, vegetarian women are at increased risk of developing iron-deficiency anaemia. In countries such as India, where religious beliefs promote vegetarianism, women are vulnerable to the development of iron-deficiency anaemia (Burke, Leon, and Suchdev 2014).

When iron deficiency develops due to poor diet, dietary iron intake cannot meet iron needs. In long-term deficiency of iron, the body's iron storage will have been reduced, resulting in a decreased supply of iron required for the formation of red blood cells and the outcome is decreased haemoglobin concentration (WHO 2017).

Iron status is also affected by the various factors that either increase or decrease iron absorption. Calcium, phenolic compounds, and phytates inhibit iron absorption (Collings et al. 2013). Other risk factors for low iron levels in pregnant women are reduced iron intake, malaria, intestinal infections, adolescent pregnancy, multiple pregnancies, low socioeconomic status, and the country of residence (Bothwell 2000; Cao and O'Brien 2013; Milman 2011). Social and psychological factors may reduce adherence to iron supplementation and

compliance, which can affect the prevalence of iron-deficiency anaemia (Tran et al. 2013). Vitamin C enhances iron absorption (Collings et al. 2013). Other factors, such as the programmes for anaemia control, the economic situation, the agricultural productivity of the locale, and policies for fortification with micronutrients should also be considered (Pasricha et al. 2013).

Iron-deficiency anaemia is a hypochromic, microcytic anaemia. Deficiency of iron levels in the mother can be transferred intergenerationally to the child. Various studies done previously have shown that if the mother possesses iron-deficiency anaemia, then there is an increased risk of iron deficiency and anaemia in her infants. The extent to which iron deficiency and/or iron-deficiency anaemia during pregnancy affects foetal iron levels is debated (Colomer et al. 1990; Kilbride et al. 1999). Approximately 50% of all cases of anaemia among non-pregnant and pregnant women are due to deficiency of iron (Stevens et al. 2013).

An adult woman has about 2 g of iron in her body, out of which erythrocytes contain 60–70% of iron, with the remaining iron stored in the bone marrow, liver, and spleen. There is an increase in iron demand in pregnancy, i.e. about 1 g additional iron supplement is required. During pregnancy the additional iron requirement is 300 mg for the placenta and foetus, 200 mg that compensates for excretion and 500 mg for enhanced maternal haemoglobin levels. Therefore, the iron intake should be increased during pregnancy. As about 10% of iron is absorbed from food (Table 7.3), additional oral iron should be given to a pregnant woman (Kozuma 2009).

Women's iron needs increase over the course of pregnancy. The iron requirement is 0.8 mg per day during the first trimester and 7.5 mg/day during the third trimester (Balarajan et al. 2011).

Severe consequences occur due to iron deficiency during pregnancy and they affect not only the mother but also her infant (Burke, Leon and Suchdev 2014).

Iron deficiency during pregnancy either due to low iron stores or due to low intake results in an enhanced risk of mortality of mother and infant, low birth weight, and premature birth (WHO 2001). It causes anaemia with symptoms such as reduced immune response, weakness, fatigue, and a decrease in cognitive performance. Emphasising the importance of iron to foetal brain development, a deficiency of iron in a pregnant woman results in reduced iron stores and a deficiency of iron in the infant at birth, and these are associated with behavioural and cognitive deficits. The deficiency of iron in a pregnant woman also enhances the risk of iron deficiency during infancy and iron-deficiency anaemia during lactation. To reduce the risk of iron-deficiency anaemia, iron stores of at least 500 mg are recommended before pregnancy. Over 20% of women in developed countries enter pregnancy with very low iron stores, with a higher figure in developing countries. The combination of iron with folic acid is the most effective treatment for iron deficiency in pregnant women. Folic acid is included to prevent neural tube

defects. Iron supplementation may need to start before conception to prevent iron deficiency in pregnant women. Weekly iron–folic acid supplementation programmes are recommended by WHO in areas with increased occurrence of anaemia in women of reproductive age. Worldwide, it is recommended that daily iron supplementation should be given to pregnant women. Due to adverse effects, e.g. gastrointestinal upset and uncertain benefits in iron-replete women, iron supplementation is not recommended in some developed countries. Poor adherence to iron supplementation is common due to gastrointestinal side effects as well as lack of reliable access to supplements. Further, iron supplements often contain iron of lower bioavailability (Burke, Leon, and Suchdev 2014).

Iron-fortified foods would help to decrease deficiency of iron among pregnant women, though these may be insufficient alone to satisfy iron needs without additional supplementation. Multiple micronutrient powders containing iron may have good potential for reducing iron deficiencies. In future, there is a need for further research on fortified food in order to determine their level of benefit (Bhutta et al. 2008).

According to WHO, oral supplements of iron and folic acid daily for pregnant women are required to prevent maternal anaemia. The requirement of iron is 30–60 mg of elemental iron (the equivalent of this is 300 mg of ferrous sulphate heptahydrate, 500 mg of ferrous gluconate, or 180 mg ferrous fumarate) and 0.4 mg for folic acid. Intake of folic acid should be initiated at the earliest opportunity, ideally before conception, to prevent neural tube defects. If daily iron is not advisable due to side effects, then to improve maternal outcomes in pregnant women, intermittent oral iron supplementation with 120 mg of elemental iron (the equivalent of this is 600 mg of ferrous sulphate heptahydrate, 1,000 mg ferrous gluconate, or 360 mg ferrous fumarate) and 2.8 mg folic acid once in a week is recommended (Peña-Rosas et al. 2015).

The supplementation of iron would raise the concentration of mean blood haemoglobin by 10.2 g/L (95% CI: 6.1–14.2) in women during pregnancy. Iron supplementation cures 50% of anaemia in women (Organização Mundial da Saúde 2015) (Table 7.2).

A reduced level of folate resulting in megaloblastic anaemia is the second most common cause of anaemia during pregnancy (Sifakis and Pharmakides 2006). Folate is a B-vitamin. It supports blood volume expansion in pregnancy. It is also involved in the synthesis and maintenance of DNA. There is an increase in the requirement of folate throughout pregnancy (Stamm and Houghton 2013). Reduction in the folate level during pregnancy is strongly correlated with an enhanced risk of neural tube defects and other congenital abnormalities. Folate is needed for synthesis of haem and a deficiency of folate can cause microcytic, normocytic, or sideroblastic anaemia. Folic acid-deficiency anaemia can be treated by the administration of folic acid at a dose of 500–1,000 µg/day. It can also be added to wheat and maize flour to enhance the folate intake by women (Kozuma 2009). Folate intake should be

Table 7.2 Estimated Percentage (95% CI) of Anaemia[a] that is Amenable to Iron Supplementation (WHO 2011, used with permission; Organização Mundial da Saúde 2015)

WHO region	Number of countries covered for survey	Pregnant women aged 15–49 years
African region	35	44 (42 to 47)
Region of the Americas	13	60 (52 to 68)
South-East Asia region	10	47 (42 to 54)
European region	11	62 (54 to 71)
Eastern Mediterranean region	11	49 (46 to 54)
Western Pacific region	14	61 (49 to 72)
Global	94	50 (47 to 53)

CI: credibility interval.

[a] Anaemia is defined as blood haemoglobin concentration <110 g/L for pregnant women.

increased before and during pregnancy. It can be consumed either by using tablets or fortified grain-based foods. The suggested tolerable safe upper limit of folate during pregnancy is 1,000 μg/day. Around 10% of women consume folic acid greater than the suggested dose of 1,000 μg/day during pregnancy (Hoyo et al. 2011), in addition to folate ingestion as part of their normal diet, e.g. cereal, bread, or pasta. Excessive folate consumption produces a negative effect on genetic programming and neurodevelopmental outcomes in offspring (Wiens and Desoto 2017).

The effect of riboflavin (vitamin B2) deficiency on the metabolism of iron includes a decrease in mobilisation of iron from stores, a reduction in absorption of iron, and an increase in iron loss (Rohner et al. 2007), as well as the impairment of globin production (Fishman, Christian, and West 2000). Thus, a deficiency of riboflavin may contribute to the occurrence of anaemia. A greater effect on haemoglobin concentration can be obtained by supplementing riboflavin with iron (Rohner et al. 2007). The deficiency of riboflavin is common with low intakes of milk/milk products and meat in pregnancy (Powers 2003). The deficiency of nutrients such as vitamin B12 (cobalamin) and folate affect the synthesis of DNA, cell division, and thus the formation of red blood cells. Vitamin B12 deficiency is common with decreased dietary intake of the nutrients, specifically in case of a vegetarian diet or diet with less animal source food (Allen 2008).

The occurrence of vitamin B12 deficiency anaemia is 10–28% in uncomplicated pregnancies (Koebnick et al. 2002). Animal products are rich source of vitamin B12 (Milman et al. 2006). Foetal vitamin B12 stores should be 25–50 μg at term (Korenke et al. 2004). A physiological reduction in vitamin B12 levels occurs in 20% of cases in pregnancy, with the lowest levels during the third trimester (Koebnick et al. 2002; Milman et al. 2006; Pardo, Gindes, and Orvieto 2004). Inadequate diets are the most common etiological factor for

vitamin B12 deficiency (Molloy et al. 2008). Vitamin B12 is involved in the formation of DNA, in the multiplication of cells during pregnancy, and in the development of the foetus (Koebnick et al. 2002; Milman et al. 2006). A decrease in vitamin B12 levels results in hyperhomocysteinaemia associated with placental vasculopathy, which affects foetal growth (Milman et al. 2006; Relton, Pearce, and Parker 2005).

Anaemia can be diagnosed by determining haemoglobin levels; the cut-off point in the last trimester is 11.0 g/dL. Additional tests can be performed to discover the exact cause of the anaemia (Breymann 2002; Scholl and Hediger 1994). Measurement of serum vitamin B12 level and urinary methylmalonic acid level can be done to detect vitamin B12-deficiency anaemia (Hoffbrand and Provan 1997; Korenke et al. 2004; Weatherall 1997).

Vitamin B12 is transferred from mother to foetus during pregnancy by active transport into foetal circulation, resulting in increased foetal serum level than that of maternal serum levels (Ray and Blom 2003).

Typical symptoms of megaloblastic anaemia are vomiting, diarrhoea, and pyrexia. In the later stages, oedema and albuminuria may occur (Akhtar and Hassan 2012).

Vitamin B12-deficiency anaemia can be treated with loading doses of daily to weekly parenteral hydroxocobalamin injections of 1 mg. Injections should be given over 1 to 3 months to replenish body stores of vitamin B12, followed by a maintenance regimen (Hoffbrand and Provan 1997; Solomon 2007).

Other less common anaemias during pregnancy are aplastic anaemia and haemolytic anaemia. Thalassaemia, sickle cell anaemia, and glucose-6-phosphate dehydrogenase-deficiency anaemia are haemolytic anaemias. HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome is the commonest form of haemolytic anaemia found during pregnancy. It occurs from the late pregnancy period to the puerperal period. Sickle cell anaemia can cause high-risk pregnancy. Multidisciplinary management of sickle cell anaemia is required for a proper maternal and neonatal outcome (Elenga et al. 2016). Because of the intensive maternal and foetal observations of experienced haematologists and obstetricians, women with beta thalassaemia major may have successful pregnancy outcomes. This type of anaemia should be treated with a blood transfusion and the supplementation of folic acid. The use of iron preparations is contraindicated in this type of anaemia (Sharma and Shankar 2010).

Various micronutrients are supplied by food. The food sources are animal sources (for vitamin B12 and iron), fruits, vegetables, dairy products, and eggs (for folate). Animal sources are the richest dietary source of various micronutrients, with the only dietary source of heam iron and vitamin B12 being animal sources. Meat, fish, and poultry are good sources of iron. Because of this, there is an increase in the deficiency of iron and vitamin B12 in vegetarians. Globally, the prevalence of vitamin B12-deficiency is high in countries

Table 7.3 Nutraceuticals: Food Source and Application (Picciano 2003; WHO 2017)

Nutraceutical	Recommended intake	Food source	Application
Iron	27 mg/day	Beans and peas, meat, poultry, prunes and prune juice, raisins, seafood, spinach, whole grain and enriched cereals and breads	Iron-deficiency anaemia
Folic acid	600 μg/day	Legumes and green,leafy vegetables, whole grains, fruits, and fruit juices such as oranges	Megaloblastic anaemia
Vitamin B12	2.6 μg/day	Shellfish, beef liver, other meats, fish and poultry, dairy products	Megaloblastic anaemia

with a high number of vegetarians as compared to countries with a high number of non-vegetarians. Plant sources such as legumes and maize are high in non-heam iron. Other iron-rich sources are tortillas and beans (Allen 2008). Dietary products as a good source of folate are vegetables, beans, chickpeas, and fruits (Table 7.3) (Partearroyo et al. 2017). Less folate content is found in cereals, milk, and meat (Allen 2008).

Another important point of concern is the interaction between various micronutrients. Even when the supplements for micronutrients are taken in the proper amounts to treat anaemia, the interaction between them can affect the outcome adversely. In the fasting state, high amounts of iron can interfere with the uptake of zinc. Zinc in modest concentrations produces a positive effect on immune functioning, while in high concentrations, it can interfere with iron absorption and can adversely affect immune function. High concentrations of folate also reduce the absorption of zinc. Thus, supplements having zinc with iron and folate should be taken with meals to overcome the inhibitory effect on zinc. Consumption of copper with high iron intake affects the absorption of copper. Calcium is known to inhibit the absorption of both heam and non-heam types of iron, therefore during the first trimester of pregnancy, the absorption of iron is reduced in women taking high-dose calcium supplements. Thus, two separate supplements of iron and calcium should not be taken at different times. Ascorbic acid increases the absorption of iron when taken with meals. Iron and folate supplements are recommended to be used shortly after meals to reduce side effects. Maternal malnutrition is common in developing countries, therefore the requirement of a multiple-micronutrient supplement regimen is a must. Hence, it can be seen that interactions between micronutrients have important implications for supplements during pregnancy (Ladipo 2000).

The use of dietary supplements as nutraceuticals helps to implement future campaigns emphasising the use of dietary supplements in pregnancy in order

to ensure adequate micronutrient intakes and reduce the risk of pregnancy-associated anaemias. In addition, it is important to understand and analyse to what extent nutraceuticals are helpful in satisfying the overall requirement of nutrients during pregnancy. Rigorous, controlled clinical trials are needed to assess the efficacy and safety of dietary supplements recommended as nutraceuticals during pregnancy.

References

Akhtar, Mahenaz, and Ismail Hassan. 2012. "Severe Anaemia during Late Pregnancy." *Case Reports in Obstetrics and Gynecology*. doi:10.1155/2012/485452.

Allen, Lindsay H. 2008. "To What Extent Can Food-Based Approaches Improve Micronutrient Status?" *Asia Pacific Journal of Clinical Nutrition*. doi:10.1016/j.drugalcdep.2017.06.044.

Ansari, Shahid H, Baby Chauhan, Nazia Kalam, and Gopal Kumar. 2013. "Current Concepts and Prospects of Herbal Nutraceutical: A Review." *Journal of Advanced Pharmaceutical Technology & Research*. doi:10.4103/2231-4040.107494.

Balarajan, Yarlini, Usha Ramakrishnan, Emre Özaltin, Anuraj H. Shankar, and S. V. Subramanian. 2011. "Anaemia in Low-Income and Middle-Income Countries." *The Lancet*. doi:10.1016/S0140-6736(10)62304-5.

Bhutta, Zulfiqar A., Tahmeed Ahmed, Robert E. Black, Simon Cousens, Kathryn Dewey, Elsa Giugliani, Batool A. Haider, et al. 2008. "What Works? Interventions for Maternal and Child Undernutrition and Survival." *The Lancet*. doi:10.1016/S0140-6736(07)61693-6.

Bothwell, Thomas H. 2000. "Iron Requirements in Pregnancy and Strategies to Meet Them." *American Journal of Clinical Nutrition*. doi:10.1093/ajcn/72.1.257S.

Breymann, Christian. 2002. "Iron Deficiency and Anaemia in Pregnancy: Modern Aspects of Diagnosis and Therapy." *Blood Cells, Molecules, and Diseases*. doi:10.1006/bcmd.2002.0597.

Breymann, Christian, Xu Ming Bian, Lourdes R. Blanco-Capito, Christopher Chong, Ghazala Mahmud, and Rakhshanda Rehman. 2011. "Expert Recommendations for the Diagnosis and Treatment of Iron-Deficiency Anaemia during Pregnancy and the Postpartum Period in the Asia-Pacific Region." *Journal of Perinatal Medicine*. doi:10.1515/JPM.2010.132.

Van Den Broek, Nynke. 1996. "The Aetiology of Anaemia in Pregnancy in West Africa." *Tropical Doctor*. doi:10.1177/004947559602600103.

Brower, V. 1998. "Nutraceuticals: Poised for a Healthy Slice of the Healthcare Market?" *Nature Biotechnology*. doi:10.1038/nbt0898-728.

Burke, Rachel M., Juan S. Leon, and Parminder S. Suchdev. 2014. "Identification, Prevention and Treatment of Iron Deficiency during the First 1000 Days." *Nutrients*. doi:10.3390/nu6104093.

Cao, Chang, and Kimberly O. O'Brien. 2013. "Pregnancy and Iron Homeostasis: An Update." *Nutrition Reviews*. doi:10.1111/j.1753-4887.2012.00550.x.

Collings, Rachel, Linda J. Harvey, Lee Hooper, Rachel Hurst, Tracey J. Brown, Jennifer Ansett, Maria King, and Susan J. Fairweather-Tait. 2013. "The Absorption of Iron from Whole Diets: A Systematic Review." *American Journal of Clinical Nutrition*. doi:10.3945/ajcn.112.050609.

Colomer, Julia, Concepción Colomer, Dolores Gutierrez, Angeles Jubert, Andres Nolasco, Joaquín Donat, Rafael Fernandez-Delgado, Francisco Donat, and Carlos Alvarez-Dardet. 1990. "Anaemia during Pregnancy as a Risk Factor for Infant Iron Deficiency: Report from the Valencia Infant Anaemia Cohort (VIAC) Study." *Paediatric and Perinatal Epidemiology*. doi:10.1111/j.1365-3016.1990.tb00638.x.

De-Regil, L. M., J. P. Peña-Rosas, M. N. Garcia-Casal. 2014. "Anemias de origen nutricio." In *Nutriología médica, 4th ed.*, edited by M. Kaufer-Horwitz, A. B. Pérez-Lizaur, P. Arroyo. Mexico City, Editorial Panamericana, 401–33.

Elenga, Narcisse, Aurélie Adeline, John Balcaen, Tania Vaz, Mélanie Calvez, Anne Terraz, Laetitia Accrombessi, and Gabriel Carles. 2016. "Pregnancy in Sickle Cell Disease Is a Very High-Risk Situation: An Observational Study." *Obstetrics and Gynecology International*. doi:10.1155/2016/9069054.

Erdman, John W., Ian A. MacDonald, and Steven H. Zeisel. 2012. *Present Knowledge in Nutrition: Tenth Edition*. doi:10.1002/9781119946045.

FAO. 2017. *The State of Food Security and Nutrition in the World. Food and Agriculture Organization of the United Nations*. doi:10.1176/appi.ap.30.6.528.

Fishman, Steven M., Parul Christian, and Keith P. West. 2000. "The Role of Vitamins in the Prevention and Control of Anaemia." *Public Health Nutrition*. doi:10.1017/S1368980000000173.

Hoffbrand, V., and D. Provan. 1997. "ABC of Clinical Haematology: Macrocytic Anaemias." *British Medical Journal* 314 (7078): 430–33.

Hoyo, Cathrine, Amy P. Murtha, Joellen M. Schildkraut, Michele R. Forman, Brian Calingaert, Wendy Demark-Wahnefried, Joanne Kurtzberg, Randy L. Jirtle, and Susan K. Murphy. 2011. "Folic Acid Supplementation before and during Pregnancy in the Newborn Epigenetics STudy (NEST)." *BMC Public Health*. doi:10.1186/1471-2458-11-46.

Kalaivani, K. 2009. "Prevalence & Consequences of Anaemia in Pregnancy." *Indian Journal of Medical Research*. doi:10.1542/peds.2005-1156.

Kassebaum, Nicholas J., Tom D. Fleming, Abraham Flaxman, David E. Phillips, Caitlyn Steiner, Ryan M. Barber, Sarah Wulf Hanson, et al. 2016. "The Global Burden of Anaemia." *Hematology/Oncology Clinics of North America*. doi:10.1016/j.hoc.2015.11.002.

Kilbride, Julia, Terry G. Baker, Liakat A. Parapia, Sami A. Khoury, Saher W. Shuqaidef, and David Jerwood. 1999. "Anaemia during Pregnancy as a Risk Factor for Iron-Deficiency Anaemia in Infancy: A Case-Control Study in Jordan." *International Journal of Epidemiology*. doi:10.1093/ije/28.3.461.

Koebnick, Corinna, Ulrike A. Heins, Pieter C. Dagnelie, Sunitha N. Wickramasinghe, Indrika D. Ratnayaka, Torsten Hothorn, Annette B. Pfahlberg, Ingrid Hoffmann, Jan Lindemans, and Claus Leitzmann. 2002. "Longitudinal Concentrations of Vitamin B12 and Vitamin B12-Binding Proteins during Uncomplicated Pregnancy." *Clinical Chemistry* 48 (6): 928–33.

Korenke, G. Christoph, Donald H. Hunneman, Stefan Eber, and Folker Hanefeld. 2004. "Severe Encephalopathy with Epilepsy in an Infant Caused by Subclinical Maternal Pernicious Anaemia: Case Report and Review of the Literature." *European Journal of Pediatrics*. doi:10.1007/s00431-004-1402-4.

Kozuma, Shiro. 2009. "Approaches to Anaemia in Pregnancy." *Japan Medical Association Journal* 52 (4): 214–8.

Ladipo, Oladapo A. 2000. "Nutrition in Pregnancy: Mineral and Vitamin Supplements." *American Journal of Clinical Nutrition*. doi:10.1093/ajcn/72.1.280S.

McLean, Erin, Mary Cogswell, Ines Egli, Daniel Wojdyla, and Bruno De Benoist. 2009. "Worldwide Prevalence of Anaemia, WHO Vitamin and Mineral Nutrition Information System, 19932005." *Public Health Nutrition*. doi:10.1017/S1368980008002401.

Milman, Nils. 2011. "Iron in Pregnancy - How Do We Secure an Appropriate Iron Status in the Mother and Child?" *Annals of Nutrition and Metabolism*. doi:10.1159/000332129.

Milman, Nils, Keld Erik Byg, Thomas Bergholt, Lisbeth Eriksen, and Anne Mette Hvas. 2006. "Cobalamin Status during Normal Pregnancy and Postpartum: A Longitudinal Study Comprising 406 Danish Women." *European Journal of Haematology*. doi:10.1111/j.0902-4441.2006.t01-1-EJH2550.x.

Molloy, Anne M, Peadar N. Kirke, Lawrence C. Brody, John M. Scott, and James L. Mills. 2008. "Effects of Folate and Vitamin B 12 Deficiencies during Pregnancy on Fetal,

Infant, and Child Development." *Journal of Psychomatic Obstetrics and Gynaecology*. doi:10.1177/156482650802925114.
Organização Mundial da Saúde. 2015. "The Global Prevalence of Anaemia in 2011." WHO Report. doi:10.1017/S1368980008002401.
Pardo, J., L. Gindes, and R. Orvieto. 2004. "Cobalamin (Vitamin B12) Metabolism during Pregnancy." *International Journal of Gynecology and Obstetrics*. doi:10.1016/S0020-7292(03)00257-1.
Partearroyo, Teresa, María de Lourdes Samaniego-Vaesken, Emma Ruiz, Josune Olza, Javier Aranceta-Bartrina, Ángel Gil, Marcela González-Gross, Rosa M. Ortega, Lluis Serra-Majem, and Gregorio Varela-Moreiras. 2017. "Dietary Sources and Intakes of Folates and Vitamin B_{12} in the Spanish Population: Findings from the ANIBES Study." *PLoS ONE*. doi:10.1371/journal.pone.0189230.
Pasricha, Sant Rayn, Hal Drakesmith, James Black, David Hipgrave, and Beverley Ann Biggs. 2013. "Control of Iron Deficiency Anaemia in Low- and Middle-Income Countries." *Blood*. doi:10.1182/blood-2012-09-453522.
Peña-Rosas, Juan Pablo, Luz Maria De-Regil, Maria N. Garcia-Casal, and Therese Dowswell. 2015. "Daily Oral Iron Supplementation during Pregnancy." *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD004736.pub5.
Picciano, Mary Frances. 2003. "Pregnancy and Lactation: Physiological Adjustments, Nutritional Requirements and the Role of Dietary Supplements." *The Journal of Nutrition*. doi:10.1093/jn/133.6.1997S.
Powers, Hilary J. 2003. "Riboflavin (Vitamin B-2) and Health." *American Journal of Clinical Nutrition*. doi:10.1093/ajcn/77.6.1352.
Rahman, Md Mizanur, Sarah Krull Abe, Md Shafiur Rahman, Mikiko Kanda, Saki Narita, Ver Bilano, Erika Ota, Stuart Gilmour, and Kenji Shibuya. 2016. "Maternal Anaemia and Risk of Adverse Birth and Health Outcomes in Low- and Middle-Income Countries: Systematic Review and Meta-Analysis." *American Journal of Clinical Nutrition*. doi:10.3945/ajcn.115.107896.
Ray, J. G., and H. J. Blom. 2003. "Vitamin B12 Insufficiency and the Risk of Fetal Neural Tube Defects." *QJM - Monthly Journal of the Association of Physicians*. doi:10.1093/qjmed/hcg043.
Relton, Caroline L., Mark S. Pearce, and Louise Parker. 2005. "The Influence of Erythrocyte Folate and Serum Vitamin B12 Status on Birth Weight." *British Journal of Nutrition*. doi:10.1079/BJN20041395.
Rohner, Fabian, Michael B. Zimmermann, Rita Wegmueller, Andreas B. Tschannen, and Richard F. Hurrell. 2007. "Mild Riboflavin Deficiency Is Highly Prevalent in School-Age Children but Does Not Increase Risk for Anaemia in Coôte d'Ivoire." *British Journal of Nutrition*. doi:10.1017/S0007114507665180.
Ross, A. C., B. Caballero, R. J. Cousins, K. L. Tucker, T. R. Ziegler. 2012. *Modern Nutrition in Health and Disease*. 11th ed. Wolters Kluwer Health Adis (ESP).
Scholl, Theresa O., and Mary L. Hediger. 1994. "Anaemia and Iron-Deficiency Anaemia: Compilation of Data on Pregnancy Outcome." *American Journal of Clinical Nutrition*. doi:10.1093/ajcn/59.2.492S.
Schütz L. F., J. Bernardo, M. Le, T. Thomas, C. Nguyen, D. Zapata, H. Sanford, J. D. Bowman, B. M. Mitchell, M. Choudhury. 2017. "Application of Nutraceuticals in Pregnancy Complications: Does Epigenetics Play a Role?" In *Handbook of Nutrition, Diet, and Epigenetics*, edited by V. Patel and V. Preedy. Springer, Cham.
Sharma, J. B., and Meenakshi Shankar. 2010. "Anaemia in Pregnancy." *JIMSA*. doi:10.5005/jp-journals-10006-1177.
Sifakis, S., and G. Pharmakides. 2006. "Anaemia in Pregnancy." *Annals of the New York Academy of Sciences*. doi:10.1097/00007611-193901000-00023.
Solomon, Lawrence R. 2007. "Disorders of Cobalamin (Vitamin B12) Metabolism: Emerging Concepts in Pathophysiology, Diagnosis and Treatment." *Blood Reviews*. doi:10.1016/j.blre.2006.05.001.

Stamm, Rosemary A., and Lisa A. Houghton. 2013. "Nutrient Intake Values for Folate during Pregnancy and Lactation Vary Widely around the World." *Nutrients*. doi:10.1007/978-3-319-59876-5_53.

Stevens, Gretchen A., Mariel M. Finucane, Luz Maria De-Regil, Christopher J. Paciorek, Seth R. Flaxman, Francesco Branca, Juan Pablo Peña-Rosas, Zulfiqar A. Bhutta, and Majid Ezzati. 2013. "Global, Regional, and National Trends in Haemoglobin Concentration and Prevalence of Total and Severe Anaemia in Children and Pregnant and Non-Pregnant Women for 1995–2011: A Systematic Analysis of Population-Representative Data." *The Lancet Global Health*. doi:10.1016/S2214-109X(13)70001-9.

Tran, Thach Duc, Beverley Ann Biggs, Tuan Tran, Gerard J. Casey, Sarah Hanieh, Julie Anne Simpson, Terence Dwyer, and Jane Fisher. 2013. "Psychological and Social Factors Associated with Late Pregnancy Iron Deficiency Anaemia in Rural Viet Nam: A Population-Based Prospective Study." *PLoS ONE*. doi:10.1371/journal.pone.0078162.

Trottier, Greg, Peter J. Boström, Nathan Lawrentschuk, and Neil E. Fleshner. 2010. "Nutraceuticals and Prostate Cancer Prevention: A Current Review." *Nature Reviews Urology*. doi:10.1038/nrurol.2009.234.

Weatherall, David J. 1997. "ABC of Clinical Haematology: The Hereditary Anaemias." *BMJ*. doi:10.1136/bmj.314.7079.492.

WHO/NMH/NHD/MNM/11.1. 2011. "Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity." *Micronutrients Indicators*. doi:2011.

WHO. 2001. Iron Deficiency Anaemia: Assessment, Prevention and Control, a Guide for Program Managers. Geneva: WHO. doi:10.1136/pgmj.2009.089987.

WHO. 2008. "Worldwide Prevalence of Anaemia 19932005." *WHO Report*. doi:10.1017/S1368980008002401.

WHO. 2017. *Nutritional Anaemias : Tools for Effective Prevention*. *World Health Organization*. doi:10.1111/j.1532-950X.2006.00216.x.

Wiens, Darrell, and M. Catherine Desoto. 2017. "Is High Folic Acid Intake a Risk Factor for Autism?—a Review." *Brain Sciences*. doi:10.3390/brainsci7110149.

8

Nutraceuticals in Maternal Infections

Param Patel, Sujan Patel, Parth Amin, and Yashwant Pathak

Contents

Introduction

The outreach of public health care has immensely reduced the number of mortalities with the help of modern medicine. Through copious amounts of research, public healthcare specialists are able to prevent many infections and disruptions of homeostasis during pregnancy. Maternal infections have been correlated to increased rates of maternal mortality, stillbirths, and developmental effects if untreated. Infections occur when there is an invasion of microorganisms including viruses, parasites, and bacteria. When infections occur there tends to be a different appearance in tissue where the invasion has occurred. In 2010 a global study was done on the deaths of the 7.6 million infants who were less than the age of five when they died; and about 4.8 million of those deaths can be attributed to infectious diseases in infants and during pregnancy [1]. One of the main causes of infantile infections is due to early breastfeeding measurements through a breastfeeding instrument called MomSense. Breast milk contains enormous amounts of nutraceuticals that are essential to the development of an infant. Research has shown that through the use of proper breastfeeding and preventive sterile measures, the overall probability of infections occurring during maternity and infancy is greatly reduced. Breastfeeding

also has a great effect on the development of the body's natural immune system. The immune system is responsible for fighting off numerous amounts of viruses that can creep into the body. With the annual rate of maternal deaths and infantile deaths being in the millions, research is constantly being done on the treatment and prevention of possible infections. Through the use of modern medicine, pharmaceutical advancements, and nutraceuticals, doctors are able to treat maternal infections.

One of the leading causes of premature births is poor diet and unhygienic practices [2]. Poor diet has been known to weaken the immune system since the body does not have enough energy to fight foreign invasive bacteria and viruses. Hygienic practices when using maternal equipment such as a breast pumps and the sterilization of equipment are both essential for reducing the probability of infections. In rural areas this is especially important since the risk of infection is higher than in more developed areas of the globe. Through advancements in public health care there have been many infantile care organizations that specialize in educating the public about practices that reduce the risk of maternal infections during the development of the embryo until birth. Organizations like these have helped immensely in the reduction of maternal mortality and stillbirths.

In formula milk, additives are normally used to maximize the number of nutrients that a developing infant should be receiving for mothers who are not able to produce breast milk. The prenatal period for the mother is absolutely vital for the development of the foetal immune system. When mothers are not able to produce breast milk after pregnancy, this usually relates to malnutrition during pregnancy. The nutritional intake of a pregnant women is essential to the development of the foetal immune system. With the research on micronutrients, supplements, and additives a great amount of light has been shed on aiding the foetus. Evidence has shown that certain supplements, micronutrients, and additives are able to help develop the immune system. The introduction of such micronutrients and supplements to a developing mother has shown to have a direct effect on the development of the foetal immune system [3].

The Role of Nutraceuticals in Fighting Maternal Infections

Maternal infections or inflammations cause preterm births, which can lead to many chronic diseases such as cardiovascular diseases, asthma, and obesity. Research indicates that abnormal responses to childhood infections, such as parvovirus B19, combined with epigenetic alteration may influence cancer. There is a link between maternal infections followed by epigenetic alteration in the foetus and the mechanisms involved. Recent studies have offered some clues for this, with recurring urinary tract infections, common in pregnant women, causing preterm birth and low birth weight.

Whether or not a maternal infection with a urinary tract pathogen makes epigenetic changes in the foetus is not known. However, there is a possibility in which neonatal exposure to pathogens could lead to alterations in the epigenetic landscape of the foetus, which increases the susceptibility to chronic disease or cancer. Viruses and bacteria are represented as biological stressors that make epigenetic alterations either directly or indirectly through the induction of inflammation. Epigenetic alterations are induced by bacterial infections, such as from the bacterium *Listeria monocytogenes*, a food-borne pathogen that is dangerous to both pregnant women and the foetus. Maternal nutrition has a huge impact on foetal metabolic programming. High-fat diets, micro- and macronutrient deficiencies, and low-protein consumption during pregnancy through to lactation can be harmful to foetal development [4].

Further research has indicated that nutraceuticals obtained from spices such as red pepper, turmeric, black pepper, ginger, liquorice, garlic, clove, coriander, and cinnamon target inflammatory pathways, preventing neurodegenerative diseases. There are practices related to antenatal care for managing a variety of conditions from early nausea and vomiting symptoms in relation to pregnancy. Maternal education is the most important factor in determining good health. Imbalances in maternal nutrition can affect foetal growth and development. Foetal growth is hindered in developing countries and has been connected with negative short- and long-term outcomes, with increases in mortality, childhood morbidity, perinatal morbidity, and child morbidity. Children who go through a shortage of foetal growth are more likely to show signs of difficulties with cognitive development and of neurological impairment. Energy during pregnancy does not change and weight gain is very low in the first trimester, more energy is suggested in the second and third trimester. It is indicated by research that about 340 to 450 kcal per day is recommended. There is a very close relationship between glucose consumption during pregnancy and proper growth of the foetus. Glucose is an essential component required by both the mother and foetus as it helps regulate foetal glycaemia and maternal blood glucose. Glucose accounts for around 90% of the energy expenditure of the foetus. Pregnant mothers require polyunsaturated fatty acids and lipid soluble vitamins to sustain the metabolic processes required by the foetus. During parts of the third trimester, the mother is vulnerable to infections. A proper supply of long-chain polyunsaturated fatty acids and fatty acids are needed for foetal immune development and to sustain the mother's immunity. Mothers require a higher protein intake at each stage of pregnancy. During the first trimester, the protein intake requirement for the mother is the same as normal. However, during the second the and third trimesters the protein intake requirement jumps up 15% and 25% respectively. Another essential component for pregnant mothers is the proper intake of choline as it plays a major role in the development of the hippocampus and alters the biochemical properties of the foetal brain [5] (Tables 8.1 and 8.2).

Table 8.1 Beneficial Nutraceuticals for Pregnant Mothers [5]

Nutraceutical	Benefits for mother/foetus
Flax seeds and rye	Cardiovascular health, immunity
Soybeans and soy products	Brain health, immunity, reduction in risk for coronary heart disease (CHD)
Citrus foods, carrot, pumpkin	Antioxidant defence
Dairy products	Immunity, bone growth
Onion, garlic, scallions	Immunity, detoxification, cardiovascular health
Whole grains, fruit, honey	Calcium absorption, gastrointestinal (GI) health
Kale, radish, broccoli	Detoxification, antioxidant defence
Cocoa, nuts, berries, cinnamon	Cardiovascular health, urinary tract development
Peas, apples, beans	Reduction in risk for CHD

Table 8.2 Nutraceutical Components Required for Pregnant Women [6]

Nutraceutical component	Benefits
Energy (kcal)	Depending on maternal age, body mass, rate of weight gain and physiological appetite.
Protein (g)	This refers to the use of complete proteins. Also it looks back at maternal requirements for maintaining nitrogen equilibrium, in addition to protein deposition requirements of pregnancy.
Lysinea (mg/kg)	Plays a vital role in protein synthesis.
Omega-3 fatty acids (g)	Important in developing the brain and central nervous system.
Iron (mg)	75% of iron comes from haem sources such as meat and poultry.
Folate (μg)	This is required for cellular reactions, including DNA, nucleic acid synthesis, and widespread for sustained cell division.

The Effects of Maternal Iron Deficiency on the Developing Foetus

Iron-deficiency anaemia during the pregnancy is one of the leading causes of anaemia in infants. Many women will go through an entire pregnancy without even having the minimum intake of iron. In an extensive literature review this showed that iron deficiency is a nutritional problem that affects up to 52% of pregnant women. Improper weight gain in women during pregnancy is an important predictor of iron deficiency, iron deficiency in mother leads to adverse effects on infant. Premature births and weaning off breastfeeding increase the possibility of anaemia because of reduced iron in the body. Some causes of anaemia are highlighted Table 8.3.

Nutritional factors play a vital role in preventing iron deficiency. A healthy diet can be supplemented by prophylactic doses of iron to prevent the depletion of iron stores. During pregnancy the total iron amount taken should at least be 1,000 milligrams. Normal weight gain is a sign of proper maternal nourishment. Healthy weight before pregnancy can lead to positive perinatal outcomes such as a healthy birth weight for the baby. During pregnancy, iron-deficiency anaemia challenges maternal and foetal health, and it is

Table 8.3 Common Causes of Iron-Deficiency Anaemia [7]

Causes	Examples
Physiological	Prematurity, growth spurts, pregnancy
Poor intake	Malnutrition, pseudobulbar palsy, vegan diet, chronic illness
Malabsorption	Coeliac disease, atrophic gastritis
Blood loss	Oesophageal varices, hiatus hernia, gastritis, peptic ulcer, inflammatory bowel disease, hookworm, haemorrhoids, menorrhagia

connected to an increase of morbidity and foetal death. Mothers affected by this usually experience breathing problems, fainting, tiredness, palpitations, and sleep difficulties. They also have the risk of developing perinatal infection, pre-eclampsia, and bleeding. Perinatal outcomes include prematurity, growth retardation, and low birth weight. Iron deficiency during the first trimester has a negative impact on the foetal growth, which then leads to anaemia developing. It is recommended to have iron supplementation before pregnancy in order to lower the risks of prematurity and low birth weight. Micronutrients such as copper, zinc, and vitamins A and E are important for foetal growth and development [7].

Malnutrition is when there is not enough nutrient intake in the body, and this applies to pregnant women as well. Neonatal, maternal, and postnatal nutritional immunity gives an effective approach to decrease the risk of malnutrition. Overall maternal nutrients are a key component for determining the long-term health of the offspring. Maternal malnutrition can develop a poor immune system, slow motor development and cognitive dysfunction in the children. Many epidemiological and experimental reports have showed that nutritional status during foetal development is very important in sustaining energy metabolism later in life. The nutritional status of the mother affects the brain development and cognitive abilities in the offspring. Maternal nutrition affects the developing foetus by making them prone to diseases and this why they need nutrition for growth and development. Studies have demonstrated that maternal malnutrition changes the foetal genome, creating a greater risk of neuropsychiatric disorders: depression, schizophrenia, aggression, hyperactivity, etc. It also reduces the thickness of the visual cortex, parietal neocortex, dentate gyrus, CA3, and cerebellum [8].

The prenatal and postnatal environment affects the brain growth and development, maturation, and function both positively and negatively depending on the type of environmental stimuli. The embryological and the postnatal development of the offspring are led in utero (this means “in the womb”). Improving the womb environment could help the foetus to survive in specific environments, as new-borns are exposed to many infections. In adverse environmental conditions, the most unprotected period of development affects the epigenetic status and also changes the modifications of the DNA and histones of embryo, foetus, and neonates. The changes here can impact the complete life cycle of the offspring, may be transmitted from one generation to another

and could result in the beginning of foetal programming or neonatal programming. An imbalance of maternal nutrition could lead to the pathophysiological condition known as intrauterine growth restriction. The transference of nutrients and oxygen from the pregnant mother to the foetus affects the vascular growth and capacity of the placenta. Stress or infection to the mother during the prenatal and perinatal period can also change the physiological behaviour of the stress response of the offspring. The placenta plays a vital role in maternal nutrient transport to the foetus, but placental abnormalities may prevent nutrient support to the foetus [8].

Brain development is regulated by both environmental and genetic factors. This period of rapid brain growth is the most important period of development because the brain is vulnerable. Nutrition is the most important epigenetic regulator that affects the brain function and behaviour. Lack of nutraceuticals during pregnancy changes the epigenetic of the foetal genome and can have a permanent devastating effect. The right amount of nutrient supply, which includes iron, zinc, folate protein, choline, vitamin A, and polyunsaturated fatty acids, helps brain function, behaviour, and cognitive development. A deficiency of nutrients can have a major impact on neuroanatomy, neurochemistry, neurophysiology, and neuropathology of the nervous system [8].

The Effects of Human Milk as a Nutraceutical

With many steps taken to prevent neonatal and infant mortality, it has been shown that early breastfeeding is one of the most important. Due to human breast milk, many microbial, anti-inflammatory, and immunoregulatory parts, which are known as colostrum, help in protecting the infants by serving as a source of nutrition. Human colostrum can prevent or reduce many diseases in new-borns. Some of the nutraceutical properties of milk proteins are that they are carriers of minerals, vitamins, and fatty acids, and anticancer, hypotensive, immunomodulatory, and antibacterial properties, as well as stimulating intracellular glutathione. There are many bioactive factors such lysozyme, gastrointestinal hormones, immunoglobulins, lactoferrin, oligosaccharide enzymes, growth factors, and cellular components that protect the host against infections, but bioactive factors also actively balance the immune response. Figure 8.1 shows an iron molecule and how it binds with different lactoferrin molecules [1].

Lactoferrin plays a vital role in the maternal immune defence mechanism as it helps combat against infection and excessive embryonic inflammation. Lactoferrin reacts with B cells to promote antigen presentation and facilitate interactions with T cells. This is an important function for the mother's immune response to infections. Lactoferrin also controls the maturation, movement, and function of both the embryonic and maternal immune cells. It is responsible for activating T cells so that a proper immune response is initiated upon infection [9].

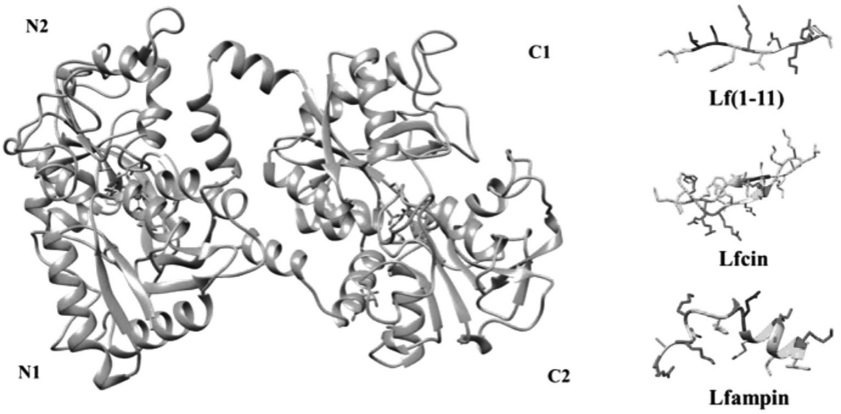


Figure 8.1 *Iron and lactoferrin binding [9].*

The Impact of Prenatal Infections on Infants

Maternal infections in general increase the risks for many neurological disorders in infants. One of the biggest of these includes schizophrenia, which is associated with infants with larger lateral ventricles. This disease impacts about 1% of the world and much of it has not been fully understood. Maternal infections are directly correlated to higher risk of schizophrenia. Prenatal viral infections are major contributing factors to the behavioural abnormalities associated with the illness [10]. Research indicates that various gestational periods are related to the increased risk of maternal infections. If the foetus is exposed during those periods, then its neurodevelopment is slowed down and chances of brain damage increase. These infections hinder the foetus from properly carrying out key processes such as cell differentiation and proliferation. With an increased risk of infection, the developing nervous system of the foetus can experience setbacks with target selection, cell migration, and synapse maturation, which ultimately leads to neurological abnormalities [11].

Maternal infections change many physiological processes in the foetus. As soon as the mother gets an infection, the foetus increases its cytokine levels, which either hinder or completely halt the normal cellular process that occur in the foetal brain. These changes that occur as a result of maternal infections cause long-term neurological impacts. Maternal infections occur in about 60% of pregnancies, however, not all infections negatively impact the foetus. Infections from rubella, Toxoplasmosis gondii, Herpes simplex, and cytomegalovirus are all associated with neurodevelopmental issues for the child that lead to cognitive delay and learning disabilities. There is also a direct correlation between maternal infections in the third trimester and increased chances of developing cognitive abnormalities. A Danish national cohort study was conducted with mothers from across Denmark. Around 200,000 mothers were asked about their exposure to infections during pregnancy. Of the 200,000

Table 8.4 Danish National Birth Cohort Study of Prenatal Exposure to Infection [12]

Maternal age	Children exposed to infection (%)	Children with neurological disabilities (%)
≤24	12.6	12.1
25–29	41.4	15.1
30–34	34.5	13.3
≥35	11.5	14.6

mothers, about 20,000 stated that they were exposed to infections. Of those mothers with infections, almost 20% had children with neurodevelopmental disabilities. This is an indicator that there is a correlation between those who are exposed to infections and the risk of neurological disabilities [12]. Table 8.4 shows the results from the study, indicating the maternal age, the percentage of children exposed to infection, and the percentage of children with neurological disabilities.

Autism has a similar relationship between maternal infections and a heightened risk of the foetus being affected, in the same way as with schizophrenia. Research shows that the brain and peripheral immune system are deregulated as a result of maternal infections. When a mother gets infected, pro-inflammatory cytokines are induced as a result of the infection. More specifically, the cytokine 1L-6 is a biomarker that is useful for identifying children with and without autism. As 1L-6 is increased, the brain of the developing foetus starts to display abnormal brain gene expression. Laboratory testing on mice showed that injecting excess 1L-6 resulted in the offspring having abnormal gene expression and behaviours. Future research aims to use therapeutic methods to manipulate the abnormal brain behaviours induced from the cytokine 1L-6. A possible method to counter the additional release of 1L-6 is to treat the developing foetus with N-acetyl-cysteine. As N-acetyl-cysteine is released, more calcium ions are released and bind to the glutamate receptors, which ultimately suppress the foetal inflammatory response from an infection. The cytokine 1L-10 is also able to suppress the negative impacts of maternal infections. 1L-10 is vital as it helps with improving the natural defence mechanisms of the foetus [13].

Maternal infections pose a higher risk for infants of cerebral palsy (CP). CP is a motor disability that affects about 1.5% of low-birth-weight babies and has been related to maternal infections. A study with randomly selected infants whose mothers had an infection. These include but are not limited to urinary tract infections (UTIs), chorioamnionitis, maternal infection, and maternal fever. Results indicated that mothers who had children with CP were more likely to have been exposed to some type of infection. Those that had maternal infections were twice as likely to develop CP. The research study isolated those with CP only and results showed that preterm infants had a 19.7% chance of getting the disease. These results indicated that there is some correlation between maternal infections and the increased chance of CP [14].

Table 8.5 Maternal Infection and Prevalence of CP for Term, Preterm, and Very Preterm Deliveries [14]

Gestational age (weeks)	Developed maternal infection? (Yes/No)	Cases in that category (%)
Term deliveries		
≥37	Yes	57.3
≥37	No	4.2
<37	Yes	29.4
<37	No	9.0
33–36	Yes	31.1
33–36	No	3.6
≤32	Yes	45.0
≤32	No	19.8
Preterm deliveries		
33–36	Yes	31.1
33–36	No	3.6
≤32	Yes	45.0
≤32	No	19.8
Very preterm deliveries		
≤32	Yes	45.0
≤32	No	19.8

Table 8.5 indicates the stratified results, which include the risk of CP in term, preterm, and very preterm infants.

Nutraceuticals and Various Uses to Combat Maternal Infections

There are many nutraceuticals that the mother can take to reduce the negative impacts of maternal infections on the foetus. These include vitamin D, antioxidants, omega-3 fatty acids, fibre, and calcium. Regular intake of these has shown signs of reduction in children born with cardiovascular diseases and atherosclerosis. Maternal calcium intake has been associated with the better response of the foetus during the first or second trimester [15]. Tables 8.6 and 8.7 show various nutraceuticals that are beneficial for the developing foetus to prevent various conditions as a result of maternal infections.

There are a wide variety of plants that protect against maternal infections. Plants used by Cameroonians have been shown to have antifungal, anti-inflammatory, anti-asthmatic, antimicrobial, and antihepatotoxic effects pre-gestation. This indicates that many of these substances have benefits for both the mother and foetus. Issues such as foetal mal-positioning can be treated mainly by *Senecio biafrae*, which is a plant that healers use to treat maternal infections. Other plants such as *Bidens pilosa* and *Tetrapleura tetraptera* are beneficial for placental retention and foetal development [17].

Table 8.6 Nutraceuticals for Combating Adverse Effects of Maternal Infections [15]

Condition	Preventive nutraceuticals during pregnancy
Obesity	Calcium supplements Fibre
Diabetes	Cod liver oil Vitamin D Omega-3 fatty acids
Hypercholesterolaemia	Pectin Fibre Glucomannan Vitamin C Vitamin E Mandarin juice
Hypertension	Omega-3 fatty acids Calcium supplements

The interactions between the maternal and foetal portions are vital for the maternal immune system's ability to aid in placental and foetal development. The proper development of the foetal immune system is heavily reliant on tolerance against foreign antigens and infections. If the foetal immune system is not properly regulated, then the central nervous system of the embryo cannot properly develop. Maternal antibodies, cytokines, and immune imbalance in cytokine expression have the possibility of negatively impacting the developing brain of the foetus. Essential processes such as cell

Table 8.7 Nutraceuticals Used by Nigerian Mothers during Pregnancy [16]

Nutraceutical	Dosage	Usage frequency
Pure body drops (with zeolites)	4 drops	Thrice a day
OmegaRX	2 gel capsules	Twice a day
Stem-Kine	1 capsule	Twice a day
NeuroBright	2 capsules	Twice a day
Probiotics	1 capsule	Once a day
Aroga Immune	1 capsule	Twice a day
Aroga brain and nerve	1 capsule	Twice a day
Aroga gut	1 capsule	Twice a day
Aroga endocrine	1 capsule	Twice a day
Supergreens (combination of enzymes and probiotics)	1 capsule	Thrice a day
Vitaloe (mammose polysaccharide complex)	1 scoop of the powder	Once a day
Protandim (synergizes NRF2)	1 caplet	Once a day
Gastrex (contains nutrient complex for GI health)	1 capsule	Thrice a day
Melatonin	1 capsule	Once a day

migration, dendritic tree maturation, and axonal elongation can be slowed down if the foetus experiences a foreign antigen due to an infection. Nutraceuticals are essential for the foetus, as it is always vulnerable to infections, stressors, and malnutrition. The foetus is especially vulnerable each time new tissue is added by precursors of immune cells depending on the embryonic cell type. There is strong evidence that shows how many nutraceuticals can aid the foetus to induce efficient neurodevelopment [3].

The Prevention, Identification, and Common Outcomes of Maternal Infections

With the amount of food derivatives for consumption available on the market growing at an outstanding rate, governmental organizations are having a tough time researching the long-term effects of these nutraceuticals. Through the help of research companies a considerable amount of information can be shed on the role of nutraceuticals in our body. When it comes to the consumption of nutraceuticals during pregnancy it is essential to evaluate the intake amount of different nutraceuticals since the embryo absorbs everything the mother takes in. The development of the embryo is crucial and profoundly affects the outcome of development of childhood till adulthood. Identifying specific nutraceuticals has allowed mothers and families to take a proactive step in stopping disorders and infections by maintaining and improving the homeostasis of the human body. Through research mothers and families are able to consume nutraceuticals to prevent certain neurological diseases such as Parkinson's, Alzheimer's, and autism spectrum disorders. Research has found that taking bioactive phytocompounds during pregnancy has been shown to reduce the effects of Alzheimer's, Parkinson's, and autism spectrum disorders in the future. The consumption of bioactive phytocompounds can be naturally found in foods but also can be found in supplements [18]. Most of these compounds can be found in fruit and vegetables that aid in the prevention of long-term diseases. With over 20% of the known plants being used in pharmaceutical studies, many studies have shown a gallery of specific molecular compounds that the body observes. Many of these fruit and vegetables include such compounds such as carotenoids, tocopherol, phenolics, and anthocyanins [19] (Table 8.8).

During pregnancy, common infections include yeast infections, group B streptococcus, and bacterial vaginosis. One of the most common ways to discover a way of stopping the invasive bacteria is to work out the metabolic pathways of the bacteria. Bacterial by-products are known to be slightly acidic, causing the surrounding tissue to be under slightly acidic conditions. The disruptions of tissues could lead to a number of issues when it is time for birth. Some of the complications that are likely to occur without treatment of infections usually lead to premature births. Premature births can lead to numerous long-term and short-term effects from childhood to adulthood. Premature births cause the body to not be fully developed to take on every metabolic pathway it

Table 8.8 Classifications of Certain Nutraceuticals [19]

Classification	Distinguishing
Carotenoids	Yellow, red or orange pigments that give things like cherries and red leaves their colour
Tocopherol	Various forms of vitamin E
Phenolics	Organic compounds that contain hydroxyl group
Anthocyanins	Blue and violet pigments found naturally in plants

should be able to process. This impediment of metabolism has caused many difficulties for people who were born prematurely. In order to stop premature births, many experiments and clinical trials have been conducted. There are both primary and secondary ways to stop and prevent such infections. There are several ways an infection can occur but the main reason why infections occur are due to unhygienic practices. One of the biggest factors causing women to go into premature labour is that of unfavourable living conditions [16]. With poverty being a global problem, it is hard to afford hygienic products such as tampons and pads, that help prevent these infections. However, through the help of public aid and public healthcare systems there are many ways to maintain hygienic practices during pregnancy.

The development of the embryo until birth plays a crucial role in the health risk factors that may affect childhood and adulthood years. Common untreated infections can lead to premature births that in turn can lead to a number of health risks, since organs and other bodily structures have not been properly formed. The human body has built in mechanisms that aid in fighting off infectious bacteria. By initiating an inflammatory response the body is easily able to degrade the invasive bacteria. The ability to release these inflammatory responses greatly depends on the body's ability and agility to react to the affected tissue. Immune responses greatly depend on both genetics and the physical and mental stresses being put on the body. A lot of research and many experiments have been conducted on the consumption of micronutrients and nutraceuticals that affect the development of the foetal immune system [3]. Even though these micronutrients can be taken to boost the immune system, there is no guaranteed immunity towards infections. Preterm births that take place due to infections commonly could relate to an underdeveloped gastrointestinal tract, causing intestinal problems, hearing loss, or vision problems. Premature births affect the whole body rather than a single organ or a single area of the body, hence an array of deformations is possible. Underdevelopment of the brain, which can lead to a number of neurological disorders such as cerebral palsy, or underdevelopment of the lungs, which could lead to asthma or chronic lung disease, could occur [20]. All of these developmental effects depend on how far along the development process the embryo is. A child who is seven weeks premature is more likely to have health risks and problems than a child who is two or three week premature. This is because, over time, the embryo is able to grow with the nutrients received from the mother. Overall, maintaining hygienic practices greatly reduces the risk of vaginal infection leading to

premature births. Premature births are known to cause a variety of health problems such as asthma, cerebral palsy, chronic lung disease, and hearing loss. With the help of micronutrients and nutraceuticals, a mother can have a proactive approach in having and delivering a healthy baby.

The immunodeficiency virus is another infection that occurs with or without pregnancy. If the mother has the virus from unprotected sex, then the baby will also contain the immunodeficiency virus. In cases like these many studies have looked at reducing the effects of the virus in the foetal embryo as well as in later adulthood. Treatment of HIV and AIDs has been a complicated procedure over the years since there is no known cure. However, there are many ways to slow down the progression of the virus on the body. Research has shown that the intake of vitamin A and vitamin D, for example, has an adverse effect on a pregnant woman with HIV and AIDs. In contrast, research has also shown that consumption of multi-micronutrient supplements can slow down the effects of HIV and AIDs. With the rise of HIV and AIDs it is essential to communicate to the public the effects and the prevention of such disease. With this being said, people who are infected have weakened immune systems and, since the immune system is greatly weakened, this can give rise to many other infections. In order to prevent this and boost the immune system, research has shown that zinc, for example, can reduce the number of infections and reinfections [21]. For a person who is pregnant and female, having a higher risk of infection can also lead to premature birth. The adverse effects of premature births have shown to be very detrimental in the development of the child into adulthood. Although complications can occur it is essential to take pre-emptive measures to stop these infections from happening. Many of these diseases can be stopped by using protected sex and proper hygienic practices. We are also able to slow down or prevent the effects of certain infections by taking vitamin supplements and nutraceuticals.

Melatonin is an important neurotransmitter that can counter the foetal inflammatory response after a maternal infection has occurred. The up-regulation of foetal antioxidant enzymes occurs as melatonin is released [22]. Dietary needs are also essential for a pregnant mother because the mother's consumption of organic material greatly affects the embryo. There are several nutraceuticals that help in the maintenance of homeostasis pathways [2] (Table 8.9).

Although the effects of a reduction of the nutraceuticals mentioned above are necessary for the proper development of the embryo, if an expecting mother does not meet the required daily dietary needs for one day, it won't be as harmful as when a woman has not met the required dietary needs for months continuously.

Conclusion

The proper intake of nutraceuticals has a profound impact on the way the human body defends itself from infections. Nutraceuticals play a major role

Table 8.9 Effects of Different Types of Nutraceuticals on the Body [2]

Nutraceuticals	Effect from disruption
Salt concentration	The salt concentration must be carefully looked at in the body. When pregnant the kidneys will retain more sodium and water. A reduction of sodium intake leads to a reduction of a number of other things such cholesterol, calcium, and zinc.
Calcium	Reducing the intake of calcium leads to increased incidence of disease. In most cases low calcium intake is due to a lack of dietary intake or malnutrition. Pregnant women who have low calcium intake also can suffer from hypertension and preeclampsia.
Iron and folate	Reduction of iron and folate intake is usually rare since most of the necessary intake can be found in daily meals. When a reduction of absorption does occur it can lead to gestational hypertension.
Magnesium	The body naturally needs larger amounts of magnesium when compared to the other nutrients that the body needs daily. Just like iron, magnesium is another nutrient that can be received from daily meals. Reduction of magnesium intake can lead to a disruption of the regulation of temperature and protein synthesis. Due to these symptoms, the embryo could greatly be affected by a reduction of magnesium intake.
Fish oil	Blood pressure is extremely important to the bodily organs for many reasons. High blood pressure means that the heart is being put through a lot of stress. High blood pressure also greatly affects expecting mothers leading to premature birth. Fish oils help maintain the homeostasis of blood pressure.

in helping the body's immune system and development of the embryo. Even though the proper dietary values for a healthy human are known, people in many areas of the globe lack in nutritional intake. In developing countries where the average level of malnutrition is elevated compared to developed countries, there is a higher risk of infection, and with this higher risk of infection there is also a higher risk of a child having a multitude of complications at birth. Therefore, with the help of nutraceuticals, the body is able to boost the immune response and decrease the risk of infection. Although preemptive measures can be taken, not all infections can be stopped. Untreated infections in pregnant women lead to premature births, neurological defects in the child, and many other complications. All these outcomes can greatly affect the development of the child into adulthood. In order to reduce the risk of infection, more public education on hygienic practices needs to be implemented and more studies must be done to evaluate the role of nutraceuticals in combating maternal infections.

References

1. Gupta, Ritika. Pasteurized human donor milk as nutraceutical. 2017. *Journal of Childhood & Developmental Disorders*, Vol. 3 (4). pp. 1–3.
2. Lim, Ratana. et al. Dietary phytophenols curcumin, naringenin and apigenin reduce infection-induced inflammatory and contractile pathways in human placenta, foetal membranes and myometrium. 2013. *Molecular Human Reproduction*, Vol. 19 (7). pp. 451–462.

3. Marques H, Andrea. et al. The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. 2013. *Neuroendocrine Science*, Vol. 7. pp. 1–12.
4. Claycombe J, Kate. et al. Epigenetics of inflammation, maternal infection, and nutrition. 2015. *The Journal of Nutrition*, Vol. 145 (5). pp. 1109–1115.
5. Pushpangadan P. et al. Functional foods and nutraceuticals with special focus on mother and child care. 2014. *Annals of Phytomedicine*, Vol. 3 (1). pp. 4–24.
6. Abu-Saad, Kathleen and Dora Fraser. Maternal nutrition and birth outcomes. 2010. *Epidemiologic Reviews*, Vol. 32 (1). pp. 5–25.
7. Abu-Our M. Noran and M. Mohammed. The impact of maternal iron deficiency and iron deficiency anaemia on child's health. 2015. *Saudi Medical Journal*, Vol. 36 (2). pp. 146–149.
8. Sinha, Shrstha. et al. Maternal protein malnutrition: Current and future perspectives of spirulina supplementation in neuroprotection. 2018. *Nutrients*, *Neurotransmitters, and Brain Energetics*, Vol. 12. pp. 932–966.
9. Giansanti, Francesco. et al. Lactoferrin from milk: Nutraceutical and pharmacological properties. 2016. *Pharmaceuticals*, Vol. 9 (4). p. 61.
10. Yilmaz, Yusuf. et al. Helicobacter pylori: A role in schizophrenia. 2008. *Medical Science Monitor*, Vol. 14 (7). pp. 13–16.
11. Meyer, Urs. et al. The neurodevelopmental impact of prenatal infections at different times of pregnancy: The earlier the worse? 2007. *SAGE Journals*, Vol. 13 (3). pp. 241–256.
12. Werenberg, Julie. et al. Prenatal exposure to fever and infections and academic performance: A multilevel analysis. 2017. *American Journal of Epidemiology*, Vol. 186 (1). pp. 29–37.
13. Atlemimi, Ammar. et al. Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. 2017. *National Centre for Biotechnology Information*, Vol. 6 (4). p. 42.
14. Neufeld, Michael. et al. Maternal infection and risk of cerebral palsy in term and preterm infants. 2005. *Journal of Perinatology*, Vol. 25. pp. 108–113.
15. Pignatelli, Pasquale and Stefania Basili. Nutraceuticals in the early infancy. 2010. *Clinica Medica Universita Sapienza*, Wiley Online Library, Vol. 28 (4). pp. 185–186.
16. Ajibade, A. Possible effects of nutraceuticals in the management of some neurodevelopmental disorders in Nigerian children. 2018. *Annals of Ibadan Postgraduate Medicine*, Vol. 16 (2). pp. 142–149.
17. Emmanuel, Asongalem. et al. Effects of Cameroonian folk natural substances, nutraceuticals, and foods on pre, peri, and post gestation. 2012. *Rapporti Istisan*, Vol. 12 (49). pp. 166–179.
18. Pistollato, Francesca and Magdalini Sachana. Prevention of neurodegenerative disorders by nutraceuticals. 2016. Academic Press, NCBI, Vol. 1. pp. 15–28.
19. Altemimi, Ammar. et al. Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. 2017. *National Centre for Biotechnology Information*, Vol. 6 (4). pp. 42.
20. Solomons W, Noel. Malnutrition and infection: An update. 2007. *British Journal of Nutrition*, Vol. 98. pp. 5–10.
21. Bhutta A, Zulfiqar. et al. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? 2013. *The Lancet*, Vol. 382. pp. 452–477.
22. Shaw, Oriana and Jerome Yager. Preventing childhood and lifelong disability: Maternal dietary supplementation for perinatal brain injury. 2019. University of Alberta, Elsevier, Vol. 139. pp. 228–242.

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9

Nutraceuticals and Hormonal Balance in Pregnancy

Ashley Oake, Michaela McMahon, and Yashwant V. Pathak

Contents

9.1 Introduction

The use of medically beneficial natural supplements and food is becoming increasingly popular compared with the use of pharmaceutical drugs throughout the United States (1). These supplements can range from vitamins to medical foods (1). Research on specific nutraceuticals started with Stephen DeFelice at the Foundation for Innovation in Medicine in 1989 when the term was defined as "food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease (1)." Throughout the last 2,000 years most medical practices have been focused on a specific diet to treat a disease rather than medication (1). For example, Hippocrates, who was a Greek physician, once stated "let food be your medicine" during 400 BCE (1). A Polish biochemist named Kazimierz Funk defined the term vitamins following his discovery of a nitrogen-containing amine base in the shell of rice in 1912 (1). He concluded that without these "vitamins" found in specific foods, there would be an appearance of disease (1). A study published in the *American Journal of Obstetrics & Gynecology* states that one in ten women have used them and about 9.4 % use them during pregnancy (2).

These ideals are currently reaching other countries including the UK, Japan, and India (3). The United States diet has the highest number of calories and processed foods in the world, but Europe is also having issues with obesity and cardiovascular issues (3). It is advised that children start their initial diet with six months of breastfeeding, to be followed by two years in total of this combined with a diet full of nutrients (3). After two years children should be fed complex carbohydrates, fruits, and vegetables full of dietary fiber, vitamins, and probiotics to prevent chronic diseases (3). A diet consisting of mainly fruits, vegetables, and whole grains reduce the risk of developing complications throughout life (3). Cardiovascular disease (CVD) and cancer are two of the main causes of death in most developed countries, with CVD contributing to 60% of deaths (3). According to 206 different studies, a diet of raw, cruciferous, and allium vegetables may help reduce the risk of cancer (3). Complications dealing the gastrointestinal tract, including ulcerative colitis and Crohn's disease, all result from the nutrients we consume (3). These may arise from an imbalance in microbial flora, so consumption of prebiotics and probiotics may help prevent the onset of disease (3). Medicinal plants are being used in Africa due to the lack of pharmaceuticals to treat nausea and to give relief during childbirth (4). plants used for nutritional supplements and relief include *Allium sativum* L. and *Cucurbita pepo* L. (4)

Nutraceuticals found in food products are categorized as dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, and antioxidants (5). Dietary fiber is plant material such as celluloses, lignin, dextrins, and starches, and it can be divided into insoluble and soluble dietary fiber (5). By consuming these components in food, the stomach empties more slowly and makes the body feel fuller (5). The many benefits include increased insulin receptor binding, improved glucose tolerance, lower blood pressure, the aid of weight loss, and lowering the risk of stroke, diabetes, and gastrointestinal disorders (5). Adults are recommended to consume 20–35 grams of dietary fibre a day, which can be found in many foods including fruits, oats, barley, and beans (5). Polyunsaturated fatty acids, specifically the n-3 and n-6 families, are recommended for their beneficial effects on cardiovascular and inflammatory diseases (6). These are commonly found in fish oil supplements and can be a regular part of an individual's everyday diet (6). Foods rich in omega-3 fatty acids are mainly fatty fishes, fish oil, nuts, flaxseed, and soybeans, while omega-6-fatty acids are found in vegetable oils and some meat and poultry (5). Consumption of this product benefits individuals by preventing heart disease and lipid buildup (5). Antioxidant vitamins include vitamins E and C and beta-carotene, and they mainly focus on treating degenerative diseases by preventing oxidation reactions (5). Vitamin E can be used to protect the polyunsaturated fatty acids in the membranes and help prevent lipid peroxidation (5). These vitamins can be found in many vegetables and fruits including most citrus fruits and leafy greens (5).

Prebiotics and probiotics are very important for overall digestion and balance of the bacteria in your body (5). Probiotics are live bacteria that are beneficial to the body and can be improved with prebiotics, which are bifidogenic,

non-digestible oligosaccharides that increase the bacteria in your gastrointestinal tract (5). Lactobacilli, gram-positive cocci, and bifidobacteria are all found in the body; they regulate gastrointestinal conditions and can even help prevent systemic conditions (5). These probiotic strains can be classified as aiding with metabolism, inflammatory and functional disorders, infections, and allergies (5). Certain doses of these probiotics are needed for specific complications and usually range 10^6–10^8 cfu/g depending on the location (5). Adding prebiotics to an individual's diet can improve metabolism, help treat lactose intolerance, and reduce cholesterol levels (5). Foods containing probiotics are yogurts and fermented foods, while prebiotics can be found in bananas, beans, onions, garlic, and apples (5).

9.2 Hormone Balance in Pregnancy

When a woman becomes pregnant, many physiological alterations occur, which include the endocrine and metabolic system, aiding in the success of the pregnancy (7). An increase in the production of specific hormones is in part to the corpus luteum, which is an endocrine gland within the ovaries that plays a key role in both the menstrual cycle and early pregnancy (7). Several hormones that are crucial for the first six weeks of gestation are produced by the corpus luteum including estradiol, relaxin, and, most importantly, progesterone (8). Progesterone is a steroid hormone produced and secreted by the corpus luteum and utilized for preparation of the endometrium if there is potential for a woman to become pregnant after ovulation (8). This plays a huge role in preventing maternal rejection of the fetus by adapting the immune system (8). If conceiving is successful, progesterone production and secretion is continued to provide for the blood vessels in the endometrium that will be supplying food to the fetus (8). After the first trimester, the main source of progesterone comes from the placenta for the maintenance of the uterine lining and helps the smooth muscle create room for the fetus to grow (9). Maintaining elevated progesterone levels (first trimester: 9–47 ng/ml; second trimester: 17–146 ng/ml; third trimester: 49–300 ng/ml) prevents the body from producing more eggs and prepares the breasts for milk production.

Assisted by relaxin, progesterone is responsible for the aching feeling women get during mid- to late-pregnancy, as it loosens joints and softens cartilage to help with child birth (9). This also gives rise to heartburn and indigestion as the gastrointestinal tract makes more room for the fetus (9). Estrogen has similar functions, including the maintenance of the uterine lining and the growth of breast tissue, but it also helps to develop the organs and bones in the fetus (9) As progesterone is responsible for the aching, estrogen may make women feel like they are developing a cold as it causes blood to flow to the mucous membranes and creates color change in skin, giving either a blotchiness or a glow (9). Estrogen production increases rapidly during the first trimester and finally reaches its peak during the third trimester (9).

During embryo development in uterus, the pregnancy hormone human chorionic gonadotropin (HcG) is secreted by syncytiotrophoblast cells, and later in pregnancy it is produced by the placenta as a placental hormone. The body produces HcG during pregnancy for many reasons, including preparing the mother's body for the growing fetus by aiding in the release of other hormones, which can also result in a positive pregnancy test. After the egg has been fertilized and attaches to the uterine wall, HcG nourishes the egg for continued development (10). It promotes progesterone production by the corpus luteum, uterine growth in line with the growth of the fetus, growth and differentiation of fetal organs, and the growth of the umbilical cord. HcG receptors found in the hippocampus, hypothalamus, and brain stem of an adult brain take part in nausea and vomiting, affecting 50%–90% of pregnant women (7). There is a strong peak in HcG levels during the first trimester, typically doubling every 72 hours, until 8–11 weeks of pregnancy, where the hormone will then level off (10). Studies have also correlated the structure of HcG and the thyroid-stimulating hormone to suggest the reaction between them stimulates the thyroid gland (10).

9.2.1 Reduced Hormones during Pregnancy

During pregnancy, women experience an increase in hormone levels, however, an increase in certain hormones can cause a reduction in others. The follicle-stimulating hormone is produced by the pituitary gland and is directly responsible for the stimulation of the ovaries to produce estrogen. Once estrogen is being produced, it inhibits the production of the follicle-stimulating hormone, so women do not ovulate and produce more eggs during pregnancy. Estrogen also encourages the luteinizing hormone to secrete and release an egg for possible fertilization. This luteinizing hormone causes the follicle to burst and create the corpus luteum, which nourishes the fetus and produces progesterone. Progesterone that is produced by the corpus luteum inhibits the production of the luteinizing hormone during the remainder of the pregnancy. A lack of either of these initial hormones can cause many complications for the mother, including polycystic ovarian syndrome.

When progesterone levels begin to increase after successful conception, T helper 2 (Th2) cytokines are stimulated and T helper 1 (Th1) cytokines are reduced (11). Pregnancy offers a bias toward the increased production of Th2 cytokines over Th1 cytokines as a means of protecting the fetus (11). Th1 cytokines are pro-inflammatory signal molecules that have been shown to cause a risk of poor neonatal outcomes and can lead to preterm labor or recurrent miscarriages (11). The suppression of Th1 cytokine aids in the success of a full-term pregnancy (11). Th2 cytokines are anti-inflammatory signal molecules that aid in the suppression of the maternal immune system to prevent the rejection of the fetus (11). Estrogen and the placenta have been found to release several thyroid stimulatory factors such as HcG to support the

pregnancy (11). Women who are pregnant may develop different endocrine disorders, including hypothyroidism, that affect the production and secretion of thyroid hormones that are essential for a woman to produce during pregnancy (12). A reduction in thyroid hormones can lead to a list of complications that women who are pregnant will experience, especially if they have hypothyroidism, such as preterm birth, low birthweight, and respiratory distress in the infant (12).

9.3 Hormone Balance in Non-Pregnant Women Compared to Pregnant Women

Hormone levels in pregnant women compared to non-pregnant women vary significantly (13). When a woman becomes pregnant, several thyroid hormone levels such as total thyroxine 4 (TT4), total thyroxine 3 (TT3), free thyroxine 4 (FT4), free triiodothyronine 3 (FT3), and thyroid stimulating hormone (TSH) are all affected (13). TT4 levels in healthy non-pregnant women were shown to be 81.42 ± 30.1 (13). Levels of TT4 are shown to increase each trimester of a pregnant woman, reaching its highest levels of 102.17 ± 40.11 in the third trimester (13). TT3 levels in non-pregnant women are around 2.83 ± 1.27 and increase up until the second trimester of a pregnant woman (13). FT3 hormone levels are 14.96 ± 6.21, and FT4 levels are recorded at around 6.38 ± 2.98 in non-pregnant women, which are shown to decrease when a woman becomes pregnant progressively throughout each trimester (13). The TSH level is approximately 2.68 ± 1.11 in non-pregnant women, but only shows an increase in a pregnant woman's first trimester, slowly decreasing to normal levels during the second and third trimester (13).

Estrogen, progesterone, and HcG levels all increase when a woman becomes pregnant (14). Before pregnancy, estrogen is mainly for development and maintenance of female sexual characteristics, fat distribution, and bone development (14). It is produced not only by the ovaries but also by the breasts and adrenal glands (14). The average level that a menstruating woman should have is 15 to 350 pg/mL, which changes over the course of the day as it is released in bursts (14). After the menopause the levels may drop all the way to 10 pg/mL (14). When levels are too high it can indicate complications due to early pregnancy and tumors in the ovaries (14). Lower levels can indicate ovarian failure or even polycystic ovarian syndrome (14). Progesterone in a menstruating woman is responsible for the preparation of pregnancy throughout the cycle (15). Progesterone ranges throughout a woman's menstrual cycle from 0.1 to 0.7 ng/mL in the follicular stage (the first stage), while during the luteal stage (the final stage) of the menstrual cycle, progesterone levels range from 2 to 25 ng/mL (15). HcG levels in non-pregnant women should remain less than 5 mIU/mL and show significant increases every 72 hours once a woman becomes pregnant (10).

The follicle-stimulating hormone and lutenizing hormone are produced in a woman's body for the ovulation cycle and are inhibited during pregnancy. Both hormones are usually around 5–20 mIU/mL during the cycle, but the day before ovulation starts the luteinizing hormone (LH) rises to 25–40 mIU/mL. After ovulation occurs the hormone returns to the normal level. Women suffering from polycystic ovarian disease usually have three times the amount of LH compared to follicle stimulating hormone (FSH), while an average woman has around a one to one ratio. All women also produce small amounts of testosterone which range from 6 to 86 ng/dL and dehydroepiandrosterone which range from 35 to 430 μg/dL.

9.4 Nutraceuticals in Pregnancy

During the initial stages of pregnancy, many hormonal changes occur with the development of the placenta (16). The first two trimesters of the pregnancy are specifically dedicated to preparation for the third trimester's rapid fetal growth, so a proper diet is necessary for development (16). Out of the 21 micronutrients, 14 increase their need during pregnancy: they consist of 7 vitamins, 5 minerals, and choline (16). Folic acid, found in leafy greens and citrus, is critical in development due to its prevention of birth defects regarding the brain and spinal cord (16). Most defects occur in the first month of pregnancy and 70% of these conditions can be completely prevented through a proper diet (16). In addition to prevention of defects, folic acid also aids in producing blood cells, producing DNA, and supporting the growth of the placenta (16). It is recommended that women intake at least 800 micrograms a day during pregnancy through a diet of fortified foods or supplements, especially in the first trimester (16). The use of a multivitamin during pregnancy can reduce the risk of multiple complications and aid in fertility, including higher rates of twins (17).

A study conducted in Israel followed the pregnancy of 45,300 children to look at the effects of taking folic acid and a multivitamin during pregnancy to prevent autism spectrum disorder (ASD) (18). The multivitamin contained a combination of vitamins A, B, C, and D throughout the trials (18) Only 572 children, or 1.3% of children, received the diagnosis of ASD (18). The results showed that taking folic acid and multivitamins before the pregnancy significantly lowered the risk of being diagnosed, but taking the supplements during pregnancy still lowered the risk compared to taking nothing before pregnancy (18).

Studies have shown that the use of folic acid during pregnancy may aid in reducing the risk of neural tube defects in the fetus (19). Having a child born below the 10th percentile for birthweight can lead to many complications, including cardiovascular disease, diabetes, and mental health issues (19). A study was done in the UK focusing on the time folic acid supplementation was initially taken regarding the conception of the fetus compared to the

birthweight (19). The results shown favored taking the supplement before conception of the fetus compared to just taking it while pregnant (19). There was a reduced risk of children being below the 10th percentile when mothers were taking folic acid before conception compared to the mothers that took the folic acid during the pregnancy (19). While folic acid may provide many benefits to the fetus when taken during pregnancy, this study concludes that there was no effect on the proportion of lower-weight children when only taken postconception (19).

At the start of the second trimester an increase of iron in the diet is recommended for the production of hemoglobin (16). It is recommended that the mother consume at least 30 mg a day to ensure prevention of iron-deficiency anemia (16). Calcium is also important for fetal development with a need of over 1,300 mg a day (16). If the necessary amount of calcium is not acquired, the fetus takes the calcium from the mother's own supply, resulting in a change in calcium metabolism (16). Reduced levels can result in hypertensive disorders in the fetus and preterm delivery (16). Vitamin A is responsible for the development of many structures including membranes, the immune system, reproduction, and vision (16). Unlike many other nutrients, vitamin A has a maximum recommendation of 8,000 IU per day with over 10,000 increasing the risk of birth defects to 1 in 57 (16). Vitamin D is primarily focused on for helping the body to absorb calcium in the same way that vitamin C enhances iron absorption (16). Studies have shown a combination of 25 mg of vitamin C and 5 mg of vitamin K can treat 91% of morning sickness (16).

Moringa oleifera is a tree in the Himalayas studied mainly for its use in developing iron nutraceuticals (20). In the Middle East and African cultures, it is used to help clean water and even used in medicine (20). It is high in essential nutrients, including minerals, vitamins, and protein, which can help fight cancer and diabetes (20). Now these crops are being grown in Central and South America as well as India (20). A study with 60 women tested the effects of moringa treatment on hemoglobin levels while taking 100 mg per day (20). The group taking the supplements showed an increase of hemoglobin levels in 23 out of the 30 participants, while the placebo group showed an increase in 3 out of 30 participants (20). Lack of proper nutrition during pregnancy can lead to anemia, which affects over 38.2% of women (20). Both the moringa leaf and the iron-folic acid combination have been tested as possible solutions to help prevent this complication (20). Moringa leaves contain iron, calcium, and vitamins A, B, and C, so they contain antioxidant properties (20). A study was done with 70 pregnant women split into two groups of 35 each, either taking a moringa leaf supplement or a 60 mg folic acid supplement (20). The group with the folic acid supplement had a slightly larger increase in hemoglobin levels compared to the group with the moringa leaf supplement, but both showed a significant enough increase to conclude that they could be used to prevent anemia in pregnant women (20).

A clinical trial was done in Bangladesh regarding the use of lipid-based nutrient supplements. These supplements were given to a total of 4,011 women

split into groups, with some groups given folic acid and iron while others were given the lipid-based nutrient supplements and 22 vitamins and minerals. The children born from the mothers taking the lipid-based nutrient supplements had higher weights and measurements overall (2,629 ± 408 g in the lipid-based nutrient supplements (LNS) group compared to 2,588 ± 413 g in the folic acid group). This treatment also reduced the risk of stunting and being born with a smaller head. Results have shown that using these supplements, when taken to term, increase the weight and measurements of children. A similar trial was done with lipid-based nutrient supplements to measure the effects they have on anemia and iron deficiency (21). The 4,011 children were also tested on their hemoglobin, serum ferritin, and soluble transferrin receptors (21). The children who took LNS or had mothers who took LNS showed lower levels of soluble transferrin receptors and higher levels of hemoglobin and serum ferritin (21). Results have shown that taking LNS during pregnancy reduced the risk of developing anemia or an iron deficiency (21).

Docosahexaenoic acid levels during pregnancy aid in the development of baby's pre- and postnatal brain, eyes, and nervous system (22). It can also increase birthweight, cognitive development, and psychomotor developments (22). Foods containing docosahexaenoic acid are cold-water fish including tuna, salmon, herring, and cod (22). A study done with 804 Chinese women tested their blood throughout different periods of pregnancy and filled out a docosahexaenoic acid-specific (docosahexaenoic acid (DHA)-specific) semiquantitative food-frequency questionnaire (22). The results show that women later in pregnancy had higher levels of docosahexaenoic acid than those in the first and second trimesters (22). An increase in the DHA levels is crucial during the course of pregnancy due to the neurodevelopment occurring (23). An underdevelopment of any of the essential structures can cause severe issues with brain function for the rest of an individual's life (23). One of the structures to start development during the last trimester, which is when DHA levels need to be the highest, is the hippocampus, which forms the limbic system and has an impact on emotional learning (23). Studies show that the levels of choline also have an effect on this development as well as signaling in neural and liver cells, neural tube closure, and hepatic transport (23). A study in India tested the effects of choline and DHA in the development of neural structures in pregnant rats (23). The rats were given a normal control, saline control, choline, or DHA, or they were given choline and DHA over the course of pregnancy (23). The rats that were given either choline or DHA showed an increase ($p < 0.05$) in neural cells compared to the rats that were given the control or saline during pregnancy (23). Rats that were given both the DHA and choline showed a significant increase ($p < 0.001$) in the amount of neural cells compared to the control and saline groups (23). Results support the use of choline and DHA supplements over the course of pregnancy to aid in the development of the hippocampus and other brain structures (23).

9.5 Mood Disorders

Many women experience a depressive state during pregnancy due to the hormonal changes the body is undergoing (22). Studies have shown that depression during pregnancy has affected almost 16% of the population and 5% have a major depressive disorder (22). These mood disorders can have negative effects on the fetus and result in complications during delivery, including low birthweight, preterm birth, and abnormalities with development (22). Severe anxiety can also cause complications with neurodevelopment with the fetus and a shorter gestation (22). Taking antidepressants during pregnancy may cause adverse effects on both the child and the mother (24). Selective serotonin reuptake inhibitor (SSRI) antidepressants have been shown to result in developmental complications to the fetus as well as during the delivery (24). They can also cause lower gestation periods and premature delivery (24).

Research has shown that taking omega-3 supplements may aid in lowering the risk of these disorders (24). They can contain eicosapentaenoic acid (EPA) and DHA that provide many health benefits, and societies with high amounts in their food have much lower levels of depression. An eight-week trial was conducted with 36 pregnant women with China Medical University Hospital in Taiwan regarding the effect that omega-3 polyunsaturated fatty acids could have on these mood disorders (24). Of the women who completed the trial, 13 took the omega-3 supplement and 11 took a placebo (24). The results showed that the women taking the omega supplement had lower scores for depressive symptoms and a higher response rate during weeks 6–8, which was 62% compared to 27% (24). Researchers use the Hamilton Depression Rating Scale (HAM-D), Edinburgh Postnatal Depression Scale (EPDS), and Beck Depression Inventory (BDI) systems to analyze the symptoms and results from the study (24). No adverse effects were observed on both the fetuses and maternal figures during this experiment (24). Taking fish oil supplements may be very beneficial for these mood disorders. A study in Iran with 150 participants observed the affects that fish oil had on raising the omega-3 content in the body (25). For the second two trimesters of pregnancy women were given 1,000 mg supplements that contained both EPA and (DHA (25). A rise in fatty acid levels was observed during weeks 35–37 in the participants and results showed that taking the supplement aided in the drop in omega-3 levels usually observed during pregnancy (25).

9.6 Obesity and Nutraceuticals

Obesity has become a major health issue in the United States, and this can negatively affect the development on the fetus and the mother (26). Mothers with a high BMI can develop gestational diabetes mellitus, preeclampsia, cardiovascular issues, and cancer (26). There is evidence that the mother's nutritional status can impact the function of the placenta (26). The macronutrient

transport capacity will increase and cause fetal overgrowth, which leads to complications with the hormone receptors (26). This could lead to placental inflammation, and oxidative stress and studies have shown that docosahexaenoic acid can prevent these complications by reducing inflammation markers (26). A study published in *The Journal of Clinical Endocrinology & Metabolism* analyzed the results of 38 pregnant women with a body mass index (BMI) of over 30 kg/m^2 who took an algal oil supplement (26). Blood samples were taken before the study and at week 36, and 35 placentas were collected after birth (26). The results shown indicated that there was a reduction in inflammatory markers and amino acid transport, but not in fatty acid (26). There was an increase of DHA in the placental membrane, a decrease in inflammation, but there may have been no beneficial effect on the maternal figure (26). Inflammation, BMI, and gestation length were not affected in the mothers by this trial (26).

Women with a body mass index in the obesity range have an excess amount of adipose tissue and adipocytes (27). These cells release hormones and cytokines throughout the body that influence both the physiology and the metabolism (27). Aromatase is released in the body to convert androgens to estrogens, so with more fat there is a greater rate of conversion than with more estrogen (27). There is a higher amount of cortisol in the system due to the conversion of cortisone to cortisol by excess 11β-hydroxysteroid dehydrogenase (27). Levels of leptin, tumor necrosis factor α, and adiponectin are also increased (27). A chart by the Institute of Medicine created a Pregnancy Risk Assessment Monitoring System that established a range of healthy weights that women should follow (27). Studies show that only one in three women actually follow these guidelines, but race and ethnicity play a huge role in weight gain (27). Asian women usually gain under the recommended amount of weight and African American women are more likely to gain over the recommended weight while women other than these race remain around the recommended weight on average (27).

9.7 Conclusion

Natural supplements are becoming increasingly popular with pregnancy throughout many cultures due to the immense amount of benefits they may provide without adverse effects on the fetus. The need for many of these nutrients increases with pregnancy as they may help reduce the risk of complications that can arise from hormone imbalance. Folic acid is involved in preventing many of the birth defects that can occur as well as aiding in producing blood cells, DNA, and the growth of the placenta. It is recommended that women start taking it before pregnancy as well as during to improve the overall well-being of the child. Iron, calcium, and vitamin A consumption reduces the risk of preterm birth and helps develop essential structures that include the immune system. Lipid-based nutrient supplements help increase

the overall measurements and birthweight of the child while also reducing the risk of anemia. Docosahexaenoic acid supplementation focuses on development of the brain, eyes, and nervous system, and increases birthweight, cognitive development, and psychomotor developments. Omega-3 supplements can be taken by women experiencing depression or anxiety in order to reduce the risk of developing a mood disorder which may have adverse effects on the child. A proper diet is also necessary for the overall health of the mother as obesity may cause a release of excess amounts of hormones from the adipose tissue.

References

1. Bull E, Rapport L, & Lockwood B (2000) What is a nutraceutical? *The Pharmaceutical Journal. 265*(7104):45.
2. Cosgrove J (2010) *Supplements during pregnancy.* Nutraceuticals World.
3. Cencic A, & Chingwaru W (2010) The role of functional foods, nutraceuticals, and food supplements in intestinal health. *Nutrients. 2*(6): 611–625.
4. Ahmed SM, Nordeng H, Sundby J, Aragaw YA, & de Boer HJ (2018) The use of medicinal plants by pregnant women in Africa: a systematic review. *Journal of Ethnopharmacology. 224*: 297–313.
5. Das L, Bhaumik E, Raychaudhuri U, & Chakraborty R (2012) Role of nutraceuticals in human health. *Journal of Food Science and Technology. 49*(2): 173–183.
6. Andlauer W, & Fürst P (2002) Nutraceuticals: a piece of history, present status and outlook. *Food Research International. 35*: 171–176.
7. Baerwald AR, Adams GP, & Person RA (2010) Form and function of the corpus luteum during the human menstrual cycle. *Ultrasound in Obstetrics & Gynecology. 25*(5): 498–507. doi: 10.1002/uog.1891
8. Kumar P, & Magon N (2012) Hormones in pregnancy. *Nigerian Medical Journal. 53*(4): 179–183. doi: 10.4103/0300-1652.107549
9. Wilson, DR (2017) *What Bodily Changes Can You Expect During Pregnancy?* Healthline.
10. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, & Mebazaa A (2016) Physiological changes in pregnancy. *Cardiovascular Journal of Africa. 27*(2): 89–94. doi: 10.5830/CVJA-2016-021
11. Sykes L, MacIntrye D, Yap XJ, Ponnammpalam S, Teoh TG, & Bennett PR (2012) Changes in the Th1 : Th2 cytokine bias in pregnancy and the effects of the anti-inflammatory cyclopentenone prostaglandin 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2. *Mediators of Inflammation. 2012*: 416739. doi: 10.1155/2012/416739
12. Sahay RK, & Nagesh VS (2012) Hypothyroidism in pregnancy. *Indian Journal of Endocrinology and Metabolism. 16*(3): 364–370. doi: 10.4103/2230-8210.95667
13. Manjunatha S, Basavraja GN, Veena HC, & Patil RS (2014) Thyroid status in non-pregnant & pregnant women. *Scholars Journal of Applied Medical Sciences. 2*(6G):3349–3352.
14. Wilson DR (2017) *What is An Estradiol Test?* Healthline.
15. Freeborn D, & Haldeman-Englert C (2018) *Progesterone.* University of Rochester.
16. Clow M, & Beck S (2002) *Women's Health.* Nutraceuticals World.
17. Picciano MF, & McGuire MK (2008) Use of dietary supplements by pregnant and lactating women in North America. *American Journal of Clinical Nutrition. 89*(2): 663S–667S. doi: 10.3945/ajcn.2008.26811B
18. Levine SZ, Kodesh A, Viktorin A, Smith L, Uher R, Reichenberg A, & Sandin S (2018) Association of maternal use of folic acid and multivitamin supplements in the periods

before and during pregnancy with the risk of autism spectrum disorder in offspring. *JAMA Psychiatry. 75*(2):176–184. doi: 10.1001/jamapsychiatry.2017.4050
19. Hodgetts VA, Morris RK, Francis A, Gardosi J, & Ismail KM (2014) Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis. *International Journal of Obstetrics & Gynaecology. 122*(4). doi: 10.1111/1471-0528.13202
20. Nurdin MS, Thahir AIA, & Hadju V (2018) Supplementations on pregnant women and the potential of Moringa Oleifera supplement to prevent adverse pregnancy outcome. *International Journal of Science and Healthcare Research. 3*(1): 71–75.
21. Matias SL, Mridha MK, Young RT, Khan MSA, Siddiqui Z, Ullah MB, Vosti SA, & Dewey KG (2018) Prenatal and postnatal supplementation with lipid-based nutrient supplements reduces anemia and iron deficiency in 18-month-old Bangladeshi children: a cluster-randomized effectiveness trial. *Journal of Nutrition. 148*(7):1167–1176. doi: 10.1093/jn/nxy078
22. Schetter CD, & Tanner L (2015) Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. *Current Opinion in Psychiatry. 25*(2): 141–148. doi: 10.1097/YCO.0b013e3283503680
23. Rajarethnem HT, Bhat KMR, Jc M, Gopalkrishnan SK, Golpalram RBM, & Rai KS (2017) Combined supplementation of choline and docosahexaenoic acid during pregnancy enhances neurodevelopment of fetal hippocampus. *Neurology Research International.* 2017(8748706):9 doi: 10.1155/2017/8748706
24. Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, & Pariante CM (2008) Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry. 69*:4.
25. Farshbaf-Khalili A, Mohamad-Alizadeh S, Darabi M, Hematzadeh S, Mehdizadeh A, Shaaker M, & Ostadrahimi A (2017) The effect of fish oil supplementation on serum phospholipid fatty acids profile during pregnancy: a double blind randomized controlled trial. *Women Health. 57*(2):137–153. doi: 10.1080/03630242.2016.1159269
26. Lager S, Ramirez VI, Acosta O, Meireles C, Miller E, Gaccioli F, Rosario FJ, … Powell TL (2017) Docosahexaenoic acid supplementation in pregnancy modulates placental cellular signaling and nutrient transport capacity in obese women. *Journal of Clinical Endocrinology & Metabolism. 102*(12): 4557–4567. doi: 10.1210/jc.2017-01384
27. Leddy MA, Power ML, & Schulkin J (2008) The impact of maternal obesity on maternal and fetal health. *Reviews in Obstetrics & Gynecology. 1*(4): 170–178.

10

The Role of Nutraceuticals in Preeclampsia and Eclampsia

Nafiseh Shokri Mashhadi and Reza Ghiasvand

Contents

10.1 Introduction

10.1.1 The Definition of Eclampsia and Preeclampsia

The determination of nutraceuticals' application for the prevention of preeclampsia must begin with a discussion of the definition and perception of the etiology of preeclampsia. Hypertensive disorders of pregnancy constitute the clinically challenging pregnancy complications that are responsible for a significant number of the medical problems and deaths during pregnancy around the world. Gestational hypertension (GH) is defined as hypertension that appears in pregnancy after 20 weeks' gestation and returns to normal within 12 weeks. Pregnancy-induced hypertension (PIH) and preeclampsia (PE), usually identified as GH, remain unresolved in both developed and

developing countries [1]. The World Health Organization identifies high blood pressure as the major cause of maternal mortality in industrialized countries leading to 16% mortality [2].

Classically, preeclampsia is known as a systemic syndrome by gestational hypertension plus proteinuria (the urinary excretion of protein). In the absence of proteinuria, hypertension is diagnosed as preeclampsia, which may progress and contribute to neurological aspects and ultimately cause eclampsia [3]. Currently, the American College of Obstetricians and Gynecologists (ACOG), introduce preeclampsia as "a hypertensive a combined with the multi-system disorder of pregnancy that significantly related to maternal and fetal mortality" [4].

Several classifications have been proposed for disease severity in preeclampsia which causes poor placental perfusion and an increased risk of some comorbidity as well as the need for neonatal intensive care. Moreover, small for gestational age (SGA) may be seen in infants born following preeclampsia; they may also have higher levels of blood pressure in childhood and adolescence than infants born from other pregnancies [5].

10.1.2 The Pathogenesis and Prevention of Eclampsia and preeclampsia

In a normal pregnancy, in order to supply the blood flow to the embryo, invasion of the myometrial portion begins in the latter half of the first trimester and is completed by 18–20 weeks' gestation. It has been proposed that the failure of the cytotrophoblast to penetrate the myometrial portion in early pregnancy leads to the production of spiral vessels that can reduce placental perfusion during pregnancy. [6]. Placental cell death is also increased in patients with PE [7].

Interestingly, some studies have indicated that activation of a maternal inflammatory response and immunologic intolerance of the fetus lead to endothelial dysfunction. In addition, evidence supporting the importance of the maternal immune system in the pathogenesis of PE [8]. Other theories include angiogenic factors, cardiovascular incompatibility, and vasoconstriction as well as lack of progesterone in early pregnancy, genetic predisposition, and platelet activation [9–11].

Based on the fact that all patients with reduced placental perfusion do not experience preeclampsia or gestational hypertension Roberg et al. recently proposed other practical risk factors (such as antiphospholipid antibody syndrome, chronic hypertension, chronic renal disease, body mass index, maternal age, multiple gestation, nulliparity, history of preeclampsia in a previous pregnancy, and pregestational diabetes mellitus) that can lead to endothelial dysfunction and give rise to the risk of preeclampsia. Additionally, hyperhomocysteinemia is one of the risk factors for PE. Cotter et al. have indicated that maternal serum homocysteine levels were significantly increased in a preeclampsia group compared with a control group. Increasing homocysteine

level in early pregnancy leads to endothelial dysfunction and can increase the risk of developing severe preeclampsia [12].

Several studies showed the advantage of using biochemical markers, such as activin, inhibin, and placental protein 13, for the prediction of PE at early stages of pregnancy [13, 14]. However, to our knowledge, none of these markers has sufficient predictive value in a clinical practice, though their combination probably improves the prediction of this disorder.

Treatment options are limited, so therapies that prevent preeclampsia, or delay its onset, or decrease its severity would be helpful. Studies showed that one of the best agents for the prevention of preeclampsia is aspirin [15]. In addition to low-dose aspirin, other methods used to prevent or treat preeclampsia include antioxidants [16]. In many studies, using antioxidants to reduce the incidence of PE has been investigated due to the effect of oxidative stress in the pathogenesis of PE. Recently, emerging research indicates the potential benefits of other nutritional factors, called nutraceuticals, in pregnancies complicated by preeclampsia. These factors should be monitored more intensively to regulate their use and eventually reduce the potential complications associated with these agents.

10.2 Nutraceuticals in the Prevention of Eclampsia and preeclampsia

10.2.1 The Definition of Nutraceuticals

A broad range of interventions has been evaluated for the prevention of preeclampsia. Epidemiological, clinical, and laboratory evidence suggest a significant role of the maternal dietary component in hypertensive disorders of pregnancy such as preeclampsia [17–19]. Dietary qualities and components associated with preeclampsia and eclampsia include macronutrients, micronutrients, dietary fiber, and individual foods as well as medicinal foods.

According to DeFelice [20], the term “nutraceutical” can be defined as a food that includes micronutrients, dietary supplements, and functional foods and has health benefits, together with the possibility of being used for the prevention or treatment of a disease. Currently, there is considerable interest in nutraceuticals due to their potential nutritional properties and treatment benefits [21].

However, there are differences in the definition of nutraceuticals and the terminology, and the definitions are not identical in different countries. Nonetheless, nutraceuticals are usually defined as concentrated and purified forms of bioactive metabolites, which can be consumed via normal food, as ingredients with naturally occurring contents or in the form of enriched foods [19].

Sometimes nutraceutical compounds can contribute to certain pharmacological disadvantages. Also, there has been conflicting scientific evidence for the

efficacy of some nutraceuticals. Nevertheless, it has been claimed that they protect our bodies against certain chronic disorders, including obesity, diabetes, inflammation status, cancer, and cardiovascular diseases [22–24], and it has been revealed that most nutraceuticals have antioxidant, anti-inflammatory, anticarcinogenic, and neuroprotective abilities [22, 25, 26].

At present, there are various natural products for beneficial health effects that include vitamins and minerals, polyphenols, glucosinolates, terpenoids, functional foods, essential fatty acids, and amino acids [27, 28].

Recognizing the safety and effectiveness of nutraceuticals is essential in order to maximize their benefits without any side effects. Based on a large number of observational and clinical studies on nutraceuticals, they are generally considered safe, however, their use in pregnancy and their efficacy in special conditions such as preeclampsia and eclampsia have not been investigated comprehensively.

10.2.2 Calcium

Among several elemental deficiencies, epidemiological evidence has suggested a connection between low serum calcium levels and preeclampsia. In Ethiopia, a low prevalence of preeclampsia has been claimed where the diet contained high levels of calcium [29]. To examine the association between calcium levels during the first trimester of pregnancy and preeclampsia, one controlled case study was conducted by Udenze et al., however, they did not find significant hypocalcemia in mild and severe preeclampsia with significantly low urine calcium/creatinine levels [30]. Moreover, Gabbay et al. described that there was no significant difference in serum calcium levels of 5,233 pregnancies with mild preeclampsia [31]. And the results of the studies seem controversial. So, a recent meta-analysis study proposes that, due to publication bias and a lack of large trials in current studies, there should be caution against accepting the combined trials as definitive evidence of the benefits of calcium supplementation for preeclampsia [32]. However, they also indicated that calcium supplementation was more effective in the low-baseline intake subgroup versus the adequate-baseline calcium intake.

On the other hand, there is a growing body of evidence that points to the important role of cell calcium in vasodilation of the uterine arteries throughout pregnancy, especially from mid-gestation, since adequate uteroplacental blood flow is highly dependent on vasodilation [33]. The common activating mechanism for many vasodilators is the increase in cell calcium. Additionally, previous evidence has indicated an inverse relationship between high blood pressure and calcium intake [34, 35]. Numerous epidemiological and clinical studies have also confirmed this association [35, 36]. So, these findings suggest that calcium supplementation (≥1 g/day) could lower the risk of preeclampsia [37]. As a result, the World Health Organization (WHO) issued a strong recommendation that pregnant women

be provided a daily dosage of calcium supplements, 1.5–2.0 g elemental calcium, to prevent preeclampsia [38].

Also, an earlier Cochrane review involving 13 high-quality studies reported that calcium supplementation was associated with a significant reduction in the risk of PE (RR: 0.41; 95% CI: 0.31–0.65) mainly in women with low-calcium diets, maternal death or morbidity (RR: 0.80; 95% CI: 0.65–0.97), and preterm birth (RR: 0.76; 95% CI: 0.60–0.97) [39].

Overall, in spite of some trials showing low clinical benefits of calcium supplements, it is still prescribed to women at high risk of preeclampsia in developing countries [40]. This could be because calcium intake (>1 g/day) reduces the risk of preeclampsia in women with low-calcium diets [40]. Therefore, there is an essential need for strong evidence to support the benefits of calcium supplementation for all pregnant women with a risk of preeclampsia.

10.2.3 Magnesium

Magnesium deficiency is prevalent in women of reproductive ages in both developing and developed countries [41, 42]. The need for magnesium increases during pregnancy, and most pregnant women probably do not take in extra magnesium [42]. Magnesium deficiency or insufficiency during pregnancy may contribute to health risks for both the mother and the newborn, for whom these complications may extend into adulthood [43].

The measurement of serum magnesium is the most useful method for determining magnesium levels [44]. So many researchers proposed that optimizing magnesium status appeared to be a practical process to prevent many complications during pregnancy [45]. To estimate magnesium status and its association with oxidative stress and inflammation in preeclamptic women, de Sousa Rocha et al. conducted a controlled case study consisting of 18 preeclamptic women. The results indicated that increased plasma magnesium and decreased urinary 8-isoprostane were considered predictors of preeclampsia [46]. In addition, the serum levels of calcium, magnesium, zinc, and copper were shown to have significant relationships with preeclampsia in pregnant women in Sudan [47]. In contrast, a comparative cross-sectional study was conducted in Ghana, involving 60 pregnant women aged 18–35 years with >30 weeks' gestation. It found that serum magnesium and total calcium, therefore, seemed not to differ in preeclamptic women compared to normal pregnant women [48]. For this purpose, Čabarkapa et al. recently conducted a prospective study that included 403 pregnant women over 18 years and evaluated the importance of serum concentration of magnesium (Mg) in the first trimester of pregnancy for predicting preeclampsia (PE). Their results showed that the Mg level during the first trimester of pregnancy is a significant prediction tool for PE and could also play an important role in predicting the week of gestational outcome and birthweight of newborns [49].

Motivated by these above-mentioned reports, several randomized clinical trials have been carried out to evaluate the potential benefits of magnesium supplementation during pregnancy; they have reported that magnesium supplementation during pregnancy is likely to decrease the probability of occurrence of many complications of pregnancy, including preeclampsia [50, 51]. Since the magnesium homeostasis in normal pregnancy is different from preeclampsia, supplementation with magnesium has shown beneficial effects on high blood pressure and infant conditions [52]. A 300-mg magnesium pill was used in a randomized controlled trial with three groups, each of 60 pregnant women, and this indicated a probable decreased occurrence of many of the complications of pregnancy [50]. These results were also confirmed by other studies [53].

However, a comprehensive meta-analysis of 10 randomized trials involving 9,090 women indicated that magnesium supplementation did not reduce the risk of SGA in neonates (RR: 0.76; 95% CI: 0.54–1.07), and did not decrease the risk of preeclampsia for the mothers (RR: 0.87; 95% CI: 0.58–1.32) [54]. But it is worth noting that in one of the highest quality studies of women in the above-mentioned trials, the results have been influenced by the fact that both magnesium-supplemented groups and placebo groups consumed a multivitamin and mineral containing 100 mg of magnesium [55].

Taken together, according to the above-mentioned studies, the importance of magnesium during pregnancy has received greater understanding and magnesium supplementation during pregnancy may be able to reduce growth restriction of the fetus in preeclampsia. Using the right dose of magnesium plays a crucial role in the treatment of unwanted pregnancy disorders and so should be determined.

10.2.4 Zinc

Preeclampsia may be caused by the imbalance of increased lipid peroxides (LPOs) and decreased antioxidants. As an antioxidant trace element, zinc deficiency may cause increasing lipid peroxidation [56, 57]. Also, in pregnant women, poor zinc status can have adverse effects on maternal and neonatal outcomes. Therefore, many studies have attempted to explore the correlation between the changes in serum zinc levels in pregnant women and PE. Some studies conducted in Europe and Africa found significantly lower levels of serum zinc in PE patients than in the control group and showed an association between serum zinc concentration and the severity of preeclampsia [58–60]. But other studies indicated that the mean serum level of zinc was significantly higher in PE patients than in healthy pregnancy controls [61, 62]. Meanwhile, no difference in serum zinc levels in PE patients compared with healthy pregnancy controls was observed in yet other research [63]. Ultimately, to determine the relationship between serum zinc levels and preeclampsia, a recently performed meta-analysis by Ma et al. [64] showed that the serum zinc level in PE patients was significantly lower than that in healthy pregnant women.

Based on this fact, there is an increasing concern about the adequacy of zinc in pregnant women, especially in developing countries. Where there is a low to moderate zinc deficiency and the consumption of animal food is limited, and agents that inhibit zinc absorption, is high in cereals [65]. As a result, the World Health Organization (WHO) recommends the use of multiple micronutrient supplements that include zinc for all pregnant women in developing countries [66].

To assess the accurate dose of zinc, one study investigated a daily dose of 15 mg of zinc (zinc sulfate) in 540 healthy women at 16 weeks, however, it didn't determine significant differences in maternal outcomes, including weight gain during pregnancy and the incidence of preeclampsia [66]. Also, a previous randomized clinical trial conducted on 196 Iranian pregnant women indicated that 50 mg daily of zinc sulfate did not significantly affect maternal pregnancy complications such as preeclampsia [67]. These results were confirmed in other previous studies [68].

In conclusion, based on the absence of a positive effect of zinc supplementation on maternal or neonatal outcomes in the above-mentioned studies, the advice on using a zinc supplement during pregnancy to prevent preeclampsia is in doubt. Further investigation in this area should possibly use a higher dose of zinc or be carried out on zinc-deficient pregnant women in order to discover any positive effects of zinc supplementation.

10.2.5 Vitamin D

Vitamin D plays an significant role in regulating bone metabolism, calcium intake, and maintaining muscle function [69]. Pregnancy has essential requirements for the availability of vitamin D and calcium. In addition, vitamin D has an effect in early placental development through gene regulation and expression, which may affect the progression of preeclampsia. So vitamin D adequacy is important for the desired outcomes for mother and fetus [70].

The number of studies on vitamin D deficiency during pregnancy has increased rapidly, and numerous studies have been conducted on the lack of vitamin D in various populations. The results of these studies show that the 25-OH-D level in preeclampsia is significantly lower than in healthy pregnant mothers [71, 72]. A study on 33 women with preeclampsia, 79 women with eclampsia, and 76 healthy pregnant women was conducted by Ullah et al. It concluded that women with plasma vitamin D level <30 ng/ml were five times more likely to be diagnosed with preeclampsia and eclampsia [73]. Moreover, in another study, it was found that normal women had significantly higher vitamin D levels than women with preeclampsia in India [71]. Levels of vitamin D seem to play a role in the balance of Th1 and Th2 levels and may contribute to the overexpression of Th1 cytokines. This affects the immunological tolerance of embryo implantation. The studies revealed that the deficiency of

vitamin D could be related to a higher expression of Th1, which is observed in cases of preeclampsia [74].

Consequently, to translate the current level of knowledge into clinical recommendations, many studies have been designed to evaluate the benefits of vitamin D supplementation in prevention of preeclampsia. Some data suggested that only a 10 ng/mL increase in maternal vitamin D could give rise to a possible reduction of the risk of preeclampsia [75]. In addition, an interventional study on 142 patients with preeclampsia showed that receiving a 50,000 IU pearl vitamin D3 in the first trimester of pregnancy contributes to the prevention of preeclampsia [76]. Further, the recent systematic review and network meta-analysis of calcium and vitamin D supplementation on preeclampsia suggested that the intake of calcium plus vitamin D compared with placebo can reduce the risk of preeclampsia by approximately 50%, but data on the adverse effects of vitamin D supplementation were lacking [77]. The findings of the study on vitamin D followed by calcium supplementation are also confirmed by the latest Cochrane review. Nevertheless, combined vitamin D and calcium increased the risk of preterm birth [78].

Based on the results of conducted current evidence, the WHO guidelines for prenatal care do not recommend frequent vitamin D supplements during pregnancy to improve maternal and postnatal outcomes. However, for pregnant women with a poor vitamin D status, vitamin D supplements may be given at the current recommended nutrient intake [79]. Overall, it can be concluded that, based on the role of maternal vitamin D deficiency as a potential independent risk factor for preeclampsia, vitamin D supplementation in early pregnancy plus calcium remains a possible intervention for women with documented vitamin D deficiency.

10.2.6 Folic Acid and Vitamin B12

The concentration of homocysteine is strongly controlled by using the pathway that homocysteine can be modified to methionine and needs folic acid as a cofactor. In addition, for proper function of folic acid in this method, it requires vitamin B12 as an important co-worker.

New evidence suggests a link between high levels of circulating homocysteine in women with gestational hypertension and preeclampsia [80, 81]. The findings also indicate that changes in homocysteine metabolism can lead to systemic vascular deformation, which results in the clinical emergence of hypertension in pregnancy and can be an independent risk factor for severe PE [82]. In line with this, another study showed that plasma homocysteine was inversely related to preeclampsia among black women [83].

Also, in a cohort study in the Netherlands, pregnant women with the lowest folate levels and the highest homocysteine levels had a fourfold higher preeclampsia risk compared with women with normal levels of homocysteine and folate (OR: 4.27; 95% CI: 1.21, 15.0; $P = 0.02$) [84]. Consequently, considering the

possibility that hyperhomocysteine status may damage the vascular endothelium of the developing placenta, folic acid supplements can be used to reduce blood homocysteine levels and potentially reduce the risk of preeclampsia [85].

On the other hand, some clinical investigations suggested that the daily consumption of 400 μg of folic acid alone cannot avoid the occurrence of gestational hypertension and preeclampsia during early pregnancy [86]. However, based on the results of the large cohort study on a total of 10,041 pregnant women, folic acid supplementation and higher dietary folate intake during pregnancy reduce the risk of preeclampsia [82]. Similarly, these results were acknowledged in one recent study that indicated there is a significant relationship between the risk of preeclampsia and the duration of supplementation but not the time of use [87].

Published literature reports controversial results about the association of folic acid supplementation and PE. Based on the results of a meta-analysis, we conclude that folic acid fortification alone did not prevent the occurrence of gestational hypertension and preeclampsia. However, the above-mentioned study suggested that the supplementation of multivitamins containing folic acid could reduce the risk of gestational hypertension and preeclampsia [88].

Vitamin B12 as a water-soluble B vitamin, is one of the other factors that can modulate elevated levels of plasma homocysteine. It is also necessary as a cofactor for enzymes that produce methylcobalamin and for its function in cytosol converting homocysteine to methionine, as well as contributing to the mitochondria to catabolize branched-chain fatty acids [89].

Several studies have shown that low vitamin B12 status is associated with low birthweight (<2,500 g) and preterm delivery (<37 weeks) in pregnant women [90]. Outcomes regarding the associations between maternal vitamin B12 status and the risk of preeclampsia was diverse among vitamin B12-related biomarkers. While another study presented findings that serum levels of folic acid and vitamin B12 were not significantly different in the subjects with GH and PE than the control group [83].

Although, it has been revealed that patients with preeclampsia have hypermethylation in the MTHFR (methylenetetrahydrofolate reductase) gene promoter [1]. But no significant differences were found in serum or plasma vitamin B12 concentrations between groups [83, 91]. However, Mujawar et al. found hyperhomocysteinemia and deficiency of folic acid and vitamin B12 with increased blood pressure as a risk factor for cardiovascular disease (CVD) in preeclampsia [92]. In line with this, in another interventional study in Wistar rats, maternal vitamin B12 deficiency resulted in elevated homocysteine levels, however, n-3 PUFA supplementation in the presence of vitamin B12 supplementation reduced homocysteine levels [93].

To our knowledge, there are not enough studies to reach a conclusion about the effects of B12 supplement on preeclampsia during pregnancy and further studies are warranted.

10.2.7 Vitamins C and E

Another role for food and nutrition in the origins of preeclampsia could be the deficiency of antioxidant intake, specifically vitamins C and E. Vitamin C has a prominent role in the neutralization of both water-soluble and lipid-soluble free radicals and must be supplied by the diet [94]. In addition it was suggested that vitamin E, a powerful antioxidant, plays a significant role in preventing preeclampsia. So, supplementation with antioxidant vitamins has been proposed to diminish the risk of preeclampsia and perinatal problems [95].

In this regard, the Cochrane study on randomized controlled trials was done to assess the effects of vitamin E supplementation, alone or in combination with other separate supplements, on pregnancy outcomes. The authors concluded that there were no clear differences between the vitamin E and placebo or control groups relating to the adverse pregnancy outcomes [96]. In agreement with these results, a systematic review and meta-analysis for the effectiveness of combined vitamin C and E supplementation in the prevention of preeclampsia did not confirm this hypothesis and showed that combined vitamin C and E supplementation does not decrease the risk of preeclampsia and should not be suggested for its prevention. Furthermore, the aforesaid study indicated that combined supplementation with vitamins C and E increased the risk of gestational hypertension [97]. In a clinical trial, Spinnato et al. also revealed that the incidence of preeclampsia was not statistically significant in pregnant women who received vitamins E and C and in women who received a placebo [98]. In line with these results, another study by Rumbol et al. showed that different doses of vitamin C and E supplementation during pregnancy do not reduce the risk of preeclampsia in women or the risk of intrauterine growth restriction, or the risk of death or other serious consequences in their infants [99].

However, there is evidence that supplementation with commonly used antioxidants (mostly vitamins C and E) makes a difference in overwhelming oxidative stress [100]. A summary of the studies to date is that the combination of vitamins C and E cannot reduce the rate of adverse maternal or perinatal outcomes related to pregnancy-associated hypertension. But, in future trials, the sample size calculated on the basis of different doses of supplements should be considered to determine the effects of these antioxidants on preeclampsia.

10.2.8 Omega-3

Marine omega-3 polyunsaturated fatty acids (n-3 PUFAs) are important nutrients during the infant growth period [101]. The most potent bioactive products of n-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). So, marine n-3 PUFAs are claimed to have beneficial effects on childhood growth when ingested during pregnancy [102]. Furthermore, it has been

shown that during pregnancy there is a decrease in the maternal LC-PUFA (long-chain polyunsaturated fatty acid) status, and that the embryo development depends entirely on the supply of essential fatty acids [103].

Regarding the biological activity of n-3 saturated fatty acid, some researchers believe that eating omega-3 fatty acids may affect several pregnancy outcomes, including preeclampsia [104]. Moreover, an observational study by Wang et al. found that total n-3 polyunsaturated fatty acids were lower in women with preeclampsia [105]. Such results were also proved by other observational studies [18]. These findings encouraged researchers to determine whether maternal DHA supplementation affects these complications of pregnancy or not.

Currently, there are reasons (e.g. decreased synthesis of thromboxane A2 from arachidonic acid) for a possible beneficial effect of n-3 fatty acids on preeclampsia. In regard to these effects, Adair et al. conducted a study to investigate effect of high-dose n-3 fatty acid intake on hypertension and revealed that it can reduce maternal thromboxane A2 synthesis [106]. Also, numerous epidemiological and observational studies have assessed the influence of n-3 LC-PUFA intake during pregnancy on maternal outcomes and abundant meta-analyses have been published [104, 107]. Some studies confirmed that the odds ratios of preeclampsia are reduced by taking between 100 and 900 mg of omega-3 per day [108].

Nevertheless, despite some valuable data from these studies, there is little evidence from randomized, placebo-controlled trials for a significant effect of omega-3 on the incidence or severity of preeclampsia. Recently, a meta-analysis on randomized controlled trials that investigated the effects of fish oil supplementation in pregnant women, identified that supplementation with fish oil during the pregnancy is not associated with reduced preeeclampsia [109], while, according to Clausen et al.'s study, a high consumption of PUFA is associated with an increased risk of preeclampsia [110]. These conflicting results may be the case either because LC-PUFAs are ineffective or because the design of the analyzed trials does not take into account certain contradictory factors.

Therefore, to detect the effect of LC-PUFA supplementation on preeclampsia, we suggest the design of a large-scale clinical trial study regarding the selection of an optimal dose and timing and considering all contributory factors.

10.2.9 Probiotics

Since endothelial dysfunction is associated with the activation of the clotting cascade and has an important role in the pathogenesis of preeclampsia [111], it is hypothesized that modulation of the maternal immune system may be important in the pathogenesis of preeclampsia. So, many researchers have intended to assess the regulatory immune system effects of food or its components on preeclampsia risk [112].

Probiotics are defined as a community of live microorganisms and modulator of gastrointestinal health that are consumed as a dietary supplement or drug for the purpose of promoting health and stimulating the growth of desirable microbes which help human health through involved processes of hypertension and inflammation [113].

Evidence is also emerging that gut microbiota play an important role in energy homeostasis, inflammation, and glucose metabolism [114]. Moreover, they can change the complication of pregnancy independent of health status and diet. These benefits are similar to the improvement of metabolic syndrome in non-pregnant individuals and are likely to stimulate the physiological insulin resistance that develops during a typical pregnancy (Laitinen, 2008 #1). Sometimes, adverse health states during pregnancy may be associated with intestinal microbial changes. Maternal microbiome also may influence and reduce pregnancy complications associated with hypertension and inflammation. Therefore, altering the intestinal microbiome during pregnancy can affect both the health of the mother and fetal consequences [115].

In this regard, a study on pregnant women with overweight and obesity problems, the abundance of butyrate-producing bacteria and butyrate production in the gut microbiota was significantly negatively related to blood pressure, so increasing butyrate-producing capacity may help the maintenance of normal blood pressure in obese pregnant women [116]. Also, in another study on pregnant women in South China, there was an overall increase in pathogenic bacteria in PE pregnant women. The study suggested that there is a significant structural change in the gut microbiota in PE patients, which might be attributed to the onset and development of the disease [117].

Also, in a recent large observational study conducted by Nordqvist et al., the intake of probiotic milk products in the first half of pregnancy was connected with a reduction in risk of preeclampsia (OR = 0.80; 95% CI: 0.66, 0.96), although the association was more obvious in severe preeclampsia (OR = 0.61; 95% CI: 0.43, 0.89) [118].

In addition, earlier systematic reviews of the literature about the impact of probiotics in pregnancy and maternal outcomes clarified that probiotic usage in pregnancy could significantly decrease maternal fasting glucose levels, the incidence of GDM (gestational diabetes mellitus) and preeclampsia, and C-reactive protein levels [119]. Although few studies show the positive role of the gut in association with gestational hypertension and preeclampsia, identifying the characteristics of the mammary gland microbial profile and identifying the various factors that facilitate their changes during pregnancy may reveal important strategies for improving the pregnancy and the infant's health outcomes.

10.2.10 Carotenoids

Carotenoids are natural fat-soluble pigments found in plants and some microorganisms. So far, β-carotene, α-carotene, and lycopene are important

members of the carotene group [120]. Although some studies could not show the relationship between reduced levels of carotenoids and the risk of preeclampsia, a recent investigation demonstrated significant correlation between carotenoids status and risk of some complications during pregnancy [121]. Therefore, the role of carotenoids during pregnancy and infancy is significant [122]. For instance, the prevalence of PE in women with reduced level of antioxidants is higher than those with normal status [123, 124]. Also, analysis of the serum of pregnant women showed that lower α- and β-carotenes, and generally lower vitamin D, are associated with later development of PE [125]. Interestingly, other observational data supported these facts by the reported inhibitory effects of β-carotene on vasoconstriction in the human placenta and the decreasing risk of preeclampsia by the increased plasma concentration of lutein (OR: 0.60; 95% CI: 0.46–0.77) [64].

Thus, these findings provide a hypothesis on a potentially critical role of carotenoid deficiencies in early pregnancy for the development of PE and the need for adequate dietary intake of carotenoids. But clinical trials assessing the effects of carotenoid supplementation in PE are limited. To investigate the effect of lycopene supplements (2 mg/day up to the second trimester of pregnancy), Sharma et al. conducted a randomized controlled study of 116 women in their second trimester and showed a weakly decreasing effect of lycopene for the development of preeclampsia (8.6% vs. 17.7% cases) [126]. In contrast, a placebo-controlled β-carotene supplementation trial in a population in Asia showed that the intervention reduced pregnancy-related maternal mortality, but the study did not show the prevention effect of β-carotene supplementation in the risk of preeclampsia [127]. The results of the mentioned study agree with the other investigations [128].

To summarize, the role of carotenoids in the prevention of preeclampsia is uncertain. Thus, larger randomized controlled trials are needed to define the role of carotenoids in PE development and determine the mechanistic effects of carotenoids and other antioxidant micronutrients and bioactive compounds in interventional models.

10.3 Conclusion

The well-known pathogenesis of preeclampsia appears to be the release of inflammatory and angiogenic factors that contribute to endothelial dysfunction in PE. Currently, there are several suggestions to prevent PE and most of the evidence for the probable benefits of nutraceuticals, functional foods, or medicinal products are resulting from epidemiological studies. Thus, researchers have attempted to identify the safety and efficacy of natural agents in interventional trials. In some interventional studies, the benefits of nutraceutical supplementation, such as minerals, vitamins, omega-3 fatty acids, and food bioactive compounds, were shown by improvements in oxidative stress and the repair of the activities of antioxidant enzymes. But these results are under

the influence of some confusing factors, such as treatment with a combination of supplements in daily routine and short intervention time. So further longitudinal and well-designed clinical trials regarding comprehensive molecular mechanisms are needed to explore the potential impact of nutraceuticals and their beneficial effects for health and to address their dose-dependency as well as their synergistic effects in PE. However, it should be noted that a better understanding of the pathophysiology of PE and the definition of new molecular biomarkers could also be effective in evaluating the exact impact of nutraceuticals.

References

1. Kintiraki, E., et al., Pregnancy-induced hypertension. *Hormones*, 2015. **14**(2): p. 211–223.
2. Hutcheon, J.A., S. Lisonkova, and K. Joseph, Epidemiology of preeclampsia and the other hypertensive disorders of pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 2011. **25**(4): p. 391–403.
3. Vest, A.R. and L.S. Cho, Hypertension in pregnancy. *Current Atherosclerosis Reports*, 2014. **16**(3): p. 395.
4. Practice, A.C.o.O., ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 2002. **77**(1): p. 67.
5. Ødegård, R.A., et al., Preeclampsia and fetal growth. *Obstetrics & Gynecology*, 2000. **96**(6): p. 950–955.
6. Correa, P., et al., Etiopathogenesis, prediction, and prevention of preeclampsia. *Hypertension in Pregnancy*, 2016. **35**(3): p. 280–294.
7. Huppertz, B., Placental villous trophoblast: the altered balance between proliferation and apoptosis triggers preeclampsia. *Journal für Reproduktionsmedizin und Endokrinologie-Journal of Reproductive Medicine and Endocrinology*, 2006. **3**(2): p. 103–108.
8. Grotegut, C.A., Prevention of preeclampsia. *The Journal of Clinical Investigation*, 2016. **126**(12): p. 4396–4398.
9. Perez-Sepulveda, A., et al., Innate immune system and preeclampsia. *Frontiers in Immunology*, 2014. **5**: p. 244.
10. Chaiworapongsa, T., P. Chaemsaithong, L. Yeo, and R. Romero. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nature Reviews Nephrology*, 2014. **10**(8): p. 466.
11. Skjærven, R., et al., Recurrence of preeclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ*, 2005. **331**(7521): p. 877.
12. Cotter, A.M., et al., Elevated plasma homocysteine in early pregnancy: a risk factor for the development of severe preeclampsia. *American Journal of Obstetrics and Gynecology*, 2001. **185**(4): p. 781–785.
13. Youssef, A., et al., Uterine artery Doppler and biochemical markers (PAPP-A, PlGF, sFlt-1, P-selectin, NGAL) at 11+ 0 to 13+ 6 weeks in the prediction of late (> 34 weeks) preeclampsia. *Prenatal Diagnosis*, 2011. **31**(12): p. 1141–1146.
14. Di Lorenzo, G., et al., First trimester maternal serum PIGF, free β-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. *Placenta*, 2012. **33**(6): p. 495–501.

15. Lin, L., et al., Low-dose aspirin in the prevention of preeclampsia in China (APPEC study): protocol for a multicentre randomized controlled trial. *Trials*, 2018. **19**(1): p. 608.
16. Xu, H., et al., An international trial of antioxidants in the prevention of preeclampsia (INTAPP). *American Journal of Obstetrics and Gynecology*, 2010. **202**(3): p. 239. e1239. e10.
17. Frederick, I.O., et al., Dietary fiber, potassium, magnesium and calcium in relation to the risk of preeclampsia. *The Journal of Reproductive Medicine*, 2005. **50**(5): p. 332–344.
18. Williams, M.A., et al., Omega-3 fatty acids in maternal erythrocytes and risk of preeclampsia. *Epidemiology*, 1995: p. 232–237.
19. Nandi, A.A., N.S. Wadhwani, and S.R. Joshi, Altered metabolic homeostasis between vitamin D and long chain polyunsaturated fatty acids in preeclampsia. *Medical Hypotheses*, 2017. **100**: p. 31–36.
20. Kalra, E.K., Nutraceutical-definition and introduction. *Aaps Pharmsci*, 2003. **5**(3): p. 27–28.
21. Sauer, S. and A. Plauth, Health-beneficial nutraceuticals—myth or reality? *Applied Microbiology and Biotechnology*, 2017. **101**(3): p. 951–961.
22. Nasri, H., et al., New concepts in nutraceuticals as alternative for pharmaceuticals. *International Journal of Preventive Medicine*, 2014. **5**(12): p. 1487–1499.
23. Kramer, K., P.-P. Hoppe, and L. Packer, *Nutraceuticals in Health and Disease Prevention*. Vol. 6. CRC Press, 2001.
24. Mashhadi, N.S., et al., Influence of ginger and cinnamon intake on inflammation and muscle soreness endued by exercise in Iranian female athletes. *International Journal of Preventive Medicine*, 2013. **4**(Suppl 1): p. S11.
25. Rani, V., et al., Oxidative stress and metabolic disorders: pathogenesis and therapeutic strategies. *Life Sciences*, 2016. **148**: p. 183–193.
26. Souyoul, S.A., K.P. Saussy, and M.P. Lupo. Nutraceuticals: a review. *Dermatology and Therapy*, 2018. **8**(1): p. 5–16.
27. Souyoul, S.A., K.P. Saussy, and M.P. Lupo, Nutraceuticals: a review. *Dermatology and Therapy (Heidelb)*, 2018. **8**(1): p. 5–16.
28. Rajasekaran, A., G. Sivagnanam, and R. Xavier, Nutraceuticals as therapeutic agents: a review. *Research Journal of Pharmacy and Technology*, 2008. **1**(4): p. 328–340.
29. Segovia, B., et al., Hypocalciuria during pregnancy as a risk factor of preeclampsia. *Ginecologia y obstetricia de Mexico*, 2004. **72**: p. 570–574.
30. Udenze, I., et al., Calcium and magnesium metabolism in preeclampsia. *The West African Journal of Medicine*, 2014. **33**(3): p. 178–182.
31. Gabbay, A., et al., Calcium level during the first trimester of pregnancy as a predictor of preeclampsia. *Hypertension in Pregnancy*, 2014. **33**(3): p. 311–321.
32. Tang, R., et al., Limited evidence for calcium supplementation in preeclampsia prevention: a meta-analysis and systematic review. *Hypertension in Pregnancy*, 2015. **34**(2): p. 181–203.
33. Boeldt, D.S. and I.M. Bird, Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. *Journal of Endocrinology*, 2017. **232**(1): p. R27–R44.
34. Cormick, G., et al., *Calcium Supplementation for Prevention of Primary Hypertension*. The Cochrane Library, 2015.
35. Patrelli, T.S., et al., Calcium supplementation and prevention of preeclampsia: a meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2012. **25**(12): p. 2570–2574.
36. Milman, N., et al., Supplementation during pregnancy: beliefs and science. *Gynecological Endocrinology*, 2016. **32**(7): p. 509–516.
37. Turner, J.A., Diagnosis and management of preeclampsia: an update. *International Journal of Women's Health*, 2010. **2**: p. 327.
38. Meeting, W.E.C.o.B.S. and W.H. Organization, *WHO Expert Committee on Biological Standardization*: *Sixty-Third Report*. Vol. 980. World Health Organization, 2013.

39. Hofmeyr, G.J., et al., Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Systematic Review*, 2014. **6**(6).
40. Firoz, T., et al., Preeclampsia in low and middle income countries. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 2011. **25**(4): p. 537–548.
41. Parazzini, F., M. Di Martino, and P. Pellegrino, Magnesium in the gynecological practice: a literature review. *Magnesium Research*, 2017. **30**(1): p. 1–7.
42. Black, R.E., Micronutrients in pregnancy. *British Journal of Nutrition*, 2001. **85**(S2): p. S193–S197.
43. Dalton, L.M., et al., Magnesium in pregnancy. *Nutrition Reviews*, 2016. **74**(9): p. 549–557.
44. Ephraim, R.K.D., et al., Serum calcium and magnesium levels in women presenting with preeclampsia and pregnancy-induced hypertension: a case–control study in the Cape Coast metropolis, Ghana. *BMC Pregnancy and Childbirth*, 2014. **14**(1): p. 390.
45. Glasdam, S.M., S. Glasdam, and G.H. Peters. The importance of magnesium in the human body: a systematic literature review. *Advances in Clinical Chemistry*, 2016. **73**: p. 169–193.
46. de Sousa Rocha, V., et al., Association between magnesium status, oxidative stress and inflammation in preeclampsia: a case–control study. *Clinical Nutrition*, 2015. **34**(6): p. 1166–1171.
47. Elmugabil, A., et al., Serum calcium, magnesium, zinc and copper levels in sudanese women with preeclampsia. *PloS One*, 2016. **11**(12): p. e0167495.
48. Owusu, E.D., et al., Serum magnesium and calcium in preeclampsia: a comparative study at the Korle-Bu Teaching Hospital, Ghana. *Integrated Blood Pressure Control*, 2017. **10**: p. 9–15.
49. Čabarkapa, V., et al., Serum magnesium level in the first trimester of pregnancy as a predictor of preeclampsia–a pilot study. *Hypertension in Pregnancy*, 2018. **37**(3): p. 144–153.
50. Zarean, E. and A. Tarjan, Effect of magnesium supplement on pregnancy outcomes: a randomized control trial. *Advanced Biomedical Research*, 2017. **31**(6): p. 109.
51. Alves, J.G.B., et al., The B RAzil MAG nesium (BRAMAG) trial: a randomized clinical trial of oral magnesium supplementation in pregnancy for the prevention of preterm birth and perinatal and maternal morbidity. *BMC Pregnancy and Childbirth*, 2014. **14**(1): p. 222.
52. Rylander, R., Magnesium in pregnancy blood pressure and preeclampsia–a review. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*, 2014. **4**(2): p. 146–149.
53. Doyle, W., et al., Maternal magnesium intake and pregnancy outcome. *Magnesium Research*, 1989. **2**(3): p. 205–210.
54. Makrides, M., et al., Magnesium supplementation in pregnancy. *Cochrane Database of Systematic Reviews*, 2014(4).
55. Sibai, B.M., and E. Bray, Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial. *American Journal of Obstetrics & Gynecology*, 1989. **161**(1): p. 115–119.
56. Atamer, Y., et al., Lipid peroxidation, antioxidant defense, status of trace metals and leptin levels in preeclampsia. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2005. **119**(1): p. 60–66.
57. Bayhan, G., et al., Significance of changes in lipid peroxides and antioxidant enzyme activities in pregnant women with preeclampsia and eclampsia. *Clinical and Experimental Obstetrics and Gynecology*, 2000. **27**(2): p. 142–146.
58. Bahadoran, P., et al., The relationship between serum zinc level and preeclampsia. *Iranian Journal of Nursing and Midwifery Research*, 2010. **15**(3): p. 120.
59. Kiilholma, P., et al., Copper and zinc in preeclampsia. *Acta obstetricia et gynecologica Scandinavica*, 1984. **63**(7): p. 629–631.

60. Kim, J., et al., Serum levels of zinc, calcium, and iron are associated with the risk of preeclampsia in pregnant women. *Nutrition Research*, 2012. **32**(10): p. 764–769.
61. Harma, M., M. Harma, and A. Kocyigit, Correlation between maternal plasma homocysteine and zinc levels in preeclamptic women. *Biological Trace Element Research*, 2005. **104**(2): p. 97–105.
62. Katz, O., et al., Severe preeclampsia is associated with abnormal trace elements concentrations in maternal and fetal blood. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2012. **25**(7): p. 1127–1130.
63. Rafeeinia, A., et al., Serum copper, zinc and lipid peroxidation in pregnant women with preeclampsia in gorgan. *The Open Biochemistry Journal*, 2014. **8**: p. 83.
64. Cohen, J.M., et al., Maternal antioxidant levels in pregnancy and risk of preeclampsia and small for gestational age birth: a systematic review and meta-analysis. *PloS One*, 2015. **10**(8): p. e0135192.
65. Caulfield, L., and R. Black, *Zinc Deficiency. Comparative Quantification of Health Risks: The Global and Regional Burden of Disease due to 25 Selected Major Risk Factors. Cambridge, MA: World Health Organization*. Harvard University Press, 2004.
66. Zahiri sorouri, Z., H. Sadeghi, and D. Pourmarzi, The effect of zinc supplementation on pregnancy outcome: a randomized controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2016. **29**(13): p. 2194–2198.
67. Aminisani, N., et al., Zinc supplementation during pregnancy: a randomized controlled trial. *Iranian Journal of Pharmacology and Therapeutics*, 2009. **8**(2): p. 67–0.
68. Mahomed, K., et al., Zinc supplementation during pregnancy: a double blind randomised controlled trial. *BMJ*, 1989. **299**(6703): p. 826–830.
69. Pérez-López, F.R., Vitamin D: the secosteroid hormone and human reproduction. *Gynecological Endocrinology*, 2007. **23**(1): p. 13–24.
70. Heyden, E. and S. Wimalawansa, Vitamin D: effects on human reproduction, pregnancy, and fetal well-being. *The Journal of Steroid Biochemistry and Molecular Biology*, 2017. **1**(180): p. 41–50.
71. Singla, R., et al., Relationship between preeclampsia and vitamin D deficiency: a case control study. *Archives of Gynecology and Obstetrics*, 2015. **291**(6): p. 1247–1251.
72. Umar, N., et al., Serum 25-Hydroxy vitamin D level in preeclamptic and normotensive pregnancies. *Journal of the College of Physicians and Surgeons Pakistan*, 2016. **26**(8): p. 673–676.
73. Ullah, M., et al., Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. *Hormone and Metabolic Research*, 2013. **45**(09): p. 682–687.
74. Hyppönen, E., Vitamin D for the prevention of preeclampsia? A hypothesis. *Nutrition Reviews*, 2005. **63**(7): p. 225–232.
75. Mulligan, M.L., et al., Implications of vitamin D deficiency in pregnancy and lactation. *American Journal of Obstetrics and Gynecology*, 2010. **202**(5): p. 429. e1429. e9.
76. Behjat Sasan, S., et al., The effects of Vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia. *Obstetrics and Gynecology International*, 2017. **75**(1): p. 2081–2089.
77. Khaing, W., et al., Calcium and vitamin D supplementation for prevention of preeclampsia: a systematic review and network meta-analysis. *Nutrients*, 2017. **9**(10): p. 1141.
78. De-Regil, L.M., et al., Vitamin D supplementation for women during pregnancy. *Sao Paulo Medical Journal*, 2016. **134**(3): p. 274–275.
79. Organization, W.H., *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*. World Health Organization, 2016.
80. Hogg, B.B., et al., Second-trimester plasma homocysteine levels and pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction. *American Journal of Obstetrics & Gynecology*, 2000. **183**(4): p. 805–809.

81. Dodds, L., et al., Effect of homocysteine concentration in early pregnancy on gestational hypertensive disorders and other pregnancy outcomes. *Clinical Chemistry*, 2008. **54**(2): p. 326–334.
82. Sun, F., et al., Correlation of maternal serum homocysteine in the first trimester with the development of gestational hypertension and preeclampsia. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, 2017. **23**: p. 5396.
83. Patrick, T.E., et al., Homocysteine and folic acid are inversely related in black women with preeclampsia. *Hypertension*, 2004. **43**(6): p. 1279–1282.
84. Bergen, N., et al., Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2012. **119**(6): p. 739–751.
85. Wang, Y., et al., Folic acid supplementation and dietary folate intake, and risk of preeclampsia. *European Journal of Clinical Nutrition*, 2015. **69**(10): p. 1145.
86. Li, Z., et al., Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. *Hypertension*, 2013. **61**(4): p. 873–879.
87. De Ocampo, M.P., et al., Folic acid supplement use and the risk of gestational hypertension and preeclampsia. *Women and Birth*, 2018. **31**(2): p. e77–e83.
88. Yang, X., et al., Periconceptional folic acid fortification for the risk of gestational hypertension and preeclampsia: a meta-analysis of prospective studies. *Maternal & Child Nutrition*, 2016. **12**(4): p. 669–679.
89. Finkelstein, J.L., A.J. Layden, and P.J. Stover, Vitamin B-12 and perinatal health–3. *Advances in Nutrition*, 2015. **6**(5): p. 552–563.
90. Rogne, T., et al., Associations of maternal vitamin B12 concentration in pregnancy with the risks of preterm birth and low birth weight: a systematic review and meta-analysis of individual participant data. *American Journal of Epidemiology*, 2017. **185**(3): p. 212–223.
91. Makedos, G., et al., Homocysteine, folic acid and B12 serum levels in pregnancy complicated with preeclampsia. *Archives of Gynecology and Obstetrics*, 2007. **275**(2): p. 121–124.
92. Mujawar, S.A., V.W. Patil, and R.G. Daver, Study of serum homocysteine, folic acid and vitamin B 12 in patients with preeclampsia. *Indian Journal of Clinical Biochemistry*, 2011. **26**(3): p. 257–260.
93. Khaire, A., et al., Supplementation with omega-3 fatty acids during gestation and lactation to a vitamin B12-deficient or-supplemented diet improves pregnancy outcome and metabolic variables in Wistar rats. *Reproduction, Fertility and Development*, 2015. **27**(2): p. 341–350.
94. Taghiyar, M., et al., The effect of vitamin C and e supplementation on muscle damage and oxidative stress in female athletes: a clinical trial. *International Journal of Preventive Medicine*, 2013. **4**(Suppl 1): p. S16.
95. Aris, A., et al., Detrimental effects of high levels of antioxidant vitamins C and E on placental function: considerations for the vitamins in preeclampsia (VIP) trial. *Journal of Obstetrics and Gynaecology Research*, 2008. **34**(4): p. 504–511.
96. Rumbold, A., et al., Vitamin E supplementation in pregnancy. *Cochrane Database Systematic Review*, 2015. **9**(08).
97. Basaran, A., M. Basaran, and B. Topatan, Combined vitamin C and E supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. *Obstetrical & Gynecological Survey*, 2010. **65**(10): p. 653–667.
98. Rumbold, A.R., et al., Vitamins C and E and the risks of preeclampsia and perinatal complications. *New England Journal of Medicine*, 2006. **354**(17): p. 1796–1806.
99. Spinnato, J.A., et al., Antioxidant therapy to prevent preeclampsia: a randomized controlled trial. *Obstetrics & Gynecology*, 2007. **110**(6): p. 1311–1318.
100. Tenório, M., et al., Oral antioxidant therapy for prevention and treatment of preeclampsia: meta-analysis of randomized controlled trials. *Nutrition, Metabolism and Cardiovascular Diseases*, 2018. **28**(9): p. 865–876.

101. McCann, J.C. and B.N. Ames, Is docosahexaenoic acid, an n– 3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals–. *The American Journal of Clinical Nutrition*, 2005. **82**(2): p. 281–295.
102. Innis, S.M., Dietary (n-3) fatty acids and brain development. *The Journal of Nutrition*, 2007. **137**(4): p. 855–859.
103. Haggarty, P., Effect of placental function on fatty acid requirements during pregnancy. *European Journal of Clinical Nutrition*, 2004. **58**(12): p. 1559.
104. De Giuseppe, R., C. Roggi, and H. Cena, n-3 LC-PUFA supplementation: effects on infant and maternal outcomes. *European Journal of Nutrition*, 2014. **53**(5): p. 1147–1154.
105. Wang, Y., H.H. Kay, and A.P. Killam, Decreased levels of polyunsaturated fatty acids in preeclampsia. *American Journal of Obstetrics & Gynecology*, 1991. **164**(3): p. 812–818.
106. Adair, C.D., et al., The effect of high dietary n-3 fatty acid supplementation on angiotensin II pressor response in human pregnancy. *American Journal of Obstetrics and Gynecology*, 1996. **175**(3 Pt 1): p. 688–691.
107. Voortman, T., et al., Effects of polyunsaturated fatty acid intake and status during pregnancy, lactation, and early childhood on cardiometabolic health: a systematic review. *Progress in Lipid Research*, 2015. **59**: p. 67–87.
108. Olafsdottir, A.S., et al., Relationship between high consumption of marine fatty acids in early pregnancy and hypertensive disorders in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2006. **113**(3): p. 301–309.
109. Chen, B., et al., Fish oil supplementation does not reduce risks of gestational diabetes mellitus, pregnancy-induced hypertension, or preeclampsia: a meta-analysis of randomized controlled trials. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, 2015. **21**: p. 2322.
110. Clausen, T., et al., High intake of energy, sucrose, and polyunsaturated fatty acids is associated with increased risk of preeclampsia. *American Journal of Obstetrics and Gynecology*, 2001. **185**(2): p. 451–458.
111. Roberts, J.M., and H.S. Gammill, Preeclampsia: recent insights. *Hypertension*, 2005. **46**(6): p. 1243–1249.
112. James, J.L., G.S. Whitley, and J.E. Cartwright, Preeclampsia: fitting together the placental, immune and cardiovascular pieces. *The Journal of Pathology*, 2010. **221**(4): p. 363–378.
113. Lye, H.-S., et al., The improvement of hypertension by probiotics: effects on cholesterol, diabetes, renin, and phytoestrogens. *International Journal of Molecular Sciences*, 2009. **10**(9): p. 3755–3775.
114. Cani, P.D. and N.M. Delzenne, Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. *Current Opinion in Pharmacology*, 2009. **9**(6): p. 737–743.
115. Brantsæter, A.L., et al., Intake of probiotic food and risk of preeclampsia in primiparous women: the Norwegian Mother and Child Cohort Study. *American Journal of Epidemiology*, 2011. **174**(7): p. 807–815.
116. Gomez-Arango, L.F., et al., Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy. *Hypertension*, 2016. **68**(4): p. 974–981.
117. Liu, J., et al., Remodeling of the gut microbiota and structural shifts in preeclampsia patients in South China. *European Journal of Clinical Microbiology & Infectious Diseases*, 2017. **36**(4): p. 713–719.
118. Nordqvist, M., et al., Timing of probiotic milk consumption during pregnancy and effects on the incidence of preeclampsia and preterm delivery: a prospective observational cohort study in Norway. *BMJ Open*, 2018. **8**(1): p. e018021.

119. Lindsay, K.L., et al., Probiotics in pregnancy and maternal outcomes: a systematic review. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2013. **26**(8): p. 772–778.
120. Stahl, W. and H. Sies, Bioactivity and protective effects of natural carotenoids. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 2005. **1740**(2): p. 101–107.
121. Zhang, C., et al., Plasma concentrations of carotenoids, retinol, and tocopherols in preeclamptic and normotensive pregnant women. *American Journal of Epidemiology*, 2001. **153**(6): p. 572–580.
122. Cohen, J.M., et al., The association between maternal antioxidant levels in midpregnancy and preeclampsia. *American Journal of Obstetrics and Gynecology*, 2015. **213**(5): p. 695. e1695. e13.
123. Böhm, F., et al., β-Carotene with vitamins E and C offers synergistic cell protection against NOx. *FEBS Letters*, 1998. **436**(3): p. 387–389.
124. Sharma, J., et al., Oxidative stress markers and antioxidant levels in normal pregnancy and preeclampsia. *International Journal of Gynecology & Obstetrics*, 2006. **94**(1): p. 23–27.
125. Palan, P.R., M.S. Mikhail, and S.L. Romney, Placental and serum levels of carotenoids in preeclampsia. *Obstetrics & Gynecology*, 2001. **98**(3): p. 459–462.
126. Sharma, J., et al., Effect of lycopene on preeclampsia and intra-uterine growth retardation in primigravidas. *International Journal of Gynecology & Obstetrics*, 2003. **81**(3): p. 257–262.
127. Antartani, R., and K. Ashok, Effect of lycopene in prevention of preeclampsia in high risk pregnant women. *Journal of the Turkish German Gynecological Association*, 2011. **12**(1): p. 35.
128. Banerjee, S., S. Jeyaseelan, and R. Guleria, Trial of lycopene to prevent preeclampsia in healthy primigravidas: results show some adverse effects. *Journal of Obstetrics and Gynaecology Research*, 2009. **35**(3): p. 477–482.

11

The Role of Nutraceuticals in Gestational Diabetes Mellitus

Neda Roshanravan and Hamed Mohammadi

Contents

11.1 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) or glucose intolerance is the most general metabolic disorder of our times that is prevalent among pregnant women. Recent clinical investigations have indicated an increasing prevalence of GDM by 10–100% over the past 20 years (1). This disease increases the risk of adverse perinatal outcomes after delivery and maladies in the offspring in later life. Normally, pregnancy is associated with insulin resistance (IR) and

hyperinsulinemia around mid-pregnancy, and IR progression during the third trimester (1, 2).

Some hormones and adipokines such as tumor necrosis factor (TNF-α), human placental lactogen, and human placental growth hormone are responsible for IR in pregnancy. Furthermore, increases of hormones with diabetogenic effects such as estrogen, progesterone, and cortisol during pregnancy contribute to the disruption of the glucose homeostasis (3). The increase of maternal adipose deposition, decreased physical activity, and increased caloric intake during pregnancy are independent risks for this state of relative glucose intolerance (4).

Dietary strategies and lifestyle interventions have been considered to be the mainstay of treatment to optimize pregnancy outcomes in GDM women.

11.2 Nutraceuticals

The term "nutraceutical" is a hybrid of "nutrition" and "pharmaceutical" and was coined by Dr. Stephen L. DeFelice, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, New Jersey, in 1989 for the first time (5). The concept of "nutraceuticals" has evolved over the years and the definition varies across countries. It can be defined as "a food (or a part of food) that provides medical or health benefits, including the prevention and or treatment of a disease" (6). According to Health Canada's definition "nutraceuticals are concentrated forms of food or food constituents that can be taken in pills, powder, or other medicinal forms that have specific health benefits." In Europe, it is defined as "concentrated sources of nutrients; or other substances with a nutritional or physiological effect." And the Japanese know nutraceuticals as foods with health claims (7).

In general, nutraceuticals as natural functional/medical foods or bioactive phytochemicals are natural ingredients derived from foods, used in the medicinal form and type of pills, capsules, potions, and liquids, and they provide physiological benefits or protect against chronic disease (8). Such products may vary from isolated nutrients, specific diets, and dietary supplements to genetically modified foods (GM foods), also known as genetically engineered foods (GE foods), and processed foods such as cereals, soups, vegetable juices, beverages, and even herbal products (5).

According to the Bureau of Nutritional Sciences of the Food Directorate of Health Canada, the definitions of "nutraceutical" and "functional food" have been defined as follows (9):

11.2.1 Nutraceutical

"A product isolated or purified from foods that is generally sold in medicinal forms not usually associated with the food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease." (10)

11.2.2 Functional food

"[A food] consumed as part of a usual diet, and is demonstrated to have physiological benefits and/ or reduce the risk of chronic disease beyond basic nutritional functions." (10)

In this review we have considered functional foods within the scope of nutraceuticals.

Surveillance of nutraceuticals/natural health products differs from country to country. Some countries treat natural health products in the same manner as foods, for example Japan and China. In these countries there are no legal or regulatory differences between food and medication forms. In the United States, there is a distinction between foods and natural health products (dietary supplements) without any significant differences in rules (the same generic claims are available to food and to dietary supplements). New Zealand deals with natural health products (dietary supplements) like food but does not allow claims in this context (including disease risk reduction claims). However, the regulatory rules for dietary supplements are somewhat weak. The European Union (EU) limits food supplements to only approved vitamins and minerals. Some countries put natural health products in a grey area (without any clear rules) between food and drugs. In Australia, Brazil, and Canada all the rules that relate to natural health products differ from those for food, using a product-specific system. In South Korea there are restricted rules regarding functional foods and natural health products with licenses being required (10).

The potential health effects of nutraceuticals form current research topics in the area of the prevention, management, and treatment of degenerative diseases such as cancer, diabetes, cardiovascular, non-alcoholic fatty liver, neurodegenerative diseases.

11.3 Categories of Nutraceuticals and Their Role in Gestational Diabetes Mellitus

In the same way as for food sources, nutraceuticals can be classified using their mechanism of action and chemical nature. Nutraceuticals can be categorized as (11): antioxidant vitamins, minerals, dietary fibers, polyunsaturated fatty acids.

11.3.1 Antioxidant Vitamins

This includes clinical research aimed to investigate the antioxidant and anti-inflammatory activities of vitamins as nutraceuticals. The high blood glucose level in women with GDM decreases antioxidant defenses and induces oxidative stress. The exact pro-oxidant status and antioxidant status in women

with gestational diabetes is still unclear (12). Nevertheless, the intake of vitamins with antioxidant and insulinotropic properties has been shown to have beneficial effects on the glycemic status of women with gestational diabetes. Antioxidant vitamins, with properties of scavenging free reactive radicals, have been considered as the first line of defense against reactive free radical attack (13). The key vitamins are vitamins A, D, and E, nicotinamide, pyridoxine, folic acid, and vitamin B12.

11.3.2 Vitamin A

Vitamin A (VA) is a generic term for a group of fat-soluble retinoids with similar patterns of biologic activity, such as retinol, retinal, and retinoic acid. The term "retinoids" includes both natural forms of VA and many synthetic analogs to retinol. This vitamin acts in the retina, participating in the visual cycle, and acts in all tissues and organ systems of the body, interfering in the growth and integrity of cells (14).

Diabetes mellitus (DM) as a chronic pathological process is involved in metabolic disorders and is represented by insulin secretory deficiency, or disturbance in its function, or in both, with resulting glucose intolerance and high blood sugar. Considerable research effort has been focused on the association between GDM and serum retinol levels. According to pioneering studies, women with GDM may be considered as a group as having an increased risk of presenting reduced VA levels (15–17). Studies indicated that there was a significant decrease of vitamin A levels in a pregnant group with gestational diabetics as compared to a healthy pregnant group (16, 17). Insulin resistance is a causative factor during the gestational period that makes pregnant women susceptible to displaying a marginal biochemical state or vitamin A deficiency (18).

Retinol's plasma transportation is feasible due to its bond with a transporter protein with determined function, retinol-binding protein (RBP). RBP as an adipocytokine with potential susceptibility in enhancing hepatic gluconeogenesis and reducing insulin sensitivity was known in 2005. It is mainly synthesized in a higher extension by hepatocytes and adipose tissues (RBP4) (19). RBP dissolves liposoluble vitamin in the serum and protects it against oxidative demolition, and it keeps a constant concentration in the blood circulation (20). VA is transferred in blood in two ways: complex retinol-RBP and chylomicrons. Complex retinol-RBP is responsible for more than 95% of the VA existing in the circulation in the fasting state (21). According to previous evidence the expression level of glucose transporter 4 (GLUT4) as an insulin-regulated glucose transporter is reduced in the adipocytes of obese and insulin resistance subjects (22). Recently, studies have indicated that the decrease in GLUT4 expression is accompanied by an increased expression and secretion of the RBP. Raised levels of RBP have been found to impair insulin signaling and are a contributor to insulin resistance. In GDM, hyperglycemia is an important factor for the imbalance between retinol levels and RBP (12). Due to the different methodologies, some results in this field are still

conflicting and the exact mechanism responsible for alterations in vitamin A levels and the presence of GDM has not been completely clarified. However, the need to monitor vitamin A during gestation seems to be necessary mainly if it is accompanied by gestational diabetes mellitus.

11.3.3 Vitamin D

Vitamin D, or calciferol, has two main, functionally distinct forms, vitamin D2 (ergocalciferol), or the synthetic form of vitamin D, is made by irradiating ergosterol steroids in plants, which can then be used as a dietary supplement, and vitamin D3 (cholecalciferol), which is found in animal-based foods and is made when cholesterol in subcutaneous fat cleaves by ultraviolet rays (23). Both forms are considered as pro-hormones and are active after they have been hydroxylated twice: first in the liver to make 25-hydroxyl vitamin D (25[OH] D), and then again in the kidney to make the biologically active hormone, calcitriol (1,25-dihydroxyvitamin D) (24).

The best-accepted functions of vitamin D are in the regulation and preservation of calcium and phosphorus homeostasis, but there is now some evidence that vitamin D protects against certain types of chronic disease, such as cancer, multiple sclerosis, and diabetes (25). In recent years, vitamin D deficiency has been investigated as one of the potential contributors with increasing prevalence of GDM (26–28). Many researchers demonstrated that vitamin D concentrations were lower in women with GDM compared with healthy pregnant women (29–31).

Results from randomized trials indicated that vitamin D supplementation in women with GDM can decrease the risk of poor neonatal outcomes, such as neonatal hypoglycemia and "small for gestational age," caused by GDM (32). The observed inverse association of vitamin D levels with GDM risk is supported by the direct and/or indirect effects of vitamin D on insulin sensitivity and insulin secretion. In addition, vitamin D can normalize glucose intolerance via the facilitation of intestinal calcium absorption (33). Evidence from previous studies showed that an increased risk of GDM may be associated with vitamin D deficiency (27, 34); however, to support routine high-dose vitamin D supplementation during pregnancy, further clinical research must be done.

11.3.4 Vitamin E

In much of the literature, increased levels of free radicals are constantly observed in women with GDM (35). Vitamin E is known as a strong antioxidant which is found in plants and consists of a chromanol ring and an isoprenoid side chain. This term refers to tocopherols and tocotrienols and can be divided into alpha-, beta-, gamma-, and delta-isomers. Vitamin E with similar molecular structure to the thiazolidinedione (TZD) drugs has been linked to improved metabolic status through PPAR-γ-mediated

up-regulation of adiponectin as a major adipokine with insulin-sensitizing action (35, 36). The antioxidant activity of vitamin E has contributed to its hydroxyl group on the chromanol ring, which donates hydrogen for reducing the free radicals (37).

Animal studies have indicated that there are reduced concentrations of vitamin E in both the embryos and livers of fetuses from diabetic mothers (38). In addition, cord plasma vitamin E levels are significantly decreased in GDM women (39, 40). Some previous studies have claimed that dietary vitamin E intake or even its supplementation on its own or simultaneously with other antioxidants may give reduced GDM occurrence (41–43). Nevertheless, more clinical studies are required to understand the short- and long-term effects of vitamin E supplementation in pregnant women with GDM.

11.3.5 Nicotinamide

Niacin or nicotinic acid as a water soluble vitamin exists in two forms, nicotinamide or nicotinic acid. Niacin in the food ingredients often exists in the form of nicotinamide (44). It has been reported that nicotinamide, with its antioxidant and free radical scavenging effects, may protect pancreatic islets from inflammation (45, 46). Besides its functions as a B group vitamin, it can be considered as a wonder drug for correcting lipid metabolic disorders (47). Contrary to previous beliefs, some evidence is now available that indicates it has a moderate effect on the fasting blood glucose and hemoglobin A1c levels (48, 49).

There have been many animal studies that have indicated that the enhancement of antioxidant defenses is necessary for normoglycemia and normal immune functions in women with gestational diabetes mellitus. In a rat study the ability of nicotinamide to improve oxidative stress in gestational diabetic rats was proven (50, 51). Supplementation with nicotinamide may reverse insulin levels through improvement of C-peptide release (50, 52). The positive effects of nicotinamide on pro-oxidant/antioxidant status as well as its immunomodulatory effects should be taken into account when considering using this food supplement as an adjunct to the pharmacotherapeutic approach in gestational diabetes. However, more human clinical trials must be done to provide further support for its usage.

11.3.6 Pyridoxine

Pyridoxine or vitamin B6 is found generally in foods and can be used as a dietary supplement to increase dietary intake or partially reduce disease risk (53). Some clinical examinations have indicated far-reaching beneficial effects of using pyridoxine in the prevention or amelioration of GDM. Early studies showed that blood concentration of vitamin B6 is significantly decreased in diabetic animals and patients (54–57). Bennink and colleagues demonstrated that pregnant women with GDM who were treated with vitamin B6

(pyridoxine), 100 mg/day for two weeks, improved oral glucose tolerance considerably (58). Vitamin B6 deficiency is found to reduce circulating insulin levels and has been related to degenerative changes in pancreatic β-cells (59, 60). Beyond that, the health benefits of pyridoxamine (amine form of vitamin B6) can be attributed to the inhibition of the production of oxidative stress markers or scavenging the reactive oxygen species (61). There seems to be an increased requirement/utilization of vitamin B6 in GDM, accordingly various studies are needed to reach a definitive and overall conclusion regarding adjuvant therapy of vitamin B6 in the prevention of GDM complications.

11.3.7 Folate and Vitamin B12

It has been established that folate and vitamin B12 can be used in the regulation of homocysteine synthesis involved in the pathogenesis of GDM (62). It has been reported that elevated levels of homocysteine have been linked with insulin resistance (63). Some previous studies suggested that high plasma levels of folate and low plasma concentration of vitamin B12, resulting in a high plasma concentration of homocysteine, could be correlated with a higher plasma glucose level and the likelihood of GDM during pregnancy (62). A cohort study in China reported that daily folate supplementation in the first trimester of pregnancy may be associated with higher chances of GDM later in pregnancy (64). The association between vitamin B12 insufficiencies with higher GDM risk has also been shown in other studies (65, 66). An imbalance in these two B vitamins may be responsible for higher prevalence of GDM. On other hand, vitamin B12 insufficiency inhibited the conversion of 5-methyltetrahydrofolate to tetrahydrofolate. It has been proved that disruption in the production of purines and thymidine for DNA/RNA synthesis can be associated with the development of insulin resistance and impaired fasting glucose (67). However, the exact mechanisms for linking the effects of low vitamin B12 concentration and high folate level on glucose intolerance and insulin resistance are still unclear and not defined.

11.4 Minerals

11.4.1 Magnesium

It has been shown that pregnancy induces losses of magnesium (Mg). Beyond this, hypomagnesemia has been revealed as a major cause of insulin resistance. Some previous studies demonstrate that Mg supplementation has a beneficial effect on glucose metabolism and on insulin action (68, 69). Pioneering epidemiological studies have demonstrated an opposing relationship between the risk of diabetes and the ingestion of food rich in magnesium (70). These beneficial effects of Mg can be attributed to the participation of Mg in the process of gene expression (such as PPAR-γ, FPG, and LDLR), which is involved in insulin and lipid metabolism (71).

11.4.2 Zinc

Zinc, as a mineral, affects pancreatic function and insulin secretion. Some previous reports indicated that in pregnancy, as a result of prenatal iron and folic acid supplementation, zinc absorption is disrupted. In addition, pregnant women require higher levels of zinc due to various physiological conditions (72–74).

Zinc deficiency may be related to carbohydrate intolerance. Previous studies indicate the important role of zinc deficiency in glucose intolerance, insulin resistance, and diabetes mellitus (75). There is strong evidence that maternal zinc supplementation improves hyperglycemia in diabetic mothers and plays a key role in the regulation of carbohydrate metabolism (73, 76, 77). Furthermore, it also appears that zinc may favorably alter carbohydrate metabolism in patients with zinc deficiency or diseases causing zinc deficiency such as diabetes (78).

Zinc with insulin mimetic and hypoglycemic properties plays an important role in improving peripheral insulin sensitivity and may potentiate insulin-stimulated glucose transport (79). In conclusion, some initial comprehensive, systematic reviews and meta-analyses on the effects of zinc supplementation in GDM mothers demonstrate that zinc supplementation has beneficial effects on glycemic control. However, further studies are required to achieve more definitive results.

11.4.3 Iron

Iron, with its strong pro-oxidant ability and generation of reactive oxygen species, can be involved in oxidative stress and cell injury. Pancreatic beta cells, due to their weak antioxidative defense mechanisms are vulnerable to oxidative stress. However, adequate iron levels are necessary for beta cell function and glucose homeostasis (80). Pregnant women are especially vulnerable to iron deficiency, for this reason they are routinely recommended for iron supplementation. Emerging evidence has raised potential concerns about this routine supplementation. (81). Significant associations have been seen between higher iron stores and disruption of glucose homeostasis and also an increase in the risk of diabetes (82). A comprehensive review in recent years investigated the role of iron in the development of GDM. Data from this study showed that high dietary heme iron is strongly and significantly associated with GDM risk, whereas results with respect to non-heme iron are inconclusive. However, findings do not provide conclusive results regarding the intake of iron supplements and the risk of GDM. These contradictory results between iron supplements and dietary heme iron can be attributed to the fact that the majority of iron supplements contain non-heme iron such as ferrous sulfate, ferric sulfate, and ferrous fumarate (83). Overall, the impact of maternal responses to dietary or supplemental iron on glucose metabolism may be dependent on differences in the mother's underlying iron status and

metabolism. In general it can be said that additional studies should also be investigated for a more definitive conclusion.

11.5 Dietary Fiber

Dietary fibers, including pectin, oat gum, guar gum, resistant starch, and non-digestible oligosaccharides such as fructo-oligosaccharides, galacto-oligosaccharides, trans-oligosaccharides, polyfructan inulin, and lactulose, have been proven to have beneficial effects in the prevention of diabetes (84). Dietary fibers can be divided into insoluble and soluble forms based on their relative solubility in water. Insoluble fibers can bind with carcinogens, mutagens, and other toxic chemicals, and may be involved in reducing the risk of inflammatory disease, colon cancer, malignancies, obesity, diabetes, and cardiovascular disease (85).

Non-digestible fibers are selectively fermented by beneficial microbiota to short-chain fatty acids (e.g. acetate, propionate, and butyrate). Dietary fibers may reduce appetite, delay gastric emptying, and lower total energy intake. The relationship between dietary fiber and glucose homeostasis can be explained by these possible mechanisms (86). Substantial evidence from epidemiologic and clinical studies has demonstrated associations between dietary fiber and dietary glycemic index and load in diabetic patients. Studies on the role of these dietary fibers in the development of GDM are rare (86). A large prospective study of women demonstrated that consumption of dietary total fiber and fruit fiber were significantly and inversely associated with GDM risk (86).

Further to the results of pioneering studies, more research is needed to explore the plausible mechanisms and confirm these findings.

11.6 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) play a key role during pregnancy for both the health of the pregnant woman and for the growth and development of their fetus. PUFAs regulate placental angiogenesis, inflammatory status, oxidative stress levels, and some hormone production (e.g. leptin). It has been proved that a significant decrease in the placental transport of PUFAs has been associated with GDM (87). Previous research has demonstrated that there are different plasma fatty acid profiles in women with and without GDM. This difference can be attributed to possible changes in the metabolism of fatty acids in GDM (88). Animal-based studies indicated that the use of PUFAs as a dietary treatment in pregnant mildly diabetic rats can improve maternal dyslipidemia and fetal overgrowth and can increase the utilization of peripheral glucose (88, 89). Despite increasing evidence regarding the beneficial effects of PUFA treatment on improved insulin sensitivity and glucose metabolism in animals and humans (90, 91), contradictory results in the epidemiological

literature have been reported (92). Overall, there is not enough evidence to support or refute the routine supplementation of PUFAs during pregnancy for the prevention or treatment of GDM and it seems necessary to conduct randomized trials in order to evaluate the role of PUFA supplementation in GDM.

11.7 Conclusion

In recent decades with the advent of hectic life schedules, many women develop gestational diabetes during pregnancy. Nowadays, healthy foods are of greater value than costly medication. Thus, the general availability and use of nutraceuticals are on the rise. Most of the nutraceuticals have been proven to keep diseases away and maintain good health. Nowadays, the accumulated knowledge regarding safe and effective usage of nutraceuticals causes an undoubted challenge for food and pharmacy professionals. However, further studies seem to be necessary for receiving a definite conclusion.

References

1. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care*. 2007;30(Supplement 2):S141–S6.
2. Association AD. Gestational diabetes mellitus. *Diabetes Care*. 2004;27:S88.
3. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care*. 2007;30(Supplement 2):S112–S9.
4. Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. *Jama*. 1997;278(13):1078–83.
5. Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of nutraceuticals in human health. *Journal of Food Science and Technology*. 2012;49(2):173–83.
6. Dillard CJ, German JB. Phytochemicals: nutraceuticals and human health. *Journal of the Science of Food and Agriculture*. 2000;80(12):1744–56.
7. Keservani RK, Sharma AK, Ahmad F, Baig ME. Nutraceutical and functional food regulations in India. *Nutraceutical and Functional Food Regulations in the United States and Around the World*, 2nd Edition. Elsevier; 2014. pp. 327–42.
8. Kailasapathy K. Encapsulation technologies for functional foods and nutraceutical product development. *CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources*. 2009;4(033):1–19.
9. Lippert MC, McClain R, Boyd JC, Theodorescu D. Alternative medicine use in patients with localized prostate carcinoma treated with curative intent. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1999;86(12):2642–8.
10. Malla S, Hobbs JE, Sogah EK. Functional foods and natural health products regulations in Canada and around the world: nutrition labels and health claims. Saskatoon, Saskatchewan, Canada: Report prepared for the Canadian Agricultural Innovation and Regulation Network. 2013:447–54.
11. Kokate C, Purohit A, Gokhale S. *Nutraceutical and Cosmaceutical. Pharmacognosy*, 21st Edition, Pune, India: Nirali Prakashan; 2002. pp. 542–9.
12. Lira LQD, Dimenstein R. Vitamin A and gestational diabetes. *Revista da Associação Médica Brasileira*. 2010;56(3):355–9.

13. Jovanovic-Peterson L, Peterson CM. Vitamin and mineral deficiencies which may predispose to glucose intolerance of pregnancy. *Journal of the American College of Nutrition*. 1996;15(1):14–20.
14. Zempleni J, Suttie JW, Gregory III JF, Stover PJ. *Handbook of Vitamins*: CRC Press; 2013.
15. Tuitoek P, Lakey J, Rajotte R, Ziari S, Tsin A, Basu T. Effect of insulin treatment or zinc supplementation on vitamin A status in streptozotocin-induced diabetic rats. *Journal of Clinical Biochemistry and Nutrition*. 1995;19(3):165–73.
16. Suhail M, Patil S, Khan S, Siddiqui S. Antioxidant vitamins and lipoperoxidation in non-pregnant, pregnant, and gestational diabetic women: erythrocytes osmotic fragility profiles. *Journal of Clinical Medicine Research*. 2010;2(6):266.
17. Krzyzanowska K, Zemany L, Krugluger W, Schernthaner G, Mittermayer F, Schnack C, et al. Serum concentrations of retinol-binding protein 4 in women with and without gestational diabetes. *Diabetologia*. 2008;51(7):1115–22.
18. Stupin J, Arabin B. Overweight and obesity before, during and after pregnancy: part 1: pathophysiology, molecular biology and epigenetic consequences. *Geburtshilfe und Frauenheilkunde*. 2014;74(7):639.
19. Su Y-X, Hong J, Yan Q, Xu C, Gu W-Q, Zhang Y-F, et al. Increased serum retinol-binding protein-4 levels in pregnant women with and without gestational diabetes mellitus. *Diabetes & Metabolism*. 2010;36(6):470–5.
20. Wolf G. Identification of a membrane receptor for retinol-binding protein functioning in the cellular uptake of retinol. *Nutrition Reviews*. 2007;65(8):385–8.
21. Green MH, Green JB, Akohoue SA, Kelley SK. Vitamin A intake affects the contribution of chylomicrons vs. retinol-binding protein to milk vitamin A in lactating rats. *The Journal of Nutrition*. 2001;131(4):1279–82.
22. Garvey WT, Maianu L, Zhu J-H, Hancock JA, Golichowski AM. Multiple defects in the adipocyte glucose transport system cause cellular insulin resistance in gestational diabetes: heterogeneity in the number and a novel abnormality in subcellular localization of GLUT4 glucose transporters. *Diabetes*. 1993;42(12):1773–85.
23. Mahan LK, Raymond JL. *Krause's Food & the Nutrition Care Process-e-book*: Elsevier Health Sciences; 2016.
24. Omdahl JL, Morris HA, May BK. Hydroxylase enzymes of the vitamin D pathway: expression, function, and regulation. *Annual Review of Nutrition*. 2002;22(1):139–66.
25. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *The American Journal of Clinical Nutrition*. 2007;85(6):1586–91.
26. Burris HH, Camargo CA. Vitamin D and gestational diabetes mellitus. *Current Diabetes Reports*. 2014;14(1):451.
27. Dovnik A, Mujezinović FJ. The association of vitamin D levels with common pregnancy complications. *Nutrients*. 2018;10(7):867.
28. Bao W, Song Y, Bertrand KA, Tobias DK, Olsen SF, Chavarro JE, et al. Prepregnancy habitual intake of vitamin D from diet and supplements in relation to risk of gestational diabetes mellitus: a prospective cohort study: 孕前习惯从饮食以及补充剂中摄入的维生素 D 剂量与妊娠糖尿病风险的关系: 一项前瞻性队列研究. *Journal of Diabetes*. 2018; 10(5):373–9.
29. Zhang C, Qiu C, Hu FB, David RM, Van Dam RM, Bralley A, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. *PloS One*. 2008;3(11):e3753.
30. Lacroix M, Battista M-C, Doyon M, Houde G, Ménard J, Ardilouze J-L, et al. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. *Acta Diabetologica*. 2014;51(4):609–16.
31. Al-Ajlan A, Al-Musharaf S, Fouda MA, Krishnaswamy S, Wani K, Aljohani NJ, et al. Lower vitamin D levels in Saudi pregnant women are associated with higher risk of developing GDM. *BMC Pregnancy and Childbirth*. 2018;18(1):86.

32. Weinert LS, Reichelt AJ, Schmitt LR, Boff R, Oppermann MLR, Camargo JL, et al. Serum vitamin D insufficiency is related to blood pressure in diabetic pregnancy. *American Journal of Hypertension*. 2014;27(10):1316–20.
33. Beaulieu C, Kestekian R, Havrankova J, Gascon-Barré M. Calcium is essential in normalizing intolerance to glucose that accompanies vitamin D depletion in vivo. *Diabetes*. 1993;42(1):35–43.
34. Dawodu A, Akinbi H. Vitamin D nutrition in pregnancy: current opinion. *International Journal of Women's Health*. 2013;5:333.
35. Lappas M, Hiden U, Desoye G, Froehlich J, Mouzon SH-d, Jawerbaum A, et al. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. *Antioxidants & Redox Signaling*. 2011;15(12):3061–100.
36. Xita N, Tsatsoulis A. Adiponectin in diabetes mellitus. *Current Medicinal Chemistry*. 2012;19(32):5451–8.
37. Chin KY, Ima-Nirwana S. The role of vitamin E in preventing and treating osteoarthritis-a review of the current evidence. *Frontiers in Pharmacology*. 2018;9:946.
38. Siman CM, Eriksson UJ. Vitamin E decreases the occurrence of malformations in the offspring of diabetic rats. *Diabetes*. 1997;46(6):1054–61.
39. Sobki SH, Al-Senaidy AM, Al-Shammari TA, Inam SS, Al-Gwiser AA, Bukhari SA. Impact of gestational diabetes on lipid profiling and indices of oxidative stress in maternal and cord plasma. *Saudi Medical Journal*. 2004;25(7):876–80.
40. Biri A, Onan A, Devrim E, Babacan F, Kavutcu M, Durak I. Oxidant status in maternal and cord plasma and placental tissue in gestational diabetes. *Placenta*. 2006;27(23):327–32.
41. Yang ZJ. Diet and nutrition interventions prevent gestational diabetes mellitus. *Zhonghua yu fang yi xue za zhi* [*Chinese Journal of Preventive Medicine*]. 2018;52(1):101–6.
42. Ley S, Hanley A, Sermer M, Zinman B, O'connor D. Lower dietary vitamin E intake during the second trimester is associated with insulin resistance and hyperglycemia later in pregnancy. *European Journal of Clinical Nutrition*. 2013;67(11):1154.
43. Maktabi M, Jamilian M, Amirani E, Chamani M, Asemi Z. The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. *Lipids in Health and Disease*. 2018;17(1):163.
44. DiPalma JR, Thayer WS. Use of niacin as a drug. *Annual Review of Nutrition*. 1991;11(1):169–87.
45. Maiese K, Chong ZZ, Hou J, Shang YC. The vitamin nicotinamide: translating nutrition into clinical care. *Molecules*. 2009;14(9):3446–85.
46. Velikiĭ N, Obrosova I, Efimov A, Babicheva E, Sokil O. Nicotinamide coenzymes in the regulation of cellular metabolism in various types of diabetes. *Voprosy Meditsinskoi Khimii*. 1992;38(4):45–52.
47. Shah TZ, Ali AB, Jafri SA, Qazi MH. Effect of Nicotinic Acid (Vitamin B3 or Niacin) on the lipid profile of diabetic and non–diabetic rats. *Pakistan Journal of Medical Sciences*. 2013;29(5):1259.
48. Reasner C. Rational therapy of mixed dyslipidaemia in a patient with diabetes. *The British Journal of Diabetes & Vascular Disease*. 2007;7(1):25–30.
49. Goldberg RB, Jacobson TA, editors. Effects of niacin on glucose control in patients with dyslipidemia. Mayo Clinic Proceedings; 2008: Elsevier.
50. John C, Ramasamy R, Al Naqeeb G, Al-Nuaimi A, Adam A. Nicotinamide supplementation protects gestational diabetic rats by reducing oxidative stress and enhancing immune responses. *Current Medicinal Chemistry*. 2012;19(30):5181–6.
51. Feng J, Li H, Wang X, Huo Y, Liu S, Li L. Nicotinamide phosphoribosyltransferase enhances beta cell expansion during pregnancy. *European Review for Medical and Pharmacological Sciences*. 2016;20(23):4965–71.

52. Polo V, Saibene A, Pontiroli A. Nicotinamide improves insulin secretion and metabolic control in lean type 2 diabetic patients with secondary failure to sulphonylureas. *Acta Diabetologica*. 1998;35(1):61–4.
53. Intakes IoMSCotSEoDR. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*: National Academies Press (US); 1998.
54. Ellis JM, Folkers K, Minadeo M, VanBuskirk R, Xia L-J, Tamagawa H, et al. A deficiency of vitamin B6 is a plausible molecular basis of the retinopathy of patients with diabetes mellitus. *Biochemical and Biophysical Research Communications*. 1991;179(1):615–9.
55. Davis R, Calder J, Curnow D. Serum pyridoxal and folate concentrations in diabetics. *Pathology*. 1976;8(2):151–6.
56. Hamfelt A, Soderhjelm L. Plasma pyridoxal phosphate in diabetics. *The American Journal of Clinical Nutrition* 1984;39(5):841–2.
57. Jovanovic-Peterson L, Peterson CM. Vitamin and mineral deficiencies which may predispose to glucose intolerance of pregnancy. *Journal of the American College of Nutrition*. 1996;15(1):14–20.
58. Bennink H, Schreurs W. Improvement of oral glucose tolerance in gestational diabetes by pyridoxine. *BMJ*. 1975;3(5974):13–5.
59. Makris A, Gershoff SN. Insulin sensitivity in vitamin B6-deficient rats. *Annals of Nutrition and Metabolism*. 1974;16(6):337–51.
60. Toyota T, Kai Y, Kakizaki M, Ohtsuka H, Shibata Y, Goto Y. The endocrine pancreas in pyridoxine deficient rats. *The Tohoku Journal of Experimental Medicine*. 1981;134(3):331–6.
61. Metz TO, Alderson NL, Chachich ME, Thorpe SR, Baynes JW. Pyridoxamine traps intermediates in lipid peroxidation reactions in vivo: evidence on the role of lipids in chemical modification of protein and development of diabetic complications. *Journal of Biological Chemistry*. 2003.
62. Lai JS, Pang WW, Cai S, Lee YS, Chan JK, Shek LP, et al. High folate and low vitamin B12 status during pregnancy is associated with gestational diabetes mellitus. *Clinical Nutrition*. 2018;37(3):940–7.
63. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N, et al. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham offspring study. *Diabetes Care*. 2001;24(8):1403–10.
64. Zhu B, Ge X, Huang K, Mao L, Yan S, Xu Y, et al. Folic acid supplement intake in early pregnancy increases risk of gestational diabetes mellitus: evidence from a prospective cohort study. *Diabetes Care*. 2016;39(3):e36–e7.
65. Krishnaveni G, Hill J, Veena S, Bhat D, Wills A, Karat C, et al. Low plasma vitamin B12 in pregnancy is associated with gestational 'diabesity'and later diabetes. *Diabetologia*. 2009;52(11):2350–8.
66. Knight BA, Shields BM, Brook A, Hill A, Bhat DS, Hattersley AT, et al. Lower circulating B12 is associated with higher obesity and insulin resistance during pregnancy in a non-diabetic white British population. *PLoS One*. 2015;10(8):e0135268.
67. Zheng LD, Linarelli LE, Liu L, Wall SS, Greenawald MH, Seidel RW, et al. Insulin resistance is associated with epigenetic and genetic regulation of mitochondrial DNA in obese humans. *Clinical Epigenetics*. 2015;7(1):60.
68. Sales CH, Pedrosa LD. Magnesium and diabetes mellitus: their relation. *Clinical Nutrition*. 2006;25(4):554–62.
69. Asemi Z, Karamali M, Jamilian M, Foroozanfard F, Bahmani F, Heidarzadeh Z, et al. Magnesium supplementation affects metabolic status and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition*. 2015;102(1):222–9.

70. Fung TT, Manson JE, Solomon CG, Liu S, Willett WC, Hu FB. The association between magnesium intake and fasting insulin concentration in healthy middle-aged women. *Journal of the American College of Nutrition*. 2003;22(6):533–8.
71. Mizuarai S, Irie H, Kotani HJ. Gene expression-based pharmacodynamic biomarkers: the beginning of a new era in biomarker-driven anti-tumor drug development. *Current Molecular Medicine*. 2010;10(6):596–607.
72. Salimi S, Yaghmaei M, Joshaghani H, Mansourian AJ. Study of zinc deficiency in pregnant women. *Iranian Journal of Public Health*. 2004;33(3):15–8.
73. Roshanravan N, Alizadeh M, Hedayati M, Asghari-Jafarabadi M, Alamdari NM, Anari F, et al. Effect of zinc supplementation on insulin resistance, energy and macronutrients intakes in pregnant women with impaired glucose tolerance. *Iranian Journal of Public Health*. 2015;44(2):211.
74. Sharifi F, Hedayati M, Mirmiran P, Mehrabi Y, Azizi F. The serum level of Zinc, Cu, iron in elementary students of 23 province of Iran in 1996. *Iranian Journal of Endocrinology & Metabolism*. 1999;1(4):275–85.
75. Nokhostin F, Bavar A, Hedayati M, Zahedi Asl S, Latifi MJ. The frequency of diabetes in pregnant women with pyelonephritis in Imam Khomeini hospital of Ahwaz (13701382). *Iranian Journal of Endocrinology & Metabolism*. 2005;7(4):325–9.
76. Genova MP, Atanasova B, Todorova-Ananieva K, Velisarova M, Hristova J, Tzatchev KJ, et al. Zinc and insulin resistance in pregnancy complicated with gestational diabetes. *International Journal of Health Sciences*. 2016;6(12):191–7.
77. Karamali M, Heidarzadeh Z, Seifati S-M, Samimi M, Tabassi Z, Talaee N, et al. Zinc supplementation and the effects on pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Experimental and Clinical Endocrinology & Diabetes*. 2016;124(01):28–33.
78. Jayawardena R, Ranasinghe P, Galappatthy P, Malkanthi R, Constantine G, Katulanda P, et al. Effects of zinc supplementation on diabetes mellitus: a systematic review and meta-analysis. *Diabetology & Metabolic Syndrome*. 2012;4(1):13.
79. Tang X-h, Shay NF. Zinc has an insulin-like effect on glucose transport mediated by phosphoinositol-3-kinase and Akt in 3T3-L1 fibroblasts and adipocytes. *Journal of Nutrition*. 2001;131(5):1414–20.
80. Hansen JB, Moen I, Mandrup-Poulsen T. Iron: the hard player in diabetes pathophysiology. *Acta Physiologica*. 2014;210(4):717–32.
81. Obstetricians ACo, Obstetrics G. ACOG practice bulletin No. 95: anemia in pregnancy. *Obstetrics and Gynecology*. 2008;112(1):201.
82. Montonen J, Boeing H, Steffen A, Lehmann R, Fritsche A, Joost H-G, et al. Body iron stores and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *Diabetologia*. 2012;55(10):2613–21.
83. Zhang C, Rawal SJ. Dietary iron intake, iron status, and gestational diabetes. *The American Journal of Clinical Nutrition*. 2017;106(suppl_6):1672S–80S.
84. Shin D, Lee KW, Song WO. Dietary patterns during pregnancy are associated with risk of gestational diabetes mellitus. *Nutrients*. 2015;7(11):9369–82.
85. Theuwissen E, Mensink RP. Water-soluble dietary fibers and cardiovascular disease. *Physiology & Behavior*. 2008;94(2):285–92.
86. Zhang C, Liu S, Solomon CG, Hu FB. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. *Diabetes Care*. 2006;29(10):2223–30.
87. Araújo JR, Keating E, Martel F. Polyunsaturated fatty acids and gestational diabetes. *Nutrition and Diet in Maternal Diabetes*: Springer; 2018. pp. 451–63.
88. Lardinois CK, Starich GH. Polyunsaturated fats enhance peripheral glucose utilization in rats. *Journal of the American College of Nutrition*. 1991;10(4):340–5.
89. Capobianco E, Fornes D, Roberti SL, Powell TL, Jansson T, Jawerbaum A. Supplementation with polyunsaturated fatty acids in pregnant rats with mild diabetes normalizes placental PPARγ and mTOR signaling in female offspring developing gestational diabetes. *The Journal of Nutritional Biochemistry*. 2018;53:39–47.

90. Zhou SJ, Yelland L, McPhee AJ, Quinlivan J, Gibson RA, Makrides MJ. Fish-oil supplementation in pregnancy does not reduce the risk of gestational diabetes or preeclampsia. *The American Journal of Clinical Nutrition*. 2012;95(6):1378–84.
91. Flachs P, Rossmeisl M, Kopecky J. The effect of n-3 fatty acids on glucose homeostasis and insulin sensitivity. *Physiological Research*. 2014;63:S93.
92. Bo S, Menato G, Lezo A, Signorile A, Bardelli C, De Michieli F, et al. Dietary fat and gestational hyperglycaemia. *Diabetologia*. 2001;44(8):972–8.

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12

The Role of Nutraceuticals in Depression during Pregnancy and Postpartum Well-Being

Reza Amani and Shirin Amini

Contents

12.1 Introduction

Depression is a mood disorder with significant disability and mortality in people worldwide (1). The prevalence of depression in the world is about 10–15% and is twice as high in women as in men. Women, between the ages of 25 and 44, may have experienced depression during times of hormonal change including menstruation, prenatal and postpartum (2–4). During pregnancy and lactation, some nutrients are more needed compared with non-pregnant women. Hence, it may be difficult to meet these needs by a normal diet and the maternal stores can be decreased (2). In the last decade, studies have assessed the role of nutraceuticals in the prevention and/or treatment of mood disorders in women and have reported that some nutraceuticals may be involved in the regulation of brain serotonin through their effects on the proper function of the thyroid, the hypothalamic–pituitary–adrenal (HPA) axis, and the immune system(2).

12.2 Definitions

12.2.1 Depression during Pregnancy

Depression during pregnancy is a prevalent mood disorder that affects 10% to 20% of pregnant women (5). This disorder is identified by persistent sadness, sleeping disorders, loss of interest in life events, anxiety, and feelings of worthlessness and guilt (6).

12.2.2 Postpartum Depression

Postpartum depression (PPD) is a major depressive disorder that onsets within 4 weeks of delivery and may be continued to 12 months after childbirth (7). This disorder is identified by irritability, hopelessness, tearfulness, fatigue, sleeping disorders, poor memory, disinterest in life events, feelings of inadequacy, and inability to care for the child (8).

12.3 Epidemiology

Pre- and postnatal depression are prevalent mood disorders that occur in 10% and 13% of women worldwide in pregnancy and after childbirth, respectively (9). Evidence indicates that, in developing countries, these mental disorders are higher, i.e. 15.6% and 19.8% during pregnancy and after delivery, respectively (10). Recent studies estimated approximately 8.5% of women in Canada, 5–13% in Denmark, and 13–36% in Chile and Brazil experience clinical symptoms of PPD in the first month after childbirth (1). In Asian countries, the highest prevalence of PPD was reported as 63% in Pakistan and the lowest rate was 3% in Malaysia (11).

12.4 Pathophysiology

Although psychological, biological, and environmental factors are involved in depression, the exact pathophysiology of depression pre- and postdelivery remains unclear. Evidence has suggested that several different mechanisms are involved in prenatal depression (2). Firstly, fluctuations in levels of hormones such as estrogen and progesterone, influenced by the HPA axis, regulate the serotonin (5-HT) system, thyroid hormones, and proinflammatory biomarkers, through which, they may play role in this mood disorder (4).

Secondly, hyperactivation of the HPA axis during pregnancy, which results from placental production of corticotropin-releasing hormone (CRH), if continued persistently, leads to increased levels of glucocorticoids (4). Some evidence showed that increased levels of glucocorticoids may increase the risk of depressive disorders, through their effect on neuronal transmission and synaptic plasticity (12). Thirdly, estradiol, which rises greatly during pregnancy and enhances neurotransmitter function and serotonin levels and then drops sharply immediate after childbirth, may affect the mood balance. This event has a great impact on the monoamine-rich regions of the brain that can modulate the mood (4).

Fourthly, the neurotrophin family, particularly the brain-derived neurotrophic factor (BDNF), which binds with the tropomyosin receptor kinase B (TrkB) receptor, and the nerve growth factor (NGF), which binds with the tropomyosin receptor kinase A receptor, are important in the protection, survival, and proper function of the synaptic cell in the central and peripheral nervous systems (13, 14). Low concentrations of some nutraceuticals increase downregulation of neurotrophic factors and may, therefore, increase depressive symptoms (2).

Finally, in some studies, the levels of thyroid hormones have been positively associated with serotonin levels, giving rise to the proposition that thyroid dysfunction during pregnancy and/or declined levels of T3 and T4 in postpartum may lead to depressive disorder (4) (Figure 12.1).

12.5 Risk Factors for Depression during Pregnancy and Postpartum

A history of previous depression, recent psychological stress, the mother's age, inadequate socioeconomic support, a poor marital relationship, or an unwanted pregnancy are risk factors that affect maternal mood during pregnancy and postpartum (3, 6). Inadequate nutrition and micronutrient deficiencies have also been considered as other risk factors for depression in this period. Studies showed nutritional status has an important role in the appropriate function of neurotrophin family, HPA axis, and immune system (6, 16) (Figure 12.2).

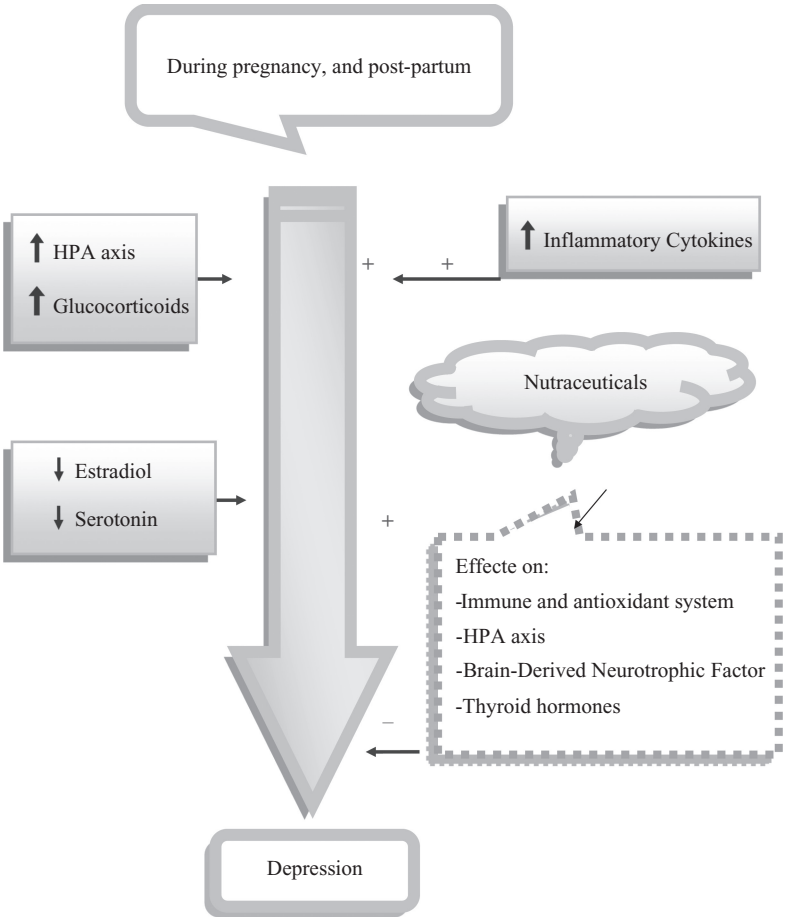

Figure 12.1 *Etiology of prenatal depression (2, 4, 15).*

12.6 Effective Nutraceuticals in the Prevention and Treatment of Prenatal Depression

12.6.1 Omega-3 Fatty Acids

Linolenic (18:3n-3) and linoleic acid (18:2n-6) acids, are polyunsaturated fatty acids (PUFAs) that humans cannot synthesize through a de novo pathway (17) and, hence, they are called essential fatty acids (EFAs). They need to be obtained from dietary sources. Linolenic acid is mainly found in the forms of alpha-linolenic acid (ALA; 18:3n-3) in plant oils (e.g. canola oil), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3), and in fish and other seafoods (17, 18).

Evidence demonstrates that EPA and DHA exert critical roles in brain development and function (19). During pregnancy and lactation, the need for omega-3

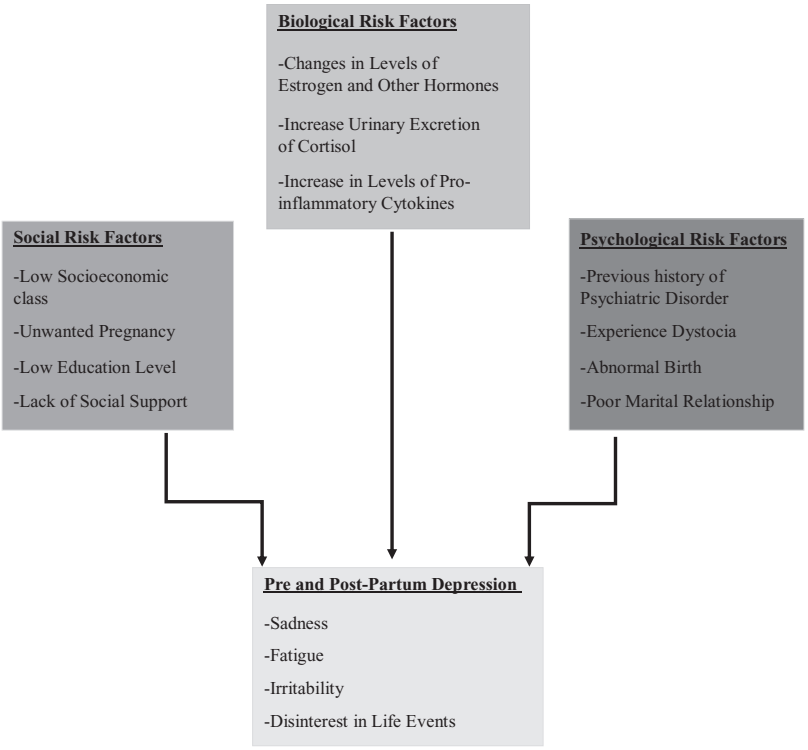

Figure 12.2 *Risk factors associated with prenatal depression (2, 6).*

fatty acids increases due to increased transmission of DHA and EPA to the fetus and infant (20). PUFAs are one of the structural components of phospholipids in the neuronal membranes of the brain cells. The major fatty acid found in the brain cells is DHA. By increasing the concentration of DHA in the membrane, the sensitivity of the serotonin receptors increases (21).

Omega-3 fatty acid deficiency is linked to the increased occurrence of depression in prenatal period in follow-up studies (22, 23). Some studies suggested that n-3 PUFA may be effective in prevention and/or treatment of depressive symptoms in women (22, 24, 25), but, up to now, there have not been adequate high-quality clinical trials assessing the effect of DHA and EPA in the treatment of depression in the pre- and postpartum periods.

There are three mechanisms proposed to explain the inverse relationship between n-3 PUFA and depressive symptoms (21). The first mechanism is a psychoneuroimmunological hypothesis that demonstrates n-3 PUFA can inhibit the synthesis of pro-inflammatory cytokines and eicosanoids and, hence, reduce inflammation (22, 24). The second is a neuronal hypothesis that explains n-3 PUFAs regulate and facilitate the metabolism of serotonergic neurotransmitters, both playing a significant role in lowering clinical symptoms of depression (21). Finally, n-3 PUFAs play a role in the production of specific

leukotrienes and prostaglandins with a vasodilatory action that inhibits platelets aggregation (21, 22) (Table 12.1).

Overall, considering the health effect of EPA and DHA on the fetus and mother dyad, only scarce randomized controlled trials (RCTs), with contradictory results, are available in this area, and the World Health Organization (WHO) recommendation in which women need to use 250–500 mg/day of n-3 PUFA (about 1–2 servings of fish/week) for a healthy pregnancy and postpartum period seems appropriate (30, 31).

12.6.2 Vitamin D

Vitamin D is a fat-soluble neurosteroid molecule and its serum levels in the body are linked to sunlight exposure and diet (32). In recent decades, vitamin D deficiency (VDD) is a prevalent micronutrient deficiency among women of reproductive age (32, 33). This may result from reduced sunlight exposure and a decreasing rate of vitamin D-rich foods consumption. Among the foods, fish oil contains significant amounts of vitamin D while dairy products and eggs contain lower amounts (32, 33).

Evidence demonstrates that vitamin D plays a part in brain development and function (34, 35), and VDD is linked to increased occurrence of depression (36). Several follow-up studies reported that low concentrations of serum 25 hydroxy vitamin D (25[OH]D) during pregnancy and postpartum could increase the risk of pre- and postpartum depression (37–40). In one study, supplementation with 2,000 IU vitamin D3 daily for 12 weeks in pregnant women until childbirth significantly prevented PPD ($p < 0.001$) (41). Moreover, in a recent study, supplementation with 50,000 IU vitamin D3 fortnightly for a period of 8 weeks was shown to decrease clinical symptoms of depression in patients with PPD ($p < 0.006$) (42). Several biological mechanisms have been proposed explaining vitamin D could affect brain development and neuronal function and reduce the risk of depression during pregnancy and at postpartum (43):

1- Vitamin D inhibits NF-κB (nuclear factor kappa light chain enhancer of activated B cells) activation in macrophages, so decreases the production of pro-inflammatory cytokines (44, 45).
2- The active form of vitamin D enhances glutathione function in the brain and lowers oxidative degeneration in neurons (45).
3- If high levels of glucocorticoid stimulate the hippocampal cell for a long period, apoptosis occurs in this area. Vitamin D affects the HPA axis and decreases the production of glucocorticoids, thus, preventing apoptosis in the hippocampal cells (46).

Overall, up to now, few RCTs are available in this area and as women usually have modest sun exposure during pregnancy and the postpartum period, this recommendation might logically indicate to be appropriate to use the dose of 1,000 to 2,000 IU per day to reduce the risk of depression during this period (43).

Table 12.1 Summary of Studies of Supplementation with EPA and DHA in the Treatment of Pre- and Postpartum Depression

Study (year)	Dose	n	Design	Duration of trial	Result
Llorente et al. (26) (2003)	200 mg DHA	138	Randomized double-blind clinical trial	4 months (starting after childbirth)	No significant differences were observed in the mean EPDS* scores between omega-3 fatty acids and placebo groups
Marangell et al. (24) (2004)	2.96 g/day EPA and DHA	7	Open-label	Variable,starting at 34–36 weeks of pregnancy	No significant differences were observed in the mean EPDS scores between DHA and placebo groups
Freeman et al.(27) (2006)	1.9 g/day EPA and DHA	15	Open-label, flexible dose	59 days in pregnancy	About 50% decrease was observed in mean EPDS scores
Freeman et al. (25) (2006)	0.5 g/day, 1.4 g/day, or 2.8 g/day EPA and DHA	16	Randomized double-blind clinical trial	8 weeks in postpartum	No significant differences were observed between three groups overall a 51.5% decrease was observed in mean EPDS scores
Freeman et al. (28) (2008)	1.9g/day EPA and DHA	51	Randomized double-blind clinical trial	8 weeks	No significant differences were observed in mean EPDS scores between omega-3 fatty acids and placebo groups
Mozurkewich et al. (19) (2013)	900 mg DHA + 180 mg EPA or 274 mg DHA + 1,060 mg EPA	118	Double-blind, randomized controlled trial	Early pregnancyuntil 26–28 weeks, 34–36 weeks, and 6–8 weeks after delivery	No significant differences were observed in mean BDI** scores in any of the 3 times that were assessed after supplementation
Dos Santos et al. (29) 2017	1.08 g EPA + 0.72 g DHA	60	Double-blind, randomized controlled trial	16 weeks	Daily supplementation with EPA and DHA had no significant effect on mean EPDS scores during the prenatal period

* EPDS, Edinburgh Postnatal Depression Scale; **BDI, Beck Depression Inventory

12.6.3 Vitamin A

Vitamin A is a fat-soluble molecule that particularly found in cod liver oil, fish, and eggs.

Fortified milk, butter, and cheese are other rich sources of retinoids (47). Evidence suggests that high levels of vitamin A and its derivatives, particularly retinoids, are linked to increases in the risk of depressive symptoms (47). Serum concentrations of retinol-binding protein (RBP) could be a predictor of depression in pregnancy and the first week after childbirth (48). Researchers proposed that high vitamin A accumulates in the brain, breast, and liver and may potentially be toxic in late pregnancy (49). The excess accumulation of vitamin A in the liver can impair the secretion and mobilization of RBP, hence increased serum concentrations of circulating retinyl esters and retinoic acids may cause depression (49, 50).

Considering the retinoid toxicity hypothesis, researchers proposed the theory that breastfeeding may decrease the occurrence of PPD, secondary to reduced stores of vitamin A in women's bodies (50).

12.6.4 B Vitamins

B vitamins (B1, B2, B3, B6, B9, and B12) are a family of water-soluble molecules with similar structures. These vitamins are found in unprocessed foods, especially B1, B3, and B6 in unprocessed cereals, B2 in dairy products, B9 in beans and green leafy plants, and B12 in animal foods (e.g. eggs and meats) (2). B vitamins act as coenzymes in the function of the nervous system (2). In previous studies, depressive symptoms have been linked to high serum concentrations of homocysteine. B vitamins influence the serum concentrations of pro-inflammatory amino acid homocysteine (51). B9 and B12 convert homocysteine to methionine (an essential amino acid), and B6 helps convert homocysteine into cysteine (52, 53). High levels of homocysteine as a result of low B vitamins levels (B9, B6, and B12) have been linked to major depressive disorder (MDD) (54). Low levels of B12 are correlated with depressive symptoms in the elderly (55). Moreover, low concentrations of B9 in RBCs are correlated with moderate to severe depression in adolescents (56) and non-pregnant women of reproductive age (57). Folate plays a role in sustained normal concentrations of tetrahydrobiopterin (an important cofactor in the synthesis of catecholamines and serotonin) in the brain (2).

Up to now, little research has assessed the relation between dietary intake, serum concentration of B vitamins, and depressive symptoms in pregnancy and postpartum (58). A cohort study found no correlation between serum levels of vitamin B9 in the third day of postpartum and PPD symptoms at 1, 2, and 3 months after childbirth (59). Another prospective study investigated the dietary intake of B vitamins by use of an FFQ during pregnancy and observed an inverse association only between the amount of B2 intake and the occurrence of PPD (58).

Most work done in this area has been cross-sectional, and cohort studies indicate that the correlation between B vitamin levels and depression in pregnancy and postpartum is not strong. Therefore, more longitudinal researches are needed and, currently, there is no recommendation for taking these vitamins to prevent depression throughout the pregnancy and postpartum period.

12.6.5 Zinc (Zn)

Zinc (Zn) is a trace element that is particularly found in red meat, seeds. and beans. Zn functions in immune and central nervous systems (60, 61). Studies demonstrated that Zn deficiency is linked to depressive symptoms in women (62, 63). In a cohort study on pregnant women, low levels of Zn were associated with the severity of PPD symptoms (64). Moreover, the result of a pilot study suggested that 7 mg of Zn daily for 10 weeks could improve depressive symptoms in young women (62).

Low levels of Zn may affect depression probably via three mechanisms. Firstly, Zn deficiency increases the production of NF-κB and modifies the balance between anti- and pro-inflammatory cytokines (65). Secondly, low levels of Zn alter the number of T and B cells and therefore contribute to immunosuppression (66). Finally, Zn is involved in the regulation of NMDA/glutamate pathway (67).

Presumably Zn deficiency contributes to mood disorders through a neuronal mechanism. The normal concentrations of Zn in hippocampal neurons may contribute to glutamate release from synaptic vesicles of these neurons (2, 67).

Low concentrations of Zn in the brain augment the down-regulation of BDNF and its receptor TrkB in the hippocampus (68). BDNF is one of the growth factors that exerts proper function of synaptic neurons in the brain and down-regulation of BDNF is linked to the pathophysiology of depressive symptoms (69).

12.6.6 Iron (Fe)

Iron is a trace element that is particularly found in liver, red meat, seeds, and beans. Iron-deficiency anemia is a common health problem prevalent among women during pregnancy and postpartum (70). Iron deficiency is associated with fatigue and poor general health in women (71, 72). Evidence proposed that low iron status can lead to thyroid malfunction. Thyroid peroxidase is a heme enzyme that requires iron for its function (73). The findings on the relationship between anemia and prenatal depression are controversial (44, 74). Several observational studies have reported that iron deficiency in pregnancy is associated with depressive symptoms in women (75–77). Also, low hemoglobin levels were risk factors for the occurrence of PPD in Saudi women (74). However, studies in the UK and China showed no relationship between maternal iron status and depressive symptoms (78, 79). Probably differences

between studies in terms of measuring iron status, severity of depression, genetic background of participants, timing, and study design may contribute to the inconsistent results obtained. Further studies are needed to demonstrate whether iron supplementation can reduce the severity of depression during pregnancy and postpartum. Although the results of the studies in this area are inconsistent, when considering the impacts of iron deficiency in health problems (70), the current Dietary Reference Intakes (DRI) recommendation is that it seems appropriate for women to have an additional daily iron intake of 27 mg/day for pregnancy and 9 mg/day for breastfeeding in order to reduce the risk of depressive disorders during these periods (80).

12.6.7 Selenium

Selenium is an essential trace element that is particularly found in seafood and organ meats such as kidney, liver, red meat, and also poultry. Muscle meats, cereals, and dairy products are other rich sources of selenium (81). Evidence has demonstrated that a diet with high levels of selenium can significantly improve mood disorders (82). Low levels of selenium may alter concentrations of neurotransmitters in the brain. Thyroid dysfunction may also affect mood and behavior. Selenium is required in thyroid hormone metabolism such as synthesis and activation stages (82). Moreover, selenium functions in the protection of the brain against oxidative damage (83). Glutathione peroxidase is a selenoprotein with antioxidant activity that protects the nerves and brain tissue from damage by scavenging hydrogen peroxides, i.e., eliminating their actions (82, 84).

The results of one study demonstrated that a history of prenatal depression in pregnancy increased the occurrence of PPD symptoms, while the consumption of selenium supplements in the prenatal period decreased depressive symptoms (85). Another clinical trial showed that the consumption of 100 μg/day of selenium in the first trimester of pregnancy until delivery significantly decreased depressive symptoms (86). The effect of selenium on women's behavior is not as well assessed, however, as the effects of other micronutrients, such as omega-3, vitamin D, zinc, and folate, therefore it seems prudent to follow the current DRI for selenium.

12.6.8 Flavonoids

Flavonoids are a group of phenolic compounds with biological activities that are found in plants. Up to now, about 5,000 types of flavonoids have been identified and, based on their chemical structure, can be classified as flavonoids, flavanones, flavones, anthocyanidins, and isoflavones (87). Animal and *in vitro* studies have suggested that flavonoids have antioxidative, neuroprotective, and antidepressant properties (87, 88).

Evidence has demonstrated that some flavonoids have shown therapeutic effects on behavioral disorders in animal studies by three mechanisms including reducing the levels of pro-inflammatory cytokine in the brain (89, 90) and

by affecting both neurotrophic factors (91–95) and neurotransmitters (dopaminergic, serotonergic, and noradrenergic systems) (89, 92, 94). Moreover, these phenolic compounds protect the brain against the destructive effects of free radicals as antioxidant agents (89, 90, 95). Some flavonoids suggested as neuroprotective in animal studies are described in Table 12.2.

Despite the positive effects on reducing depressive symptoms in animal studies, possible side effects, toxicity, and pharmacological interactions with other substances in long-term consumption have been proposed and, hence, the use of flavonoids needs to be assessed in clinical trials (96).

12.6.9 Astaxanthin

Carotenoids are a group of organic pigments with biological activities found in plants and algae (97). The role of carotenoids on women's behavior has not been as well assessed as that of other nutraceuticals. The results of several animal studies have suggested that trans-astaxanthin, a carotenoid that is a strong antioxidant, rich in algae, can decrease depressive symptoms (98, 99). The mechanism of trans-astaxanthin's action may be based on its effect on the serotonergic system (99) and inhibition of hippocampal inflammation (98). Trans-astaxanthin can help increase the serotonin/tryptophan ratio and decrease the kynurenine/tryptophan ratio in the frontal cortex and hippocampus in the brain (99). Astaxanthin may inhibit 5-alpha reductase (an enzyme that converts testosterone to dihydrotestosterone) (100).

Although no serious adverse effects of astaxanthin supplementation have been reported up to now, safe doses of astaxanthin have not been determined in pregnant or breastfeeding women. Hence, is not recommended in pregnancy and breastfeeding due to the lack of sufficient evidence (100).

12.6.10 Probiotics

Microbial dysbiosis is linked to mood and neuropsychiatric disorders by increased oxidative stress and the concentration of pro-inflammatory cytokines, gastrointestinal disorders, and lowered micronutrient absorption (101).

Probiotics are live beneficial microorganisms that are found particularly in fermented dairy foods. The consumption of these beneficial organisms enhances gut microbiota, which yields health benefits for the host (102). Several studies suggested that probiotics may improve mood disorders (103, 104) and might be used as adjuvant therapy in depression (105). The effects of *Bifidobacterium* and *Lactobacillus* strains on mental health have been assessed and have demonstrated that these two microorganisms have beneficial effects on the brain (106). A current study has assessed supplementation with the probiotic *Lactobacillus rhamnosus*, using a dose of 6×10^9 colony-forming units (cfu) daily from 14 to 16 weeks' gestation until delivery, and from childbirth up to 6 months of postpartum in breastfeeding mothers. The results of this study

Table 12.2 Summary of Results from Animal Studies on Flavonoids in Treatment of Prenatal Depression

Flavonoids	Dose and duration of treatment	Effects	Mechanism of action	References
Hesperidin	50mg/kg for 2 weeks 0.01, 0.1, 0.3, and 1 mg/kg for 3 weeks	Increased the concentrations of BDNF in the hippocampus area in mice	Effects on the 5-HT1A receptors,dopaminergic, serotonergic and noradrenergic systems Effects on the neurotrophic factors and neurotransmitter systems	Antunes et al. 2016 (92) Donato et al. 2014 (94)
Naringenin	5, 10, and 20 mg/kg for 3 weeks	Increased the concentrations of BDNF in the hippocampus area in mice	Effects on the neurotrophic factors and neurotransmitter systems	Yi et al. 2014 (91)
Quercetin	50 mg/kg for 3 weeks	Decreased depressive symptoms, particularly in diabetic rats	Antioxidative actions, reduction levels of pro-inflammatory cytokine in the brain	Demir et al. 2016 (90)
Silymarin	100 and 200 mg/kgfor 2 weeks	Increased the concentrations of 5-HT and BDNF in the hippocampus and cerebralcortex area in mice	Antioxidative actions, reduced levels of pro-inflammatory cytokine in the brain, effects on the neurotransmitter systems	Thakare et al. 2017 (89)
7,8-Dihydroxyflavone	1, 3, and 10 mg/kg,60 min before test	Increased the concentrations of BDNF in the hippocampus and prefrontal cortex area in mice	As TrkB* agonist can stimulate neurogenesis in the hippocampus area Antioxidative actions	Zhang et al. 2014 (95)
Apigenin	20 mg/kg and 40 mg/kgfor 3 weeks	Increased the concentrations of BDNF in the hippocampus area in mice	Effects on the neurotrophic factors	Weng et al. 2016 (93)

* TrkB, tropomyosin receptor kinase B

have suggested that *Lactobacillus rhamnosus* can significantly decrease the prevalence of depression in prenatal period (107).

Several mechanisms are proposed explaining that probiotics may play role in the reduction of depressive symptoms through changes in the expression of the neurotransmitter gamma aminobutyric acid (GABA) receptors in the brain (108) and/or changes in HPA axis function (109). Moreover, infant colic is associated with higher maternal depression scores, as shown in previous studies. The hypothesis was proposed that supplementation with probiotics can improve maternal mood through reduced infant colic (107). Figure 12.3 depicts a summary of nutraceuticals that may a exert preventive role in prenatal depression.

12.7 Summary

- Pre- and postnatal depression are prevalent mood disorders among women.
- Some nutrients are more useful for women during pregnancy and lactation, compared with non-pregnant women.

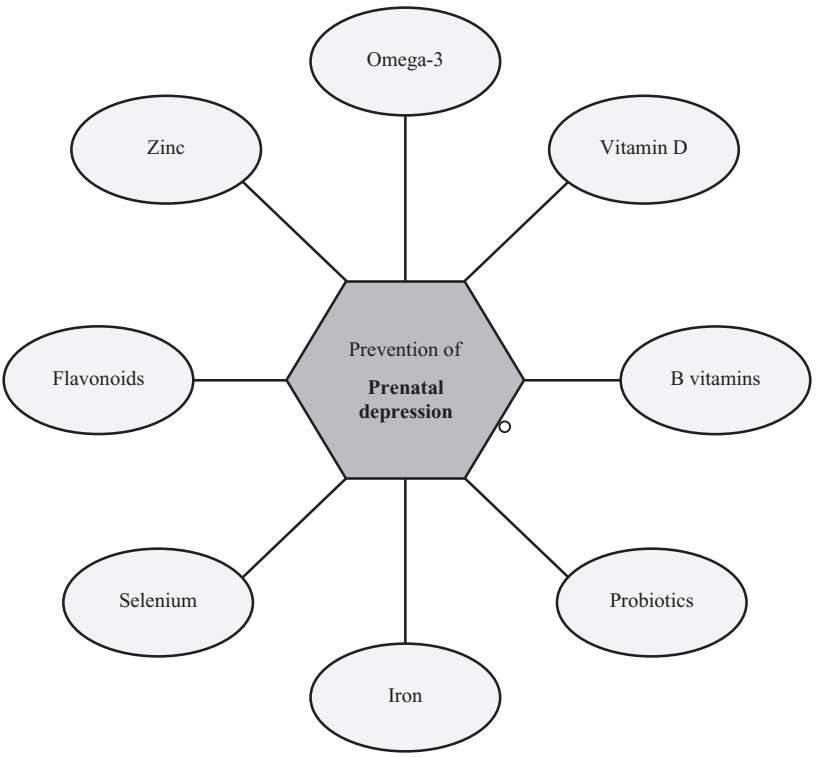

Figure 12.3 *Summary of nutraceuticals with a possible preventive role in prenatal depression.*

- EPA and DHA play important roles in brain development and function.
- Low concentrations of serum 25[OH]D during pregnancy and postpartum could increase the risk of prenatal depression.
- During pregnancy, an inverse association between the amount of B2 intake and the occurrence of PPD was observed.
- In pregnant women, low levels of Zn are associated with the severity of PPD symptoms.
- Iron deficiency in pregnancy may be associated with depressive symptoms.
- Selenium can improve mood disorders.
- Serum concentrations of RBP may be a predictor of depression in pregnancy and the first week after childbirth.
- Some flavonoids have shown therapeutic effects on the treatment of behavioral disorders in animal studies.
- Several studies suggested that probiotics may improve mood disorders

12.8 Future Research

Clinical and preclinical data have proven the role of some nutraceuticals in the prevention and/or treatment of depression during pregnancy and postpartum, however, up to now many questions in this area, such as the duration and doses of treatment with nutraceuticals, remain unanswered and require further research. In addition, more studies are warranted to examine the possible effects of other nutraceuticals on prenatal depression. For example, certain serum levels of vitamins and micronutrients in the human body may be associated with the occurrence of prenatal depression. In addition, some antioxidants and functional foods may play a role in the prevention and treatment of maternal mood disorders.

References

1. Lanes A, Kuk JL, Tamim H. Prevalence and characteristics of postpartum depression symptomatology among Canadian women: a cross-sectional study. *BMC Public Health*. 2011;11(1):302.
2. Ellsworth-Bowers E, Corwin E. Nutrition and the psychoneuroimmunology of postpartum depression. *Nutrition Research Reviews*. 2012;25(1):180–92.
3. Hosseini SH, Naghibi AA, Khademlou M. Post partum depression and its relationship with some related factors. *Journal of Babol University of Medical Sciences*. 2008;10(2):76–81.
4. Hendrick V, Altshuler LL, Suri R. Hormonal changes in the postpartum and implications for postpartum depression. *Psychosomatics*. 1998;39(2):93–101.
5. Yonkers KA, Vigod S, Ross LE. Diagnosis, pathophysiology, and management of mood disorders in pregnant and postpartum women. *Focus*. 2012;10(1):51–66.
6. Rasmussen M-LH, Strøm M, Wohlfahrt J, Videbech P, Melbye M. Risk, treatment duration, and recurrence risk of postpartum affective disorder in women with no prior psychiatric history: a population-based cohort study. *PLoS Medicine*. 2017;14(9):e1002392.

7. American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., (DSM-5). Washington, DC: American Journal of Psychiatry Associat. Association. 143–47.
8. Beck CT. State of the science on postpartum depression: what nurse researchers have contributed—Part 1. *MCN: The American Journal of Maternal/Child Nursing*. 2008;33(2):121–6.
9. Nielsen NO, Strøm M, Boyd HA, Andersen EW, Wohlfahrt J, Lundqvist M, et al. Vitamin D status during pregnancy and the risk of subsequent postpartum depression: a case-control study. *PloS one*. 2013;8(11):e80686.
10. Fisher J, Mello MCd, Patel V, Rahman A, Tran T, Holton S, et al. Prevalence and determinants of common perinatal mental disorders in women in low-and lower-middle-income countries: a systematic review. *Bulletin of the World Health Organization*. 2012;90:139–49.
11. Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. *Infant Behavior and Development*. 2010;33(1):1–6.
12. Dantzer R, Wollman E, Vitkovic L, Yirmiya R. Cytokines and depression: fortuitous or causative association? *Molecular Psychiatry*. 1999;4(4):328–32.
13. Numakawa T, Richards M, Nakajima S, Adachi N, Furuta M, Odaka H, et al. The role of brain-derived neurotrophic factor in comorbid depression: possible linkage with steroid hormones, cytokines, and nutrition. *Frontiers in Psychiatry*. 2014;5:136.
14. Gazal M, Motta LS, Wiener CD, Fernandes JC, Quevedo LÁ, Jansen K, et al. Brain-derived neurotrophic factor in post-partum depressive mothers. *Neurochemical Research*. 2012;37(3):583–7.
15. Boufidou F, Lambrinoudaki I, Argeitis J, Zervas IM, Pliatsika P, Leonardou AA, et al. CSF and plasma cytokines at delivery and postpartum mood disturbances. *Journal of Affective Disorders*. 2009;115(1):287–92.
16. Bloch M, Rotenberg N, Koren D, Klein E. Risk factors for early postpartum depressive symptoms. *General Hospital Psychiatry*. 2006;28(1):3–8.
17. Hibbeln JR, Davis JM. Considerations regarding neuropsychiatric nutritional requirements for intakes of omega-3 highly unsaturated fatty acids. *Prostaglandins, Leukotrienes and Essential Fatty Acids*. 2009;81(23):179–86.
18. Mahan LK, Raymond JL. *Krause's Food & the Nutrition Care Process-e-book*. 14 th ed. Philadelphia: Elsevier Health Sciences; 2016.
19. Mozurkewich EL, Clinton CM, Chilimigras JL, Hamilton SE, Allbaugh LJ, Berman DR, et al. The mothers, omega-3, and mental health study: a double-blind, randomized controlled trial. *American Journal of Obstetrics and Gynecology*. 2013;208(4):313. e1–. e9.
20. Campoy C, Escolano-Margarit MV, Anjos T, Szajewska H, Uauy R. Omega 3 fatty acids on child growth, visual acuity and neurodevelopment. *British Journal of Nutrition*. 2012;107(S2):S85–S106.
21. Su K-P. Biological mechanism of antidepressant effect of omega–3 fatty acids: how does fish oil act as a 'mind-body interface'? *Neurosignals*. 2009;17(2):144–52.
22. Sontrop J, Campbell MK. ω-3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. *Preventive Medicine*. 2006;42(1):4–13.
23. Markhus MW, Skotheim S, Graff IE, Frøyland L, Braarud HC, Stormark KM, et al. Low omega-3 index in pregnancy is a possible biological risk factor for postpartum depression. *PloS one*. 2013;8(7):e67617.
24. Marangell LB, Martinez JM, Zboyan HA, Chong H, Puryear LJ. Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depression and Anxiety*. 2004;19(1):20–3.
25. Freeman MP, Hibbeln J, Wisner K, Brumbach B, Watchman M, Gelenberg A. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatrica Scandinavica*. 2006;113(1):31–5.

26. Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *American Journal of Obstetrics and Gynecology*. 2003;188(5):1348–53.
27. Freeman MP, Hibbeln JR, Wisner KL, Watchman M, Gelenberg AJ. An open trial of Omega-3 fatty acids for depression in pregnancy. *Acta Neuropsychiatrica*. 2006;18(1):21–4.
28. Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *Journal of Affective Disorders*. 2008;110(12):142–8.
29. dos Santos Vaz J, Farias DR, Adegboye ARA, Nardi AE, Kac G. Omega-3 supplementation from pregnancy to postpartum to prevent depressive symptoms: a randomized placebo-controlled trial. *BMC Pregnancy and Childbirth*. 2017;17(1):180.
30. Kris-Etherton PM, Grieger JA, Etherton TD. Dietary reference intakes for DHA and EPA. *Prostaglandins, Leukotrienes and Essential Fatty Acids*. 2009;81(23):99–104.
31. Marangoni F, Cetin I, Verduci E, Canzone G, Giovannini M, Scollo P, et al. Maternal diet and nutrient requirements in pregnancy and breastfeeding. An Italian consensus document. *Nutrients*. 2016;8(10):629.
32. Holick MF. Vitamin D deficiency. *New England Journal of Medicine*. 2007;357(3):266–81.
33. Heaney RP, Weaver CM. Calcium and vitamin D. Endocrinology and Metabolism Clinics. 2003; 32(1):181–94.
34. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1α-hydroxylase in human brain. *Journal of Chemical Neuroanatomy*. 2005;29(1):21–30.
35. Bertone-Johnson ER, Powers SI, Spangler L, Larson J, Michael YL, Millen AE, et al. Vitamin D supplementation and depression in the women's health initiative calcium and vitamin D trial. *American Journal of Epidemiology*. 2012;176(1):1–13.
36. Huang JY, Arnold D, Qiu C-f, Miller RS, Williams MA, Enquobahrie DA. Association of serum vitamin D with symptoms of depression and anxiety in early pregnancy. *Journal of Women's Health*. 2014;23(7):588–95.
37. Murphy PK, Mueller M, Hulsey TC, Ebeling MD, Wagner CL. An exploratory study of postpartum depression and vitamin D. *Journal of the American Psychiatric Nurses Association*. 2010;16(3):170–7.
38. Gould JF, Anderson AJ, Yelland LN, Smithers LG, Skeaff CM, Gibson RA, et al. Association of cord blood vitamin D at delivery with postpartum depression in Australian women. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2015;55(5):446–52.
39. Fu CW, Liu JT, Tu WJ, Yang JQ, Cao Y. Association between serum 25-hydroxyvitamin D levels measured 24 hours after delivery and postpartum depression. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2015;122(12):1688–94.
40. Accortt EE, Schetter CD, Peters RM, Cassidy-Bushrow AE. Lower prenatal vitamin D status and postpartum depressive symptomatology in African American women: preliminary evidence for moderation by inflammatory cytokines. *Archives of Women's Mental Health*. 2016;19(2):373–83.
41. Vaziri F, Nasiri S, Tavana Z, Dabbaghmanesh MH, Sharif F, Jafari P. A randomized controlled trial of vitamin D supplementation on perinatal depression: in Iranian pregnant mothers. *BMC Pregnancy and Childbirth*. 2016;16(1):239.
42. Amini S, Jafari rad S, Amani R, Cheraghian B, Sayah M, Hemmati AA. The Effect of vitamin D and calcium supplementation on inflammatory biomarkers, estradiol levels and severity of symptoms, in women with post partum depression: a randomized double-blind clinical trial. PhD thesis. Ahvaz Jundishapur University of Medical Sciences. 2018.
43. Amini S, Jafarirad S, Amani R. Postpartum depression and vitamin D: a systematic review. *Critical Reviews in Food Science and Nutrition*. 2018:1–7. doi: 10.1080/10408398.2017.1423276.

44. Corwin EJ, Bozoky I, Pugh LC, Johnston N. Interleukin-1ß elevation during the postpartum period. *Annals of Behavioral Medicine*. 2003;25(1):41–7.
45. Corwin EJ, Pajer K. The psychoneuroimmunology of postpartum depression. *Journal of Women's Health*. 2008;17(9):1529–34.
46. Obradovic D, Gronemeyer H, Lutz B, Rein T. Cross-talk of vitamin D and glucocorticoids in hippocampal cells. *Journal of Neurochemistry*. 2006;96(2):500–9.
47. Bremner JD, McCaffery P. The neurobiology of retinoic acid in affective disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2008;32(2):315–31.
48. Zeng Y, Li Y, Xia H, Wang S, Zhou J, Chen D. Retinoids, anxiety and peripartum depressive symptoms among Chinese women: a prospective cohort study. *BMC Psychiatry*. 2017;17(1):278.
49. O'Reilly K, Bailey SJ, Lane MA. Retinoid-mediated regulation of mood: possible cellular mechanisms. *Experimental Biology and Medicine*. 2008;233(3):251–8.
50. Mawson AR, Xueyuan W. Breastfeeding, retinoids, and postpartum depression: a new theory. *Journal of Affective Disorders*. 2013;150(3):1129–35.
51. Smulders YM, Blom HJ. The homocysteine controversy. *Journal of Inherited Metabolic Disease*. 2011;34(1):93–9.
52. Malouf R, Evans JG. Vitamin B6 for cognition. *Cochrane Database of Systematic Reviews*. 2003. doi: 10.1002/14651858.CD004393.
53. Beydoun MA, Shroff MR, Beydoun HA, Zonderman AB. Serum folate, vitamin B-12 and homocysteine and their association with depressive symptoms among US adults. *Psychosomatic Medicine*. 2010;72(9):862.
54. Tiemeier H, Van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. *American Journal of Psychiatry*. 2002;159(12):2099–101.
55. Robinson D, O'luanaigh C, Tehee E, O'connell H, Hamilton F, Chin A, et al. Associations between holotranscobalamin, vitamin B12, homocysteine and depressive symptoms in community-dwelling elders. *International Journal of Geriatric Psychiatry*. 2011;26(3):307–13.
56. Murakami K, Miyake Y, Sasaki S, Tanaka K, Arakawa M. Dietary folate, riboflavin, vitamin B-6, and vitamin B-12 and depressive symptoms in early adolescence: the Ryukyus Child Health Study. *Psychosomatic Medicine*. 2010;72(8):763–8.
57. Nguyen B, Weiss P, Beydoun H, Kancherla V. Association between blood folate concentrations and depression in reproductive aged US women, NHANES (2011–2012). *Journal of Affective Disorders*. 2017;223:209–17.
58. Rouillon F, Thalassinos M, Miller H, Lemperiere T. Folates and post partum depression. *Journal of Affective Disorders*. 1992;25(4):235–41.
59. Miyake Y, Sasaki S, Tanaka K, Yokoyama T, Ohya Y, Fukushima W, et al. Dietary folate and vitamins B12, B6, and B2 intake and the risk of postpartum depression in Japan: the Osaka Maternal and Child Health Study. *Journal of Affective Disorders*. 2006;96(12):133–8.
60. Prasad AS, Beck FWJ, Bao B, Snell D, Fitzgerald JT. Duration and severity of symptoms and levels of plasma interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and adhesion molecules in patients with common cold treated with zinc acetate. *The Journal of Infectious Diseases*. 2008;197(6):795–802.
61. Maret W, Sandstead HH. Zinc requirements and the risks and benefits of zinc supplementation. *Journal of Trace Elements in Medicine and Biology*. 2006;20(1):3–18.
62. Sawada T, Yokoi K. Effect of zinc supplementation on mood states in young women: a pilot study. *European Journal of Clinical Nutrition*. 2010;64(3):331.
63. Amani R, Saeidi S, Nazari Z, Nematpour S. Correlation between dietary zinc intakes and its serum levels with depression scales in young female students. *Biological Trace Element Research*. 2010;137(2):150–8.
64. Wójcik J, Dudek D, Schlegel-Zawadzka Mg, Grabowska M, Marcinek A, Florek E, et al. Antepartum/postpartum depressive symptoms and serum zinc and magnesium levels. *Pharmacological Reports*. 2006;58(4):571.

65. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2009;12(6):646–52.
66. Beck F, Prasad A, Kaplan J, Fitzgerald J, Brewer G. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *American Journal of Physiology-Endocrinology And Metabolism*. 1997;272(6):E1002–E7.
67. Szewczyk B, Poleszak E, Sowa-Kucma M, Siwek M, Dudek D, Ryszewska-Pokrasniewicz B, et al. Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action. *Pharmacological Reports*. 2008;60(5):588.
68. Tae W, Kim S, Lee K, Nam E, Choi J, Park J. Hippocampal shape deformation in female patients with unremitting major depressive disorder. *American Journal of Neuroradiology*. 2011. doi: 10.3174/ajnr.A2367.
69. Numakawa T, Richards M, Nakajima S, Adachi N, Furuta M, Odaka H, et al. The role of brain-derived neurotrophic factor in comorbid depression: possible linkage with steroid hormones, cytokines, and nutrition. *Front Psychiatry*. 2014;5:136.
70. Stoltzfus RJ. Defining iron-deficiency anemia in public health terms: a time for reflection. *The Journal of Nutrition*. 2001;131 (2):565s–7s.
71. Paterson JA, Davis J, Gregory M, Holt SJ, Pachulski A, Stamford DE, et al. A study on the effects of low haemoglobin on postnatal women. *Midwifery*. 1994;10(2): 77–86.
72. Grondin M-A, Ruivard M, Perreve A, Derumeaux-Burel H, Perthus I, Roblin J, et al. Prevalence of iron deficiency and health-related quality of life among female students. *Journal of the American College of Nutrition*. 2008;27(2):337–41.
73. Zimmermann MB. The influence of iron status on iodine utilization and thyroid function. *The Annual Review of Nutrition*. 2006;26:367–89.
74. Alharbi AA, Abdulghani HM. Risk factors associated with postpartum depression in the Saudi population. *Neuropsychiatric Disease and Treatment*. 2014;10:311.
75. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for postpartum depression. *The Journal of Nutrition*. 2003;133(12):4139–42.
76. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. *The Journal of Nutrition*. 2005;135(2):267–72.
77. Albacar G, Sans T, Martín-Santos R, García-Esteve L, Guillamat R, Sanjuan J, et al. An association between plasma ferritin concentrations measured 48 h after delivery and postpartum depression. *Journal of Affective Disorders*. 2011;131(13):136–42.
78. Patterson AJ, Brown WJ, Powers JR, Roberts DC. Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health. *Quality of Life Research*. 2000;9(5):491–7.
79. Armony-Sivan R, Shao J, Li M, Zhao G, Zhao Z, Xu G, et al. No relationship between maternal iron status and postpartum depression in two samples in China. *Journal of Pregnancy*. 2012. doi: 10.1155/2012/521431.
80. Kaiser L, Allen LH. Position of the American dietetic association: nutrition and lifestyle for a healthy pregnancy outcome. *Journal of the American Dietetic Association*. 2008;108(3):553–61.
81. Rayman MP. Food-chain selenium and human health: emphasis on intake. *British Journal of Nutrition*. 2008;100(2):254–68.
82. Sher L. Role of thyroid hormones in the effects of selenium on mood, behavior, and cognitive function. *Medical Hypotheses*. 2001;57(4):480–3.
83. Hoffmann PR, Berry MJ. The influence of selenium on immune responses. *Molecular Nutrition & Food Research*. 2008;52(11):1273–80.
84. Duntas L. Selenium and inflammation: underlying anti-inflammatory mechanisms. *Hormone and Metabolic Research*. 2009;41(06):443–7.
85. Leung BM, Kaplan BJ, Field CJ, Tough S, Eliasziw M, Gomez MF, et al. Prenatal micronutrient supplementation and postpartum depressive symptoms in a pregnancy cohort. *BMC Pregnancy and Childbirth*. 2013;13(1):2.

86. Mokhber N, Namjoo M, Tara F, Boskabadi H, Rayman MP, Ghayour-Mobarhan M, et al. Effect of supplementation with selenium on postpartum depression: a randomized double-blind placebo-controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2011;24(1):104–8.
87. German-Ponciano LJ, Rosas-Sánchez GU, Rivadeneyra-Domínguez E, Rodríguez-Landa JF. Advances in the preclinical study of some flavonoids as potential antidepressant agents. *Scientifica*. 2018. doi: 10.1155/2018/2963565.
88. Paladini A, Marder M, Viola H, Wolfman C, Wasowski C, Medina J. Flavonoids and the central nervous system: from forgotten factors to potent anxiolytic compounds. *Journal of Pharmacy and Pharmacology*. 1999; 51(5):519–26.
89. Thakare VN, Aswar MK, Kulkarni YP, Patil RR, Patel BM. Silymarin ameliorates experimentally induced depressive like behavior in rats: involvement of hippocampal BDNF signaling, inflammatory cytokines and oxidative stress response. *Physiology & Behavior*. 2017;179:401–10.
90. Demir EA, Gergerlioglu HS, Oz M. Antidepressant-like effects of quercetin in diabetic rats are independent of hypothalamic–pituitary–adrenal axis. *Acta neuropsychiatrica*. 2016;28(1):23–30.
91. Yi L-T, Liu B-B, Li J, Luo L, Liu Q, Geng D, et al. BDNF signaling is necessary for the antidepressant-like effect of naringenin. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2014;48:135–41.
92. Antunes MS, Jesse CR, Ruff JR, de Oliveira Espinosa D, Gomes NS, Altvater EET, et al. Hesperidin reverses cognitive and depressive disturbances induced by olfactory bulbectomy in mice by modulating hippocampal neurotrophins and cytokine levels and acetylcholinesterase activity. *European Journal of Pharmacology*. 2016;789:411–20.
93. Weng L, Guo X, Li Y, Yang X, Han Y. Apigenin reverses depression-like behavior induced by chronic corticosterone treatment in mice. *European Journal of Pharmacology*. 2016;774:50–4.
94. Donato F, de Gomes MG, Goes ATR, Borges Filho C, Del Fabbro L, Antunes MS, et al. Hesperidin exerts antidepressant-like effects in acute and chronic treatments in mice: possible role of L-arginine-NO-cGMP pathway and BDNF levels. *Brain Research Bulletin*. 2014;104:19–26.
95. Zhang L-M, Wang H-L, Zhao N, Chen H-X, Li Y-F, Zhang Y-Z. Involvement of nitric oxide (NO) signaling pathway in the antidepressant action of the total flavonoids extracted from Xiaobuxin-Tang. *Neuroscience Letters*. 2014;575:31–6.
96. Galati G, O'brien PJ. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. *Free Radical Biology and Medicine*. 2004;37(3):287–303.
97. Saini RK, Nile SH, Park SW. Carotenoids from fruits and vegetables: chemistry, analysis, occurrence, bioavailability and biological activities. *Food Research International*. 2015;76:735–50.
98. Zhou X-y, Zhang F, Hu X-T, Chen J, Tang R-X, Zheng K-Y, et al. Depression can be prevented by astaxanthin through inhibition of hippocampal inflammation in diabetic mice. *Brain Research*. 2017;1657:262–8.
99. Jiang X, Zhu K, Xu Q, Wang G, Zhang J, Cao R, et al. The antidepressant-like effect of trans-astaxanthin involves the serotonergic system. *Oncotarget*. 2017;8(15):25552.
100. Anderson M. Method of inhibiting 5α-reductase with astaxanthin. Google Patents; 2001. Available at: https://patents.google.com/patent/US6277417B1/en.
101. Dawson S, Dash S, Jacka F. The importance of diet and gut health to the treatment and prevention of mental disorders. *International Review of Neurobiology*. 2016;131: 325–46. Elsevier.
102. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology and Hepatology*. 2014;11(8):506.

103. Dinan TG, Cryan JF. The impact of gut microbiota on brain and behaviour: implications for psychiatry. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2015;18(6):552–8.
104. Barthow C, Wickens K, Stanley T, Mitchell EA, Maude R, Abels P, et al. The Probiotics in Pregnancy Study (PiP Study): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy. *BMC Pregnancy and Childbirth*. 2016;16(1):133.
105. Logan AC, Katzman M. Major depressive disorder: probiotics may be an adjuvant therapy. *Medical Hypotheses*. 2005;64(3):533–8.
106. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. *Journal of Neuroscience*. 2014;34(46):15490–6.
107. Slykerman R, Hood F, Wickens K, Thompson J, Barthow C, Murphy R, et al. Effect of lactobacillus rhamnosus HN001 in pregnancy on postpartum symptoms of depression and anxiety: a randomised double-blind placebo-controlled trial. *EBioMedicine*. 2017;24:159–65.
108. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences. 2011:201102999.
109. Collins SM, Kassam Z, Bercik P. The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications. *Current Opinion in Microbiology*. 2013;16(3):240–5.

13

The Prevalence of Anemia in Postnatal Women

Arti Patel and Yashwant Pathak

Contents

Introduction

Anemia during pregnancy and the postpartum period is a critical public health issue affecting more than 56 million women worldwide.[1] The main factors affecting postpartum anemia include prenatal iron-deficiency anemia and hemorrhage or blood loss. Hemoglobin levels less than 110 g/L are an indication of iron-deficiency anemia in patients.[2] Iron-deficiency anemia affects both maternal and fetal health, thus it is a topic of concern for many obstetrics/gynecology (OB/GYN) practitioners. Pregnant women with iron-deficiency anemia are reported to experience symptoms such as fatigue, palpitations, and an increase in respiratory effort. Iron-deficiency women are also at a higher risk of perinatal infections, preeclampsia, and bleeding. Iron-deficiency anemia is also linked to low fetal birthweight and premature delivery.[2] This occurs when pregnancy and lactation increase iron demands; therefore, various treatment options have been made available for anemic women. These options include nutraceuticals such as dietary supplements and fortified foods. These topics will be addressed in this chapter as well as treatment options available for anemic individuals/patients.

Pathophysiology of Anemia

Iron is necessary for various cellular functions such as respiration, oxygen transport, DNA synthesis, and electron transfer. A tightly regulated homeostatic system allows iron levels to stay within a normal range and avoid

toxicity.[3] Iron deficiency can be classified as microcytic with reduced cell volume, normocytic with normal cell volume, or macrocytic, which is an increase in cell volume. Furthermore, B12 and folate deficiency can lead to macrocytic anemia. Microcyctic anemia and hyperchromic anemia include various conditions such as iron-deficiency anemia, thalassemia syndromes, anemia of chronic diseases, and congenital sideroblastic anemias.[4] Iron deficiency and anemia occur when the balance between iron absorption, iron transport, and iron storage is disrupted. This develops as a result of increased iron requirements, limited external supply, and increased blood loss. Anemia is a condition where blood contains low levels of hemoglobin. The hemoglobin that is found in red blood cells contains iron which is used to bind and transport oxygen. These hemoglobin levels are then used to indicate iron deficiency. During pregnancy, most women have a lower than normal level of hemoglobin because of an elevated accumulation of fluid. Anemia is generally classified as a hemoglobin level of less than 120 g/L. Hemoglobin levels less than 100 g/L indicate anemia during any stage of pregnancy and should be treated as soon as possible in an effort to reduce any risks to the mother and fetus.[5] Serum ferritin levels are also used to indicate iron deficiency. Iron deficiency is classified as a serum ferritin level of less than 20–30 μg/L. Moderate iron deficiency is a serum ferritin level less than 70–100 μg/L. However, serum ferritin is an acute phase reactant that is raised during infections and inflammation. Therefore, ruling out inflammation by testing for inflammatory markers is also advised when looking at iron deficiency. The most definitive way of testing iron deficiency is through bone marrow testing; however, this procedure is invasive and not widely used.

A protein that plays a valuable role in iron metabolism is hepcidin. Hepcidin is made by hepatocytes and secreted into an individual's blood circulation. Since hepcidin can be detected in urine, it is useful for indicating that regulation has been triggered at production sites. During pregnancy, fetal hepcidin is responsible for the transfer of iron from the mother's plasma to the fetus's circulation. If hepcidin levels are low, then iron will enter the blood plasma at a high rate. If hepcidin levels are high, then ferroportin is internalized and iron gets trapped in enterocytes and macrophages. During pregnancy and lactation, more external iron is required to meet increased demands and to support the mother's blood volume. Moreover, an increase in iron will also help the fetus and placenta develop.[5] The postpartum period usually refers to the six weeks after delivery. Postpartum anemia can cause symptoms such as palpations, shortness of breath, fatigue, and an increased risk of infections.

Prevalence and Risk Factors

In 2003 around 6% of pregnancy-related discharges from US hospitals had the diagnosis of obstetric bleeding. One out of five of those diagnosed with obstetric bleeding had anemia. Around the world, countries are showing an increase

in pregnancy-related hemorrhage and postpartum anemia. In Australia, the rate of hemorrhage is about 13.1% of deliveries. During the years 1998 to 2003, postpartum anemia had increased in Germany from 12.2% to 15.6%. One study done in Germany showed that on the second day after giving birth, 1 in 5 women were moderately anemic and 1 in 30 were severely anemic.[6] The prevalence of postpartum anemia is 50–80% in developing countries, making it slightly higher than in developed countries.[7] Another study done in Switzerland showed that 31.8% of the subjects showed a decrease in iron stores, and 18.5% of those were diagnosed with anemia. The prevalence of iron-deficiency anemia was higher in individuals from Yugoslavia and other developing countries, compared to its neighboring developed countries.[8] In Jordan, maternal iron deficiency has been linked to gestational age, BMI, history of prior surgeries, and multivitamin use.[9] In Ethiopia, chronic illnesses and deficiency of iron or folic acid have been linked to maternal anemia.[10]

A retrospective cohort study conducted in the United States found that the prevalence of postpartum anemia was 27%. Anemia rates were higher for minority, Hispanic, and African American women at 48%.[11] Furthermore, African American women had a lower mean hemoglobin level and higher prevalence of postpartum anemia compared to other ethnic groups. A study of over 9,000 women showed that although they had normal hemoglobin levels during their third trimester of pregnancy, around 21% had postpartum anemia after delivery.[12] Risk factors for postpartum anemia include prenatal anemia, maternal obesity, multiple births, and not breastfeeding. Maternal iron deficiency anemia during pregnancy doubles the risk of preterm delivery and triples the risk for low birthweight infants. The reasons for preterm births are not fully understood, however, it is hypothesized to be because of hypoxia in the placenta, increased oxidative stress that cannot be neutralized by dietary antioxidants, and reduced immune function leading to inflammatory cytokines and the secretion of corticotropin-releasing hormones.[13] The rate of fetal congenital abnormalities was not increased in anemic women who received iron supplementation. Low-income women in the United States have an 8% prevalence of anemia in the first trimester, 12% in the second trimester, and 29% in the third trimester.[14]

A study done by Infante-Torres et al. found that the duration of the second stage of labor beyond 4 hours is safe for women who have not previously given birth. However, for multiparous women monitoring should increase if the second stage of labor exceeds 3 hours because of an increased risk of postpartum anemia.[15] Studies have shown an increased risk of postpartum anemia from an episiotomy, primiparity, and prior cesarean section. A study by Rubio-Alvarez et al. found that perineal trauma, tearing, and episiotomy tripled the risk of postpartum anemia.[16]

The type of delivery plays a role in postpartum anemia and hemorrhage. A study by Brichs et al. found that 82.3% of births using instruments such as forceps and vacuums increased the risk of postpartum anemia. Postpartum

anemia was influenced by delivery types such as venthouse at 67%, cesarean sections at 58.2%, and vaginal births at 37.2%.[17] Another study by Daru et al. showed that the chances of maternal death were doubled in those who had severe anemia compared to the individuals who did not have anemia. Anemia was linked to poor maternal outcomes because of postpartum hemorrhage, antenatal sepsis, and postnatal sepsis.[18] Teenage mothers are a high-risk group because of their own particular nutritional requirements, and growth spurts. Since they generally have suboptimal nutritional values, they are at a higher risk of developing iron-deficiency anemia during and after pregnancy.[19]

Treatments, Interventions, and Nutraceuticals

Iron supplementation is necessary for treating anemia during pregnancy and during the postpartum period. For maximum benefits, iron supplementation should be started before conception.[19] Additionally, the use of contraceptives prior to pregnancy has been found to lower the risk of low iron stores. This could be because contraceptives decrease the menstrual blood loss by 50%.[20] However, further studies should be done to establish the potential contraceptives have as a preventative measure for anemia.

Supplements of other micronutrients should also be consumed in order to aid with fetal growth and development. These micronutrients include but are not limited to zinc, copper, vitamin A, vitamin E, vitamin B12, and folate. Folate, B12, and iron are necessary for active erythropoiesis to take place because they play a role in the accompanying DNA synthesis.[21] During pregnancy, iron and folic acid levels decrease because of hematopoiesis, fetal cell division, and elevated urinary loss of nutrients. Although supplement levels differ depending on deficiency levels, the World Health Organization recommends pregnant women to take at least 60 mg of elemental iron supplements and 400 μg of folic acid supplements per day.[21] Vitamin B12 and folate deficiency can cause megaloblastic anemia. Additionally, vitamin B12 deficiency may be caused by dietary restrictions, ineffective absorption, or metabolic inhibition. This B12 deficiency can be improved by consuming B12-rich foods such as milk, cheese, and eggs.[22] Vitamin B12 deficiency can also be treated with intramuscular injections of hydroxocobalamin or oral supplements of cyanocobalamin.[22] Folate is increasingly utilized during pregnancy, and therefore can cause women to become deficient. Consuming greater amounts of green vegetables and oral folic acid supplements can help combat folate deficiency. Correcting folate deficiency is crucial not only for the mother, but also for the health of the fetus. Folate plays a major role in the development of a fetal brain and spinal cord, therefore folate deficiency during pregnancy has been linked to various congenital birth defects.

Women who had an early diagnosis of anemia but were not treated with iron supplementation showed a shorter gestational period and a higher rate of preterm births. However, this increased rate of preterm births was not found

in anemic women who were treated for anemia in their first trimester of pregnancy. Severe nausea and vomiting were reduced in individuals who took iron supplementation.[23] Although various treatments exist to help boost iron levels during anemia, it is important to weigh the harms and benefits of treatments on both the mother and fetus.

The following treatment options include nutraceuticals such as oral iron and folate supplements, as well as treatment options for severe anemia brought on by postpartum hemorrhage.

Oral iron therapy: Nutraceutical oral iron therapy can be ingested in the form of pills, capsules, and extended-release tablets. Oral iron supplements can contain ferrous fumarate, ferrous gluconate, or ferrous sulfate, all of which contain specific amounts of elemental iron that will be absorbed by the body. Oral iron is one of the main treatments for general anemia in most of the population as well as in patients who are pregnant. Oral iron treatment is used for individuals that have mild to moderate anemia. The body absorbs the iron from the stomach and intestines. Treatment is usually given for several months. However, some adverse effects that may discourage individuals from completing treatment include nausea and constipation.[24] When iron reserves are low in the body, it will increase gastrointestinal iron absorption. Therefore, oral iron treatment can be beneficial for postpartum iron deficiency or bleeding. To optimize the benefits and absorption of oral iron therapy, it is beneficial to take it in between meals in order to avoid interference with food iron sources as well as side effects.[25] A recent study showed that lactoferrin treatment for replenishing iron could be a better treatment option compared to ferrous sulfate. This is because it produces fewer gastrointestinal side effects and therefore increases compliance.[26] Some studies in the past showed that taking oral iron supplements with vitamin C increased iron absorption by the body, however, more recent studies show that ingesting both simultaneously can actually cause toxicity and gastrointestinal side effects.[27]

Folate: Folic acid and vitamin B9 are necessary for DNA synthesis, cell proliferation, and growth. Folic acid is used as an adjunct with other iron treatments to help increase iron and folate levels in the body.

Parenteral iron therapy: As an alternative to oral iron therapy, parenteral iron therapy can be given intravenously or with injections. Various types of parenteral iron products include iron dextran, ferric gluconate, and iron sucrose.[28] An advantage of iron dextran is that the patient can be treated with a full dose in one hospital visit. However, iron dextran has been associated with more adverse effects such as hypertension, malaise, abdominal pain, and nausea after the administration. Parenteral iron therapies generally have more pain and irritation at the injection site, as well as allergic reactions noted with their use. Intravenous iron therapy given in the first trimester can help replenish iron supplies and decrease the need for blood transfusions in the postpartum period. Intravenous iron produces a faster and higher concentration of hemoglobin compared to iron.[29] Parenteral iron therapy is

preferred for cases of impaired absorption or intolerance of oral iron.[30] A study by Seid et al. compared the efficacy of ferric carboxymaltose with oral ferrous sulfate and found that patients tolerated and benefited more from carboxymaltose injections. The study noted that patients achieved greater hemoglobin levels and a faster rate and obtained higher serum transferrin and ferratin levels.[31] Studies investigating the benefits of parenteral iron therapy over the gold standard oral treatment are continuously being carried out, bringing us closer to the best treatment option for patients with postpartum anemia.

Erythropoietin: When oxygen levels are low, erythropoietin is produced by the kidneys. This hormone stimulates blood formation in the bone marrow. Erythropoietin was originally used to treat anemia associated with kidney disease, then it was used to treat postpartum anemia as a substitute for blood transfusions. However, because of various adverse effects and links to hematological cancers, it is now rarely being used for postpartum anemia.[32] Most women suffering from postpartum anemia have normal immune function and still have high endogenous erythropoietin levels, therefore rhEPO (recombinant form of the hormone erythropoietin) treatment does not have any major effect. Receiving external erythropoietin treatment is beneficial if the patient has low serum erythropoietin levels, infections, or inflammatory disorders. A study done using recombinant human erythropoietin treatment for postpartum anemia showed that anemia should be treated by rhEPO for 5 days postpartum, and for 15 days postpartum in the case of severe anemia.[33] Extended use of rhEPO treatment increases the hemoglobin and hematocrit levels at a faster rate.

Blood transfusions: Postpartum anemia, especially that resulting from excessive bleeding during birth, can be treated using allogeneic blood transfusions. Cesarean section is one of the greatest risk factors for postpartum anemia because of the major blood losses associated with it.[34] Blood transfusion should be considered when hemoglobin levels go below 60 g/l.[34]

References

1. Goonewardene, M., Shehata, M., & Hamad, A. (2012). Anaemia in pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 26(1), 3–24. doi:10.1016/j.bpobgyn.2011.10.010
2. Abu-Ouf, N., & Jan, M. (2015). The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi Medical Journal*, 36(2), 146–149. doi:10.15537/smj.2015.2.10289
3. Percy, L., & Mansour, D. (2017). Iron deficiency and iron-deficiency anaemia in women's health. *The Obstetrician & Gynaecologist*, 19(2), 155–161. doi:10.1111/tog.12368
4. Thomas, A. (2017). Investigation and management of anaemia. *Medicine*, 45(4), 209–213. doi:10.1016/j.mpmed.2017.02.015
5. Khalafallah, A. A., & Dennis, A. E. (2012). Iron deficiency anaemia in pregnancy and postpartum: Pathophysiology and effect of oral versus intravenous iron therapy. *Journal of Pregnancy*, 2012, 630519. doi:10.1155/2012/630519

6. Bergmann, R. L., Richter, R., Bergmann, K. E., & Dudenhausen, J. W. (2010). Prevalence and risk factors for early postpartum anemia. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 150(2), 126–131. doi:10.1016/j.ejogrb.2010.02.030
7. Infante-Torres, N., Molina-Alarcón, M., Rubio-Álvarez, A., Rodríguez-Almagro, J., & Hernández-Martínez, A. (2018). Relationship between duration of second stage of labour and postpartum anaemia. *Women and Birth*, 31(5). doi:10.1016/j.wombi.2017.11.009
8. Bencaiova, G., Burkhardt, T., & Breymann, C. (2012). Anemia—prevalence and risk factors in pregnancy. *European Journal of Internal Medicine*, 23(6), 529–533. doi:10.1016/j.ejim.2012.04.008
9. Al-Mehaisen, L., Khader, Y., Al-Kuran, O., Issa, F. A., & Amarin, Z. (2011). Maternal anemia in rural Jordan: Room for improvement. *Anemia*, 2011, 1–7. doi:10.1155/2011/381812
10. Haidar, J. (2010). Prevalence of anaemia, deficiencies of iron and folic acid and their determinants in Ethiopian women. *Journal of Health, Population and Nutrition*, 28(4). doi:10.3329/jhpn.v28i4.6042
11. Bodnar, L. M., Scanlon, K. S., Freedman, D. S., Siega-Riz, A. M., & Cogswell, M. E. (2001). High prevalence of postpartum anemia among low-income women in the United States. *American Journal of Obstetrics and Gynecology*, 185(2), 438–443. doi:10.1067/mob.2001.115996
12. Bodnar, L. M., Scanlon, K. S., Freedman, D. S., Siega-Riz, A. M., & Cogswell, M. E. (2001). High prevalence of postpartum anemia among low-income women in the United States. *American Journal of Obstetrics and Gynecology*, 185(2), 438–443. doi:10.1067/mob.2001.115996
13. Bánhidy, F., Ács, N., Puhó, E. H., & Czeizel, A. E. (2011). Iron deficiency anemia: Pregnancy outcomes with or without iron supplementation. *Nutrition*, 27(1), 65–72. doi:10.1016/j.nut.2009.12.005
14. Bodnar, L. M., Scanlon, K. S., Freedman, D. S., Siega-Riz, A. M., & Cogswell, M. E. (2001). High prevalence of postpartum anemia among low-income women in the United States. *American Journal of Obstetrics and Gynecology*, 185(2), 438–443. doi:10.1067/mob.2001.115996
15. Infante-Torres, N., Molina-Alarcón, M., Rubio-Álvarez, A., Rodríguez-Almagro, J., & Hernández-Martínez, A. (2018). Relationship between duration of second stage of labour and postpartum anaemia. *Women and Birth*, 31(5). doi:10.1016/j.wombi.2017.11.009
16. Rubio-Álvarez, A., Molina-Alarcón, M., & Hernández-Martínez, A. (2018). Incidence of postpartum anaemia and risk factors associated with vaginal birth. *Women and Birth*, 31(3), 158–165. doi:10.1016/j.wombi.2017.09.020
17. Brichs, X. U., Carballeira, M. R., Fernández, A. G., & Picañol, E. P. (2016). Anaemia in pregnancy and in the immediate postpartum period. Prevalence and risk factors in pregnancy and childbirth. *Medicina Clínica (English Edition)*, 146(10), 429–435. doi:10.1016/j.medcle.2016.06.050
18. Daru, J., Zamora, J., Fernández-Félix, B. M., Vogel, J., Oladapo, O. T., Morisaki, N., … Khan, K. S. (2018). Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: A multilevel analysis. *The Lancet Global Health*, 6(5). doi:10.1016/s2214-109x(18)30078-0
19. Abu-Ouf, N., & Jan, M. (2015). The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi Medical Journal*, 36(2), 146–149. doi:10.15537/smj.2015.2.10289
20. Bencaiova, G., Burkhardt, T., & Breymann, C. (2012). Anemia—prevalence and risk factors in pregnancy. *European Journal of Internal Medicine*, 23(6), 529–533. doi:10.1016/j.ejim.2012.04.008

21. Woude, D. A., Vries, J. D., Wijk, E. M., Verzijl, J. M., & Pijnenborg, J. M. (2014). A randomized controlled trial examining the addition of folic acid to iron supplementation in the treatment of postpartum anemia. *International Journal of Gynecology & Obstetrics*, 126(2), 101–105. doi:10.1016/j.ijgo.2014.02.013
22. Roddie, C., & Davis, B. (2009). Iron, B12 and folate. *Medicine*, 37(3), 125–128. doi:10.1016/j.mpmed.2008.12.009
23. Bánhidy, F., Ács, N., Puhó, E. H., & Czeizel, A. E. (2011). Iron deficiency anemia: Pregnancy outcomes with or without iron supplementation. *Nutrition*, 27(1), 65–72. doi:10.1016/j.nut.2009.12.005
24. Dodd, J., & Dare, M. (2003). Treatment for women with postpartum iron deficiency anaemia. *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.cd004222
25. Milman, N. (2011). Postpartum anemia II: Prevention and treatment. *Annals of Hematology*, 91(2), 143–154. doi:10.1007/s00277-011-1381-2
26. Hashim, H. A., Foda, O., & Ghayaty, E. (2017). Lactoferrin or ferrous salts for iron deficiency anemia in pregnancy: A meta-analysis of randomized trials. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 219, 45–52. doi:10.1016/j.ejogrb.2017.10.003
27. Munoz, M., Garcia-Erce, J. A., & Remacha, A. F. (2010). Disorders of iron metabolism. Part II: Iron deficiency and iron overload. *Journal of Clinical Pathology*, 64(4), 287–296. doi:10.1136/jcp.2010.086991
28. Silverstein, S. B., & Rodgers, G. M. (2004). Parenteral iron therapy options. *American Journal of Hematology*, 76(1), 74–78. doi:10.1002/ajh.20056
29. Milman, N. (2011). Postpartum anemia II: Prevention and treatment. *Annals of Hematology*, 91(2), 143–154. doi:10.1007/s00277-011-1381-2
30. Thomas, A. (2017). Investigation and management of anaemia. *Medicine*, 45(4), 209–213. doi:10.1016/j.mpmed.2017.02.015
31. Seid, M. H., Derman, R. J., Baker, J. B., Banach, W., Goldberg, C., & Rogers, R. (2008). Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: A randomized controlled clinical trial. *American Journal of Obstetrics and Gynecology*, 199(4). doi:10.1016/j.ajog.2008.07.046
32. Dodd, J., & Dare, M. (2003). Treatment for women with postpartum iron deficiency anaemia. *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.cd004222
33. Tsiara, S., Kaiafas, P., Kapsali, E., Christou, L., & Bourantas, K. L. (2009). Recombinant human erythropoietin for the treatment of refractory anemia in lymphoproliferative disorders: Preliminary results. *European Journal of Haematology*, 60(5), 317–319. doi:10.1111/j.1600-0609.1998.tb01048.x
34. Milman, N. (2011). Postpartum anemia II: Prevention and treatment. *Annals of Hematology*, 91(2), 143–154. doi:10.1007/s00277-011-1381-2

14

Nutraceuticals Impacting Uterine Growth, Gestational Age and Mortality Rate

Shrushti Patil, Natalia Mercado, Yashwant Pathak, and Priyanka Bhatt

Contents

Introduction

Herbs have been an integral part of our society for centuries for both medicinal and non-medicinal use. Herbal medicine has been in existence for thousands of years and still persists today, even with the presence of modern medicine, as people become aware of the side effects and potency of the latter (Nikam et al. 2012). It encompasses herbs, herbal materials, herbal preparations, and finished herbal products that consist of parts of plants, or plant materials, or combinations, as active ingredients (Kamboj 2000, Al-Ramahi et al. 2013). Over decades, by means of local tradition, familiarity, and even social pressure, women have turned toward the consumption of herbal medicine during

pregnancy to combat their physiological symptoms and to enhance the health of the mother as well as their baby (Ahmed et al. 2017). The most commonly reported clinical indications of using herbal medicine includes nausea, vomiting, induction of labor, swollen feet, constipation, and backache (Zamawe et al. 2018; Samavati et al. 2017).

There is also a certain amount of dissatisfaction related to conventional healthcare in terms of the holistic approach herbal and alternative therapies proclaim. It is commonly believed that herbal medicines or nutraceuticals are better and safer compared to conventional medicines (Chan et al. 2003). There is no licensed medicine associated with the aforementioned pregnancy-related morning sickness or insomnia (Holst et al. 2009). However, pregnant women view herbal medicine as a prime method of cure without considering their complex physiopathological and pharmacological aspects. Social demographics, such as geopolitical zones and educational attainment, can play an important role on the mind-set of the women about the safety of herbal medicine along with their effects for the fetus (Mothupi 2014). However, they fail to recognize the possible toxicity of certain chemicals in the herbal drugs could have, triggering malformations in the fetus (Tiran 2003). The embryonic period of a fetus in the first trimester is a very critical time due to the level of vulnerability it poses for the development of an embryo to fetus. A fetus may develop major physical malformations or have its metabolism influenced via epigenetic modifications if exposed to harmful chemical and biological agents, drugs, and radiation as well as if deprived of certain nutrients (Chuang et al. 2006) (Table 14.1).

The World Health Organization (WHO) has estimated that about 80% of the developing countries' population relies on traditional medicine to provide their primary healthcare needs due to its natural origins and ease of availability (Mukherjee et al. 2006). The use of herbal medicine for maternal health has been researched in developed countries such as Norway and the United States. It was found that the prevalence of herbal as well as other alternative

Table 14.1 Some Common Symptoms Experienced by Women in the United Kingdom

Symptoms experienced	Percentage of women experiencing symptoms during pregnancy
Morning sickness	70
Insomnia	66–94
Heartburn	30–50
Ankle edema	12
Anemia	14–52
Urinary tract infections	1–13
Constipation	11–38

Source: Holst et al. (2009).

therapies ranged from about 9% to 36%, which is mostly associated with higher education and with cultural minorities (Mothupi 2014). The prevalence of nutraceuticals is up to 60% in developed countries, in particular Asian countries, which are known to be pioneers of traditional healthcare systems such as Ayurveda and Chinese medicine (Mukherjee et al. 2006). It is not an unusual sight to see medicinal plants along with their preparation widely available in condimental and homeopathic Asian stores. People often visit traditional healers to seek herbal medicine for their ailments (Ahmed et al. 2017). These herbal medicine extracts are sold over the counter in several countries, including the United States and the United Kingdom, without having to submit proof of safe consumption since they are categorized as food. In African countries, herbal medicine continues to play a crucial role in pregnancy and labor alongside their healthcare systems. Traditional medicine is used depending on the severity of the illness and availability of medicine (Van der Kooi et al. 2006). In urban sub-Saharan Africa, the use of herbal medicine during pregnancy, labor, or the postpartum period ranges from 30% to 70% (Mothupi 2014). For instance, the rural population of Africa highly depends on herbal medicine due to the lack of healthcare facilities in their proximity. The rest of the population with access to Western medicine has also returned to alternative medicine especially without any detailed knowledge or advice of a healthcare professional. Unfortunately, the incidence of threatened miscarriage has increased along with a decrease in the size of newborns of an adequate gestational age in females self-medicating on herbal supplements (Ahmed et al. 2017).

Background of Nutraceuticals Used during Pregnancy

The consumption of nutraceuticals is most common during the first and third trimesters of pregnancy to prevent disorders and nutrient deficiency. Glucosamine, ginseng, echinacea, folic acid, cod liver oil, omega-3, calcium-enriched orange juice, and green tea are some popular nutraceuticals.

Folic Acid

Folic acid supplements have been recognized as a crucial nutrient before conception and during the first trimester of pregnancy because they can reduce the risk of neural tube defects in children. Neural tube defects are birth defects of the brain and spinal cord and occur when the neural tube doesn't close early in embryonic development. In 1992, the US Public Health Service recommended that all fertile women consume 400 μg of folic acid daily in order to reduce the number of spina bifida and other neural tube defects. A report indicated that the number of pregnancies affected by neural tube defects in the United States dropped from 4,000 in 1995–1996 to 3,000 in 1999–2000 after women started using folic acid supplements (CDC 2004). A study was conducted in order to determine how common neural tube

defects were among several women who never used multivitamins before or after conception and women who did (Milunsky et al. 1989). The study concluded that among women who never used multivitamins before or after conception, the occurrence of neural tube defects was 3.5 per 1,000 (Milunsky et al. 1989). The study also demonstrated that neural tube defects were lower (0.9 per 1,000) among women who consumed folic acid multivitamins during the first 6 weeks of pregnancy (Milunsky et al. 1989). However, recent studies in mice and infants show that the intake of folic acid supplements during pregnancy can have unfavorable effects on respiratory health in early life (Whitrow et al. 2009). It has been established that folic acid supplements can modify the status of methylation-sensitive, DNA-binding proteins (Whitrow et al. 2009). When tested on mice, it was demonstrated that DNA changes caused by folic acid supplements can affect the expression of T-helper type 2 cytokines during fetal development, which in turn modify the inflammatory response and therefore increases the risk of allergic airways disease in the offspring (Whitrow et al. 2009). A study was conducted in Norway to investigate the correlation between folic acid supplements during pregnancy and the risk of lower respiratory tract infections and wheeze in children up to 18 months of age (Håberg et al. 2009). The study found that folic acid supplements taken during pregnancy were related to an increase in wheeze and lower respiratory tract infections (Håberg et al. 2009).

Docosahexaenoic Acid and Fish Oil

Docosahexaenoic acid (DHA) is abundant in fish and it is critical for the growth and development of the brain in children (Horrocks and Yeo, 1999). The supplementation of DHA improves mental development since the brain prefers taking up DHA to other fatty acids. Deficiencies of DHA are linked with fetal alcohol syndrome, attention deficit hyperactivity disorder, cystic fibrosis, phenylketonuria, unipolar depression, aggressive hostility, and adrenoleukodystrophy (Horrocks and Yeo, 1999). A cognitive assessment was done on children who were 2½ years old and whose mothers received fish oil supplements during pregnancy. The study found that the children whose mothers consumed fish oil supplements during pregnancy had higher scores for eye and hand-eye coordination than those whose mothers didn't consume the fish oil supplements (Dunstan, Simmer & Dixon 2008). Another study tested the effect of fish oil on pregnant women and on the risk of persistent wheeze or asthma in their offspring (Bisgaard et al. 2016). That study found that consuming fish oil supplements in the third trimester of pregnancy lowered the risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by one third (Bisgaard et al. 2016).

Many benefits have been related to the consumption of omega-3 fatty acids during pregnancy, including improvements in neurodevelopment in the child. Omega-3 fatty acids play a critical role during pregnancy because they are the building blocks of fetal brain and retina (Coletta 2010). Studies have been

done on animals and have demonstrated a link between a lack of omega-3 fatty acids during pregnancy and visual and behavioral deficits (Coletta 2010). A further study used different tests to evaluate neurodevelopmental outcomes among children whose mothers consumed fish oil and mothers who didn't. The study found that higher consumption of fish during pregnancy resulted in higher visual recognition memory and higher scores of verbal intelligence (Coletta, 2010).

Ginger

Ginger is often used for its anti-nauseant and anti-emetic properties to curb nausea and hyperemesis gravidum (Laelago 2018). Based on a review conducted on four different studies, a daily intake of 1 g of ginger is more effective against nausea and vomiting than the placebo, without any detectable side effects for the following three weeks (Holst et al. 2009). This natural root also seemed to have the highest percentage of users (47%) in the aforementioned study. GraviFrisk, sold in Denmark and containing 6 g of dried ground ginger, was advertised for pregnant females but soon withdrawn for having a high amount of ginger and limited documentation on safety (Holst et al. 2009). At a concentration of more than 1,000 mg of daily usage, ginger can trigger blood thinning, discomfort in the stomach, and heartburn (Laelago 2018).

Blue Cohosh

Blue cohosh or *Caulophyllum thalictroides* is a small perennial plant that grows mostly in the northeast of American. Native American women were the first to begin brewing the roots as tea, in order to curb the pain associated with menstrual cramps and childbirth (Dugoua et al. 2008). Traditionally, expectant mothers consume blue cohosh with a combination of herbal medicines such as squaw vine, raspberry, black cohosh, and false unicorn, especially during their third trimester called mother's cordial or *partus preparatus*. Approximately 64% of the certified nurse midwives in 1999 claimed to use blue cohosh during labor preparation. Even in modern times, in countries like the United States, blue cohosh is frequently utilized as a labor inducer to aid the process of childbirth and make it quick as well as painless for the mother (Dugoua et al. 2008).

Ginseng

Ginseng is consumed to improve immunity, sexual performance, and energy (Tiran 2003). According to one study, about 9.1% of pregnant women in the United States and 10% of pregnant women from Asian countries consumed ginseng supplements (Chan et al. 2003). The effects of oral consumption versus direct treatment of ginseng extract starting at 50 mg/kg to 2,000 mg/kg were investigated in vitro using pregnant mice throughout the gestation period (Belanger et al. 2016). Although oral consumption did not have a negative

effect at any point during the pregnancy, the direct treatments of ginseng had detrimental effects on the preimplantation development in vitro (Belanger et al. 2016). On the other hand, Chin's study (1991) concluded that 88% of pregnant women had a high risk of adverse fetal outcome and some minor side effects such as diarrhea, vaginal bleeding, insomnia, tender breasts, dizziness, headaches, and, in certain severe cases, mania (Tiran 2003).

Mwanamphepo

Mwanamphepo is a term used to describe local Malawian herbal medicines, which are often given to expectant mothers to induce or hasten labor (Zamawe et al. 2018). A group of researchers conducted a cross-sectional analysis in rural Malawi over a period of 5 years to scrutinize the adverse effects of mwanamphepo on maternal and neonatal outcomes (Zamawe et al. 2018). Expectant mothers have also been known to drink raspberry leaf tea, as it is said to tone the uterus for labor, preventing postmaturity and, less painful yet more effective, Braxton Hicks contractions. Over the decades, women and medicinal herbalists have prescribed raspberry tea, however, it should be avoided in the third trimester and by women with uterine scars and a history of preterm labor (Tiran 2003) (Table 14.2).

Table 14.2 Herbs Commonly Consumed by Expectant Mothers for Easing Pregnancy-Related Symptoms

Common name	Scientific name	Symptoms cured and benefits	References
Echinacea/coneflower	*Echinacea purpurea*	Prevent or treat cold	Holst et al. (2009)
Ginger	*Zingiber officinale*	Nausea/sickness	Wilkinson et al. (2000)
Chamomile	*Matricaria chamomilla*	Insomnia, joint pain, gastrointestinal tract irritation	Holst et al. (2009)
St. John's wort	*Hypericum perforatum*	Depression/relaxation	Al-Ramahi et al. (2013)
American cranberry	*Vaccinium macrocarpon*	Urinary tract infections	Al-Ramahi et al. (2013)
Blue cohosh	*Caulophyllum thalictroides* L. Michx	Labor induction	Al-Ramahi et al. (2013)
Raspberry leaf	*Rubus idaeus*	Prepare uterus for labor contractions, increase milk production, and relieve nausea	Tiran, (2003) Al-Ramahi et al. (2013)
Ginseng	*Panax ginseng*	Improve immunity and energy	Belanger et al. (2016)
Peppermint	*Mentha spicata*	Nausea, vomiting, flatulence, indigestion, and heartburn	Al-Ramahi et al. (2013)
Clary sage	*Salvia sclarea*	Increase in oxytocin levels during labor	Tadokoro et al. (2017)

Impact on Uterine Growth

Native Americans have a long history of using blue cohosh for gynecological issues. Blue cohosh is found in a variety of forms in North America. Black cohosh is often used in conjunction with blue cohosh, which has been known to have oxytocic and abortifacient effects. According to a survey conducted for certified nurse-midwives, this labor-inducing herb has caused complications in about 21% of cases (Irikura & Kennelly 1999). These complications included nausea, meconium-stained fluid, and transient fetal tachycardia. The amount of glycosides—caulosaponin and caulophyllosaponin—present in blue cohosh were the main reason for its oxytocic effects. Moreover, there have been findings of some seriously toxic alkaloid extracts in blue cohosh, namely:

- Anagyrine—hazardous if present in a concentration of 290 ppm, this teratogen is found in grazing animals and causes congenital deformations. Its activity in humans is not known at this time, but the FDA discourages the consumption of anagyrine at any concentration.
- N-methylcytisine—hazardous if present in a concentration of 20 ppm, this potentially harmful chemical has caused malformation in rat embryos, has restricted growth, and caused morphogenesis in the embryos. It has an effect similar to nicotine.
- Taspine—hazardous if present in a concentration of 0.5 ppm, this compound has been known to kill rat embryos at a concentration of 5 ppm. It is highly cytotoxic and a possible human teratogen (Irikura & Kennelly 1999).

Green tea or *Camellia sinensis* originated in East Asia and is now consumed by people all over the world, primarily for its antioxidant effects as well as anti-inflammatory benefits (Laelago 2018). Although this miracle tea has a myriad of beneficial qualities, it contains caffeine, which has been shown to put pregnant women at risk of spontaneous abortion if consumed in large doses, for example of about 375 mg or more. According to a study conducted on 62 pregnant women, those who consumed over 300 mg/day caffeine conceived babies with low birthweights (Laelago 2018). The effect of green tea extract was analyzed in Winstar rats, which were given either water or green tea extract diluted in water and had either controlled or high-fat diets during pregnancy. The offspring of the rats consuming the green tea extract, regardless of the diet, displayed modification in the inflammatory cytokines and p-NFκB p50 (primary antibodies), which resulted in a pro-inflammatory environment in their adipose tissues. Therefore, this extract is capable of altering the metabolic development of their offspring in utero (Hachul et al. 2018).

Impact on Gestational Age

Golden ragwort (*Senecio aureus* L.) is a short-lived perennial forb that belongs to the Aster family. Cherokee Indians used the roots and leaves of this plant in

teas for heart trouble and for preventing pregnancy (USDA NRCS). Moreover, other Native Americans have used it for the following reasons:

1. Help with childbirth
2. Regulate menstruation
3. Treat lung disease (such as tuberculosis)
4. External ointments for ulcers and wounds
5. Treat urinary tract diseases

Later, through research, it was discovered that the leaves of this plant contained a low toxicity alkaloid called pyrrolizidine (USDA NRCS). Pyrrolizidine alkaloids (PA) are plant toxins, which cause human as well as plant diseases. During the metabolism process of this plant, the liver converts the alkaloids into highly reactive electrophiles that react with the macromolecules to form an adduct, further resulting in either acute or chronic toxicity. PAs are also known to act as teratogens and as abortifacients (Prakash et al. 1999). All herbal abortifacients are to be avoided during pregnancy since the side effects can be harmful to the pregnant mother.

Raspberry leaf has not yet been shown to significantly affect either the mother or the baby, as demonstrated by a blind, placebo-controlled randomized study. This study also revealed that there was no reduction in the first stage of labor; however, it depicted a distinct decrease in the second stage of labor, including a reduced rate of deliveries using forceps (Dog 2009).

Fennel (*Foeniculum vulgare*) has been investigated for its ability to reduce the contractions and gestational age. The fennel essential oil tested on pregnant rats using different dosages led to a significant decrease in the induced contractions at lower concentrations of 0.93 mg/ml (Samavati et al. 2017). A cohort study consisting of 630 expecting mothers revealed that, upon regular consumption of fennel during pregnancy, the gestational age was shortened compared to women who did not consume fennel during the course of their pregnancy.

Impact on Mortality Rate

Birth defects of the spinal cord can lead to significant illness and mortality depending on the location and severity of the lesion. Anencephaly is the most severe and usually ends in a miscarriage or leads to death in days or weeks. The less severe lesions are spina bifida and a variety of morbidities, such as urinary and fecal incontinence and paralysis of the lower limbs (Krista 2011). A research study was conducted to evaluate the effect of folic acid supplementation on neonatal mortality due to neural tube defects (London School of Hygiene and Tropical Medicine; Blencowe et al. 2010). That study found that folic acid supplementation reduces neonatal mortality from neural tube disorders.

Another study was performed to illustrate a correlation between taking folate during pregnancy and a reduction in neonatal deaths and low birthweight babies (Lassi et al. 2013), but it found that there was no association. Pregnant women have also used ginseng, but since its safety hasn't been established in humans, it is not recommended. According to the *Natural Standard Herb and Supplement Guide*, neonatal death and the development of male characteristics were seen in a baby whose mother used ginseng during pregnancy (Ulbricht 2010).

Ginger is frequently used as a cure for morning sickness, but the 6-gingerol that is responsible for the spicy taste of ginger has teratogenic properties. This compound has affected some essential embryonic developmental processes, for instance, disruption of angiogenesis (Samavati et al. 2017). During one study, it was confirmed that ginger inhibited the proliferation as well as tube formation of primary cultured human endothelial cells via down-regulation of cyclidin D. Meanwhile, in mice, it was seen that tumor growth was inhibited by its anti-angiogenic properties. It is supposedly very embryotoxic in the second and third trimesters of pregnancy for reasons shown in Figure 14.1 (Samavati et al. 2017).

Regulation and Safety of Herbal Medication

A large proportion of the population uses herbal remedies for minor aches and complaints rather than rushing to a clinic. Herbal medicine is neither studied as extensively as its conventional counterpart nor does it undergo a standard regulatory process (Mansoor et al. 2017). The lack of evidence of

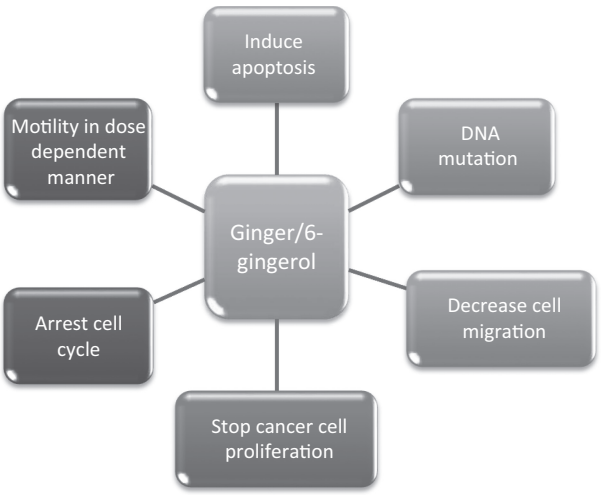

Figure 14.1 *Displays the crucial reasons why ginger should be avoided in the second and third trimesters as a remedy for morning sickness in pregnant women.*

the effectiveness as well as the safety of these nutraceuticals has definitely raised some concerns among public health practitioners (Chuang et al. 2006). These herbal drugs are distributed in the form of water decoctions or ethanolic extracts rather than in their fresh or crude form (Kamboj 2000). Creating cheaper alternatives of herbal medicines can result in serious health issues. Adulteration of herbal drugs using heavy metals, pesticides and other contaminants can be very harmful for consumers. The term nutraceutical can be difficult to define since the exact concentration of active ingredients present is often unknown. For instance, blue cohosh is known to contain vasoactive glycosides and alkaloids that have demonstrated harmful effects on the myocardium during animal testing. Although primary public health programs for women have encouraged the consumption of 400 μg of folic acid daily, not many women have complied. A recent study in the UK demonstrated that women planning a pregnancy only slightly increased their intake of folic acid supplements. Due to the lack of compliance, many countries have been implementing mandatory fortification programs to enhance their effects and lower the risks of neural tube defects (Krista 2011).

Regulations have also been placed for the mandatory fortification of wheat flour with folic acid in 53 countries (Krista 2011). A minimum level of folic acid fortification has been implemented in countries such as the United States, Canada, Chile, South Africa and Costa Rica (Krista 2011). Mandatory fortification of cereal grain products with folic acid was implemented in the US in 1998. However, research shows that folic acid might need to be added to further food products in order to reach all women effectively (Krista 2011) (Table 14.3).

Future Applications

Nutraceuticals should be created with plants that are free from harmful pesticides, heavy metals, and radioactive chemicals, and free of any microbial contamination. The extract from the herbs must be thoroughly analyzed for the indicated biological activity in vitro model before use. This active ingredient

Table 14.3 The Classification of Herbs According to their Safety and Therapeutic Use

Therapeutic use	Safe to use	Use with caution	Not recommended	Forbidden	No human data available
Laxative	Senna	Flaxseed (2nd and 3rd trimester)	Fenugreek	—	Rhubarb, flaxseed (1st trimester)
Anti-emetic	Ginger (1st trimester)	Fennel, ginger (2nd and 3rd trimester)	—	Cannabis	—

Source: Samavati, R. et al. (2017).

must then go through a standardization process followed by a stabilization process to ensure a shelf life of at least a year before being marketed for public use. Advanced standardization techniques, such as chromatographic fingerprinting, HPLC, HPTLC, LC-Mass Spectrophotometry, and LC-NMR, must be carefully controlled to detect impurities and possible toxins (Nikam et al. 2012). Certain herbal drugs should be dispensed as prescription drugs or over the counter (OTC) products based on the type of treatment/ailment (Kamboj 2000).

Conclusion

Based on most of the aforementioned research studies, contrary to the popular belief that herbal remedies are safe, they can cause harm as they are not regulated. Pregnant women tend to use herbal medicine alongside the prescribed medicine as they consider the former safe compared to the latter. Factors associated with this decision are level of education, ethnicity, and, most importantly, the use of herbal medicine by friends and family (Pallivalipila et al. 2017). It is essential that health professionals and/or midwives ask their patients about consumption of any herbal remedies and/or nutraceuticals for treating their symptoms (Holst et al. 2009). The use of herbal products by expectant mothers should be accompanied by appropriate counseling as well (Al-Ramahi et al. 2013).

References

Ahmed M, Hwang JH, Choi S & Han D 2017 Safety classification of herbal medicines used among pregnant women in Asian countries: a systematic review. *BMC Complementary and Alternative Medicine* 17 489. doi:10.1186/s12906-017-1995-6.

Al-Ramahi R, Jaradat N & Adawi D 2013 Use of herbal medicines during pregnancy in a group of Palestinian women. *Journal of Ethnopharmacology* **150** 79–84. doi:10.1016/j.jep.2013.07.041.

Al-Ramahi R, Jaradat N & Adawi D 2013 Use of herbal medicines during pregnancy in a group of Palestinian women. *Journal of Ethnopharmacology* **150** 79–84 [doi:10.1016/j.jep.2013.07.041].

Belanger D, Calder MD, Gianetto-Berruti A, Lui EM, Watson AJ & Feyles V 2016 Effects of American ginseng on preimplantation development and pregnancy in mice. *American Journal of Chinese Medicine* **5** 981–995. Available at: (http://ezproxy.lib.usf.edu/login?url=http://search.ebscohost.com/)login.aspx?direct=true&db=edsbl&AN=RN607556049&site=eds-live [doi:10.1142/S0192415X16500543].

Blencowe H, Cousens S, Modell B & Lawn 2010 Folic acid to reduce neonatal mortality from neural tube disorders. *International journal of epidemiology* **39** Suppl 1 i110–i121.

Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos AMM, et al. 2016 Fish oil–derived fatty acids in pregnancy and wheeze and asthma in offspring. *New England Journal of Medicine* **375** 2530–2539.

Centers for Disease Control and Prevention (CDC) 2004 Spina bifida and anencephaly before and after folic acid mandate—United States, 1995–1996 and 1999–2000. *MMWR. Morbidity and Mortality Weekly Report* **53** 362–365.

Chan LY, Chiu PY & Lau TK 2003 An in-vitro study of ginsenoside Rb_1-induced teratogenicity using a whole rat embryo culture model. *Human Reproduction* **18**, 1 October 2166–2168. doi:10.1093/humrep/deg401.

Chin RK 1991 Ginseng and common pregnancy disorders. *Asia-Oceania Journal of Obstetrics and Gynaecology* **17** 379–380 [doi:10.1111/j.1447-0756.1991.tb00289.x].

Chuang CH, Doyle P, Wang J-D, Chang P-J, Lai J-N & Chen P-C 2006 Herbal medicines used during the first trimester and major congenital malformations: an analysis of data from a pregnancy cohort study. *Drug Safety* **29** 537–548. doi:10.2165/00002018-200629060-00007.

Coletta M. Jaclyn 2010 *Omega-3 fatty acids and pregnancy. Reviews in Obstetrics & Gynecology* **3** 163–171.

Dog TL 2009 The use of botanicals during pregnancy and lactation. *Alternative Therapies in Health and Medicine* **15** 54–58.

Dugoua JJ, Perri D, Seely D, Mills E & Koren G 2008 Safety and efficacy of blue cohosh (Caulophyllum thalictroides) during pregnancy and lactation. *Canadian Journal of Clinical Pharmacology = Journal Canadien de Pharmacologie Clinique* **15** e66–e73.

Dunstan JA, Simmer K, Dixon G & Prescott SL 2008 Cognitive assessment of children at age 2½ years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. *Archives of Disease in Childhood. Fetal and Neonatal Edition* **93** F45–F50 [doi:10.1136/adc.2006.099085].

Håberg SE, London SJ, Stigum H, Nafstad P & Nystad W 2009 Folic acid supplements in pregnancy and early childhood respiratory health. *Archives of Disease in Childhood* **94** 180–184 [doi:10.1136/adc.2008.142448].

Hachul ACL, Boldarine VT, Neto NIP, Moreno MF, Ribeiro EB, do Nascimento CMO & Oyama LM 2018 Maternal consumption of green tea extract during pregnancy and lactation alters offspring's metabolism in rats. *PLOS ONE* **13** e0199969. doi:10.1371/journal.pone.0199969.

Holst L, Wright D, Haavik S & Nordeng H 2009 The use and the user of herbal remedies during pregnancy. *The Journal of Alternative and Complementary Medicine* **15** 787–792 [doi:10.1089/acm.2008.0467].

Horrocks LA & Yeo YK 1999 Health benefits of docosahexaenoic acid (DHA). *Pharmacological Research* **40** 211–225. Sep [doi:10.1006/phrs.1999.0495].

Irikura B & Kennelly EJ 1999 Blue cohosh: a word of caution. *Alternaticve Therapeutics Womens Health* **1** 81–83.

Kamboj VP 2000 Herbal medicine. *Current Science* **78** 35–39.

Krista CS 2011 *Folic Acid Food Fortification—Its History, Effect, Concerns, and Future Directions. 3(3)*, 370–384, 15 March.

Laelago T 2018 Herbal medicine use during pregnancy: benefits and Untoward Effects. In *Herbal Medicine. IntechOpen*.

Lassi ZS, Salam RA, Haider BA & Bhutta ZA 2013 Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. *Cochrane Database of Systematic Reviews* **3** CD006896 [doi:10.1002/14651858.CD006896.pub2].

Milunsky A, Jick H, Jick SS, Bruell CL, MacLaughlin DS, Rothman KJ & Willett W 1989 Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *JAMA* **262** 2847–2852 [doi:10.1001/jama.262.20.2847].

Mothupi MC 2014 Use of herbal medicine during pregnancy among women with access to public healthcare in Nairobi, Kenya: a cross-sectional survey. *BMC Complementary and Alternative Medicine* **14** 432. doi:10.1186/1472-6882-14-432.

Mukherjee PK & Wahile A 2006 Integrated approaches towards drug development from Ayurveda and other Indian system of medicines. *Journal of Ethnopharmacology* **103** 25–35 [doi:10.1016/j.jep.2005.09.024].

Nikam PH, Kareparamban J, Jadhav A & Kadam V 2012 Future trends in standardization of herbal drugs. *Journal of Applied Pharmaceutical Science* **2** 38–44.

Pallivalipila AR, Stewart D, Shetty A, Pande B, Rore C, Izzati N, Hail MA & McLay JS 2017 Pregnancy and the use of herbal medicines. *Reproductive Toxicology* **72** 16–17 [doi:10.1016/j.reprotox.2017.06.071].

Plant fact sheet. Available at: (https://plants.usda.gov/factsheet/pdf/fs_paau3.pdf): United States Department of Agriculture National Resources Conservation Service (USDA NRCS).

Prakash AS, Pereira TN, Reilly PE & Seawright AA 1999 Pyrrolizidine alkaloids in human diet. *Mutation Research* **443** 53–67 [doi:10.1016/s1383-5742(99)00010-1].

Samavati R, Ducza E, Hajagos-Tóth J & Gaspar R 2017 Risks and safety of herbal laxatives and antiemetics in pregnancy. *Reproductive Toxicology* **72** 16. doi:10.1016/j.reprotox.2017.06.069.

Tadokoro Y, Horiuchi S, Takahata K, Shuo T, Sawano E & Shinohara K 2017 Changes in salivary oxytocin after inhalation of clary sage essential oil scent in term-pregnant women: a feasibility pilot study. *BMC Research Notes* **10** 717 [doi:10.1186/s13104-017-3053-3].

Tiran D 2003 The use of herbs by pregnant and childbearing women: a risk-benefit assessment. *Complementary Therapies in Nursing and Midwifery* **4** 176–181. Available at: (http://ezproxy.lib.usf.edu/login?url=http://search.ebscohost.com/)login.aspx?direct=true&db=edsbl&AN=RN138382690&site=eds-live. Accessed January 10, 2019 [doi:10.1016/S1353-6117(03)00045-3].

Ulbricht, CE 2010 *Natural Standard Herb & Supplement Guide: An Evidence-Based Reference*. E-book. Elsevier Health Sciences.

Van der Kooi R & Theobald S 2006 Traditional medicine in late pregnancy and labour: perceptions of Kgaba remedies amongst the Tswana in South Africa. *African Journal of Traditional, Complementary and Alternative Medicines* **3** 11–22 [doi:10.4314/ajtcam.v3i1.31135].

Whitrow MJ, Moore VM, Rumbold AR & Davies MJ 2009 Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. *American Journal of Epidemiology* **170** December 1486–1493 [doi:10.1093/aje/kwp315].

Wilkinson JM 2000 Effect of tea on the fetal development of Sprague-Dawley rats. *Reproductive Toxicology* **14** 507–512 [doi:10.1016/S0890-6238(00)00106-4].

Zamawe C, King C, Jennings HM & Fottrell E 2018 Associations between the use of herbal medicines and adverse pregnancy outcomes in rural Malawi: a secondary analysis of randomised controlled trial data. *BMC Complementary & Alternative Medicine*: N.PAG. Available at: (http://ezproxy.lib.usf.edu/login?url=http://search.ebscohost.com/)login.aspx?direct=true&db=edb&AN=129785734&site=eds-live **18** 166 [doi:10.1186/s12906-018-2203-z].

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Nutraceuticals for Bone Health in Pregnancy

Rupal Jani

Contents

Introduction

Nutraceuticals for Bones

Bones are an integral and important part for a sound body and a healthy life. Bone well-being is particularly essential for all age groups as it is the main foundation that provides support and protection to the body. By following healthy diet and exercises we can build strong bones and avoid long-term, dependable, and painful medical issues. Milk is the key component in the eating regimen that is most effective for bone health. At one time people would consume milk from the animals. In the later phase of the twentieth century, research acknowledged milk's significance as a part of balanced eating regimen (Braithwaite et al. 2014).

In the mid-nineteenth century raw milk was distributed in metal buckets and could still be warm from the dairy animals it came from when it arrived at its destination. This technique of distribution was not appropriate for the delivery of fresh milk in cities, however, therefore over time the methods of collection and distribution of milk have changed. The consumption of raw milk can be hazardous to health, as harmful bacteria may be present, for example, salmonella, E. coli, and listeria which are responsible for some food-borne ailments. Pasteurization, homogenization, fortification, and, finally, packaging in plastic containers were developed to address distribution and food safety issues (Braithwaite et al. 2014).

Pasteurization, invented by Louis Pasteur in 1863, is a technique that involves heating the milk to a temperature greater than 161 °F for a short period of time; this kills 99% of bacteria, molds, and yeast. The pasteurization technique was an initial innovation, extending the shelf life of milk by around half a month but along with destroying infectious bacteria, it also destroys essential minerals such as vitamins, enzymes, and some beneficial bacteria. Additionally, milk may also be purified by microfiltered processes, by being passed forcefully through ceramic filters to remove bacteria that are then homogenized to prevent separation into butter–fat globules and milk fluid. In the homogenization process, milk is emulsified under intense pressure as it is pumped through narrow tubes in which the fat globules are broken down into smaller ones, and, in turn, it does not lose the milk's nutritional value or its effectiveness. In further developments, the dairy industry has gone through numerous progressions to raise milk production, quality, and distribution (Varoni & Iriti 2016).

Nutraceuticals and Functional Foods

The term "nutraceuticals" was derived from the words "nutrient" (a food component) and "pharmaceutical" (a medical drug), coined in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine, an American organization located in Cranford, New Jersey.

"Nutraceuticals" is a broad term used to indicate any product derived from food sources that has extra health benefits in addition to the basic nutritional value found in the food. They are considered to be non-specific biological treatments that can be utilized to promote general well-being and control symptoms of any disorders.

The hypothesis behind the utilization of nutraceuticals is to prevent several types of disorders and illness, with the goal of improving the health of human beings by daily diet (Varoni & Iriti 2016).

Classification of Nutraceuticals

Nutraceuticals and related products can generally be characterized on the basis of their natural sources, pharmacological conditions, and chemical constitution of the products. Most frequently they are grouped in the following classes: (1) dietary supplements, (2) functional foods, (3) medicinal foods, (4) pharmaceuticals.

Dietary Supplement

A dietary supplement contains nutrients derived from food products that are available in the form of liquids, capsules, powders, or pills. They are regulated by the Food and Drug Administration (FDA) as foods that differs from drugs and other food regulations.

Functional Food

Functional food includes whole foods and fortified foods containing enriched or enhanced dietary components that may decrease the risk of chronic disease and provide a health benefit beyond the traditional nutrients it contains.

Medicinal Food

Medicinal food is formulated to be consumed or administered internally, under the supervision of a certified physician. It is used for specific dietary management of a disease or condition for which nutritional requirements prerequisites are established by the medicinal assessment.

Pharmaceutical

Pharmaceuticals are valuable medical components obtained from modified agricultural crops or animals. Advocates of this concept believe that utilizing crops (and potentially even animals) as pharmaceutical factories is considerably more cost-effective than conventional methods of production, with higher income for agricultural producers.

Maternal Behavior and Bone Development

Bone Structure and Function

Bone is a composite of stringy collagen strands, which can be compared to the steel rebar in concrete, and a stronger solidified, mineralized core, which contains a higher content of calcium, again in a similar way to concrete. However, bone is a living tissue that, although it may look inactive at first glance, is persistently breaking down and reforming new bone so that it remains adapted to mechanical burdens and stresses. The human body made up of 206 bones and other connective tissues called tendons, ligaments, and cartilage. Bones are connected to each other by ligaments whereas tendons connect bones to muscles, and cartilage furnishes bones with greater flexibility and acts as a cushion in the joints between bones. The skeleton gives protection and structural support for all the other organ systems in the body. The skull, or cranium, protects the eyes, ears, and brain. The ribs help to form a cage that surrounds and protects the lungs and heart. In addition to this, red blood cells (RBCs) and white blood cells (WBCs) and platelets are synthesized in bone marrow. Bones also contain a complex network of canals, blood vessels, and nerves that provide storage for minerals, such as calcium, phosphorous, and magnesium, allowing nutrient transport and contact with other organ systems (Mine & Shahidi 2005).

Bone Anatomy and its Structure

It is essential to understand bone anatomy to consider bone health through nutrition. The skeleton is made up of two principal parts, the hub or axial, and the appendicular parts. The hub skeleton is made of 88 bones and comprises the skull, vertebral column, and rib cage. The appendicular skeleton is made of 126 bones and comprises of the shoulder girdle, pelvic girdle, and upper and lower extremities. Bones are likewise classified by size and shape, which allows for their different functions. There are four kinds of bone: long bones, short bones, flat bones, and sporadic/irregular bones. The longest bone in the human body is the femur (or "thigh" bone), which stretches out from the hip to the knee, and supports the body's weight when standing, walking, or running. The wrist is made of eight irregular-shaped bones, which take account of the intricate movements of the hands. The twelve ribs on each side of the body are bent flat bones that protect the heart and lungs (Trisha 2003) .

Bones are made of approximately 65% mineralized matrix grid (inorganic material), which mostly consists of crystallized hydroxyl apatite of bone tissue and is responsible for its rigid structure. The other 35% of bone is mostly fibrous protein, collagen (organic material). The collagen fibers are arranged throughout the bone tissue, which gives flexibility and strength. The bones' inorganic and organic materials are organized into two distinct tissue types. There is spongy bone, called trabecular or cancellous bone, and compact bone called cortical bone (Figure 15.1). These two tissue types contrast in their microstructural design and porosity. Trabecular bone is 50% to 90% porous, making up around 20% of the adult skeleton, and it shows a lattice-like structure under the microscope. It is found at the ends of long bones, in the centers of vertebrae, and in the pelvis. The more dense cortical bone is about 10% porous and makes up about 80% of the adult skeleton. It looks like many concentric circles sandwiched together (Figure 15.2). Cortical bone tissue surrounds all trabecular tissue and is the main tissue in the shafts of long bones (Pandey et al. 2018).

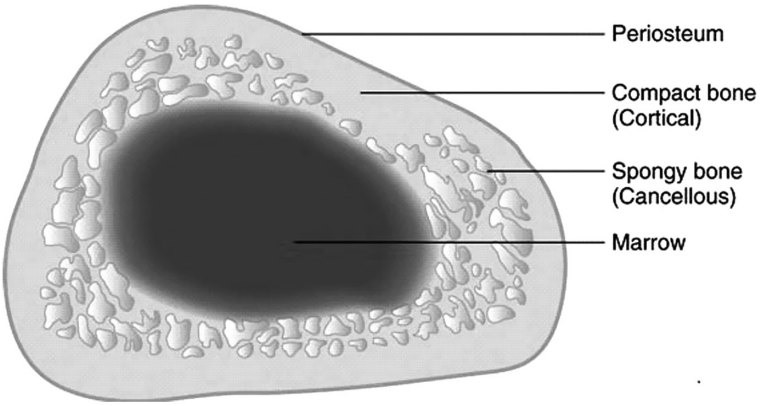

Figure 15.1 *Different parts of bone tissues.*

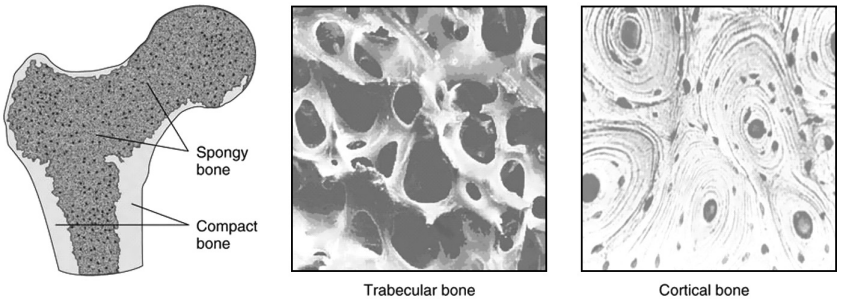

Figure 15.2 *Basic types of bones.*

Osteoporosis and Nourishment

Osteoporosis is a widely spread inflated bone disorder which results in gradual thinning and weakening of the bones. If this weakening of bones goes untreated, at some point the bones are probably going to break or crack with minor injury or with little trauma. Importantly, women are at a higher risk of developing osteoporosis than men as women experience a rapid loss of bone from the skeleton due to the decrease in estrogen production. The process of breaking down and rebuilding of bone by osteoclasts and osteoblasts respectively is a nearly perfectly coupled system, with one phase stimulating the other. Bone contains an extracellular protein matrix (mostly collagen fibers) interspersed with bone cells (osteocytes), with a mineral segment comprising calcium salts and other minerals, including sodium, magnesium, and fluoride, laid on to this. Osteoclasts resorb bone at a specific site, undergo programmed cell death, and in turn replace the protein matrix (osteoid) and mediate its remineralization. During remineralization, the osteoblasts are enclosed within the calcified material and become osteocytes, which maintain the structure of the bone. Bone turnover, mediated by the osteoclasts and osteoblasts, occurs throughout life and is known as "remodeling." Estrogen insufficiency postpones the customized cell passing or apoptosis of osteoclasts, in this way prompting a net bone loss. As an individual ages, the rebuilding framework separates and the two procedures (restoration and renewal) become out of synchronization. The reasons for this are not clear. A few people have an extremely high turnover rate of bone and some have an exceptionally slow turnover, yet the breakdown of bone, in the long term, overwhelms the development. Since the examples of changing and reabsorbing bone frequently shift from patient to tolerant, specialists trust various diverse components represent this issue. Vital hormones, such as estrogen and parathyroid hormone, vitamin D, and blood factors that influence cell development, are associated with this procedure. Changes in the dimensions of any of these elements could assume a role in the improvement of osteoporosis. Postmenopausal women regularly undergo hormone replacement therapy to make up for the lowering of their normal estrogen levels. Hormone replacement therapy is generally not recommended before a patient is extremely close to the levels of bone loss that can prompt osteoporotic fractures. Since calcium is a basic element of bone, it is believed to be important to have satisfactory calcium intake either as part of the normal diet or by taking supplements. Without vitamin D calcium cannot be consolidated into the bone and, subsequently, sufficient vitamin D intake is required as well. As well as being a good protein source, ox-like milk is regularly a primary dietary source for calcium and nutrient D. Milk proteins and their consequences for bone malady have been the focal point of a lot of research. The proteins found in milk incorporate immunoglobulin, development factors, ox-like serum egg whites, alpha-lactalbumin, beta-lactoglobulin, and an extensive number of caseins, which are all phosphor proteins. These proteins, except for casein, are additionally present in whey. Milk is known to contain an assortment of mitogenic proteins and

proteins that might be included straightforwardly in bone rebuilding. In this way, we can say that bone is a living tissue that constantly adjusts to mechanical issues while progressing toward redesigning. For bone tissue to redesign, certain supplements, such as calcium, phosphorus, magnesium, fluoride, nutrient D, and nutrient K, are required (Ahmadieh & Arabi 2011).

The skeletal structure helps in movement, provides support and protects organs, synthesizes platelets and RBC and WBC, and serves as storage for minerals, for example, calcium. The skeleton is made up of connective tissues including bones, ligaments, and tendons. Bones are comprised of a periosteum that encompasses a smaller bone, which encompasses the trabecular bone. Bone marrow resides inside the trabecular bone. Bone tissue cells are osteoprogenitor cells, osteoblasts, osteoclasts, and osteocytes. Bone is a living tissue that adjusts to mechanical pressure through the remodeling procedure. Bone remodeling is a multifaceted procedure including four stages: osteocyte activation, osteoclast-intervened bone resorption, surface formation, and osteoblast-mediated bone structure. The bone remodeling process requires certain supplements, such as calcium, phosphorus, magnesium, fluoride, vitamin D, and vitamin K7.

The Burden of Osteoporotic Fracture

There are numerous kinds of resources to be taken into consideration when assessing the cost of osteoporosis, including:

1. The direct expense of treating fractures that result in hospitalization (including treatment, restoration, and outpatient visits).
2. The direct expense of treating fractures that do not result in hospitalization (for example, GP and A&E facilities); medical and nontherapeutic expenses after fracture.
3. The cost of accommodation for individuals diagnosed to have osteoporosis; and the costs of treating different conditions for which osteoporosis is a contributory cause.

These are not the full scope of assets related to treating, distinguishing, and considering individuals with osteoporosis. These are probably going to be noteworthy since osteoporotic breaks can place a huge burden on casual parental figures. Understanding the magnitude of the expenses is especially important for well-being since it gives an indication of the assets exhausted from mediations went for diminishing the weight of osteoporosis. The connection between osteoporosis and various other, different conditions has only recently come to be recognized. This incorporates a few conditions (pain in joints other than back pain) that are owing to different conditions yet are actually the outcomes from osteoporotic breaks (e.g. vertebral fractures). This sort of misdiagnosis can prompt noteworthy consumption of medicinal services. However, osteoporosis is additionally a hazard factor for some regular

body movement and joint functions, with the increased seriousness of those conditions being related to the increased seriousness of osteoporosis. The financial burden alludes to the additional expenses related to the condition, but not to the absolute expenses related to treating and considering individuals with osteoporosis (King et al. 2012).

Bone Tissues and Cells

Bone tissue contains various cell types that always resize and reshape bones all through development and adulthood. Bone tissue cells incorporate osteoprogenitor cells, osteoblasts, osteoclasts, and osteocytes. The osteoprogenitor cells are cells that have not yet developed. When they are invigorated, some will progress toward becoming osteoblasts, the bone manufacturers, and others will move toward becoming osteoclasts, the cells that separate bone. Osteocytes are the most copious cells in bone tissue. Osteocytes are star-molded cells that are organized throughout the bone by means of their long cytoplasmic arms (National Institutes of Health 2011).

Bone Modeling and Remodeling

During the early stages of life, bones are ceaselessly developing and changing shape through two procedures called development (or hardening) and displaying. In the primary year of life, just about 100% of the bone tissue in the skeleton is replaced. During the time spent displaying, bone tissue is destroyed at one site and developed at an alternate site. In adulthood, our bones stop developing and displaying, however, they continue to experience the procedure of bone remodeling. During the time spent remodeling, bone tissue is corrupted and developed in a similar area. Around 10% of bone tissue is remodeled every year in grown-ups (Peters & Martini 2010) (Figure 15.4).

The initial phase in bone remodeling is osteocyte initiation (Figure 15.3). Osteocytes identify changes in mechanical power, calcium homeostasis, or hormone levels. In the second step, osteoclasts are selected to the site of the change. Osteoclasts are extensive cells with a profoundly sporadic unsettling film. These cells combine firmly deep down and emit hydrogen particles, which ferment and break up the minerals in the bone tissue grid. This procedure is called bone resorption and looks like pit unearthing. Our bodies unearth pits in our bone tissue since bones go about as storage facilities for calcium and different minerals. Bones supply these minerals to other body tissues as the need arises. Bone tissue can rebuild and fix itself when it breaks. In addition, on the off chance that you choose to prepare to run a long distance race, your bones will rebuild themselves by remodeling to better support the powers of their new capacity (Gallo 1996).

After a specific period of time the bone became older, the osteoclasts start to die and bone resorption stops. In the next step of bone renovating, the site

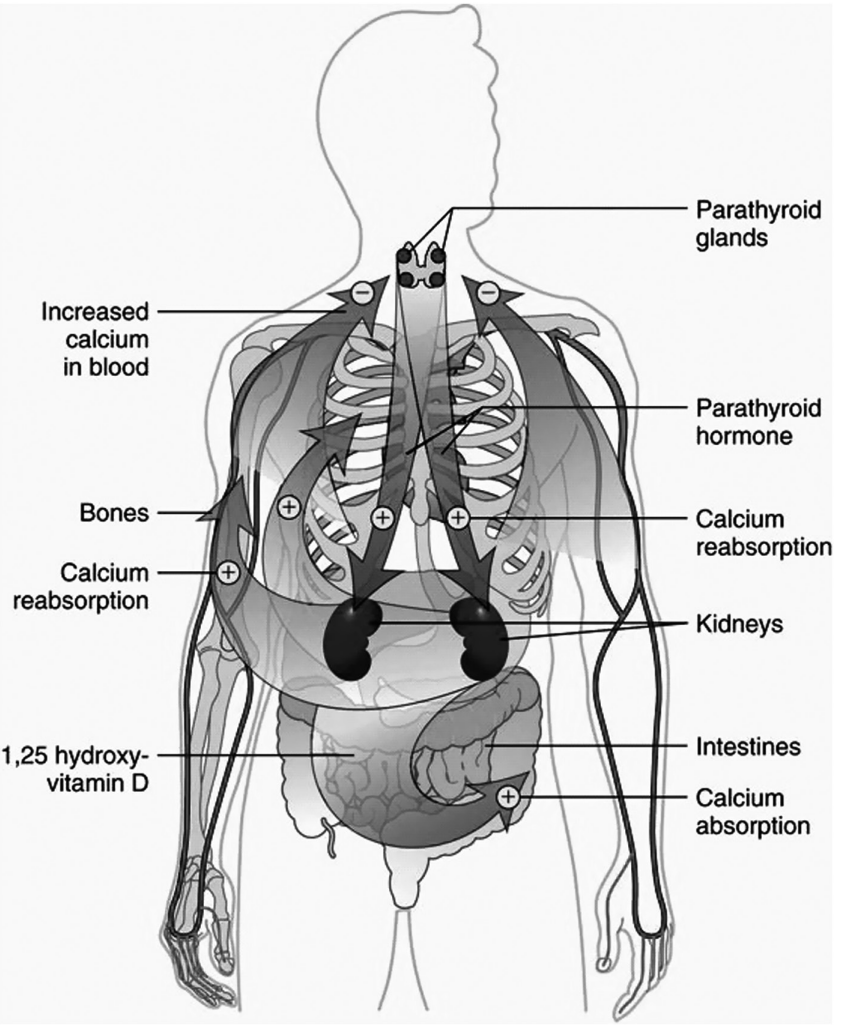

Figure 15.3 *Effect of calcium level on PTH release.*

is set up for structure. In this stage, sugars, and proteins along the bone's surface form a concrete line which acts to frame a solid bond between the old bone and the new bone that will be made. These initial three stages take around half a month to finish. In the last advance of bone renovating, osteoblasts set down new osteoid tissue that tops off the depressions that were unearthed during the resorption procedure. Osteoid is bone framework tissue that is made out of proteins, for example, collagen, and isn't mineralized yet. To make collagen, nutrient C is required. An indication of nutrient C lack (known as scurvy) is bone agony, which is brought about by lessened bone redesigning. After the osteoid tissue is developed, the bone tissue starts to mineralize. The last advance of bone renovating proceeds for a considerable

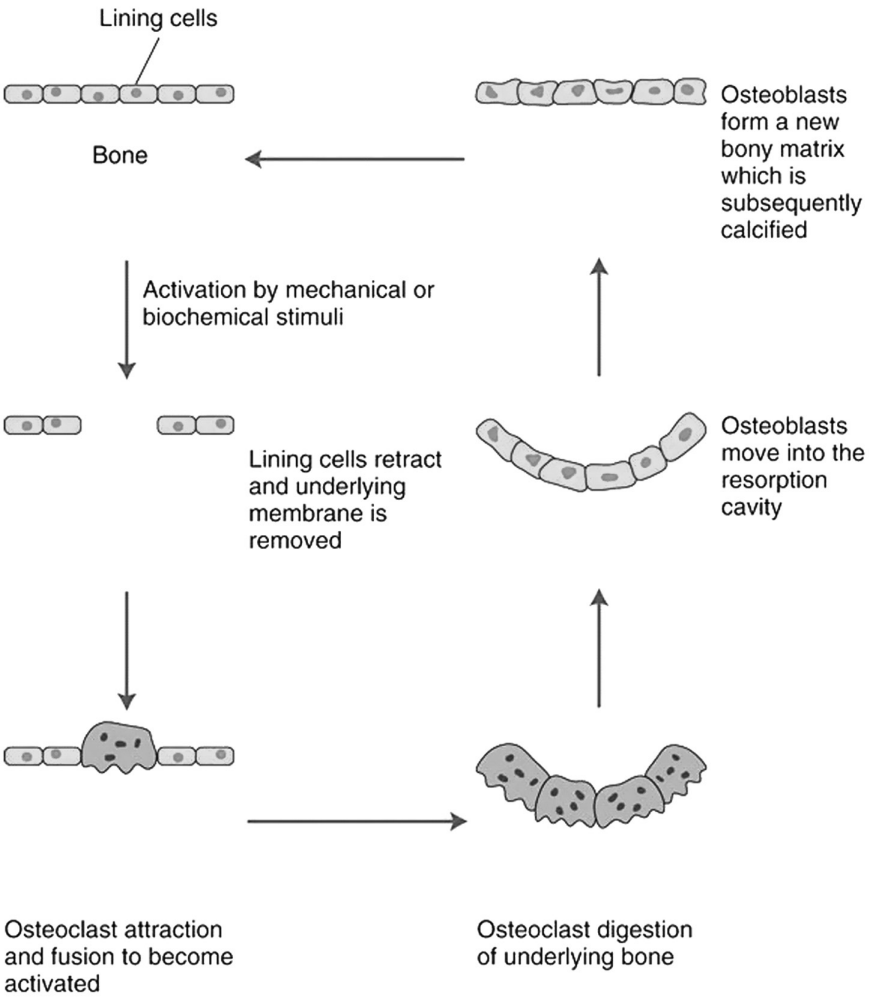

Figure. 15.4 *Process of bone remodeling.*

length of time, and for an any longer time thereafter the mineralized bone is ceaselessly pressed in a progressively thick manner (Prynne et al. 2006).

Maternal Pregnancy Factors Influencing Bone Outcomes in the Offspring

Osteoporosis is progressively perceived as an illness with its roots in early life events and exposures. Bone growth in early life may set the stage for peak bone mass accomplished in puberty, and suboptimal peak bone mass is an entrenched indicator of fracture risk. Since bone development and bone mass accretion proceed all through adolescence, it is imperative to take the way of life impacts of eating routine and movement of the youngster into record, just

as infections and restorative medications that may affect skeletal development (Tucker et al. 1999).

Neonatal Programming of Bone Status/Skeletal Development

During embryonic and fetal development a great part of the skeleton starts as a cartilaginous scaffold, which is dynamically reabsorbed and replaced by bone. Endochondral bone formation proceeds until the development plates combine during puberty. At all life stages sufficient conveyance of mineral is required for the skeleton to accomplish and keep up suitable mineral substance and quality. During fetal development the placenta effectively transports calcium, phosphorus, and magnesium. Postnatally, passive and after that active absorption from the intestine turns into the primary supply of minerals to the skeleton. Animal and human data demonstrate that fetal bone development requires parathyroid hormone (PTH) and PTH-related protein but not vitamin D/calcitriol, calcitonin, or (perhaps) sex steroids. During the postnatal period, when intestinal calcium absorption becomes an active process, skeletal development begins to rely on vitamin D/calcitriol, however, this prerequisite can be circumvented by expanding the calcium substance of the eating routine or by controlling irregular calcium imbuement (König et al. 2018). The calciotropic hormones play different roles during the fetal and neonatal periods regulating skeletal improvement and mineralization. The epidemiological proof supporting a role for maternal dietary nutrient D and conceivably calcium in fetal, neonatal, and grown-up bone results was generally limited in the consultations of the audit board in modifying the DRIs for calcium and nutrient D (Rabin 2013).

Overview of Bone Development in Fetal/Neonatal

These osteochondral ancestors start to be osteoblasts at the site of intra membranous bone arrangement (vault of the skull and a couple of different bones), though in the greater part of the creating skeleton they become chondroblasts that expansion endochondral bone development. Chondroblasts and osteoclasts assimilate the apoptosed chondrocytes and adjacent framework, vascular attack happens, and afterward osteoblasts set out the essential spongiosa (osteoid) and it will progress toward becoming mineralized. What's more, this essential hardening happens in the vertebrae and long bones between the eighth to twelfth weeks of pregnancy, yet it isn't until the third trimester that the main part of skeletal mineralization happens. Resorption and remodeling of the essential spongiosa to make auxiliary spongiosa happens in utero and resorption will strangely increment when the embryo is constrained by maternal hypocalcemia. At the 34th seven-day stretch of development, auxiliary solidification focuses on the structure in the femurs—making genuine development plates—however, generally, most epiphyses are cartilaginous until after birth. The development plates become intertwined during adolescence, after that linear development is never again conceivable (König et al. 2018).

Supplements during Pregnancy/Maternal Nutrition: The Basis of the Dietary Reference

Consistently throughout everyday life, a healthy and varied diet is imperative. In any case, it is vital during pregnancy. The maternal eating routine must give adequate energy, calories, and supplements to meet the mother's standard prerequisites, and furthermore the necessities of the developing fetus, and enable the mother to set down stores of supplements required for fetal development and for lactation. The dietary requirements for pregnant women are in reality fundamentally the same as those for different grown-ups, however, with a couple of striking special cases. The primary proposal is to pursue a solid, adjusted eating routine dependent on the Balance of Good Health. Specifically, pregnant women should endeavor to expend immense of iron- and folate-rich substances, and an everyday supplement of nutrient D (10 μg/day) is required for pregnancy. In the UK there are no official proposals for weight gain during pregnancy. For women with a solid pre-pregnancy weight, a normal weight gain of 12 kg (extended to 10–14 kg) has been delineated to be connected with the most reduced danger of issues during pregnancy and work and with decreased danger of having a low birth weight newborn child. Weight gain during pregnancy increases the risk of obesity in the mother after the birth (Leidi et al. 2012).

Concerning the all-inclusive community, pregnant women should endeavor to consume no less than two servings of fish every week, one of which ought to be oil-rich. In 2004, the Food Standards Agency (FSA) issued new guidelines on the consumption oil-rich fish and suggested that pregnant women (and individuals who are trying to conceive) consume two segments of oil-rich fish every week. Oil-rich fish contains long-chain n-3 unsaturated fats which are considered to help prevent coronary illness. Moreover, these kinds of unsaturated fats are required for fetal cerebrum and sensory system development. For instance, veggie lovers and vegetarians may find it difficult to meet their requirements for specific nutrients and minerals, especially riboflavin, nutrient B12, calcium, iron, and zinc. However, most veggie lovers and vegan women ought to have the capacity to meet their supplement necessities during pregnancy, with needful dietary arranging, while those on extremely bound weight-control plans may likewise need to use more potent supplements. Pregnancy during puberty raises various health concerns. A high proportion of young high school women have low intake of a variety of nutrients that are urgent during pregnancy, particularly folate, calcium, and iron (Hernlund et al. 2013).

Keeping up a solid, adjusted eating routine during pregnancy and remaining physically active is vital to promote general health and prosperity, and furthermore to help prevent high maternal weight gain. Studies do propose that standard, oxygen-consuming activity during pregnancy helps safeguard physical wellness and self-perception. It is prescribed that pregnant women

should proceed with their normal physical activity for whatever length of time that feels good, and endeavor to keep active once a day, for example by walking. Swimming is also a good activity, despite the fact that it is a good idea to avoid strenuous or enthusiastic physical activity during pregnancy (Sesso et al. 2012).

Dietary proposals for women before and during pregnancy are fundamentally the same as those for different grown-ups, however, with a couple of differences. The fundamental suggestion is to eat a healthy, adjusted diet as proposed by the Balance of Good Health publication. Be that as it may, there are some dietary guidelines specifically for pregnancy, for example taking folic acid supplements to help diminish the danger of neural tube defects (NTDs). There are also suggestions with respect to sanitation, for example the avoidance of specific foods to limit the danger of food contamination from unsafe microorganisms (Cranney et al. 2007).

Dietary Methodologies for Bone Health

Osteoporosis is a general medical issue for grown-ups around the world. Osteoporosis causes 2 million broken bones and $19 billion in related costs each year (Ahmadieh and Arabi 2011). Verifiably, calcium and vitamin D are the main supplements used to counteract osteoporosis in older adults. Other prescribed defenses include taking part in standard exercise, abstaining from smoking, and limiting alcohol intake. Over the past two decades, a few headways have been made, which grant re-examination of existing dietary systems for osteoporosis counteractive action. To date, many studies have linked supplements with bone health, for example, vitamins A, B, C, E, and K; minerals (potassium, magnesium, and silicon); and macronutrients (protein and fats). It is imperative to review this collection of work to determine which dietary methodologies could be counterproductive for bone health and the prevention of osteoporosis. In this chapter, we survey investigative thoughts on the connection between bone health and supplements, nourishments, and dietary examples starting from the Framingham Osteoporosis Study (Weaver 2017).

Products of the Soil

Foods grown in soil contain a large number of micronutrients, for example, vitamin K, folate, magnesium, potassium, for example, vitamin C and carotenoids. Green leafy vegetables inhibition have been related with higher bone mineral density (BMD) and less BMD loss after some time. A review of eight investigations presumed that in postmenopausal women, cross-sectional examinations bolster the sober-minded connection among foods grown from the ground consumption with bone health; nonetheless, the proof of a functional impact of products of the soil in osteoporosis avoidance in planned associates and randomized controlled preliminaries is less clear. A later report

in moderately aged and older people suggested that consuming less than the suggested five servings/day of vegetables increased the risk for hip fracture.

Vitamin C

A few studies have related oxidative stress to the pathogenesis of osteoporosis. Cancer prevention agents, for example, vitamin C, subdue osteoclast activity through their antioxidant action. Furthermore, vitamin C acts as a cofactor in advancing osteoblasts and goes about as a cofactor for collagen formation and the synthesis of hydroxyproline and hydroxylysine required for the arrangement of stable triple helixes (Tranquilli et al. 1994).

Carotenoids

Curiously, a connection of carotenoids and lycopene with biochemical markers of bone turnover has recently been delineated in postmenopausal women. In any case, a couple of longitudinal investigations have considered the relation between carotenoids other than β-carotene with bone loss or fracture hazard. In the Framingham study, the relationship between administering all carotenoids and individual carotenoids were assessed against bone loss at the hip, spine, and outspread shaft in more than four long periods of development. In women, the use of lycopene was effective against lumbar spine BMD loss more than 4 years. In men, the intake of all carotenoids, β-carotene, and lycopene were effective against bone loss. Further, members in the most astounding tertile of absolute carotenoids admission had a 46% decrease in hip fracture and members with higher lycopene consumption had a 34% l lower risk of hip fracture and a 34% less risk of non-vertebral break. The results of different studies confirm the link between individual carotenoids and a decrease in the risk of hip fracture (Wang et al. 1999a).

Folate and B_{12}

In the United States, refined grain items, including enlarged bread, oats, and flour, alongside foods grown from the ground, have turned into a prefamous wellspring of folate since the 1998 FDA order on folic acid stronghold. Information from the Framingham study was among the first to distinguish raised plasma homocysteine fixation as a solid risk factor for hip fracture. While the biological system connecting homocysteine to bone health stays questionable, McLean's underlying discoveries distributed in 2004 animated a flood in research exploring the relation between folate and vitamin B12 with bone health since a deficiency in these vitamins is a predominant determinant of raised homocysteine in older adults. In contrast to folate, vitamin B12 is absent in vegetables, it is found in animal items and fortified breakfast grains. Since modification of dietary intake of folate and vitamin B12 can effectively lower blood homocysteine focuses, these supplements were conjectured as pivotal dietary intercession for improving bone health (Albisetti et al. 2013).

Vitamin K

In Western eating regimens the key type of dietary vitamin K is phylloquinone (vitamin K1). Vitamin K is a fundamental factor for the carboxylation of osteocalcin, a bone-unconventional protein blended by osteoblasts that is among the most lavish bone lattice proteins and furthermore assumes a role in bone mineralization. Inadequate vitamin K may prompt under carboxylation of osteocalcin and add to age-related bone loss and fractures.

Potassium, Magnesium, and Alkaline Diets

Research suggests that a watery eating regimen may prevent bone loss and fracture. Potassium and magnesium are two dietary constituents found in foods grown from the ground that understanding to a higher basic state inside the body. Higher intake of potassium and magnesium were related to less BMD loss at the hip in men. Dietary intake of potassium and magnesium were comparable over the genders, suggesting that sex difference could be expected to contribute to contrasting hormonal changes that occur with age (Carpenter et al. 2006b).

Fish

The positive connection between fish consumption with BMD is likely because of its numerous nourishing components. Notwithstanding protein, certain fish are rich in polyunsaturated unsaturated fats (PUFA), and explicitly the n-3 unsaturated fat (FA) family, which have been emphatically connected with bone health because of their calming properties.

Omega-3 Fatty Acids

In synopsis, unimportant affiliations were seen with intake of individual PUFA and BMD in either sex; be that as it may, women whose eicosapentaenoic corrosive (EPA) + docosahexaenoic corrosive (DHA) intake (both n-3 FA) were ≥ middle (0.14 g daily) had higher femoral neck BMD with higher admission of the n-6 FA arachidonic corrosive (AA). This collaboration was likewise seen in men where people in the most elevated quartile of AA intake lost more hip BMD than those with the least intake, yet just among people with low EPA+DHA utilization. In this manner, the defensive impacts of an eating regimen high in AA might be dependent upon sufficient EPA+DHA intake. Likewise, plasma phosphatidylcholine (PC) centralizations of individual PUFA (n-3 FA DHA, and n-6 FA's AA and linoleic corrosive) were connected with femoral neck BMD. In women, no critical affiliations were studied; be that as it may, in men a move toward higher BMD was seen with higher plasma PC AA (Carpenter et al. 2006a).

Dietary methodologies can be a key procedure for the prevention of osteoporosis. Increasing evidence shows that diet at the dimension of vitamins,

minerals, nutritional categories, and dietary examples assumes a key role in skeletal health. This section discussed the current understanding of how vitamins, minerals, and macrovitamins present inside nutrition classes and dietary examples relate to bone health in adults and older adults, with a focus on the discoveries from the Framingham Osteoporosis Study cross-sectional and planned examinations. Numerous investigations show that the inclusion of leafy foods, fish, and specific dairy items in the diet, in addition to limiting alcohol intake, are beneficial for bone health. Further research comparing the use of supplements versus dietary sources of the nutrients discussed herein would aid our comprehension of and ability to make suggestions for the prevention of osteoporosis. Planned examinations for break result and controlled preliminaries are expected to indicate whether treatment with unconventional dietary enhancements can improve BMD or reduce crack hazard. Observational investigations have both bolstered and appeared with controlled preliminaries. Longer-term imminent mediation ponders are expected to additionally look at the dietary consequences for bone loss and crack (Song et al. 2007).

Potential of Natural Agents against Bone Loss

It is estimated that there is a high frequency of fractures related to osteoporosis globally. Milk is a readily available source of calcium and vitamin D, however one glass of milk daily doesn't provide the required daily intake of these nutrients and numerous individuals have hypersensitivity to dairy items or prefer not to consume them. Other great sources of calcium and vitamin D are soybeans, parsley, kale, salmon, broccoli, eggs, fish, beans, and enriched items, for example, soymilk, rice milk, and almond milk. As you read this section you will become familiar with the aim of building and protecting healthy bones through appropriate eating regimen and exercise. Whatever you choose, realize that your bone health is connected to your diet and way of life decisions for a considerable length of time to come.

In light of the standards of physiological bone recovery and the role of osteoblasts and osteoclasts, clearly the rate of supply of new osteoblasts and osteoclasts, and the planning of the demise of these cells by apoptosis, are prevailing determinants of bone recovery. The exercises of these cells are mostly connected with sex steroid deficiency, senescence, and glucocorticoid plenitude; besides, at menopause, the rate of bone redesigning decreases sharply. The loss of sex steroids up-regulates the age of osteoclasts and osteoblasts in the marrow by up-regulating the generation and activity of cytokines, including IL-6, TNF, IL-1, and macrophage settlement animating elements (M-CSF) which control osteoclastogenesis and osteoblastogenesis. The irregular characteristics between bone resorption and arrangement are because of an expansion of the working life expectancy of the osteoclasts and shortening of the working life expectancy of the osteoblasts. The measure of bone shaped during each rebuilding cycle decays with age in both sexes.

Glucocorticoid abundance lowers intestinal calcium retention and hypercalciuria because of inadequate vitamin D digestion. These progressions result in expanded bone resorption, diminished osteoblast outfit and biosynthetic movement, and a lack of sex hormones, just as hyperparathyroidism. A reduction in the abundance of glucocorticoid affects osteoblastogenesis in the bone marrow and furthermore helps the apoptosis of osteoblasts and osteocytes. Glucocorticoids legitimately smother bone morphogenetic protein-2 (BMP-2) and center restricting factor α-1 (Cbfα-1), two basic components for osteoblastogenesis, and may likewise diminish the creation of insulin-like development factors (IGFs) while stimulating the transcriptional movement of peroxisome proliferator-initiated receptor-γ (PPAR-γ) (Varoni & Iriti 2016; Varoni & Iriti 2016; Ryder et al. 2005).

There are a few risk factors that contrast among people and are connected to the improvement of osteoporosis and add to the probability of developing the disease. These variables can be assembled into two classifications, the first being non-modifiable factors, for example, sex, age, body size, ethnicity, and family ancestry, the other modifiable elements are sex hormones, anorexia nervosa, calcium and vitamin D admission, drug use, way of life, cigarette smoking, and liquor consumption, etc. Physical exercise, dietary enhancement, and pharmacotherapy are commonly utilized for the prevention and treatment of osteoporosis. The pharmacotherapy for osteoporosis is typically centered around pleasing the estrogen level or bone redesign. The systems include numerous highlights, for example, animating parathyroid hormone (PTH) orchestrates; inciting the statement of OPG (osteoprotegerin); diminishing IL-1, 4, 6 and M-CSF; expanding estrogens or like-estrogens; enhancing Ca and P in bones; repressing the multiplication of osteoclast and prompting osteoclast apoptosis; and upgrading the expansion and separation of osteoblasts. The medications utilized basically incorporate estrogens, parathyroid hormone, different bisphosphonates, the specific estrogen-receptor modulators (SERM) (raloxifene, calcitonin, and sodium fluoride), calcium, and vitamin D (Carpenter et al. 2006b).

Calcium supplementation alone gives little gainful impact on bone mineral thickness through postmenopausal life and may marginally decrease break rates, and vitamin D might be a useful treatment for individuals that have low vitamin D levels. The long-haul hormone treatment for osteoporosis in postmenopausal women is dubious, in light of the increase in the danger of breast cancer, endometrial malignant growth, and cardiovascular illness. Hormone treatment is only a temporary solution for menopause in symptomatic women with a high risk of osteoporotic fracture. Bisphosphonates can decrease the danger of vertebral breaks and non-vertebral cracks including hip breaks. The dosing routine (which required the patience to quick and remain stanscion for at any rate 30 minutes) and upper gastrointestinal reactions are regularly holding components in everyday bisphosphonate treatment. Their range of physiological impact is ambiguous, however, bone turnover markers can remain stifled for no less than 5 years after their endpoint. Specific estrogen-receptor

modulators (counting raloxifene, arzoxifene, and lasofoxifene) are an artificially assorted arrangement of aggravates that don't have the steroid structure of estrogen yet have a tertiary structure that enables authority of the estrogen receptor to express particular agonist or foe impacts on various estrogen target tissue. Predominant reactions include a higher risk of venous thrombosis similarly to that with hormone treatment and worsening of hot flushes. The already unveil treatments act for the most part to diminish bone resorption and the anabolic specialist parathyroid hormone basically animates bone development. The initial clinical trials in postmenopausal women portrayed PTH diminished the danger of cracks with 20 μg portion. Nonetheless, the development as far as bone mineral thickness appeared to wind down after cessation except if pursued by an antiresorptive operator. What's more, strontium ranelate is a genuinely new anti-osteoporotic operator that has been affirmed in the European Union for the treatment of postmenopausal osteoporosis. It increases bone development while lessening bone resorption, anyway its component of activity stays questionable.

Estrogens, bisphosphonates, calcitonin, calcium items, ipriflavone, and anabolic steroids are clinically utilized as powerful drugs; nonetheless, every one of them has created some symptoms. Numerous therapeutic plants have for some time been utilized to forestall and treat osteoporosis in numerous nations. These normal medications obtained from plants cause fewer symptoms and are more appropriate for long-haul use than blended medications. These plant-based drugs containing a few combined constituents generally exhibit their restorative impacts through multi-pathways and have multi-targets, this property is parallel with the numerous components of osteoporosis pathogenesis. In this chapter, we outline ongoing investigations about anti-osteoporotic restorative plants with specific conspicuousness on the compound constituents, systems of activity, and remedial applications. This will give more data to the utilizations of therapeutic plants in the prevention and treatment of osteoporosis (Carpenter et al. 2006b)

Resveratrol: Bone Health

Resveratrol (RSV), a natural polyphenolic compound with anti-inflammatory properties (3,5,4′-trihydroxy-trans-stilbene), is normally present in red wine and an assortment of plant substances, for example, grapes, cranberries. Moreover, RSV inflammation-independent effects have been outlined in connection to the bone. RSV also stimulates differentiation of osteoblast which inhibits osteoclast activity, and prevents bone loss in rats, immobilized rats, and mature–aged mice. The effects of RSV have been analyzed on biochemical markers of bone turnover in a randomized placebo-controlled trial designed to scrutinize potential effects of high-dose RSV supplementation on substrate metabolism, insulin sensitivity, and body composition. Obese men were randomly assigned to either a placebo or 1,500 mg RSV daily for 4 weeks.

RSV treatment of bone cells produces strong defense mechanism, yet dose translation from *in vitro* examinations to clinically significant dosages is constrained since bioavailability isn't considered. Because of numerous activities on the two osteoblasts and osteoclasts, research has been conducted on a few animal models to examine the bone defensive impacts of RSV supplementation. Ovariectomized rat models having rapid bone loss because of estrogen-insufficiency demonstrated that RSV supplementation improved bone mass and trabecular bone without stimulating other estrogen-sensitive tissues. RSV supplementation preceding age-related bone loss was favorable. In developing rodents, RSV increased longitudinal bone development, yet had no different impacts on bone. In human clinical trials, indication for RSV's role in bone health relies upon data produced by animal studies. A greater comprehension of efficacy, safety, and molecular mechanisms of RSV on the bone will add to the assurance of dietary suggestions and treatments to reduce osteoporosis (Wang et al. 1999b).

Resveratrol is a therapeutically effective agent for degenerative diseases like osteoporosis. Osteoporosis is a prevailing public issue with an overall assessed 9 million bone fractures every year. The occurrence of osteoporosis is expected to increase as the worldwide population ages (Wang et al. 1999b).

All through life, bone is remodeled by a process including bone resorption which evacuates old bone and replaces it with new bone through the process of bone formation. Amid the development phases of childhood, adolescence, and into adulthood, bone formation surpasses the rate of bone resorption which causes bone mass acquisition. After this stage, at ~20–30 years old, bone resorption surpasses bone formation which results in progressive bone loss. Thus, enhancing peak bone mass (PBM) is a key factor for the future risk of osteoporosis during the development period. This is especially critical for women, who are at higher risk of osteoporosis than men, because of bone loss resulting from declining estrogens at menopause. Women and men both experience age-related bone loss that is regularly quickened by mechanical lade related to physical inertness and extended bed rest. Neglect-related bone loss is likewise seen in youthful patients subjected to extended bed rest as a result of damage or immobilization due to spinal cord injury.

RSV has estrogenic, anti-inflammatory, antioxidant, and proliferative properties that can affect metabolism of bone. There are no risks associated with consumption of up to 500 mg/d of RSV in animals and human beings. Because of its various bioactivities and low harmfulness, RSV is considered as an effective and safe therapeutic agent of osteoporosis. Moreover, because of the lack of human clinical trials, RSV therapeutic role on bone depends on *in vitro* studies and creature models of bone breakdown. The point of this survey is to assess the preclinical proof of RSV supplementation to improve bone, to decrease the danger of osteoporosis, and to decide potential instruments of activity. A superior comprehension of the effects of RSV on the bone will

contribute toward the improvement of dietary proposals and treatments for forestalling bone misfortune prompting osteoporosis.

Vitamins D and Essential Children's Bone Health

Essential Micronutrients for Bone Health: Calcium and Vitamin D

Calcium

Calcium is the most abundant mineral in the body, of which more than 99% of it is stored in bone tissue. It performs the most critical functions, though only 1% of the calcium in the human body is present in the blood and soft tissues. Blood calcium levels are carefully controlled so that if blood levels drop the body will quickly react by revitalizing bone resorption, subsequently releasing stored calcium into the blood. Thus, bone tissue forfeits its stored calcium to keep up blood calcium levels. This is the reason bone health is reliant on the intake of dietary calcium and furthermore why blood levels of calcium don't always relate to dietary intake.

Calcium's Functional Roles

Calcium plays a significant role in different functions in the body.

Bone Formation

The most outstanding calcium function is to build and fortify bones and teeth. When bone tissue first forms during the modeling or remodeling process, it is unhardened, protein-rich osteoid tissue. In the osteoblast-coordinated procedure of bone mineralization, calcium phosphates (salts) are deposited on the protein matrix. The calcium salts progressively crystallize into hydroxyapatite, which ordinarily makes up around 65% of bone tissue. At the point when your diet is calcium insufficient, the mineral content of bone declines making it fragile and feeble. Subsequently, increased calcium intake builds the mineralized substance of bone tissue. More prominent mineralized bone tissue compares to a more prominent BMD and to more prominent bone strength. The discrete arrangements of the calcium-rich hydroxyapatite crystals on bone tissue's protein matrix contribute to most differing bone's mechanical properties. In tooth enamel, hydroxyapatite crystals are densely packed, making it the most mineralized tissue (greater than 95%) in the human body having incredible strength and sturdiness. The mineralized bone tissue in human teeth is so strong that back molars can withstand bite forces surpassing four hundred pounds pressure (Wang et al. 1999b).

Nerve Impulse Transmission

Calcium facilitates electrical impulse transmission from one nerve cell to another by binding to vesicles that contain neurotransmitters, causing a discharge into the neural synapses (junction between nerve cells). This allows the flow of ions in and out of nerve cells. If calcium is lacking, nerve-cell function will fail.

Muscle Contraction

For muscle contraction, the circulation of calcium ions along the muscle cell's surface and the influx of calcium into the muscle cell are critical. If calcium levels fall below a crucial range, the muscles can't relax after contracting. The muscles become stiff, and involuntary twitching may occur in a condition known as tetany.

Clotting Factors

At a point when a blood vessel is injured and bleeding occurs, it must be controlled, or death may result. Clotting factors and platelets are dynamically circulating in the blood in case of such an emergency. During injury, the circulating clotting factors and platelets were activated by specific factors released from the damaged tissue. Some of the clotting factors require calcium for activation. If clotting factors weren't activated blood clots would not form.

In addition to calcium's four primary functions calcium has various other minor functions that are also critical for maintaining normal physiology. For example, without calcium, the hormone insulin could not be discharged from cells in the pancreas and glycogen could not be broken down in muscle cells and used to provide energy for muscle contraction (Matias et al. 2012).

Maintaining Calcium Levels

Blood calcium level is strongly regulated by parathyroid hormone, calcitriol, and calcitonin which maintains calcium levels in the blood in the range of 9 to 11 mg/dL. Calcitriol is the active hormone synthesized from vitamin D. Parathyroid hormone and calcitriol help in elevating calcium levels in the blood, while calcitonin decreases blood calcium levels.

Parathyroid Hormone

PTH increases blood calcium levels by means of three different mechanisms. First, PTH stimulates the release of calcium stored in the bone. Second, PTH follows up on kidney cells to enhance calcium reabsorption and reduces its excretion in the urine. Third, PTH stimulates enzymes in the kidney that activate vitamin D to calcitriol which acts on intestinal cells by increasing dietary calcium absorption. Thus, stored calcium is released, more calcium is absorbed from the diet, and less calcium is excreted, resulting in elevating calcium levels in the blood (Saggese et al. 1991).

Conclusion

Osteoporosis is the most common bone disorder; it is characterized by a gradual weakening of the bones and finally leads to breakdown and fracture of

bones. Due to the high cost of currently available treatment, it is good to prevent osteoporosis. It can be possible to control the onset of osteoporosis by maintaining a healthy diet as well as taking regular exercises. Nutraceuticals are the agents that play an effective role in bone development as well as give mechanical strength to the bones. One of the most essential ways to build and maintain healthy bones is by getting enough calcium every day. Currently, there are a number of nutraceuticals available which are very good supplements of calcium. Thus, the daily intake of such type of nutraceuticals helps in the prevention as well as treatment of osteoporosis.

References

Ahmadieh H & Arabi A 2011 "Vitamins and bone health: beyond calcium and vitamin D." *Nutrition Reviews* **69** 584–598. doi:10.1111/j.1753-4887.2011.00372.x.

Albisetti W, Giarratana LS, Viganò C, Castiglioni S & Maier JA 2013 "Sclerostin: a novel player regulating bone mass in inflammation?" *European Journal of Inflammation* **11** 345–352 [doi:10.1177/1721727X1301100204].

Braithwaite MC, Tyagi C, Tomar LK, Kumar P, Choonara YE & Pillay V 2014 "Nutraceutical-based therapeutics and formulation strategies augmenting their efficiency to complement modern medicine: an overview." *Journal of Functional Foods* **6** 82–99 [doi:10.1016/j.jff.2013.09.022].

Carpenter TO, DeLucia MC, Zhang JH, Bejnerowicz G, Tartamella L, Dziura J, Petersen KF, Befroy D & Cohen D 2006a "A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls." *The Journal of Clinical Endocrinology and Metabolism* **91** 4866–4872 [doi:10.1210/jc.2006-1391].

Carpenter TO, DeLucia MC, Zhang JH, Bejnerowicz G, Tartamella L, Dziura J, Petersen KF, Befroy D & Cohen D 2006b "A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls." *The Journal of Clinical Endocrinology and Metabolism* **91** 4866–4872 [doi:10.1210/jc.2006-1391].

Cranney A, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, Atkinson S, Ward L, Moher D, Hanley D et al. 2007 "Effectiveness and safety of vitamin D in relation to bone health." *Evidence Report/Technology Assessment* **158** 1–235.

Gallo AM 1996 "Building strong bones in childhood and adolescence: reducing the risk of fractures in later life." *Pediatric Nursing* **22** 369–74, 422.

Hernlund E, Svedbom A, Ivergard M et al. 2013 "Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA)." *Archives of Osteoporosis* **8** 10, 97 10 of 11 [doi:10.1007/s11657-013-0136-1].

King L, Watson WL, Chapman K, Kelly B, Louie JC, Hughes C, Crawford J & Gill TP 2012 "Do we provide meaningful guidance for healthful eating? an investigation into consumers' interpretation of frequency consumption terms." *The Journal of Nutrition Education and Behavior* **44** 459–463 [doi:10.1016/j.jneb.2011.12.004].

König D, Oesser S, Scharla S, Zdzieblik D & Gollhofer A 2018 "Specific collagen peptides improve bone mineral density and bone markers in postmenopausal women, A Randomized Controlled Study." *Nutrients* **10** 97. doi:10.3390/nu10010097. Available at: (www.mdpi.com/journal/nutrients).

Leidi M, Dellera F, Mariotti M, Banfi G, Crapanzano C, Albisetti W & Maier JA 2012 "Nitric oxide mediates low magnesium inhibition of osteoblast-like cell proliferation." *Journal of Nutritional Biochemistry* **23** 1224–1229 [doi:10.1016/j.jnutbio.2011.06.016].

Matias CN, Santos DA, Monteiro CP, Vasco AM, Baptista F, Sardinha LB, Laires MJ & Silva AM 2012 "Magnesium intake mediates the association between bone mineral density and lean soft tissue in elite swimmers." *Magnesium Research* **25** 120–125 [doi:10.1684/mrh.2012.0317].

Mine Y & Shahidi F 2005 "Nutraceutical proteins and peptides in health and disease.". *Nutraceutical Science and Technology* 3–9 [doi:10.1201/9781420028836.sec1].

National Institutes of Health 2011 Dietary supplements: background information. Available at: (http://ods.od.nih.gov/factsheets/DietarySupplements-HealthProfessional/). Accessed on 2/3/2014.

Pandey MK, Gupta SC, Karelia D, Gilhooley PJ, Shakibaei M & Aggarwal BB "Dietary nutraceuticals as backbone for bone health." *Biotechnology Advance* 2018: Camden, NJ, USA: Department of Biomedical Sciences, Cooper Medical School of Rowan University: ELSEVIER. 27 March. doi:10.1016/j.biotechadv.2018.03.014.

Peters BS & Martini LA 2010 "Nutritional aspects of the prevention and treatment of osteoporosis." *Arquivos Brasileiros de Endocrinologia e Metabologia* **54** 179–185 [doi:10.1590/s0004-27302010000200014].

Prynne CJ, Mishra GD, O'Connell MA, Muniz G, Laskey MA, Yan L, Prentice A & Ginty F 2006 "Fruit and vegetable intakes and bone mineral status: a cross sectional study in 5 age and sex cohorts." *The American Journal of Clinical Nutrition* **83** 1420–1428 [doi:10.1093/ajcn/83.6.1420].

Rabin RC 2013 "Should we toss our vitamin Pills?" The New York Times. Available at: (http://well.blogs.nytimes.com/2013/12/16/a-challenge-tovitamins/?_php=true&_type=blogs&emc=eta1&_r=0). Accessed on 2/3/2014.

Ryder KM, Shorr RI, Bush AJ, Kritchevsky SB, Harris T, Stone K, Cauley J & Tylavsky FA 2005 "Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects." *Journal of the American Geriatrics Society* **53** 1875–1880 [doi:10.1111/j.1532-5415.2005.53561.x].

Saggese G, Federico G, Bertelloni S, Baroncelli GI & Calisti L 1991 Hypomagnesemia and the parathyroid hormone-vitamin D endocrine system in children with insulin-dependent diabetes mellitus: effects of Mg administration. *The Journal of Pediatrics* **118** 220–225 [doi:10.1016/s0022-3476(05)80486-x].

Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE & Gaziano JM 2012 "Multivitamins in the prevention of cardiovascular disease in men: the physicians' health study ii randomized controlled trial.". *JAMA*: The American Medical Association **308** 1751–1760 [doi:10.1001/jama.2012.14805].

Song CH, Barrett-Connor E, Chung JH, Kim SH & Kim KS 2007 "Associations of calcium and magnesium in serum and hair with bone mineral density in premenopausal women." *Biological Trace Element Research* **118** 1–9 [doi:10.1007/s12011-007-0011-2].

Tranquilli AL, Lucino E, Garzetti GG & Romanini C 1994 "Calcium, phosphorus and magnesium intakes correlate with bone mineral content in postmenopausal women." *Gynecological Endocrinology* **8** 55–58 [doi:10.3109/09513599409028459].

Trisha E O'Hehir 2003 "Discuss the research rationale for periodontal instrumentation. 2. Observe a radical ... The Toothpaste Secret." *Neutraceuticals* November 1.

Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW & Kiel DP 1999 "Potassium, magnesium, and fruit and vegetables intake are associated with greater bone mineral density in elderly men and women." *The American Journal of Clinical Nutrition* **69** 727–736 [doi:10.1093/ajcn/69.4.727].

Varoni EM & Iriti M 2016 "Odontonutraceuticals: pleiotropic phytotherapeutic agents for Oral Health." *Pharmaceuticals* 9 1–3. doi:10.3390/ph9010010.

Wang MC, Moore EC, Crawford PB, Hudes M, Sabry ZI, Marcus R & Bachrach LK 1999a "Influence of pre-adolescent diet on quantitative ultrasound measurements of the calcaneus in young adult women." *Osteoporosis International* **9** 532–535 [doi:10.1007/s001980050181].

Wang MC, Moore EC, Crawford PB, Hudes M, Sabry ZI, Marcus R & Bachrach LK 1999b "Influence of pre-adolescent diet on quantitative ultrasound measurements of the calcaneus in young adult women." *Osteoporosis International* **9** 532–535 [doi:10.1007/s001980050181].

Weaver CM 2017 "Nutrition and bone health." *Oral Diseases*: West Lafayette, IN, USA: Department of Nutrition Science, Purdue University **23** 412–415. doi:10.1111/odi.12515. Published by John Wiley & Sons Ltd All rights reserved www.wiley.com.

Yokoyama K, Takahashi N, Yada Y, Koike Y, Kawamata R, Uehara R, Kono Y, Honma Y & Momoi MY 2010 "Prolonged maternal magnesium administration and bone metabolism in neonates." *Early Human Development* **86** 187–191 [doi:10.1016/j.earlhumdev.2010.02.007].

16

Nutraceuticals for Maternal and Offspring's Dental Health

Amanda Rodrigues Amorim Adegboye

Contents

Dental Diseases

Dental diseases are common conditions and almost every individual has had an incidence of caries, periodontitis, or gingivitis during their life span. Despite these conditions being associated with a low mortality rate, dental diseases cause avoidable pain and anxiety, and eventually may lead to tooth loss (Sheiham et al. 2001). Tooth loss results in chewing impairment and consequently leads to the consumption of a limited diet of poor nutritional quality, which may not only have a severe impact on nutritional status, but on the overall quality of life (Sheiham et al. 2001; Sheiham & Steele 2001; Marcenes et al. 2003).

Dental caries or decay is a result of a complex interaction over time between acid-producing bacteria (e.g. *Streptococcus mutans*), fermentable carbohydrates, and host characteristics, including enamel (outer layer of the tooth) mineralization and the production and composition of the saliva. The key event for caries development is an ecological shift resulting in the overgrowth of aciduric microorganisms in the biofilm due to low pH conditions in the oral environment (Selwitz, Ismail & Pitts 2007; Takahashi & Nyvad 2008, 2011).

Periodontal disease is a chronic inflammation induced by bacterial infection which affects the supporting structures of teeth (e.g. gums). Periodontitis is then characterized by periodontal clinical attachment loss and alveolar bone

loss, which can subsequently lead to tooth loss (Krasse et al. 2006a). Gingivitis is a mild inflammation of the gingivae and tends to result in redness, swelling, and bleeding (Krasse et al. 2006).

Oral Health and Pregnancy Outcomes

Oral health has often been viewed separately from general health although oral health status influences overall well-being and quality of life over a person's life span (McGrath & Bedi 2001; Sheiham et al. 2006). Physiological hormonal changes during pregnancy make pregnant women more prone to develop periodontitis or worsen existing periodontitis with the progression of pregnancy (González-Jaranay et al. 2017). This inflammatory burden seems to have effects far beyond the oral cavity (Kane 2017). Evidence from systematic reviews suggests that women with periodontitis may be at higher risk for delivering premature (less than 37 weeks' gestation), low birthweight (less than 2.5 kg) babies (Chambrone et al. 2011, Kane 2017). Additionally, periodontitis seems implicated in preeclampsia (Moura da Silva et al. 2012; Sgolastra et al. 2013). A meta-analysis including 15 studies showed a positive association between preeclampsia and periodontitis (OR: 2.17; 95% CI: 1.38–3.41; P = 0.0008)(Sgolastra et al. 2013). However, there is conflicting evidence related to the association between periodontitis and gestational diabetes (Lima et al. 2016). Regarding maternal caries, a recent systematic review concluded that dental caries does not appear to be a substantial risk factor for preterm birth (Wagle et al. 2018).

Vertical transmission from mother to child of oral pathogens is also a concern. The earlier a child is colonized with *S. mutans* the higher the risk of caries later in life. Mother-to-child transmission of these acid-producing bacteria usually occurs during the first few weeks of life, even before the primary teeth have erupted (Doméjean et al. 2010). Periodontal pathogens are also transmitted between members of the same family. Oral colonization of periodontal pathogens has been identified in children as young as 5–7 years old (Asikainen et al. 1997). Therefore, potential low-risk, affordable interventions to prevent and treat dental diseases during pregnancy are of relevance for both mothers and their offspring.

Diet and Oral Health

The World Health Organization (WHO) has included dental diseases among the chronic diseases preventable by diet (WHO 2003). Dietary factors can impact dental health through local or systemic effects(Boyd & Lampi 2001). Local effects include the influence of diet on the oral biofilms, bacteria, or the amount, composition, and acidity level of the saliva, which are important determinants of dental disease (Bowden & Li 1997). Additionally, diet can

have systemic effects, when absorbed, nutrients and minerals have an impact on tooth development and growth, or on the individual's resistance to oral disease (Boyd & Lampi 2001). Particularly, micronutrients may be of importance here, and a specific role has been suggested for vitamin D and calcium (Grant & Boucher 2010; Adegboye et al. 2016).

A developing fetus receives all its nutrition from its mother. The early life environment, which a fetus is exposed to in the womb and during the first year of life, is important for healthy growth and body function. Therefore, it is paramount to advise pregnant women on the quality and quantity of dietary intake and provide dietary supplements when necessary.

Human tooth development is unique, as it is formed during a limited period of time and remains relatively stable in its structure and metabolism after mineralization (Jontell & Linde 1986). For human teeth to be healthy, all parts of the tooth must develop appropriately during key stages of fetal life. Thus, the intrauterine milieu, influenced by maternal nutrition, smoking habits, and alcohol consumption, can affect the formation, development, and mineralization of a child's teeth (Jontell & Linde 1986). Some nutrients have been linked to the development of enamel defects (lack of vitamin D), periodontal disease (lack of vitamin C), and caries (free sugars, lack of fluoride), but, generally, only a few experimental studies have examined the effect of nutraceuticals on the prevention, delay of disease onset, and progression and treatment of dental diseases (Varela-López et al. 2018).

The Role of Nutraceuticals on Maternal and Offspring's Dental Health

The role of nutraceuticals on dental health has not been extensively investigated in the general population and only a few studies have focused on the dental health of pregnant women and their offspring. Therefore, most of the data presented in Table 16.1 are based on studies conducted in the general population, which findings can potentially be extrapolated to the dental health of pregnant women and their offspring.

A comprehensive systematic review (Varela-López et al. 2018), with 41 studies included, investigated how different types of nutraceuticals (particularly vitamins) could ameliorate or improve periodontal health. All vitamins, with the exception of vitamin K, were investigated, and those with antioxidant properties, affecting the immune system, or implicated in bone metabolism seemed to be of some relevance for the prevention of periodontitis. Vitamins C and D were the most studied vitamins and vitamin D showed the most relevant role (Varela-López et al. 2018). One out of eight studies in the systematic review focused on pregnant women (Varela-López et al. 2018). In this study, pregnant women with moderate to severe periodontitis showed higher prevalence of vitamin D deficiency compared to healthy pregnant women (Boggess et al. 2011). Based on this finding, the authors concluded that use of vitamin D and

Table 16.1 List of Nutrients and Their Relevance for Maternal and Offspring Dental Health

Nutrients	Potential action mechanisms	Effect on maternal dental health	Effect on offspring dental health
Vitamin A	• Maintenance of mucosal tissue integrity. • Important for the immunological function and control of inflammation, potentially preventing bacteria overgrowth and over-inflammation.	• Protective effect on periodontitis.*	
Vitamin C	• Plays a role in the immunological function (e.g. phagocytosis and wound healing). • Down-regulates the expression of pro-inflammatory cytokines. • It is important for the maintenance of connective tissues (e.g. periodontium).	• Protective effect on periodontitis.	
Vitamin D	• Regulation of plasma calcium and phosphorus levels affecting bone development and metabolism. • Plays a role in the immunological function and control of inflammation, inhibiting the production of pro-inflammatory cytokines.	• Prevention of alveolar bone loss • Preservation of gingival tissue. • Protective effect on periodontitis.	• Effect on primary tooth formation and mineralization. • Protective effect on caries.
Vitamin E	• Its antioxidant activity prevents the propagation of cell membrane damage by peroxyl radicals formed by lipid oxidation and stabilizes the membrane structure by stopping the free radical chain reaction.	• Protective effect on periodontitis.*	
Calcium	• Plays a role in bone health (enhances mineral bone density). • Enhances enamel remineralization and prevents demineralization. • High concentrations of calcium and phosphate in saliva may inhibit bacterial biofilm formation.	• Prevents alveolar bone loss. • Protective effect on periodontitis and caries.	• Effect on primary tooth formation and mineralization. • Protective effect on caries

Note: * Limited evidence

calcium supplements might be recommended for individuals under physiological and/or pathological conditions that increase the risk of bone pathological alterations, and that supplementation could also contribute to preserving periodontal tissues (Boggess et al. 2011).

Regarding caries, there is evidence suggesting that higher intakes of vitamin D, calcium, and dairy products during pregnancy are associated with reduced risk of dental caries in the offspring in early childhood (Tanaka, Miyake & Sasaki 2010; Tanaka et al. 2012). Vitamin D plays an important role in calcium absorption, phosphate and calcium homeostasis, and bone health. During fetal development, vitamin D is transported to the fetus via the placenta only (Karras

et al. 2014). The formation and mineralization of deciduous teeth (known as milk or temporary teeth) starts at 13 weeks' gestation (Jontell & Linde 1986). Consequently, maternal vitamin D status might influence early tooth mineralization and consequently the offspring's susceptibility to caries. Some animal studies suggest that vitamin D can indirectly regulate dentin mineralization via the control of calcium and phosphate ratio, and that enamel mineralization might be regulated by genomic and non-genomic pathways (Llena & Forner 2008; Tanaka, Miyake & Sasaki 2010).

A systematic review investigating the effect of fluoride supplements in pregnant women for the prevention of caries in the primary teeth of their offspring found that fluoride supplements taken by women during pregnancy did not significantly prevent dental caries in their children at the age of 3 years (RR: 1.46; 95%CI: 0.75–2.85), nor at the age of 5 years (RR: 0.84; 95%CI: 0.53–1.33) (Takahashi et al. 2017). Although this review concluded that there is no substantial evidence proving that taking fluoride supplements during pregnancy effectively prevents dental caries in their offspring it included only one randomized clinical trial (RCT).

Probiotics are considered functional foods as their health benefits might extend beyond the conventional nutrition function (Lin 2003). Probiotics are living lactic acid-producing bacteria, which mainly belong to the genera *Lactobacillus* and *Bifidobacterium* (Lin 2003). Nikawa et al. (Nikawa et al. 2011), conducted a placebo-controlled trial including 50 participants and found a reduction in the oral carriage of *Mutans streptococci* and four other periodontal pathogens in healthy adults consuming yogurt-containing probiotics (*Lactobacillus rhamnosus* L8020) compared to those consuming placebo yogurt (without probiotics).

An RCT assessed the effect of *Lactobacillus reuteri* consumption on pregnancy gingivitis in 45 healthy women (24 test/21 placebo) compared to the placebo group for a period of approximately 7 weeks (Schlagenhauf et al. 2016). Offspring dental outcomes were not assessed. The authors concluded that regular consumption of *L. reuteri*-containing lozenges by healthy women during pregnancy proved to be a valuable co-adjuvant in the control of gingivitis during pregnancy (Schlagenhauf et al. 2016).

Although findings on the effects of probiotics on caries and periodontitis are promising, suggesting that probiotics can reduce bacterial plaque deposition (Krasse et al. 2006b), lower cytokine levels (a marker of inflammation), and decrease bleeding on probing (BOP) (Twetman et al. 2009) in the general population, very few studies have been conducted on pregnant women. The encouraging results of the above-mentioned trial including a cohort of healthy pregnant women (Schlagenhauf et al. 2016) may not be extrapolated to unhealthy pregnant women. Therefore, conclusions of the usefulness of probiotic administration in healthy pregnant women may not apply to women with compromised general and/or oral health and further evaluations in large clinical trials are still needed.

For probiotics to produce health benefits it is critical that products have an adequate level of viable bacteria and are administrated in an appropriate daily dose (Lin 2003). The majority of the experimental studies were short-term and applied various different probiotic strains making difficult to compare the results. Overall, the magnitude of the effects found in the literature were limited, consequently the clinical relevance of the findings is still questionable.

Therapeutic Relevance and Implications for Future Research

Although some studies suggested that the supplementation with vitamins and minerals, predominantly vitamins C and D and calcium, might prevent the development of or delay the progression of dental diseases, evidence from long-term experimental studies in humans is still limited. The effects reported in the studies included in the systematic review on nutraceuticals in periodontal health were relatively small to claim therapeutic relevance of supplementation (Varela-López et al. 2018). Additionally, some studies applied supplementation in combination with other treatments, which might have masked the independent effect of the supplementation. At present, there is no evidence supporting the notion that micronutrient supplementation alone is enough to revert the periodontium or enamel back to a healthy status. Therefore, the use of vitamin and mineral supplements cannot replace other traditional therapies.

Low vitamin D levels affect calcium absorption and metabolism. Pregnancy and lactation are periods of additional calcium demand as maternal calcium is transferred to the growing fetal skeleton and for breast-milk production (Thomas & Weisman 2006). Regardless of dental health benefits for mothers and babies, studies indicate that the consumption of calcium and vitamin D should be encouraged, particularly during pregnancy and lactation, to preserve maternal skeletal calcium stores, which are usually depleted during these two critical periods (Thomas & Weisman 2006). Since the fetus (via the placenta) and the infant (through breastfeeding) are dependent on maternal sources for the total calcium load, adequate maternal calcium and vitamin D intake can affect fetal bone health positively, including enhanced alveolar bone mass density, in addition to primary tooth mineralization. Further well-designed experimental studies are still needed to evaluate the clinical benefit of vitamins C and D and calcium supplementation as co-adjunct therapies for caries and periodontitis, particularly during pregnancy.

References

Adegboye ARA, Boucher BJ, Kongstad J, Fiehn NE, Christensen LB & Heitmann BL 2016 "Calcium, vitamin D, casein and whey protein intakes and periodontitis among Danish adults." *Public Health Nutrition* **19** 503–510. Available at: (http://www.journals.cambridge.org/abstract_S1368980015001202) [doi:10.1017/S1368980015001202].

Asikainen S, Chen C, Alaluusua S & Slots J 1997 "Can one Acquire Periodontal bacteria and Periodontitis from a Family Member?" *The Journal of the American Dental Association* **128** 1263–1271. Available at: (https://linkinghub.elsevier.com/retrieve/pii/S0002817715601489) [doi:10.14219/jada.archive.1997.0403].

Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S & Camargo CA 2011 "Vitamin D status and periodontal disease among pregnant women." *Journal of Periodontology* **82** 195–200. doi:10.1902/jop.2010.100384.

Bowden GHW & Li YH 1997 "Nutritional influences on biofilm development." *Advances in Dental Research* **11** 81–99. doi:10.1177/08959374970110012101.

Boyd LD & Lampi KJ 2001 "Importance of nutrition for optimum health of the periodontium." *The Journal of Contemporary Dental Practice* **2** 36–45 [doi:10.5005/jcdp-2-2-36]. http://www.ncbi.nlm.nih.gov/pubmed/12167932.

Chambrone L, Guglielmetti MR, Pannuti CM & Chambrone LA 2011 "Evidence Grade Associating Periodontitis to preterm Birth and/or Low Birth Weight: I. A Systematic Review of Prospective Cohort Studies." *Journal of Clinical Periodontology* **38** 795–808. doi:10.1111/j.1600-051X.2011.01755.x.

Doméjean S, Zhan L, DenBesten PK, Stamper J, Boyce WT & Featherstone JD 2010 "Horizontal transmission of mutans streptococci in children." *Journal of Dental Research* **89** 51–55. doi:10.1177/0022034509353400.

Esteves Lima RP, Cyrino RM, de Carvalho Dutra B, Oliveira da Silveira J, Martins CC, Miranda Cota LO & Costa FO 2016 "Association Between periodontitis and gestational diabetes mellitus: systematic review and meta-analysis." *Journal of Periodontology* **87** 48–57. doi:10.1902/jop.2015.150311.

González-Jaranay M, Téllez L, Roa-López A, Gómez-Moreno G & Moreu G 2017 "Periodontal status during pregnancy and postpartum". *PLOS ONE*. Ed. S Bencharit **12** e0178234. doi:10.1371/journal.pone.0178234.

Grant WB & Boucher BJ 2010 "Are hill's criteria for causality satisfied for vitamin D and periodontal disease?" *Dermato-Endocrinology* **2** 30–36. doi:10.4161/derm.2.1.12488.

Jontell M & Linde A 1986 "Nutritional aspects on tooth formation." *World Review of Nutrition and Dietetics* **48** 114–136 [doi:10.1159/000413028].

Kane SF 2017 "The effects of Oral Health on systemic health." *General Dentistry* **65** 30–34. http://www.ncbi.nlm.nih.gov/pubmed/29099363.

Karras SN, Anagnostis P, Bili E, Naughton D, Petroczi A, Papadopoulou F & Goulis DG 2014 "Maternal vitamin D status in pregnancy and offspring bone development: the unmet needs of vitamin D era." *Osteoporosis International* **25** 795–805. doi:10.1007/s00198-013-2468-5.

Krasse P, Carlsson B, Dahl C, Paulsson A, Nilsson A & Sinkiewicz G 2006a "Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri." *Swedish Dental Journal* **30** 55–60. doi:10.1902/jop.2008.080213.

Lin DC 2003 "Probiotics as functional foods." *Nutrition in Clinical Practice* **18** 497–506. doi:10.1177/0115426503018006497.

Llena C & Forner L 2008 "Dietary habits in a child population in relation to caries experience." *Caries Research* **42** 387–393. Available at: (https://www.karger.com/Article/FullText/154784) [doi:10.1159/000154784].

Marcenes W, Steele JG, Sheiham A & Walls AW 2003 "The relationship between dental status, food selection, nutrient intake, nutritional status, and body mass index in older people." *Cadernos de Saude Publica* **19** 809–816 [doi:10.1590/s0102-311x2003000300013]. http://www.ncbi.nlm.nih.gov/pubmed/12806483.

Mc Grath C & Bedi R 2001 ": Can dental attendance improve quality of life?" *British Dental Journal* **190** 262–265. doi:10.1038/sj.bdj.4800944.

Moura da Silva G, Coutinho SB, Piscoya MD, Ximenes RA & Jamelli SR 2012 "Periodontitis as a risk factor for preeclampsia." *Journal of Periodontology* **83** 1388–1396. doi:10.1902/jop.2012.110256.

Nikawa H, Tomiyama Y, Hiramatsu M, Yushita K, Takamoto Y, Ishi H, Mimura S, Hiyama A, Sasahara H, Kawahara K et al. 2011 "Bovine milk fermented with Lactobacillus rhamnosus L8020 decreases the oral carriage of mutans streptococci and the burden of periodontal pathogens." *Journal of Investigative and Clinical Dentistry* **2** 187–196. doi:10.1111/j.2041-1626.2011.00056.x.

Schlagenhauf U, Jakob L, Eigenthaler M, Segerer S, Jockel-Schneider Y & Rehn M 2016 "Regular consumption of Lactobacillus reuteri-containing lozenges reduces pregnancy gingivitis: an RCT." *Journal of Clinical Periodontology* **43** 948–954. doi:10.1111/jcpe.12606.

Selwitz RH, Ismail AI & Pitts NB 2007 "Dental caries." *Lancet (London, England)* **369** 51–59 [doi:10.1016/S0140-6736(07)60031-2]. http://www.ncbi.nlm.nih.gov/pubmed/17208642.

Sgolastra F, Petrucci A, Severino M, Gatto R & Monaco A 2013 "Relationship between periodontitis and pre-eclampsia: A meta-analysis". *PLOS ONE*. Ed. M Katoh **8** e71387. doi:10.1371/journal.pone.0071387.

Sheiham A 2006 "Dental caries affects body Weight, growth and quality of life in preschool children." *British Dental Journal* **201** 625–626. doi:10.1038/sj.bdj.4814259.

Sheiham A & Steele J 2001 "Does the Condition of the Mouth and Teeth Affect the Ability to Eat Certain Foods, Nutrient and Dietary Intake and Nutritional Status amongst Older People?" *Public Health Nutrition* **4** 797–803. Available at: (http://www.journals.cambridge.org/abstract_S1368980001000751) [doi:10.1079/PHN2000116].

Sheiham A, Steele JG, Marcenes W, Lowe C, Finch S, Bates CJ, Prentice A & Walls AW 2001 "The relationship among dental status, nutrient intake, and nutritional status in older people." *Journal of Dental Research* **80** 408–413. doi:10.1177/00220345010800020201.

Takahashi N & Nyvad B 2008 "Caries ecology revisited: microbial dynamics and the caries process." *Caries Research* **42** 409–418 [doi:10.1159/000159604]. http://www.ncbi.nlm.nih.gov/pubmed/18832827.

Takahashi N & Nyvad B 2011 "The role of bacteria in the caries process: ecological perspectives." *Journal of Dental Research* **90** 294–303. doi:10.1177/0022034510379602.

Takahashi R, Ota E, Hoshi K, Naito T, Toyoshima Y, Yuasa H, Mori R & Nango E 2017 "Fluoride supplementation (with tablets, drops, lozenges or chewing gum) in pregnant women for preventing dental caries in the primary teeth of their children." *The Cochrane Database of Systematic Reviews* **10** CD011850. doi:10.1002/14651858.CD011850.pub2.

Tanaka K, Miyake Y & Sasaki S 2010 "Intake of dairy products and the prevalence of dental caries in young children." *Journal of Dentistry* **38** 579–583. Available at: (http://linkinghub.elsevier.com/retrieve/pii/S0300571210000898) [doi:10.1016/j.jdent.2010.04.009].

Tanaka K, Miyake Y, Sasaki S & Hirota Y 2012 "Dairy products and calcium intake during pregnancy and dental caries in children." *Nutrition Journal* **11** 33. doi:10.1186/1475-2891-11-33.

Thomas M & Weisman SM 2006 "Calcium supplementation during pregnancy and lactation: effects on the mother and the fetus." *American Journal of Obstetrics and Gynecology* **194** 937–945. Available at: (http://linkinghub.elsevier.com/retrieve/pii/S0002937805007118) [doi:10.1016/j.ajog.2005.05.032].

Twetman S, Derawi B, Keller M, Ekstrand K, Yucel-Lindberg T & Stecksen-Blicks C 2009 "Short-term effect of chewing gums containing probiotic Lactobacillus reuteri on the levels of inflammatory mediators in gingival crevicular fluid." *Acta Odontologica Scandinavica* **67** 19–24. doi:10.1080/00016350802516170.

Varela-López A, Navarro-Hortal MD, Giampieri F, Bullón P, Battino M & Quiles JL 2018 "Nutraceuticals in periodontal health: A systematic review on the role of vitamins in periodontal health maintenance." *Molecules* **23** 1226. Available at: (http://www.mdpi.com/1420-3049/23/5/1226) [doi:10.3390/molecules23051226].

Wagle M, et al. 2018 "Dental caries and preterm birth: A systematic review and meta-analysis." *BMJ Open* **8** e018556. [doi:10.1136/bmjopen-2017-018556].

WHO 2003 "Diet, nutrition and the prevention of chronic diseases." *World Health Organization Technical Report Series* **916** i–viii, 1, 1–149, backcover. http://www.ncbi.nlm.nih.gov/pubmed/12768890.

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17

Role of Nutraceuticals in Atopic Dermatitis, Eczema, Allergy in Pregnancy

Meera Ratani, Yasmin Azad, Yashwant Pathak, and Priyanka Bhatt

Contents

17.1 Introduction

Atopic dermatitis, eczema, and allergy are disorders that are linked in a vast variety of ways. One factor that binds all of them together is their increasing prevalence in recent years, especially in the developed world. The current treatments have been accepted as viable ways to augment the quality of life and mitigate suffering for many patients with these disorders, but many patients still suffer from their symptoms because conventional treatment has not resulted in the desired amount of success, as complete cures for these disorders are currently unavailable. To further mitigate the symptoms presented by these disorders, there is an increasing amount of study in the field of nutraceuticals, i.e. foods with medicinal properties. This chapter will explore these newly proposed treatments both as complements to current treatment methods and as stand-alone treatments.

The conditions focused upon are atopic dermatitis, eczema, and allergy.

- Atopic dermatitis, also known as atopic eczema, can be briefly described as an inflammatory skin condition that involves atopic sensitization (Johansson et al. 2004).
- Eczema is a category of inflammatory skin conditions ranging from dyshidrotic eczema to xerotic eczema (Frisch 2017).
- Allergy is an immunological disorder in which the immune response overshoots the severity of a harmless substance (EAACI n.d.).

The conditions atopic dermatitis (a type of eczema), allergy, and food hypersensitivity, fall under the umbrella of allergic diseases. The allergic diseases are interconnected in many ways, but most famously as a part of the atopic march. The atopic march posits that atopic dermatitis can cause the development of the allergic rhinitis condition known to predispose a patient for other asthma, which can cause the development of asthma (Bantz, Zhu & Zheng 2014). Additionally, food allergy has been thought to increase the risk of atopic dermatitis because of the association of cell degranulation and histamine release as a key marker of an allergic response (Kawamoto et al. 2016; Figure 17.1).

Figure 17.1 *An illustration of the atopic march (Bantz 2014; Kawamoto 2016).*

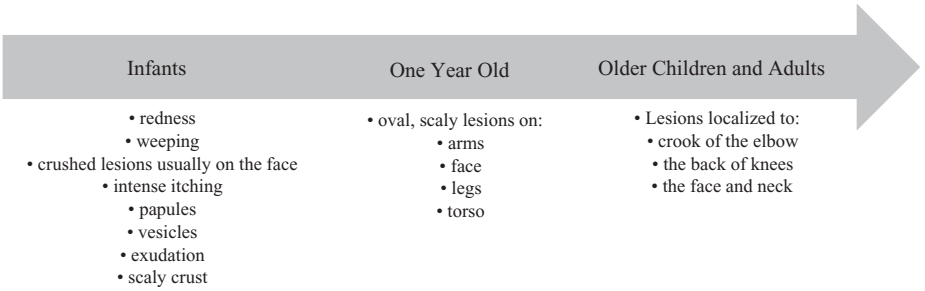

Figure 17.2 *The progression of symptoms of atopic dermatitis from infanthood to adulthood.*

17.2 Atopic Dermatitis

17.2.1 What Is Atopic Dermatitis?

Dermatitis is a series of skin disorders with a wide range of attributions including allergy and contact with a skin irritant. Of the many skin disorders that fall under the umbrella term dermatitis, atopic dermatitis is the most common with a 15–30% lifetime prevalence in children and 2–10% in adults. It often presents in infanthood and in many cases subsides by the age of three or four with few outbreaks later in life. However, atopic dermatitis, also known as atopic eczema, can also be a chronic disorder that persists past the mid-20s. The general progression of atopic dermatitis is shown in Figure 17.2. Additional symptoms of atopic dermatitis include the decreased retention of moisture in the skin, resulting in skin prone to chapping and splitting. Patients with atopic dermatitis are mostly predisposed to the disorder through the family's or individual's history of allergy, such as hay fever and asthma. The pathophysiology of atopic dermatitis has not been determined but multiple theories have been presented. A convincing argument has been made in regard to the role of the circadian rhythm in atopic dermatitis. The circadian clock genes have been found to be associated with skin hydration levels through the study of mice with knockout clock genes. The mice presented with a lack of hydration as a result of dysfunctional AQP3 proteins – transmembrane proteins that serve as facilitators of glycerol and water to maintain maximum hydration. In turn, this has been linked to nocturnal itching a symptom experienced by individuals with atopic dermatitis (Vaughn et al. 2018). Other theories include the atopic diathesis, the keratinocyte-based dogma, and the role of fibroblasts (Kang & Stevens 2003; Berroth *et al.* 2013).

17.3 Treatment – Application of Nutraceuticals

17.3.1 *Ganoderma lucidum*

Ganoderma lucidum, commonly known as the reishi mushroom, has been used for years as a part of traditional oriental medicine as an immunomodulator. Its

properties were applied and studied as a treatment of severe atopic dermatitis by Michi and Masato. The researchers administered 4–6 reishi tablets, containing the equivalent of 0.92 g of dried mushroom each, daily. In a multiple case study design, the researchers monitored the effectiveness of the reishi tablets through the Japanese Dermatological Association's severity classification, with 20 as the highest score. Four out of the five case studies demonstrated a decrease in severity score, serum IgE levels, and TARC levels. To highlight one of the case studies, a 41-year-old man who had been suffering from severe atopic dermatitis for 32 years, marked by systemic erythema and excoriations, experienced great success in symptom relief and a reduction of severity score from 20 to 10 over the course of three months. The mechanism of the reishi mushroom is thought to be its ability to suppress the signaling pathway of the protease-activated receptor-2 (PAR2). As seen in mice studies, PAR2 plays a role in skin inflammation and delay in epidermal permeability barrier recovery. Thus, suppressing PAR2 can thereby suppress itches induced by PAR2 and decrease atopic dermatitis symptoms. However, to make a concrete conclusion that *Ganoderma lucidum* is effective in the alleviation of atopic dermatitis symptoms, a much larger body of research must be conducted (Masato 2014).

17.3.2 *Arnica montana* L. and *Artemisia absinthium* L.

Arnica montana L. and *Artemisia absinthium* L. are medicinal plants originating from temperate parts of Europe and Romania. A study by Craciunescu et al. found that the plants' ethanolic extracts demonstrated antioxidant activity and cytoprotection against oxidative damage in fibroblast-like cells. This is thought to be due to the fact that the extracts consist of an abundance of flavonoids and phenolic acids. Thus, the medicinal plants have scientific evidence of their ability to act as a treatment of skin disorders (Craciunescu et al. 2012). Atopic fibroblasts have been observed to be an influencing proliferator of keratinocytes and the terminal differential process causing atopic dermatitis in the skin cultures (Berroth et al. 2013). Thus, as a contributing cause of atopic dermatitis, future research may reveal *A. montana* and *A. absinthium* as an applicable nutraceutical for the treatment of atopic dermatitis because of its ability to target fibroblast-like cells (Craciunescu et al. 2012).

17.3.3 Potential Applications

It has been found that the consumption of magnesium protects against atopic sensitization (Rosenlund et al. 2012). Therefore, foods with an abundance of magnesium may have a potential for mitigating the symptoms of or preventing against atopic dermatitis.

Magnesium-rich foods include (Cedars-Sinai n.d.):

- Nuts and seeds: sunflower seeds, almonds, sesame seeds, cashews, Brazil nuts, soybeans, peanuts, walnuts, and pecans
- Dairy products: butter and cheese

- Cereal: bran flakes, cooked oatmeal, and puffed and shredded wheat
- Bread
- Fruits: bananas, pineapples, and cherries
- Vegetables: broccoli, peas, and asparagus.

17.4 Eczema

17.4.1 What Is Eczema?

Eczema is a skin condition with a high prevalence rate and vast range of symptoms and causes. Typically, eczema presents with itchiness, erythema, and dryness, but there are several other symptoms that can be experienced (Frisch 2017). A detailed description of each type of eczema is provided in Table 17.1.

17.4.2 Eczema v. Atopic Dermatitis

Eczema and atopic dermatitis are often used interchangeably; however, there are minute but key differences that separate the two conditions. The main difference between the two disorders is that eczema is a non-specific category of skin disorders, whereas, atopic dermatitis is a specific skin disorder that falls under the non-specific category of dermatitis. The World Allergy Organization has proposed a revision of the definitions of each condition, to better differentiate between the two, in which eczema would be defined as a skin disorder with the symptoms and medical components of atopic dermatitis but with the exclusion of atopic sensitization, which would be unique to atopic dermatitis (Johansson et al. 2004; Figure 17.3).

17.5 Treatment – Application of Nutraceuticals

17.5.1 Probiotics

Probiotics are a category of nutraceuticals that have successfully reduced the risk of eczema in an increasing number of studies. Probiotics contain living bacteria that are proposed to positively affect gut flora (Fiocchi et al. 2015). In a double-blind, randomized, placebo-controlled study conducted by Rautava et al. (2012), 241 pregnant mothers with histories of allergic rhinoconjunctivitis, atopic eczema, food allergy, or asthma, which increases risk of eczema in their infants, were included in the study. The mothers were randomly assigned to receive one of three options: (1) *Lactobacillus rhamnosus* LPR and *Bifidobacterium longum* BL999 (LPR+BL999); (2) *L. paracasei* (ST11) and *B. longum* BL999 (ST11+BL999); or (3) placebo. The probiotic supplementation was begun 2 months before the predicted delivery and continued 2 more months after delivery, during breastfeeding. The probiotics were administered along with dietary supplements, including vitamins B12, A, and D, folic acid, and other micronutrients. The contraction of eczema in the infant was studied

Table 17.1 Descriptions of the Various Types of Eczema

Type of eczema	Description
Atopic eczema	• Most common • Also known as atopic dermatitis • Oftentimes there is a family history of eczema or allergy • Symptoms: atopy, increased level of IgE • Many grow out of it for the most part by their mid-20s
Pompholyx eczema	• Type of acute eczema • Small, itchy vesicles on the feet and hands break down and weep → dry, cracked skin • Unknown cause
Discoid eczema	• Typically occurs in the older demographic • Symptoms: development of well-defined, round, itchy plaques and lesions (vesicular or scaly and cracked) • Acute or chronic
Subacute eczema	• Symptoms: skin may look as though it has been burned (red and irritated), serum excretion, irritation, stinging, burning • Less severe than acute eczema
Chronic eczema	• Symptoms: lichenified (thick and leathery) skin, increased itchiness
Juvenile plantar dermatosis	• Found in children, more commonly in boys, between 4 and 8 years old • Occurs mostly during the summer • Symptoms: glazed, scaly appearing skin → development of cracks and fissures on weight-bearing areas of the forefeet
Irritant contact dermatitis	• Symptoms: soreness, itchiness, inflammation, rough and scaly skin • Occurs in response to contact with an irritant, e.g. acid, strong detergent
Allergic contact dermatitis	• Eczematous reaction to an allergen
Gravitational (varicose) eczema	• Occurs in patients with varicose veins • Venous insufficiency increases likelihood of eczematous symptoms
Asteatotic eczema (eczema craquele)	• Patients typically develop this type of eczema in the later years of their life • Risk factors: inherited, hypothyroidism, decreased lipids on skin's surface, cold weather • Symptoms: dry and itchy skin, superficial fissure running across the skin
Lichen simplex	• Eczematous reaction to frequent rubbing or scratching

Source: Frisch (2017).

through five scheduled visits at 1, 3, 6, 12, and 24 months. Of the 85% mother–infant pairs that completed the follow-up, eczema was detected in 41% of the infants and 13% of the infants were diagnosed with chronically persistent eczema. Therefore, a statistically significant reduction in risk of eczema development in the first 24 months of life was marked due to maternal probiotic supplementations. A statistically significant difference between the combination of LPR+BL999 and ST11+BL999 was not found. Due to the fact that a combination of probiotics was used, the individual benefits and possible synergistic effects could not be concluded. It is theorized that maternal probiotic supplementation controls maternal vaginal and intestinal microbiota, which offer a colonizing inoculum to the newborn infant that affects gut colonization during the neonatal stages. This theory is supported by the observation that

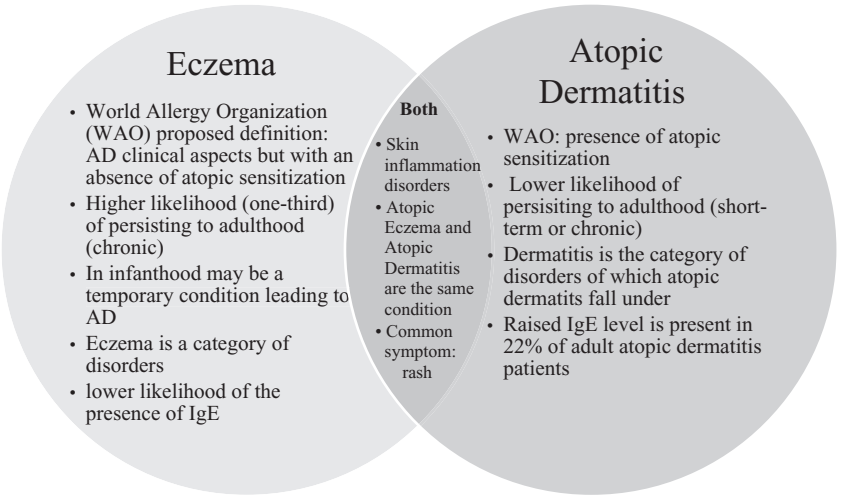

Figure 17.3 *Differentiation of eczema and atopic dermatitis.*

maternal prenatal probiotic intervention demonstrates a significant effect on placental and fetal gut immune gene expression. Although this study showed the successful reduction of eczema risk in infants as a result of maternal probiotic supplementation, a minority of studies acknowledged by a meta-analysis of 29 studies have found statistically significant data showing a lack of effect on the reduction of risk (InformedHealth.org 2017). However, the conclusion that maternal probiotic supplementation reduces risk can be reached due to the fact that studies challenging this statement fall into a minority. This notion is reflected in the World Allergy Organization's guideline that suggests pregnant mothers whose children have a high risk of developing allergic disease supplement their diet with probiotics due to the benefit of eczema prevention (Rautava et al. 2012; Fiocchi et al. 2015).

17.5.2 *Impatiens capensis, Impatiens balsamina* and Lawsone

Impatiens capensis, commonly known as jewelweed, is a plant that Native American tribes, such as the Southern Cherokee, Chippewa, Omaha, and Potawatomi, have utilized to treat rashes. *Impatiens balsamina* is the Asian relative of the jewelweed, and it has been used for the same purposes. The two flowers have been thought to alleviate the symptoms of irritant/allergic contact dermatitis (hives and rashes) caused by poison ivy. Walgreens and Burts' Bees have commercialized jewelweed's abilities to mitigate poison ivy dermatitis in their poison ivy soaps. In a study conducted by Motz et al. (2012), participants' forearms were brushed with poison ivy. The poison ivy-affected areas were treated by a variety of *I. capensis* and *I. balsamina* products, including *I. capensis* extract, mash, and soap, lawsone solution, and *I. balsamina* extract, mash, and soap. The results showed that all tested products,

with the exception of the extracts, were effective, but Dawn dish soap was the most effective in mitigating rash development. However, *I. capensis and I. balsamina* soap came in a close second and third, respectively. The researchers suggested that rather than their hypothesis of lawsone being the active component of the flowers that mitigates rash development, it is possible that saponins are the true active component. Although this study suggests that jewelweed possesses medicinal properties in regard to contact dermatitis, a concrete conclusion cannot be made due to the fact that a much larger body of evidence is needed to make such a claim with complete confidence.

17.5.3 Evening Primrose Oil and Borage Oil

Borage oil has been found to demonstrate the improvement of eczematous symptoms; however, it has also been demonstrated to have no statistical advantage over a placebo. Therefore, it has not been found to be very effective. The conclusions reached to by research regarding the effectiveness of evening primrose oil on eczema are contradictory, as evidenced by two meta-analyses. In one meta-analysis of 27 studies spanning 12 countries, the effects of the oral intake of evening primrose oil and borage oil on eczema were explored on a total of 1,596 participants. Of the 27 studies taken into consideration, 19 compared evening primrose oil to a placebo while the rest, 8, studied borage oil in comparison to a placebo. Various placebos were implemented in the studies, such as liquid paraffin, olive oil, sunflower oil, or other active eczema therapies. Most studies found that both evening primrose oil and borage oil taken orally resulted in the overall improvement of eczema through participant and/or physician reports. However, the meta-analysis concluded that the improvement in comparison to the placebo demonstrated no statistical advantage for either evening primrose oil or borage oil (Bamford 2013). In Morse and Clough's (2006) meta-analysis, 26 studies with a total of 1,207 participants were taken into consideration. This study was conducted with the purpose of further investigating the efficacy of evening primrose oil as concluded in a 1989 meta-analysis of a series of clinical trials that were randomized, double-blind, and placebo-controlled. Unlike the first-mentioned meta-analysis, Morse and Clough's study concluded that between 4 and 8 weeks the simultaneous benefits of evening primrose oil on atopic eczema – mitigation of pruritus, crusting, edema, and redness – become apparent. However, the use of potent steroids and the beneficial effects of evening primrose oil share an inverse relationship (Morse & Clough 2006). The contradictory conclusions regarding evening primrose oil are thought to be due to the inconsistencies of patient reports and because of the new developments in the two categories it has been found that people within certain categories in the variations of fatty acid metabolism unique complexities and immune response in atopic condition are not positively affected by evening primrose oil. (It works for some, but not those that have these complexities.) By further solidifying how to differentiate between responders and non-responders and later controlling for this moderating variable, the full significance of evening primrose oil can be measured.

To elaborate on the understanding of eczema's physiology and the beneficial role fatty acids can serve in its management and development, further research is needed (Morse & Clough 2006).

17.5.4 Potential Application of Nutraceuticals to Eczema

Eczema traditionally utilizes four categories of medicine as treatment. The following are the categories:

1. Anti-microbial
2. Antihistamine
3. Anti-inflammation
4. Antipruritic

There are many nutraceuticals that contain these properties but have not yet been experimented with as a treatment for eczema. These nutraceuticals are outlined in Table 17.2.

17.6 Allergy

17.6.1 What Is an Allergy?

An allergy is a disorder that results from the immune system overreacting to a foreign, but harmless, substance referred to as an allergen. Allergy symptoms include runny nose, stuffy nose, sneezing, wheezing, shortness of breath, rashes, cough, fatigue, and headache (American College of Allergy, Asthma & Immunology 2018).

Table 17.2 Potential Nutraceutical Applications with Properties

Potential nutraceutical	Why it may have potential?	References
Blackberry leaf tea	Antimicrobial and antioxidant	Evaluation of antimicrobial and antioxidant activity of leaf teas blackberry (*Morus nigra*)
Cassia pods	Antioxidant	Rehman et al. (2018)
Aloe vera	Antimicrobial, anti-inflammatory, and antioxidant	Pankaj et al. (2013), Nafis et al. (2018)
Wormwood	Antibacterial	University of South Florida (2018)
Peony root	Antioxidant	Zhang et al. (2018)
Chinese gentian	Anti-inflammatory and anti-pathogenic	Wang et al. (2018)
Dittany bark	Antipruritic	Nutrition almanac
Witch hazel	Antipruritic and potentially anti-inflammatory	Board (2017)
Dried ginger	Antioxidant	Jelled et al. (2015)
Chickweed	Antimicrobial	Komakhin et al. (2016)

Furthermore, there are two types of allergy:

1. Immediate hypersensitivity: This type of allergy occurs within an hour and is mediated by IgE. When the allergen enters the body, the body mistakes it for a harmful substance and, in the case of immediate hypersensitivity, creates antibodies to fight against the allergen. This is process is known as the sensitization phase of an allergic reaction. Next, in the symptomatic phase, the allergen binds to the IgE located on the mast cell. This "unlocks and opens" the mast cell, which then releases histamines. The histamines trigger the symptoms commonly associated with allergies, such as redness, swelling, and itchiness through vasodilation, increased vascular permeability, and nerve end stimulation respectively. Immediate hypersensitivity is linked to rhinitis and food allergy.
2. Delayed hypersensitivity: This type of allergy takes longer (up to 48 hours) to occur, as suggested by its name, and it is mediated by T cells. Delayed hypersensitivity is linked to contact eczema (EAACI n.d.)

17.6.2 Application of Nutraceuticals

17.6.2.1 Probiotics and Prebiotics

New research has been demonstrating the noteworthy effects of the gut's microbiome on the body's overall health. In line with this research, the Guidelines for Atopic Disease Prevention (GLAD-p) panel concluded that prebiotic and probiotic supplementation for infants is likely to decrease the risk of developing a food allergy (Mazzocchi et al. 2017). The positive effects of probiotic supplementation have not been confirmed by meta-analyses (Mazzocchi et al. 2017), but the World Allergy Organization still makes an undetailed suggestion that mothers of high-risk infants and infants at high risk of allergy should be recommended to take probiotics, likely due to the promising results of earlier studies (Fiocchi et al. 2015). One study involving a combination oral immunotherapy to peanut and intake of *Lactobacillus* GG resulted in the desensitization of peanut for 89.7% of the participants. It was speculated that this was due to the theorized effect of the probiotic on T-regulatory cells (Mazzocchi et al. 2017). Another review analyzed nine trials consisting of 895 pediatric cow's milk allergy patients and also found positive results. The administration of *Lactobacillus rhamnosus* GG is likely to have resulted in inducing tolerance among infants suspected of cow's milk allergy. However, the relief of symptoms cannot be stated with absolute certainty due to imprecise results and attrition bias (Tan-Lim & Esteban-Ipac 2018). All in all, probiotic and prebiotic supplementation has demonstrated positive results thus far, but has yet to be proven on a larger scale.

17.6.3 Potential Application of Nutraceuticals to Allergy

17.6.3.1 Antioxidants

Diet-derived antioxidants have the potential of serving as nutraceuticals for the control and improvement of allergy. It was proposed that, in response to oxidative stress, pulmonary and systemic oxidative stress exacerbate inflammatory responses that correspond with allergy. Oxidative stress occurs as a result of an imbalance of reactive species and antioxidants. It is an integral facet of immune defenses in regard to the fact that its purpose is to kill infecting microorganisms and prevent the overactivation of T cells. However, oxidative stress can also result in dysfunctional cell signaling and arachidonic acid metabolism and hence exacerbate inflammation. The inflammation may intensify skewing toward a T_H2 phenotype, which has been found to have an association with the development of allergic diseases. Thus, it is proposed that supplementing antioxidants to the normal diet may decrease oxidative stress and, in turn, mitigate the effects of oxidative stress that are related to allergic disease (Moreno-Macias & Romieu 2014; Figure 17.4).

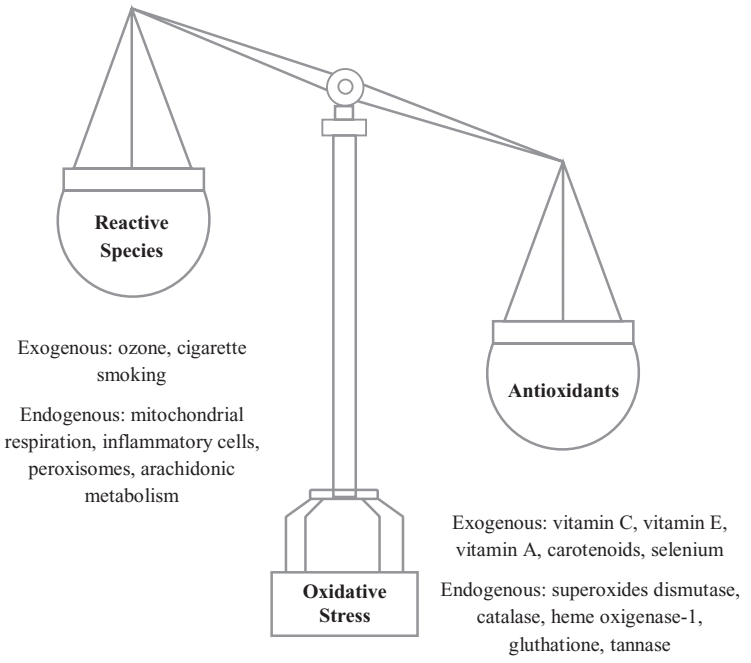

Figure 17.4 *The balance scale shows that an imbalance between reactive species and antioxidants results in oxidative stress (Ebrahimzadeh et al. 2018; Moreno-Macias & Romieu, 2014.)*

Antioxidants are molecules that delay cellular damage by eliminating oxidants or preventing them from converting into toxic compounds though the neutralization of free radicals.

As the initial defense against reactive species, antioxidants are an integral facet of the immune defense system. Diet-derived antioxidants include:

- Vitamin C:
  - Fruits: cantaloupe, citrus fruits, kiwi, mango, papaya, pineapple, strawberries, raspberries, blueberries, cranberries, and watermelon
  - Vegetables: broccoli, Brussels sprouts, cauliflower, green and red peppers, spinach, cabbage, turnip greens, sweet and white potatoes, tomatoes, and winter squash ("Vitamin C: MedlinePlus Medical Encyclopedia")
- Vitamin E: vegetable oils, margarine, nuts and seeds, and leafy greens ("Vitamin E," 2018)
- Vitamin A: cod liver oil, eggs, orange and yellow vegetables and fruits, and other sources of beta-carotene (e.g. broccoli, spinach, and most dark green, leafy vegetables) ("Vitamin A: MedlinePlus Medical Encyclopedia")
- Spices: sage, cinnamon, cloves, pepper, oregano (Stone 2009).

Epidemiologic studies offer limited support to the theoretical application of antioxidants for the treatment and prevention of allergic disease. One study conducted by Sausenthaler et al. (2009) showed vitamin E may have a protective role from allergic sensitization's development – the specific serum IgE concentration greater than or equal to 0.35 kU/1 – for adults between the ages of 29 and 54 (Sausenthaler et al. 2009). This conclusion corresponds to that reached by another study conducted by Fogarty et al. In this study, an inverse relationship was found between vitamin E intake and serum IgE concentrations and allergen sensitization; in other words, high vitamin E intake correlates to lower serum IgE concentrations and the frequency of allergen sensitization. The intake of antioxidants does show potential as a way to mitigate allergic disease; thus, a significant need for research becomes apparent in this area of immunology (Moreno-Macias & Romieu 2014).

17.6.3.2 Ginger

In a mice study, the 8-week-old Balb/c mice were separated into two groups. In one group the mice received a control diet and the other group was fed a 2% ginger diet. Both groups were sensitized by ovalbumin (OVA). The results were promising in that the group fed the ginger diet demonstrated fewer sneezes, less nasal running, and lower IgE levels. There was a significant decrease in the number of mast cells and inflammatory leukocytes that infiltrated the nasal mucosa and the proliferation of T cells. It was found that the OVA-induced allergy was potently suppressed by 2% ginger diet through the

inhibition of T-cell activation. Some researchers propose that 6-gingerol, a potent compound found in ginger, has potential as an immunosuppressive agent that contributes to ameliorate cytokine-mediated immune responses (Kawamoto et al. 2016).

17.6.3.3 Curcumin

Curcumin has also been found to improve the symptoms of allergic rhinitis, as supported by the data of an ovalbumin-sensitized mice study. The results demonstrated curcumin's suppression of inflammatory cytokines and decreases in serum histamine, IgE, and TNF-α in the ovalbumin-induced mice. Moreover, the infiltration of inflammatory mast cells in the nasal mucosa was significantly lower in the curcumin group in comparison to the control group. The researchers also found that curcumin had an influence on the signaling pathways of the MAPK molecules and NF-κB transcription factor, which are important in the control of the synthesis and release of inflammatory mediators by activated mast cells during allergic inflammation (Zhang et al. 2015). Thus, the implementation of curcumin in a treatment plan could decrease allergen-caused inflammation.

17.7 Conclusion and Future Perspectives

There is much progress in the field of applying nutraceuticals to various conditions. There is a long way to go before the full potential of the nutraceutical field is fully tapped into, but a significant start has been made. For atopic dermatitis, *Ganoderma luciudum* was able to better the condition of some patients that had stagnant or worsening conditions when using traditional allopathic treatments. Moreover, jewelweed extracts also demonstrated medicinal properties applicable to mitigating atopic dermatitis symptoms. The number of nutraceuticals that can be applied increases when opening the pool to the full category of eczema. Although studies have been conducted to specifically apply certain nutraceuticals to eczema, there are multiple substances that have as yet only been proposed as possible nutraceutical applications. The trend of only scratching the surface of alternative treatments carries on for allergic diseases. However, two main branches can be identified in the search for an effective nutraceutical to fight against allergic disease: antioxidants and probiotics.

In the future, further testing of the effectiveness of potential nutraceuticals would be the first task to tackle. Once a body of nutraceuticals has been tested in regard to whether or not significant mitigation or prevention of symptoms has been attained, researchers can proceed to isolating the potent compounds. For instance, the compound 6-gingerol has been identified as a potent compound of ginger, but whether or not other compounds are more potent or are applicable to a specific condition has not been explored.

Furthermore, the identification of these compounds could then allow for the exploration of synergistic effects between natural and synthetic compounds. Future and ongoing research along these paths will surely lead the healthcare field to produce the best medicines for conditions such as allergic diseases that currently have no cures, only treatments.

References

Abrams Motz V, Bowers CP, Mull Young L & Kinder DH 2012 The effectiveness of jewelweed, *Impatiens capensis*, the related cultivar *I. balsamina* and the component, lawsone in preventing post poison ivy exposure contact dermatitis. *Journal of Ethnopharmacology* **143** 314–318. doi:10.1016/j.jep.2012.06.038.

American College of Allergy, Asthma & Immunology 2018 Allergy symptoms. ACAAI public website. Available at: (https://acaai.org/allergies/symptoms).

Bamford JTM, Ray S, Musekiwa A, van Gool C, Humphreys R & Ernst E 2013 Oral evening primrose oil and borage oil for eczema. *Cochrane Database of Systematic Reviews* (4) CD004416 [doi:10.1002/14651858.CD004416.pub2].

Bantz SK, Zhu Z & Zheng T 2014 The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Journal of Clinical & Cellular Immunology* **5** 202 [doi:10.4172/2155-9899.1000202].

Berroth A, Kühnl J, Kurschat N, Schwarz A, Stäb F, Schwarz T, Wenck H, Fölster-Holst R & Neufang G 2013 : Role of fibroblasts in the pathogenesis of atopic dermatitis. *The Journal of Allergy and Clinical Immunology* **131** 1547–1554. doi:10.1016/j.jaci.2013.02.029.

Board ECR 2017 *Witch Hazel's Therapeutic Uses*: Salem Press.

Cedars-Sinai. n.d. Magnesium rich foods. Available at: (https://www.cedars-sinai.edu/Patients/Programs-and-Services/Documents/CP0403MagnesiumRichFoods.pdf).

Craciunescu O, Constantin D, Gaspar A, Toma L, Utoiu E & Moldovan L 2012 Evaluation of antioxidant and cytoprotective activities of *Arnica montana* L. and *Artemisia absinthium* L. ethanolic extracts. *Chemistry Central Journal* **6** 97. doi:10.1186/1752-153X-6-97.

Ebrahimzadeh SK, Navidshad B, Farhoomand P & Mirzaei Aghjehgheshlagh F 2018 Effects of exogenous tannase enzyme on growth performance, antioxidant status, immune response, gut morphology and intestinal microflora of chicks fed grape pomace. *South African Journal of Animal Science* **48** 2. doi:10.4314/sajas.v48i1.2.

European Academy of Allergy and Clinical Immunology (EAACI) What is an allergy. Available at: (https://patients.eaaci.org/what-is-allergy/).

Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, Beyer K, Burks W, Canonica GW, Ebisawa M et al. 2015 World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): probiotics. *World Allergy Organization Journal* **8** 4 [doi:10.1186/s40413-015-0055-2].

Frisch PJ 2017 *Eczema*: Salem Press.

InformedHealth.org 2017 Eczema in children: Can prebiotics or probiotics help prevent it? Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG). Feb 23 [originally published 2006]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279400/

Jelled A, Fernandes Â, Barros L, Chahdoura H, Achour L, Ferreira ICFR & Cheikh HB 2015 Chemical and antioxidant parameters of dried forms of ginger rhizomes. *Industrial Crops & Products* **77** 30–35. doi:10.1016/j.indcrop.2015.08.052.

Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, … Williams HC et al. 2004 Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *Journal of Allergy and Clinical Immunology* **113** 832–836. doi:10.1016/j.jaci.2003.12.591.

Kang K & Stevens SR 2003 Pathophysiology of atopic dermatitis. *Clinics in Dermatology* **21** 116–121. doi:10.1016/S0738-081X(02)00361-9.

Kawamoto Y, Ueno Y, Nakahashi E, Obayashi M, Sugihara K, Qiao S, Iida M, Kumasaka MY, Yajima I, Goto Y et al. 2016 Prevention of allergic rhinitis by ginger and the molecular basis of immunosuppression by 6-gingerol through T cell inactivation. *The Journal of Nutritional Biochemistry* **27** 112–122. doi:10.1016/j.jnutbio.2015.08.025.

Komakhin RA, Vysotskii DA, Shukurov RR, Voblikova VD, Komakhina VV, Strelnikova SR, Vetchinkina EM & Babakov AV 2016 Novel strong promoter of antimicrobial peptides gene pro-SmAMP2 from chickweed (*Stellaria media*). *BMC Biotechnology* **16** 43. doi:10.1186/s12896-016-0273-x.

Masato HMaK 2014 Useful treatment of severe atopic dermatitis with *Ganoderma lucidum* (reishi): a multiple-case study. *Journal of Academic* Society for Quality of Life **1** 12–15.

Mazzocchi A, Venter C, Maslin K & Agostoni C 2017 The role of nutritional aspects in food allergy: prevention and management. *Nutrients* **9** 850. doi:10.3390/nu9080850.

Moreno-Macias H & Romieu I 2014 : Effects of antioxidant supplements and nutrients on patients with asthma and allergies. *The Journal of Allergy and Clinical Immunology* **133** 1237–44; quiz 1245. doi:10.1016/j.jaci.2014.03.020.

Morse NL & Clough PM 2006 A Meta-analysis of randomized, placebo-controlled clinical trials of Efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries? *Current Pharmaceutical Biotechnology* **7** 503–524. doi:10.2174/138920106779116946.

Nafis A, Kasrati A, Azmani A, Ouhdouch Y & Hassani L 2018 Endophytic Actinobacteria of medicinal plant Aloe vera: isolation, antimicrobial, antioxidant, cytotoxicity assays and taxonomic study. *Asian Pacific Journal of Tropical Biomedicine* **8** [doi:10.4103/2221-1691.244160].

Pankaj KS, Deen Dayal G, Ritu S, Priyanka P, Sharmistha G, Atul Kumar S, …" Kapil Dev P 2013 Therapeutic and medicinal uses of aloe vera: a review. *Pharmacology & Pharmacy* **8** 599.

Rautava S, Kainonen E, Salminen S & Isolauri E 2012 Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. *Journal of Allergy and Clinical Immunology* **130** 1355–1360 [doi:10.1016/j.jaci.2012.09.003].

Rehman G, Hamayun M, Iqbal A, Ul Islam S, Arshad S, Zaman K, Ahmad A, Shehzad A, Hussain A & Lee I 2018 In vitro antidiabetic effects and antioxidant potential of cassia nemophila pods. *BioMed Research International* **2018** 1824790. doi:10.1155/2018/1824790.

Rosenlund H, Magnusson J, Kull I, Håkansson N, Wolk A, Pershagen G, Wickman M & Bergström A 2012 Antioxidant intake and allergic disease in children. *Clinical and Experimental Allergy* **42** 1491–1500 [doi:10.1111/j.1365-2222.2012.04053.x].

Sausenthaler S, Loebel T, Linseisen J, Nagel G, Magnessen H & Heinrich J 2009 Vitamin E intake in relation to allergic sensitization and IgE serum concentration. *Central European Journal of Public Health* **17** 79–85.

Stone J 2009 *Sage Advice: Measure for Measure, There Are More Antioxidants in Spices than in Any Other Foods, 50*.

Tan-Lim CSC & Esteban-Ipac NAR 2018 Probiotics as treatment for food allergies among pediatric patients: a meta-analysis. *World Allergy Organization Journal* **11** 1–13. doi:10.1186/s40413-018-0204-5.

University of South Florida 2018 Findings from Department of Biology update understanding of antibiotics (*Artemisia herba-alba Asso. Essential Oil Antibacterial Activity and Acute Toxicity*). Obesity, Fitness & Wellness Week.

Vaughn AR, Clark AK, Sivamani RK & Shi VY 2018 Circadian rhythm in atopic dermatitis-Pathophysiology and implications for chronotherapy. *Pediatric Dermatology* **35** 152–157. doi:10.1111/pde.13364.

Vitamin A: MedlinePlus medical encyclopedia. Available at: (https://medlineplus.gov/ency/article/002400.htm): MedlinePlus.
Vitamin C: MedlinePlus medical encyclopedia. Available at: (https://medlineplus.gov/ency/article/002404.htm): MedlinePlus.
Vitamin E 2018. Available at: (https://medlineplus.gov/vitamine.html): MedlinePlus.
Wang D, Wang H, Li J, Zhang W, Pan Y & Liu X 2018 Investigating the role of endophytic fungi in Gentiana scabra bge. by cross-growth period inoculation. *Indian Journal of Microbiology* **58** 319–325. doi:10.1007/s12088-018-0725-1.
Zhang N, Li H, Jia J & He M 2015. Research paper Anti-inflammatory effect of curcumin on mast cell-mediated allergic responses in ovalbumin-induced allergic rhinitis mouse. *Cellular Immunology* **298** 88–95. doi:10.1016/j.cellimm.2015.09.010.
Zhang X, Ban Q, Wang X & Wang Z 2018 Green and efficient PEG-based ultrasonic-assisted extraction of polysaccharides from tree peony pods and the evaluation of their antioxidant activity in vitro. *BioMed Research International* 2018 2121385. doi:10.1155/2018/2121385.

18

Nutraceuticals for Maternal and Offspring's Chronic Disease

Nasrin Sharifi and Reza Amani

Contents

1 Introduction

Fetal life and early childhood are the most vital periods of life because, in this period, the gene-environment interaction can affect the body health throughout the remainder of the entire life of a human (Barker 2004). Since the early 2000s, with the advent of the idea of fetal programming, a large body of research has been conducted to determine which biological events that occur during fetal life have an effect on the development of chronic diseases in adulthood. The evidence obtained revealed that the causes of many chronic diseases, such as obesity, hypertension, diabetes, and some cancers, are rooted in fetal life and early childhood (Huxley, Neil & Collins 2002; Ravelli et al. 1999; Eriksson et al. 2003). Hence, recognizing effective factors and trying to change them during this critical phase of life can be one of the most important strategies for preventing chronic disease throughout the life.

Nutritional deficiencies and inappropriate dietary patterns during pregnancy and early childhood provide conditions for the onset of chronic diseases through growth retardation and metabolic disturbances in the body (Langley-Evans 2006). As a result, efforts to reduce nutritional deficiencies and to correct dietary patterns during this critical period can play a significant role in the prevention and improvement of chronic disease during childhood and adulthood.

Nutraceuticals are among the nutritional interventions that can be used during fetal life and early childhood to prevent and treat chronic diseases (Kalra 2003; Figure 18.1). The word "nutraceutical" is composed of two terms "nutrition" and "pharmaceutical," which was suggested by Stephen DeFelice in 1989 (Kalra 2003). In this regard, a nutraceutical is defined as "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease" (DeFelice). Examples of nutraceutical also include dietary supplements such as vitamins and minerals, fortified foods, dietary fibers, herbal products, polyphenols, carotenoids, probiotics, and prebiotics (Kalra 2003).

The purpose of this chapter is to introduce nutraceuticals that, when used in fetal life and childhood, can be effective in the prevention and/or treatment of chronic diseases in later life. Chronic diseases considered in this chapter include obesity, insulin resistance, high blood pressure, and pediatric cancers. For each chronic disease, we will briefly define it and introduce its related risk factors during fetal life and childhood. After that, the effective

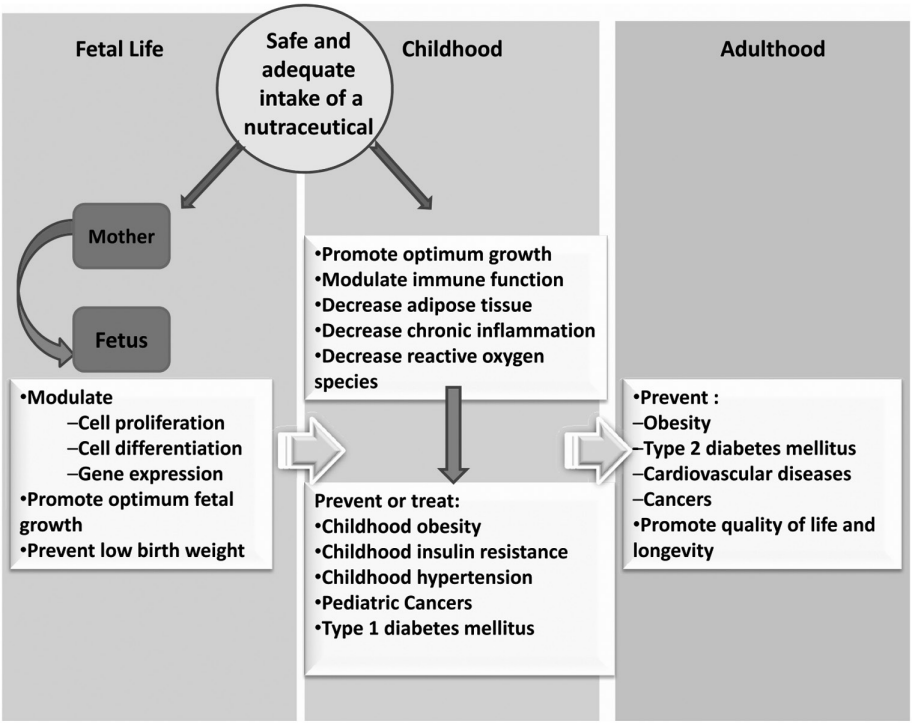

Figure 18.1 *The beneficial effects of nutraceutical intake during early life on the prevention and treatment of chronic diseases throughout the life span.*

nutraceuticals for preventing and treating these chronic diseases will be reviewed for each one.

2 Nutraceuticals and Obesity

2.1 Obesity

Obesity is defined as the extra accumulation of body fat (Gungor 2014). Recently, it has been reported that globally the rate of obesity in children and adolescents, aged 5 to 19 years, has risen tenfold in the past four decades (NCD-RisC 2017). Apart from genetic factors, a decrease in physical activity and an increase in the availability of foods with a high energy density have potentially increased the rate of childhood obesity (Han, Lawlor & Kimm 2010). Besides, nutritional deficiencies or imbalances during fetal life can also lead to obesity (Ross & Desai 2013). In fact, the important issue is that childhood obesity puts children at risk from other chronic diseases, such as diabetes mellitus, cardiovascular diseases, and cancers (Gungor 2014).

2.2 Effective Nutraceuticals in Obesity Prevention and Treatment

2.2.1 Vitamin and Mineral Supplementation

Deficiencies in some vitamins and minerals may predispose a child to being overweight or to obesity. For example, Tint et al. have found that neonates of Asian mothers with inadequate serum levels of 25-hydroxyvitamin D (25(OH) D) have higher abdominal adipose tissue (Tint et al. 2018). Several experimental and observational studies examined the relationships between maternal or fetal vitamin D status and the offspring's adiposity (Wang et al. 2018; Wen et al. 2018; Santamaria et al. 2018). The corresponding results showed that lower maternal vitamin D status was associated with the offspring's greater fat mass during childhood (Crozier et al. 2012). As suggested by a recent animal study, vitamin D deficiency (VDD) during pregnancy may interfere with the methylation of adipogenic genes and consequently promote the proliferation and differentiation of pre-adipocytes, ultimately leading to offspring obesity (Wen et al. 2018). In line with this evidence, the results of a randomized controlled trial showed that vitamin D supplementation of low birthweight infants during the first 6 months of age resulted in children with a lower body mass index (BMI) at the age of 3–6 years (Trilok-Kumar et al. 2015). As a result, an adequate intake of vitamin D during pregnancy and early infancy is emphasized to prevent obesity and other adverse outcomes of VDD. It should be noted that due to the sequestration of vitamin D in body fat stores, obese children have a higher risk of VDD when compared to their lean counterparts (Alemzadeh et al. 2008). It seems that the dietary reference intake for vitamin D (400 IU/d) might be inadequate to treat VDD in obese children (Rajakumar et al. 2008). According to a cohort study, receiving high dose of vitamin D supplements (25,000 IU/week) by obese children with VDD can be well tolerated and it effectively increases the serum vitamin D to the sufficient levels (Radhakishun et al. 2014). Therefore, it seems reasonable to revise the recommendations for the daily intake of vitamin D in obese children with VDD.

Folic acid or folate is another vitamin where deficiency during pregnancy may affect the body composition of the offspring. Interestingly, the findings from an animal study showed that maternal folate and/or vitamin B12 restriction increased visceral adiposity in rat offspring (Kumar et al. 2013). Indeed, the activity of the two lipogenic enzymes (i.e. fatty acid synthase and acetyl-CoA-carboxylase) was significantly higher in the offspring of folate-restricted female rats than in controls (Kumar et al. 2013). This finding was suggested as a reason for the increased adiposity in the offspring of rats in the above-mentioned study (Kumar et al. 2013). However, it should be taken into account that the results of a cohort study did not confirm such an effect (Lewis et al. 2009). Further studies are needed to clarify the role of folic acid in the prevention of childhood obesity.

There is evidence regarding the effects of zinc supplementation on body composition, especially during infancy and childhood (Cavan et al. 1993; Kikafunda et al. 1998). Children who have adequate zinc status show more

lean body mass and less fat mass than those with zinc deficiency (Gibson, Skeaff & Williams 2000; Friis et al. 1997). This lean tissue accretion has been attributed to the body's efficient utilization of protein and energy due to zinc supplementation (Gibson, Skeaff & Williams 2000; Golden & Golden 1992).

Calcium adequacy during fetal life and childhood may also affect body composition through its roles in lipolysis and in changing the body composition (Moore et al. 2006). Observational studies have found an inverse association between calcium intake and weight or body fat mass in children (Wang, Wu & Zhang 2016; Moreira et al. 2005). However, the results obtained from clinical trials are conflicting. For example, a one-year randomized clinical trial that examined the effects of 1,000 mg/day calcium supplementation on preschool children found a weak inverse relationship between fat mass gain and calcium intake only in supplemented children who were in the lowest tertile of dietary calcium intake (DeJongh, Binkley & Specker 2006). However, a meta-analysis of 17 randomized controlled trials (RCTs) did not show any significant effects of calcium supplementation on fat mass and lean body mass in healthy children (Winzenberg et al. 2007). On the other hand, it is still unclear whether calcium intake from dairy products or from supplements is effective in reducing body fat. Thus, until the results of the studies become clear, it is recommended that children keep their intake of calcium up to the recommended levels (700–1,000 mg/day) and provide most of their daily calcium needs from dairy products.

2.2.2 Long-Chain Polyunsaturated Fatty Acids

The n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are derived from alpha-linolenic acid (plant source) or obtained from marine oils (Scorletti & Byrne 2013).The important biological roles of n-3 LC-PUFAs in the human body include the production of anti-inflammatory mediators and involvement in gene expression (Todorcevic & Hodson 2015). The effectiveness of fish oil consumption, as a source of n-3 LC-PUFA, in the prevention and treatment of childhood obesity is under investigation. Epidemiologic studies have reported a significant association between maternal n-3 fatty acid levels and childhood adiposity (Vidakovic et al. 2016). However, the results of recent RCTs were contradictory. In a long-term follow-up of a randomized trial in mothers with obesity, Foster et al. found that DHA supplementation at 800 mg/day during the second half of pregnancy, resulted in lower BMI and adiposity in offspring at 2 and 4 years of age (Foster et al. 2017). However, in a similar study, the maternal intake of DHA-rich fish oil (800 mg/day) during the second half of pregnancy did not affect the growth or body composition of children at 3 or 5 years of age (Muhlhausler et al. 2016). Further clinical trials are needed to confirm the beneficial roles of DHA intake during fetal life in preventing childhood obesity. If mothers want to use fish oil supplements during pregnancy or when breastfeeding to take advantage of them in the growth

and development of the fetus or neonate, they should pay attention to their quality and safety. Fish oil supplements should have appropriate amounts of an antioxidant such as vitamin E to prevent lipid peroxidation (Saldeen & Saldeen 2004). Additionally, its content of dioxin and polychlorinated biphenyls (PCBs) should not exceed the established safe limit (Saldeen & Saldeen 2004). Therefore, mothers are recommended to use fish oil supplements under the supervision of healthcare providers.

Another LC-PUFA that may have anti-adipogenic effects on the human body is conjugated linoleic acid (CLA). CLA is an 18-carbon polyunsaturated fatty acid that is naturally present in the meat and dairy products derived from ruminants. It has two isomers, *cis*-9, *trans*-11 and *trans*-10, *cis*-12, with the former being found naturally in meat and dairy products. It has been reported that CLA can increase the gene expression of lipolytic enzymes such as carnitine-palmitoyl transferase and acyl-CoA oxidase, and uncoupling protein in liver, muscle, and brown adipose tissue consequently increases ß-oxidation of fatty acids (Inoue et al. 2006). Several animal studies provide evidence indicating the improvement in body composition and obesity in the offspring of mothers who have consumed CLA during pregnancy (Segovia et al. 2017; Lavandera et al. 2017). However, there are limited human studies that have evaluated the effects of CLA on obesity during childhood (Racine et al. 2010). In a clinical trial, 53 children aged 6–10 years who were overweight or obese received 3 g/day of CLA (50:50 *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers) or a placebo in chocolate milk for 7 months. After the end of the trial, it was observed that CLA supplementation significantly reduced body fatness and also significantly decreased serum levels of high-density lipoprotein (HDL) (Racine et al. 2010). As a result, more well-designed clinical trials are required to confirm the beneficial effects, as well as adverse effects, of CLA. Therefore, it is not recommended to use this supplement in children without the prescription of a nutritionist.

2.2.3 Probiotics, Prebiotics, and Synbiotics

The World Health Organization defines a *probiotic* as a "live microorganism which, when administered in adequate amounts, confers a health benefit on the host" (Tsuda & Miyamoto 2010). *Prebiotics* are non-digestible food ingredients that facilitate the growth or activity of beneficial gut microorganisms and, finally, *synbiotics* are defined as food ingredients or dietary supplements combining probiotics and prebiotics to enhance host welfare (Pandey, Naik & Vakil 2015). Today, the roles of intestinal microbiota in the development and progress of chronic diseases such as obesity are under investigation. Therefore, it is proposed that by manipulating the intestinal microbiota through probiotics, prebiotics, and/or synbiotics, it might be possible to prevent or treat obesity (Nagata et al. 2017; Hume, Nicolucci & Reimer 2017). Probiotics and/or prebiotics can decrease the gut permeability, and hence prevent the absorption of endotoxins such as lipopolysaccharides

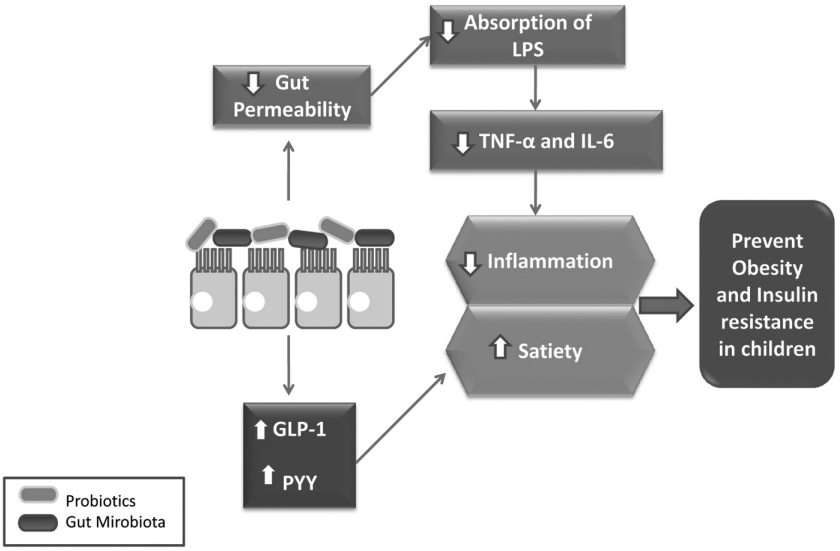

Figure 18.2 *Some of the proposed mechanisms involved in the beneficial effects of probiotics on the prevention of obesity and insulin resistance in children. GLP-1: glucagon-like peptide-1; IL-6: interleukin 6; LPS: lipopolysaccharides; PYY: peptide YY; TNF-α: tumor necrosis factor-alpha.*

(LPS), which are molecules that trigger the production of pro-inflammatory cytokines such as TNF-α and IL-6 (Figure 18.2; Sanchez, Panahi & Tremblay 2014). Consequently, by decreasing the inflammatory mediators, probiotics and/or prebiotics are involved in the prevention of atherosclerosis, obesity, and insulin resistance (Sanchez, Panahi & Tremblay 2014). Additionally, they may decrease the appetite through augmentation in the levels of gut satiety hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY(PYY) (Figure 18.2; Cani et al. 2009). There are few clinical studies regarding the roles of probiotics as a nutraceutical in the management of obesity in children. In an open prospective clinical study, Nagata et al. found that drinking beverages containing the strain *Lactobacillus casei* by obese children for 6 months, contributed to approximately 3% weight reduction in them (Nagata et al. 2017). In a recent RCT, the intake of 8 g/day of oligofructose-enriched inulin (a prebiotic) vs. maltodextrin as a placebo for 16 weeks by overweight or obese children led to a significant reduction in weight z-score, percentage of body fat and percentage of trunk fat (Nicolucci et al. 2017). Investigating the effects of probiotics, prebiotics, and synbiotics on the prevention of obesity in children would be a novel area in the field of nutraceuticals.

2.2.4 Herbal Products

Herbal products can prevent obesity through mechanisms such as stimulation of thermogenesis, reducing energy intake, increasing metabolism, and

decreasing intestinal fat absorption as well as anti-inflammatory and antioxidant activity (Payab et al. 2018). These mechanisms are carried out by phytochemicals that are part of herbal products such as polyphenols. Among the polyphenols studied, there is evidence regarding the beneficial effects of curcumin, quercetin, and catechins on obesity and body composition (Zhao et al. 2017; Suzuki et al. 2016).

Curcumin is derived from the spice turmeric and it has been shown that in primary human adipocyte it could suppress the expression of adipogenic transcription factors such as peroxisome proliferator-activated receptor γ (PPARγ) (Kim et al. 2011). Moreover, in animal models of obesity, curcumin reduced macrophage infiltration into adipocytes and, hence, decreased adipose tissue inflammation (Shao et al. 2012).

Quercetin is found in many fruits, vegetables, leaves, wine, and tea (Rauf et al. 2018). The abundant sources of this flavonoid include red onions, kale, cherries, and apple (Rauf et al. 2018). Results from *in vitro* studies have indicated that quercetin can inhibit the gene expression of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), the two key enzymes of lipogenesis (Ahn et al. 2008). It is of interest that quercetin may induce the gene expression of the uncoupling protein (UCP-1: a protein that mediates uncoupling of oxidative phosphorylation from adenosine triphosphate [ATP] synthesis) in white adipocyte mitochondria in order to increase thermogenesis and expand brown adipose tissue (Lee, Parks & Kang 2017).

Catechins are low molecular weight polyphenols mainly extracted from green tea leaves and consisting of several monomers such as catechin, epicatechin, epicatechin gallate, epigallocatechin (EGC), and epigallocatechin gallate (EGCG) (Suzuki et al. 2016). It has been reported that after catechin ingestion, dietary fat oxidation was enhanced due to increased β oxidation in liver (Murase et al. 2002). In addition, catechins can increase thermogenesis, possibly via induction of sympathetic nervous system (Dulloo et al. 2000). In a clinical trial, obese Japanese children assigned randomly to receive 576 mg catechins (catechin group) or 75 mg catechins (control group) once per day for 24 weeks (Matsuyama et al. 2008). At the end, the waist circumference in the catechin group was significantly lower than that of the control group for subjects in the above median category (Matsuyama et al. 2008).

It is noteworthy that the majority of the data regarding the effects of herbal medicines or phytochemicals on obesity treatment have been derived from cellular or animal studies (van der Spuy & Pretorius 2009). In other words, the effect of herbal supplements on human obesity has not yet been ascertained. The chemical components in herbal supplements, especially in concentrated amounts, would be harmful and may cause liver and kidney toxicity, especially in children who are more vulnerable than adults (van der Spuy & Pretorius 2009). Thus, before any recommendation is made for the use of

herbal supplements in the treatment or prevention of obesity in both adults and children, the safety of these supplements should be confirmed in valid studies.

3 Nutraceuticals and Insulin Resistance

3.1 Insulin Resistance

Insulin resistance (IR) is one of the most important components of metabolic syndrome that can cause other chronic diseases such as Type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease. The prevalence of IR is higher in children that are overweight or obese (Romualdo, Nobrega & Escrivao 2014). IR is characterized by increase in serum concentrations of insulin and a decrease in peripheral glucose uptake (Damiani et al. 2011). The results of a cross-sectional study in Brazil showed that IR was associated with lower levels of high-density lipoproteins cholesterol (HDL-c) and higher values for waist circumference measurements in children with obesity (Romualdo, Nobrega & Escrivao 2014). Interestingly, the results of the prospective cohort study in Australia revealed that maternal body size prior to pregnancy is positively correlated to increased child IR (Maftei et al. 2015). Besides, non-alcoholic fatty liver disease (NAFLD) is a hepatic feature of IR and its prevalence is increasing alarmingly among children and adolescents (Conjeevaram Selvakumar, Kabbany & Alkhouri 2018).

3.2 Nutraceuticals that May Improve Insulin Resistance

3.2.1 Vitamin and Mineral Supplementation

One of the most important nutraceuticals, which has received lots of attention in terms of improving insulin resistance during the last decade, is vitamin D. The results of experimental and observational studies demonstrated that vitamin D deficiency during early life and childhood might be a risk factor for insulin resistance, Type 1 and Type 2 diabetes mellitus (Grunwald et al. 2017; Papadimitriou 2017). However, the results of clinical trials are controversial regarding the effects of vitamin D on IR in different adult populations. For example, in a recent systematic review, we showed that vitamin D supplementation significantly reduced IR in patients with NAFLD in only one out of the six reviewed clinical trials (Sharifi & Amani 2019). Indeed, few studies have examined the effects of vitamin D supplementation on IR and/or NAFLD among children (Della Corte et al. 2016). In a recent clinical trial, Della Corte et al. found that daily DHA (500 mg) plus vitamin D (800 IU) supplementation in obese children with NAFLD improved IR, lipid profile, and hepatic enzymes. However, in two other clinical trials, vitamin D supplementation did not result in an improvement of IR and other components of metabolic syndrome (MetS). Different doses and durations of vitamin D supplementation, as

well as different populations and age groups, are possible reasons for controversies between the results obtained from previous clinical trials.

Among minerals, zinc deficiency during prenatal life and childhood may predispose children to IR and pre-diabetes (Islam et al. 2016). However, the results of a few clinical trials have supported the beneficial effects of zinc on IR in children with MetS (Mispireta et al. 2017). Iranian obese children, who received 20 mg of elemental zinc vs. their counterparts who received a placebo for 8 weeks in a cross-over RCT, showed a significant decrease in IR parameters and inflammatory biomarkers such as high-sensitive C reactive protein (hs-CRP) (Kelishadi et al. 2010). Zinc is a cofactor of antioxidant enzymes such as superoxide dismutase (SOD) (Mazani et al. 2013). As a result, it is proposed that this trace element can attenuate IR, through promoting antioxidant defense in the body (Marreiro et al. 2006).

Low serum magnesium levels may also contribute to the development of IR in children (Celik, Andiran & Yilmaz 2011). It is of interest that through an epigenetic process, low dietary intake of magnesium during pregnancy may lead to MetS in offspring in later life (Takaya 2015). Epigenetic refers to the process that biological or environmental factors affect the phenotype without changing the DNA sequence (Dupont, Armant & Brenner 2009). Binding of a protein to the specific sites of DNA, as an epigenetic change, can modify the gene expression (Takaya et al. 2011). Magnesium is proposed to be a cofactor that facilitates such binding and consequently modulates the expression of genes that are involved in MetS pathogenesis (Takaya 2015).

3.2.2 n-3 Long-Chain Polyunsaturated Fatty Acids

Most of the previous studies have evaluated the effects of n-3 LC-PUFA on metabolic parameters in children who had NAFLD (Mann et al. 2018). NAFLD is a hepatic feature of metabolic syndrome and is associated with IR. A longitudinal study showed that boys who had received n-3 LC-PUFA supplements in infancy had a reduced insulin concentration and IR at 5 years of age (Mori et al. 2018). In other RCT, Nobili et al. reported that DHA supplementation (doses of 250 and 500 mg/day) for 24 months improved IR, liver steatosis, and hepatic enzymes in children with NAFLD (Nobili et al. 2013). In addition, supplementation with 900 mg n-3 LC-PUFA daily in overweight children and adolescents for one month led to a 15% significant reduction in the homeostasis model assessment of IR (HOMA-IR) independent of weight changes (Lopez-Alarcon et al. 2011). It has been suggested that n-3 LC-PUFA might improve IR via its ability to inhibit inflammatory pathways and involvement in the gene expression (Xu et al. 2015).

3.2.3 Probiotics, Prebiotics, and Synbiotics

The early alteration in the gut microbiota by specific probiotics, prebiotics, and synbiotics may affect chronic diseases such as IR and MetS (Isolauri &

Salminen 2015). Evidence indicates the beneficial effects of probiotics on NAFLD in children (Mann et al. 2018). Using a mixture of eight probiotic strains in a supplement, named VSL#3, with a sample of children with NAFLD for 4 months resulted insignificant fatty liver improvement, although the changes in HOMA-IR were not significant between VSL#3 and placebo (Alisi et al. 2014). The other important benefit of probiotics that has attracted more attention recently is their probable ability to protect against the onset of Type 1 diabetes mellitus (T1DM) (Groele, Szajewska & Szypowska 2017). Recent evidence has indicated a significant decline in the numbers of *Lactobacillus* and *Bifidobacterium* in children with beta-cell autoimmunity (Murri et al. 2013). Additionally, in a prospective cohort study, the probiotic supplementation during the first 27 days of life was associated with a significantly lower risk of islet autoimmunity, especially in children who had a genetically higher risk of T1DM (Uusitalo et al. 2016). It should be taken into account that few human studies have investigated the effects of probiotics/prebiotics on IR, MetS, T1DM, and T2DM among children. More high-quality clinical trials are needed to establish a safe recommendation of probiotics and/or prebiotics in children with MetS.

3.2.4 Low Glycemic Index Products

The glycemic index (GI) indicates the extent to which a carbohydrate-containing food affects postprandial blood glucose levels compared with a reference product containing the same amount of available carbohydrate (Barclay et al. 2008). Consumption of low GI food is protective against IR among children (Visuthranukul et al. 2015). The GI of food products can be lowered during the production process. In this regard, the food industries can reduce the glycemic index of high-carbohydrate products through the changes made during their processes, such as the addition of fiber or resistant starch. For example, in a recent study Schuchardt et al. showed that consumption of a newly developed fiber-enriched cookie by healthy volunteers led to lower postprandial insulin concentration compared to white bread (Schuchardt et al. 2016).

3.2.5 Herbal Products and Phytochemicals

Insulin resistance and diabetes mellitus induce oxidative stress via the elevation in serum glucose and free fatty acid levels (Wei et al. 2009). Recent evidence reveals that oxidative stress can develop and exacerbate diabetes mellitus's complications (Domingueti et al. 2016). Therefore, the antioxidants are important nutraceuticals that neutralize reactive oxygen species and prevent or treat the complications that are associated with IR. The major sources of antioxidants are phytochemicals extracted from plants (D'Andrea 2015). Some phytochemicals such as quercetin, silymarin, and anthocyanins have been investigated in terms of the effects on IR and diabetes mellitus. Some proposed mechanisms underlying the beneficial effects of phytochemicals' intake on IR and T2DM has been shown in Figure 18.3.

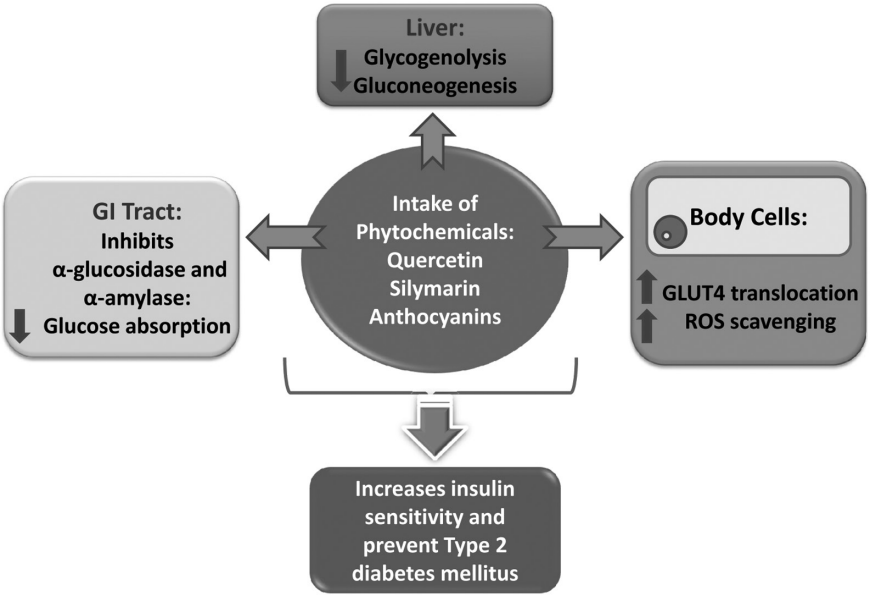

Figure 18.3 *Suggested mechanisms underlying the beneficial effects of the intake of phytochemicals on insulin resistance and Type 2 diabetes mellitus. GLUT4: glucose transporter type 4; ROS: reactive oxygen species.*

Alongside the free radical scavenging ability, quercetin might stimulate glucose uptake via the induction of glucose transporter type 4 (GLUT4) and can inhibit hepatic glycogenolysis and gluconeogenesis (Alam, Meerza & Naseem 2014). Although animal studies strongly support the beneficial effects of quercetin on IR and diabetes, the results of clinical studies are still limited and inconclusive (Pereira et al. 2016).

Silymarin is a mixture of flavonolignans extracted from the seeds of *Silybum marianum* (milk thistle) (Tuorkey, El-Desouki & Kamel 2015). Although silymarin has been known to be effective in the treatment of liver disease, its potential antidiabetic properties have been reported recently (Shin et al. 2015). The overall results of the available clinical trials revealed that silymarin supplementation (dosage range: 200 to 800 mg/day) led to improvements in glycemic control, IR, and antioxidant indices such as SOD, GPx, and total antioxidant capacity (TAC) in adults with IR and/or diabetes mellitus (DM) (Hussain 2007; Huseini et al. 2006; Ebrahimpour Koujan et al. 2015).

Anthocyanins are another subgroup of flavonoids that are supposed to have beneficial effects on IR and DM (Belwal et al. 2017). They are responsible for the red, purple, and blue colors of the plants (Belwal et al. 2017). Thus the rich sources of anthocyanins include blackberries, bilberries, cranberries, raspberries, black currant, cherry, grape, strawberry, colored cabbage, etc. (Belwal et al. 2017). It has been reported that anthocyanins may have inhibitory effects

on α-glucosidase and pancreatic α-amylase in the gut thereby limiting the glucose absorption (Tadera et al. 2006). Additionally, increased translocation of GLUT4, decreased phosphorylation of insulin receptor substrate 1 (IRS-1) as well as the inhibition of fatty acid and triglyceride synthesis are among the suggested mechanisms by which anthocyanins increase insulin sensitivity and reverse diabetic condition (Takikawa et al. 2010). However, clinical studies indicating the true effects of anthocyanins' supplementation on IR and DM among children are very limited (Belwal et al. 2017). In a placebo-controlled clinical trial, it was shown that consumption of a freeze-dried strawberry beverage (a rich source of anthocyanins) daily for 6 weeks resulted in significant decrease in hemoglobin A1c (HbA1c), lipid peroxidation, inflammatory response, and diastolic blood pressure in adults with T2DM (Amani et al. 2014; Moazen et al. 2013).

Currently, validated data is not available to establish the safe doses of phytochemicals for the prevention and/or treatment of IR. Therefore, until then, children and adults are recommended to receive such phytochemicals by increasing their intake of dietary sources such as colorful fruits and vegetables.

4 Nutraceuticals and Hypertension

4.1 Hypertension

Currently, one of the major health concerns in children is increasing trend of hypertension prevalence that can occur due to the increased prevalence of obesity and the tremendous changes in lifestyle (Falkner, Lurbe & Schaefer 2010). The significance of this health issue is better understood when we consider that the occurrence of hypertension in childhood can be continued into adulthood and, consequently, that related cardiovascular complications may arise earlier in life (Thompson et al. 2013).

4.2 Nutraceuticals that May Control Blood Pressure

4.2.1 Vitamin and Mineral Supplementation

Vitamins and minerals such as vitamin C, vitamin E, and calcium have a scientific background in terms of their beneficial effects on blood pressure (BP) control (Jamshidi & Kelishadi 2015; Block et al. 2008; Franco Mdo et al. 2009).

Vitamin C and vitamin E are antioxidants and, therefore, they can increase the nitric oxide (NO) production leading to improvements in endothelial function and arterial compliance (Plantinga et al. 2007). In a clinical trial by Rimoldi et al., the administration of 1,000 mg vitamin C plus 400 IU vitamin E to children who had been conceived by assisted reproductive technology (ART) for 4 weeks, significantly increased plasma NO levels and flow-mediated vasodilation (FMD) and attenuated pulmonary hypertension compared with placebo (Rimoldi et al. 2015).

One of the independent risk factors for cardiovascular diseases and hypertension among children is hyperhomocysteinemia (Glowinska et al. 2003). It has been reported that folic acid supplementation could decrease blood pressure through the reduction of homocysteine (Hcy) levels (Papandreou et al. 2010). Children with hyperhomocysteinemia who received a 5-mg supplement of folic acid orally twice a week for 2 months revealed a significant decrease in Hcy levels as well as systolic and diastolic blood pressure compared with the controls (Papandreou et al. 2010).

Findings from a systematic review demonstrated that higher maternal calcium intake during pregnancy was associated with a reduction in the offspring's systolic BP (SBP) (Jamshidi & Kelishadi 2015). The study by Belizan et al. was the first RCT that showed maternal calcium supplementation during pregnancy (2 g/day of elemental calcium) was associated with a lower risk of high SBP in offspring at the age of 7 years (relative risk: 0.59; 95% confidence interval: 0.39– 0.90) (Belizan et al. 1997). The mechanism of action has not been fully understood. However, Belizan et al. suggested that high maternal calcium intake could decrease maternal BP, and hence reduce fetal exposure to maternal hormones and substances that affect developmental programming, leading to high BP later in life (Belizan et al. 1997).

4.2.2 n-3 Long-Chain Polyunsaturated Fatty Acids

A growing body of evidence suggests that n-3 long-chain polyunsaturated fatty acids may exert beneficial effects on childhood hypertension. In a multicenter RCT in Europe (participants were from four centers in the UK, Belgium and Italy), children who received LC-PUFA-supplemented formula compared with those who received unsupplemented formula had lower mean BP and DBP at the age of 6 years (Forsyth et al. 2003). Of note, data from this study were used by Straub et al. to evaluate the cost-effectiveness of supplementing infant formula with LC-PUFAs on lowering blood pressure (Straub et al. 2011) and found it to be an economically worthwhile prevention strategy to decrease the rate of hypertension-related diseases in later life (Straub et al. 2011). Based on data derived from a birth cohort study in the Netherlands, van Rossem et al. reported that children who received human milk with a higher content of n-3 LC-PUFA (above the median) had significantly lower SBP and DBP at the age of 12 years (van Rossem et al. 2012). However, the effects of n-3 LC-PUFA supplementation on the offspring's BP during pregnancy have not been confirmed by longitudinal studies (Rytter et al. 2013; Rytter et al. 2012).

4.2.3 Herbal Products and Phytochemicals

Among phytochemicals, the intake of flavonoids is associated with a lower risk of hypertension and cardiovascular disease (de Jesus Romero-Prado et al. 2015; Habauzit & Morand 2012). The beneficial effects of flavonoids on hypertension are mediated through antioxidant and anti-inflammatory activities

and also by improvement in nitric oxide metabolism and endothelial function (Habauzit & Morand 2012).

Flavanols from cocoa chocolate protect vascular endothelium function by increasing NO bioavailability and improving FMD in healthy or hypertensive subjects (Grassi et al. 2012). By analyzing data from 20 RCTs, Ried et al. concluded that the intake of flavanol-rich cocoa can significantly reduce SBP (–2.77 mmHg) and DBP (–2.20 mmHg) in healthy adults compared with controls (Ried et al. 2012). Even an intake of low doses of polyphenol-rich dark chocolate (6.3 g, 30 kcal per day) by adults with pre-hypertension might effectively reduce BP (Taubert et al. 2007). Only one clinical trial has been performed on healthy children to find out the effects of dark chocolate consumption on BP (Chan et al. 2012) indicating similar SBP and DBP between the children who received dark chocolate and their controls after 7 weeks of intervention (Chan et al. 2012).

The other polyphenol-rich food that showed promising effects on BP is pomegranate juice (Shema-Didi et al. 2014; Stowe 2011). A recent meta-analysis of eight RCTs indicated a significant decrease in both systolic and diastolic blood pressure after pomegranate consumption in adults (Sahebkar et al. 2017). Interestingly, after the dose-response analysis, the decrease in SBP remained significant even when pomegranate juice had been consumed at less than 250 ml per day (Sahebkar et al. 2017). In this regard, no clinical trial has been conducted yet in children. The acceptability and easy consumption of dark chocolate and pomegranate juice by younger children are among the important advantages of these nutraceuticals, considering that even taking a small amount would be beneficial in controlling high BP (Chan et al. 2012). However, it should be noted that consuming extra amounts of dark chocolate by overweight or obese children may yield high amounts of energy.

5 Nutraceuticals and Pediatric Cancers

5.1 Pediatric Cancers

Pediatric cancers are cancers that occur at the age of 0–14 years (Childhood cancer 2017). The most prevalent cancers in children include leukemia, brain tumors, and lymphomas (Childhood cancer 2017). Nutraceuticals can be used in two ways in pediatric cancers: as chemopreventive agents and adjuvant therapies (Ferrucci et al. 2016).

5.2 Important Nutraceuticals in the Prevention and Treatment of Pediatric Cancers

5.2.1 Vitamin and Mineral Supplementation

Vitamins or minerals may exert protective effects against cancer, considering their antioxidant, anti-inflammatory, and methyl donor properties.

These nutraceuticals exert their beneficial roles in both the prevention and treatment of pediatric cancers. For example, receiving folic acid during pregnancy may reduce the risk of childhood brain and spinal cord tumors (Chiavarini, Naldini & Fabiani 2018) or supplementation with selenium might ameliorate the chemotherapy side effects in children with cancer (Vieira et al. 2015). When compared with a healthy pediatric population, children with cancer have a higher prevalence of vitamin D deficiency that predisposes them to low bone mineral density and other adverse outcomes (Revuelta Iniesta et al. 2016).

Of note, in the cancer prevention phase, the U-shaped relationship between the status of micronutrients and the risk of cancer is evident. For example, people with low selenium status may benefit from selenium supplementation, however, additional selenium intake by those who have adequate or high selenium status may increase the risk of chronic diseases such as T2DM or cancers (Rayman 2012).

5.2.2 Herbal Products and Phytochemicals

Investigators in the field of pediatric cancers are trying to find non-invasive therapies to impede cancer progression. Indeed, some of the plant-derived nutraceuticals have been found to protect against angiogenesis, tumorigenesis, and metastasis in pediatric cancers originating from brain, bone, and liver (Heger et al. 2014). One of the phytochemicals that has been shown to have anti-tumorigenic effects is curcumin (Ferrucci et al. 2016). The results of an *in vitro* study showed that curcumin administration into the cell lines of pediatric epithelial liver tumor significantly decreased their viability in a dose-dependent manner (Bortel et al. 2015). The mechanisms proposed include the inhibition of nuclear factor kappa beta (NF-κB) and decreased cyclin D, a factor that controls cell cycle and has the potential to be converted to an oncogene (Bortel et al. 2015). Of interest, curcumin can cross the blood-brain barrier due to its lipophilic properties and probably would be an effective nutraceutical to impair pediatric brain tumors (Marchiani et al. 2014).

The clinical trials investigating the effects of phytochemicals on pediatric cancers are very scarce and the majority of available evidence is derived from *in vitro* and experimental studies (Ferrucci et al. 2016). The other promising plant-derived nutraceuticals for pediatric cancer treatment include resveratrol, quercetin, diallyl trisulfide and green tea extract that have been reviewed by Ferrucci et al. (Ferrucci et al. 2016).

5.2.3 Probiotics, Prebiotics and Synbiotics

Significant alterations in gut microbiota (dysbiosis) may predispose children to increased risk of chronic diseases such as cancer (Bai, Behera & Bruner 2018). On the other hand, dysbiosis in the gut during the treatment phase

of cancer may alter chemotherapy and increase the cancer-related symptoms (Kelly et al. 2016). Additionally, dysbiosis in gut microbiota may cause alterations in mood and promote depression in patients with cancer (Naseribafrouei et al. 2014). Therefore, based on the current evidence it seems that modulation in gut microbiome by certain probiotics, prebiotics, and synbiotics may have beneficial roles in the prevention and treatment of pediatric cancers. Among the probiotic strains, *Lactobacilli* and *Bifidobacterium breve* have been shown to attenuate chemotherapy side effects such as the occurrence of fever and infections in children with cancer (Ekert et al. 1980; Wada et al. 2010). Additionally, a prebiotic supplement such as fructooligosaccharides (FOS) being taken by children during the chemotherapy phase might help the growth of beneficial gut microbiota like *Lactobacilli* and *Bifidobacteria* (Zheng et al. 2006). Unfortunately, safety concerns were not reported in previous RCTs in this regard (Wada et al. 2010; Zheng et al. 2006). Further studies are needed to determine the effective strains of probiotics and proper components of prebiotics alongside their probable side effects in the treatment of pediatric cancers.

6 Summary

- The intake of vitamin D, folate, zinc, and calcium supplements during fetal life or early childhood may prevent adiposity and obesity later in life.
- By decreasing the inflammatory mediators, probiotics and/or prebiotics are involved in prevention of atherosclerosis, obesity, and insulin resistance
- Evidence indicates the beneficial effects of curcumin, quercetin, and catechins on obesity and body composition during childhood.
- It is proposed that zinc can attenuate IR through the promotion of antioxidant defense in the body.
- Through an epigenetic process, the low dietary intake of magnesium during pregnancy may lead to metabolic syndrome in offspring later in life.
- The intake of probiotics in early childhood may protect against the onset of T1DM.
- Vitamin C, vitamin E, and calcium have scientific backgrounds in terms of beneficial effects on blood pressure control.
- The supplementation of infant formula with LC-PUFA may decrease the rate of hypertension later in life.
- In the cancer prevention phase, the U-shaped relationships between the status of micronutrients and the risk of cancer should be considered and taking extra amounts of them should be avoided.
- The promising effect of plant-derived nutraceuticals on pediatric cancer prevention and treatment include curcumin, resveratrol, quercetin, diallyl trisulfide (from garlic) and green tea extract.

7 Future Direction

Valid and reliable randomized controlled clinical trials are required in order to establish the true association between the intake of nutraceuticals during childhood and risk of chronic diseases throughout life. Additionally, safe amounts of nutraceuticals for mothers and children remain to be determined by appropriate study design. It is worth noting that nutraceuticals may have the potential to alter the programming of chronic diseases during fetal development via the epigenetic process, a novel area for future research.

References

Ahn J, Lee H, Kim S, Park J, Ha T. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochem Biophys Res Commun.* 2008;373(4):545–9.

Alam MM, Meerza D, Naseem I. Protective effect of quercetin on hyperglycemia, oxidative stress and DNA damage in alloxan induced type 2 diabetic mice. *Life Sci.* 2014;109(1):8–14.

Alemzadeh R, Kichler J, Babar G, Calhoun M. Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. *Metabolism.* 2008;57(2):183–91.

Alisi A, Bedogni G, Baviera G, Giorgio V, Porro E, Paris C, Giammaria P, Reali L, Anania F, Nobili V. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther.* 2014;39(11):1276–85.

Amani R, Moazen S, Shahbazian H, Ahmadi K, Jalali MT. Flavonoid-rich beverage effects on lipid profile and blood pressure in diabetic patients. *World J Diabetes.* 2014;5(6):962–8.

Bai J, Behera M, Bruner DW. The gut microbiome, symptoms, and targeted interventions in children with cancer: a systematic review. *Support Care Cancer.* 2018;26(2):427–39.

Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk--a meta-analysis of observational studies. *Am J Clin Nutr.* 2008;87(3):627–37.

Barker DJ. The developmental origins of chronic adult disease. *Acta Paediatr Suppl.* 2004;93(446):26–33.

Belizan JM, Villar J, Bergel E, del Pino A, Di Fulvio S, Galliano SV, Kattan C. Long-term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial. *BMJ.* 1997;315(7103):281–5.

Belwal T, Nabavi SF, Nabavi SM, Habtemariam S. Dietary anthocyanins and insulin resistance: when food becomes a medicine. *Nutrients.* 2017;9(10).

Block G, Jensen CD, Norkus EP, Hudes M, Crawford PB. Vitamin C in plasma is inversely related to blood pressure and change in blood pressure during the previous year in young Black and White women. *Nutr J.* 2008;7:35.

Bortel N, Armeanu-Ebinger S, Schmid E, Kirchner B, Frank J, Kocher A, Schiborr C, Warmann S, Fuchs J, Ellerkamp V. Effects of curcumin in pediatric epithelial liver tumors: inhibition of tumor growth and alpha-fetoprotein in vitro and in vivo involving the NFkappaB- and the beta-catenin pathways. *Oncotarget.* 2015;6(38):40680–91.

Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, De Backer F, Neyrinck AM, Delzenne NM. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am J Clin Nutr.* 2009;90(5):1236–43.

Cavan KR, Gibson RS, Grazioso CF, Isalgue AM, Ruz M, Solomons NW. Growth and body composition of periurban Guatemalan children in relation to zinc status: a longitudinal zinc intervention trial. *Am J Clin Nutr.* 1993;57(3):344–52.

Celik N, Andiran N, Yilmaz AE. The relationship between serum magnesium levels with childhood obesity and insulin resistance: a review of the literature. *J Pediatr Endocrinol Metab.* 2011;24(910):675–8.

Chan EK, Quach J, Mensah FK, Sung V, Cheung M, Wake M. Dark chocolate for children's blood pressure: randomised trial. *Arch Dis Child.* 2012;97(7):637–40.

Chiavarini M, Naldini G, Fabiani R. Maternal folate intake and risk of childhood brain and spinal cord tumors: a systematic review and meta-analysis. *Neuroepidemiology.* 2018;51(12):82–95.

Childhood Cancer: National Cancer Institute; [updated August 30, 2017]. Available from: https://www.cancer.gov/types/childhood-cancers.

Conjeevaram Selvakumar PK, Kabbany MN, Alkhouri N. Nonalcoholic fatty liver disease in children: not a small matter. *Paediatr Drugs.* 2018;20(4):315–29.

Crozier SR, Harvey NC, Inskip HM, Godfrey KM, Cooper C, Robinson SM. Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. *Am J Clin Nutr.* 2012;96(1):57–63.

Damiani D, Kuba VM, Cominato L, Damiani D, Dichtchekenian V, Menezes Filho HC. Metabolic syndrome in children and adolescents: doubts about terminology but not about cardiometabolic risks. *Arq Bras Endocrinol Metabol.* 2011;55(8):576–82.

D'Andrea G. Quercetin: a flavonol with multifaceted therapeutic applications? *Fitoterapia.* 2015;106:256–71.

de Jesus Romero-Prado MM, Curiel-Beltran JA, Miramontes-Espino MV, Cardona-Munoz EG, Rios-Arellano A, Balam-Salazar LB. Dietary flavonoids added to pharmacological antihypertensive therapy are effective in improving blood pressure. *Basic Clin Pharmacol Toxicol.* 2015;117(1):57–64.

DeFelice S. FIM Rationale and Proposed Guidelines for the Nutraceutical Research & Education Act – NREA: Foundation for Innovation in Medicine; Available from: http://www.fimdefelice.org/archives/arc.researchact.html.

DeJongh ED, Binkley TL, Specker BL. Fat mass gain is lower in calcium-supplemented than in unsupplemented preschool children with low dietary calcium intakes. *Am J Clin Nutr.* 2006;84(5):1123–7.

Della Corte C, Carpino G, De Vito R, De Stefanis C, Alisi A, Cianfarani S, Overi D, Mosca A, Stronati L, Cucchiara S, Raponi M, Gaudio E, Byrne CD, Nobili V. Docosahexanoic acid plus vitamin d treatment improves features of NAFLD in children with serum vitamin D deficiency: results from a single centre trial. *PLoS One.* 2016;11(12):e0168216.

Domingueti CP, Dusse LM, Carvalho M, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. *J Diabetes Complications.* 2016;30(4):738–45.

Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermander J. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord.* 2000;24(2):252–8.

Dupont C, Armant DR, Brenner CA. Epigenetics: definition, mechanisms and clinical perspective. *Semin Reprod Med.* 2009;27(5):351–7.

Ebrahimpour Koujan S, Gargari BP, Mobasseri M, Valizadeh H, Asghari-Jafarabadi M. Effects of *Silybum marianum* (L.) Gaertn. (silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: a randomized, triple-blind, placebo-controlled clinical trial. *Phytomedicine.* 2015;22(2):290–6.

Ekert H, Jurk IH, Waters KD, Tiedemann K. Prophylactic co-trimoxazole and lactobacilli preparation in neutropenic patients. *Med Pediatr Oncol.* 1980;8(1):47–51.

Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. *Diabetologia.* 2003;46(2):190–4.

Falkner B, Lurbe E, Schaefer F. High blood pressure in children: clinical and health policy implications. *J Clin Hypertens (Greenwich).* 2010;12(4):261–76.

Ferrucci V, Boffa I, De Masi G, Zollo M. Natural compounds for pediatric cancer treatment. *Naunyn Schmiedebergs Arch Pharmacol.* 2016;389(2):131–49.

Forsyth JS, Willatts P, Agostoni C, Bissenden J, Casaer P, Boehm G. Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial. *BMJ.* 2003;326(7396):953.

Foster BA, Escaname E, Powell TL, Larsen B, Siddiqui SK, Menchaca J, Aquino C, Ramamurthy R, Hale DE. Randomized controlled trial of DHA supplementation during pregnancy: child adiposity outcomes. *Nutrients.* 2017;9(6):566.

Franco Mdo C, Ponzio BF, Gomes GN, Gil FZ, Tostes R, Carvalho MH, Fortes ZB. Micronutrient prenatal supplementation prevents the development of hypertension and vascular endothelial damage induced by intrauterine malnutrition. *Life Sci.* 2009;85(78):327–33.

Friis H, Ndhlovu P, Mduluza T, Kaondera K, Sandstrom B, Michaelsen KF, Vennervald BJ, Christensen NO. The impact of zinc supplementation on growth and body composition: a randomized, controlled trial among rural Zimbabwean schoolchildren. *Eur J Clin Nutr.* 1997;51(1):38–45.

Gibson RS, Skeaff M, Williams S. Interrelationship of indices of body composition and zinc status in 11-yr-old New Zealand children. *Biol Trace Elem Res.* 2000;75(13):65–77.

Glowinska B, Urban M, Koput A, Galar M. New atherosclerosis risk factors in obese, hypertensive and diabetic children and adolescents. *Atherosclerosis.* 2003;167(2):275–86.

Golden BE, Golden MH. Effect of zinc on lean tissue synthesis during recovery from malnutrition. *Eur J Clin Nutr.* 1992;46(10):697–706.

Grassi D, Desideri G, Necozione S, Ruggieri F, Blumberg JB, Stornello M, Ferri C. Protective effects of flavanol-rich dark chocolate on endothelial function and wave reflection during acute hyperglycemia. *Hypertension.* 2012;60(3):827–32.

Groele L, Szajewska H, Szypowska A. Effects of Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 on beta-cell function in children with newly diagnosed type 1 diabetes: protocol of a randomised controlled trial. *BMJ Open.* 2017;7(10):e017178.

Grunwald T, Fadia S, Bernstein B, Naliborski M, Wu S, Luca F. Vitamin D supplementation, the metabolic syndrome and oxidative stress in obese children. *J Pediatr Endocrinol Metab.* 2017;30(4):383–8.

Gungor NK. Overweight and obesity in children and adolescents. *J Clin Res Pediatr Endocrinol.* 2014;6(3):129–43.

Habauzit V, Morand C. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: an update for clinicians. *Ther Adv Chronic Dis.* 2012;3(2):87–106.

Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet.* 2010;375(9727):1737–48.

Heger M, van Golen RF, Broekgaarden M, Michel MC. The molecular basis for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in relation to cancer. *Pharmacol Rev.* 2014;66(1):222–307.

Hume MP, Nicolucci AC, Reimer RA. Prebiotic supplementation improves appetite control in children with overweight and obesity: a randomized controlled trial. *Am J Clin Nutr.* 2017;105(4):790–9.

Huseini HF, Larijani B, Heshmat R, Fakhrzadeh H, Radjabipour B, Toliat T, Raza M. The efficacy of *Silybum marianum* (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. *Phytother Res.* 2006;20(12):1036–9.

Hussain SA. Silymarin as an adjunct to glibenclamide therapy improves long-term and postprandial glycemic control and body mass index in type 2 diabetes. *J Med Food.* 2007;10(3):543–7.

Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet.* 2002;360(9334):659–65.

Inoue N, Nagao K, Wang YM, Noguchi H, Shirouchi B, Yanagita T. Dietary conjugated linoleic acid lowered tumor necrosis factor-alpha content and altered expression of

genes related to lipid metabolism and insulin sensitivity in the skeletal muscle of Zucker rats. *J Agric Food Chem.* 2006;54(20):7935–9.
Islam MR, Attia J, Ali L, McEvoy M, Selim S, Sibbritt D, Akhter A, Akter S, Peel R, Faruque O, Mona T, Lona H, Milton AH. Zinc supplementation for improving glucose handling in pre-diabetes: a double blind randomized placebo controlled pilot study. *Diabetes Res Clin Pract.* 2016;115:39–46.
Isolauri E, Salminen S. The impact of early gut microbiota modulation on the risk of child disease: alert to accuracy in probiotic studies. *Benef Microbes.* 2015;6(2):167–71.
Jamshidi F, Kelishadi R. A systematic review on the effects of maternal calcium supplementation on offspring's blood pressure. *J Res Med Sci.* 2015;20(10):994–9.
Kalra EK. Nutraceutical--definition and introduction. *AAPS PharmSci.* 2003;5(3):E25.
Kelishadi R, Hashemipour M, Adeli K, Tavakoli N, Movahedian-Attar A, Shapouri J, Poursafa P, Rouzbahani A. Effect of zinc supplementation on markers of insulin resistance, oxidative stress, and inflammation among prepubescent children with metabolic syndrome. *Metab Syndr Relat Disord.* 2010;8(6):505–10.
Kelly DL, Lyon DE, Yoon SL, Horgas AL. The microbiome and cancer: implications for oncology nursing science. *Cancer Nurs.* 2016;39(3):E56–62.
Kikafunda JK, Walker AF, Allan EF, Tumwine JK. Effect of zinc supplementation on growth and body composition of Ugandan preschool children: a randomized, controlled, intervention trial. *Am J Clin Nutr.* 1998;68(6):1261–6.
Kim CY, Le TT, Chen C, Cheng JX, Kim KH. Curcumin inhibits adipocyte differentiation through modulation of mitotic clonal expansion. *J Nutr Biochem.* 2011;22(10):910–20.
Kumar KA, Lalitha A, Pavithra D, Padmavathi IJ, Ganeshan M, Rao KR, Venu L, Balakrishna N, Shanker NH, Reddy SU, Chandak GR, Sengupta S, Raghunath M. Maternal dietary folate and/or vitamin B12 restrictions alter body composition (adiposity) and lipid metabolism in Wistar rat offspring. *J Nutr Biochem.* 2013;24(1):25–31.
Langley-Evans SC. Developmental programming of health and disease. *Proc Nutr Soc.* 2006;65(1):97–105.
Lavandera J, Gerstner CD, Sain J, Farina AC, Gonzalez MA, Bernal CA. Maternal conjugated linoleic acid modulates TAG metabolism in adult rat offspring. *Br J Nutr.* 2017;118(11):906–13.
Lee SG, Parks JS, Kang HW. Quercetin, a functional compound of onion peel, remodels white adipocytes to brown-like adipocytes. *J Nutr Biochem.* 2017;42:62–71.
Lewis SJ, Leary S, Davey Smith G, Ness A. Body composition at age 9 years, maternal folate intake during pregnancy and methyltetrahydrofolate reductase (MTHFR) C677T genotype. *Br J Nutr.* 2009;102(4):493–6.
Lopez-Alarcon M, Martinez-Coronado A, Velarde-Castro O, Rendon-Macias E, Fernandez J. Supplementation of n3 long-chain polyunsaturated fatty acid synergistically decreases insulin resistance with weight loss of obese prepubertal and pubertal children. *Arch Med Res.* 2011;42(6):502–8.
Maftei O, Whitrow MJ, Davies MJ, Giles LC, Owens JA, Moore VM. Maternal body size prior to pregnancy, gestational diabetes and weight gain: associations with insulin resistance in children at 9–10 years. *Diabet Med.* 2015;32(2):174–80.
Mann JP, Tang GY, Nobili V, Armstrong MJ. Evaluations of lifestyle, dietary, and pharmacologic treatments for pediatric non-alcoholic fatty liver disease-a systematic review. *Clin Gastroenterol Hepatol.* 2019;17(8):1457–76.
Marchiani A, Rozzo C, Fadda A, Delogu G, Ruzza P. Curcumin and curcumin-like molecules: from spice to drugs. *Curr Med Chem.* 2014;21(2):204–22.
Marreiro DN, Geloneze B, Tambascia MA, Lerario AC, Halpern A, Cozzolino SM. Effect of zinc supplementation on serum leptin levels and insulin resistance of obese women. *Biol Trace Elem Res.* 2006;112(2):109–18.
Matsuyama T, Tanaka Y, Kamimaki I, Nagao T, Tokimitsu I. Catechin safely improved higher levels of fatness, blood pressure, and cholesterol in children. *Obesity (Silver Spring).* 2008;16(6):1338–48.

Mazani M, Argani H, Rashtchizadeh N, Ghorbanihaghjo A, Hamdi A, Estiar MA, Nezami N. Effects of zinc supplementation on antioxidant status and lipid peroxidation in hemodialysis patients. *J Ren Nutr.* 2013;23(3):180–4.

Mispireta ML, Caulfield LE, Zavaleta N, Merialdi M, Putnick DL, Bornstein MH, DiPietro JA. Effect of maternal zinc supplementation on the cardiometabolic profile of Peruvian children: results from a randomized clinical trial. *J Dev Orig Health Dis.* 2017;8(1):56–64.

Moazen S, Amani R, Homayouni Rad A, Shahbazian H, Ahmadi K, Taha Jalali M. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. *Ann Nutr Metab.* 2013;63(3):256–64.

Moore LL, Bradlee ML, Gao D, Singer MR. Low dairy intake in early childhood predicts excess body fat gain. *Obesity (Silver Spring).* 2006;14(6):1010–8.

Moreira P, Padez C, Mourao I, Rosado V. Dietary calcium and body mass index in Portuguese children. *Eur J Clin Nutr.* 2005;59(7):861–7.

Muhlhausler BS, Yelland LN, McDermott R, Tapsell L, McPhee A, Gibson RA, Makrides M. DHA supplementation during pregnancy does not reduce BMI or body fat mass in children: follow-up of the DHA to Optimize Mother Infant Outcome randomized controlled trial. *Am J Clin Nutr.* 2016;103(6):1489–96.

Murase T, Nagasawa A, Suzuki J, Hase T, Tokimitsu I. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. *Int J Obes Relat Metab Disord.* 2002;26(11):1459–64.

Murri M, Leiva I, Gomez-Zumaquero JM, Tinahones FJ, Cardona F, Soriguer F, Queipo-Ortuno MI. Gut microbiota in children with type 1 diabetes differs from that in healthy children: a case-control study. *BMC Med.* 2013;11:46.

Nagata S, Chiba Y, Wang C, Yamashiro Y. The effects of the Lactobacillus casei strain on obesity in children: a pilot study. *Benef Microbes.* 2017;8(4):535–43.

Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linlokken A, Wilson R, Rudi K. Correlation between the human fecal microbiota and depression. *Neurogastroenterol Motil.* 2014;26(8):1155–62.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet.* 2017;390(10113):2627–42.

Nicolucci AC, Hume MP, Martinez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. *Gastroenterology.* 2017;153(3):711–22.

Nobili V, Alisi A, Della Corte C, Rise P, Galli C, Agostoni C, Bedogni G. Docosahexaenoic acid for the treatment of fatty liver: randomised controlled trial in children. *Nutr Metab Cardiovasc Dis.* 2013;23(11):1066–70.

Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics- a review. *J Food Sci Technol.* 2015;52(12):7577–87.

Papadimitriou DT. The big vitamin D mistake. *J Prev Med Public Health.* 2017;50(4):278–81.

Papandreou D, Malindretos P, Arvanitidou M, Makedou A, Rousso I. Homocysteine lowering with folic acid supplements in children: effects on blood pressure. *Int J Food Sci Nutr.* 2010;61(1):11–7.

Payab M, Hasani-Ranjbar S, Aletaha A, Ghasemi N, Qorbani M, Atlasi R, Abdollahi M, Larijani B. Efficacy, safety, and mechanisms of herbal medicines used in the treatment of obesity: a protocol for systematic review. *Medicine (Baltimore).* 2018;97(1):e8825.

Pereira TM, Pimenta FS, Porto ML, Baldo MP, Campagnaro BP, Gava AL, Meyrelles SS, Vasquez EC. Coadjuvants in the diabetic complications: nutraceuticals and drugs with pleiotropic effects. *Int J Mol Sci.* 2016;17(8).

Plantinga Y, Ghiadoni L, Magagna A, Giannarelli C, Franzoni F, Taddei S, Salvetti A. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. *Am J Hypertens.* 2007;20(4):392–7.

Racine NM, Watras AC, Carrel AL, Allen DB, McVean JJ, Clark RR, O'Brien AR, O'Shea M, Scott CE, Schoeller DA. Effect of conjugated linoleic acid on body fat accretion in overweight or obese children. *Am J Clin Nutr.* 2010;91(5):1157–64.

Radhakishun NN, van Vliet M, Poland DC, Weijer O, Beijnen JH, Brandjes DP, Diamant M, von Rosenstiel IA. Efficacy and tolerability of a high loading dose (25,000 IU weekly) vitamin D3 supplementation in obese children with vitamin D insufficiency/deficiency. *Horm Res Paediatr.* 2014;82(2):103–6.

Rajakumar K, Fernstrom JD, Holick MF, Janosky JE, Greenspan SL. Vitamin D status and response to Vitamin D(3) in obese vs. non-obese African American children. *Obesity (Silver Spring).* 2008;16(1):90–5.

Rauf A, Imran M, Khan IA, Ur-Rehman M, Gilani SA, Mehmood Z, Mubarak MS. Anticancer potential of quercetin: a comprehensive review. *Phytother Res.* 2018;32(11):2109–2130.

Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. 1999;70(5):811–6.

Rayman MP. Selenium and human health. *Lancet.* 2012;379(9822):1256–68.

Revuelta Iniesta R, Rush R, Paciarotti I, Rhatigan EB, Brougham FH, McKenzie JM, Wilson DC. Systematic review and meta-analysis: prevalence and possible causes of vitamin D deficiency and insufficiency in pediatric cancer patients. *Clin Nutr.* 2016;35(1):95–108.

Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP. Effect of cocoa on blood pressure. *Cochrane Database Syst Rev.* 2012(8):Cd008893.

Rimoldi SF, Sartori C, Rexhaj E, Bailey DM, de Marchi SF, McEneny J, Arx R, Cerny D, Duplain H, Germond M, Allemann Y, Scherrer U. Antioxidants improve vascular function in children conceived by assisted reproductive technologies: a randomized double-blind placebo-controlled trial. *Eur J Prev Cardiol.* 2015;22(11):1399–407.

Romualdo MC, Nobrega FJ, Escrivao MA. Insulin resistance in obese children and adolescents. *J Pediatr (Rio J).* 2014;90(6):600–7.

Ross MG, Desai M. Developmental programming of offspring obesity, adipogenesis, and appetite. *Clin Obstet Gynecol.* 2013;56(3):529–36.

Rytter D, Bech BH, Halldorsson T, Christensen JH, Schmidt EB, Danielsen I, Henriksen TB, Olsen SF. No association between the intake of marine n-3 PUFA during the second trimester of pregnancy and factors associated with cardiometabolic risk in the 20-year-old offspring. *Br J Nutr.* 2013;110(11):2037–46.

Rytter D, Christensen JH, Bech BH, Schmidt EB, Henriksen TB, Olsen SF. The effect of maternal fish oil supplementation during the last trimester of pregnancy on blood pressure, heart rate and heart rate variability in the 19-year-old offspring. *Br J Nutr.* 2012;108(8):1475–83.

Sahebkar A, Ferri C, Giorgini P, Bo S, Nachtigal P, Grassi D. Effects of pomegranate juice on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res.* 2017;115:149–61.

Saldeen P, Saldeen T. Women and omega-3 Fatty acids. *Obstet Gynecol Surv.* 2004;59(10):722–30; quiz 45–6.

Sanchez M, Panahi S, Tremblay A. Childhood obesity: a role for gut microbiota? *Int J Environ Res Public Health.* 2014;12(1):162–75.

Santamaria C, Bi WG, Leduc L, Tabatabaei N, Jantchou P, Luo ZC, Audibert F, Nuyt AM, Wei SQ. Prenatal vitamin D status and offspring's growth, adiposity and metabolic health: a systematic review and meta-analysis. *Br J Nutr.* 2018;119(3):310–9.

Schuchardt JP, Wonik J, Bindrich U, Heinemann M, Kohrs H, Schneider I, Moller K, Hahn A. Glycemic index and microstructure analysis of a newly developed fiber enriched cookie. *Food Funct.* 2016;7(1):464–74.

Scorletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. *Annu Rev Nutr.* 2013;33:231–48.

See VHL, Mori TA, Prescott SL, Beilin LJ, Burrows S, Huang RC. Cardiometabolic risk factors at 5 years after omega-3 fatty acid supplementation in infancy. *Pediatrics.* 2018;142(1).

Segovia SA, Vickers MH, Gray C, Zhang XD, Reynolds CM. Conjugated linoleic acid supplementation improves maternal high fat diet-induced programming of metabolic dysfunction in adult male rat offspring. *Sci Rep.* 2017;7(1):6663.
Shao W, Yu Z, Chiang Y, Yang Y, Chai T, Foltz W, Lu H, Fantus IG, Jin T. Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes. *PLoS One.* 2012;7(1):e28784.
Sharifi N, Amani R. Vitamin D supplementation and non-alcoholic fatty liver disease: a critical and systematic review of clinical trials. *Crit Rev Food Sci Nutr.* 2019;59(4):693–703.
Shema-Didi L, Kristal B, Sela S, Geron R, Ore L. Does Pomegranate intake attenuate cardiovascular risk factors in hemodialysis patients? *Nutr J.* 2014;13:18.
Shin S, Lee JA, Kim M, Kum H, Jung E, Park D. Anti-glycation activities of phenolic constituents from Silybum marianum (Milk Thistle) flower in vitro and on human explants. *Molecules.* 2015;20(3):3549–64.
Stowe CB. The effects of pomegranate juice consumption on blood pressure and cardiovascular health. *Complement Ther Clin Pract.* 2011;17(2):113–5.
Straub N, Grunert P, von Kries R, Koletzko B. Health economic potential of early nutrition programming: a model calculation of long-term reduction in blood pressure and related morbidity costs by use of long-chain polyunsaturated fatty acid-supplemented formula. *Am J Clin Nutr.* 2011;94(6 Suppl):2030s–5s.
Suzuki T, Pervin M, Goto S, Isemura M, Nakamura Y. Beneficial effects of tea and the green tea catechin epigallocatechin-3-gallate on obesity. *Molecules.* 2016;21(10).
Tadera K, Minami Y, Takamatsu K, Matsuoka T. Inhibition of alpha-glucosidase and alpha-amylase by flavonoids. *J Nutr Sci Vitaminol (Tokyo).* 2006;52(2):149–53.
Takaya J. Small for gestational age and magnesium: intrauterine magnesium deficiency may induce metabolic syndrome in later life. *AIMS Public Health.* 2015;2(4):793–803.
Takaya J, Iharada A, Okihana H, Kaneko K. Magnesium deficiency in pregnant rats alters methylation of specific cytosines in the hepatic hydroxysteroid dehydrogenase-2 promoter of the offspring. *Epigenetics.* 2011;6(5):573–8.
Takikawa M, Inoue S, Horio F, Tsuda T. Dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. *J Nutr.* 2010;140(3):527–33.
Taubert D, Roesen R, Lehmann C, Jung N, Schomig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *JAMA.* 2007;298(1):49–60.
Thompson M, Dana T, Bougatsos C, Blazina I, Norris SL. Screening for hypertension in children and adolescents to prevent cardiovascular disease. *Pediatrics.* 2013;131(3):490–525.
Tint MT, Chong MF, Aris IM, Godfrey KM, Quah PL, Kapur J, Saw SM, Gluckman PD, Rajadurai VS, Yap F, Kramer MS, Chong YS, Henry CJ, Fortier MV, Lee YS. Association between maternal mid-gestation vitamin D status and neonatal abdominal adiposity. *Int J Obes (Lond).* 2018;42(7):1296–1305.
Todorcevic M, Hodson L. The effect of marine derived n-3 fatty acids on adipose tissue metabolism and function. *J Clin Med.* 2015;5(1).
Trilok-Kumar G, Kaur M, Rehman AM, Arora H, Rajput MM, Chugh R, Kurpad A, Sachdev HS, Filteau S. Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3–6 years: follow-up of a randomized controlled trial. *Int J Epidemiol.* 2015;44(3):894–905.
Tsuda H, Miyamoto T. Guidelines for the evaluation of probiotics in food. Report of a joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food Guidelines for the evaluation of probiotics in food. Report of a joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food, 2002. *Food Sci Technol Res.* 2010;16(1):87–92.

Tuorkey MJ, El-Desouki NI, Kamel RA. Cytoprotective effect of silymarin against diabetes-induced cardiomyocyte apoptosis in diabetic rats. *Biomed Environ Sci.* 2015;28(1):36–43.

Uusitalo U, Liu X, Yang J, Aronsson CA, Hummel S, Butterworth M, Lernmark A, Rewers M, Hagopian W, She JX, Simell O, Toppari J, Ziegler AG, Akolkar B, Krischer J, Norris JM, Virtanen SM. Association of early exposure of probiotics and islet autoimmunity in the TEDDY study. *JAMA Pediatr.* 2016;170(1):20–8.

van der Spuy WJ, Pretorius E. Is the use of resveratrol in the treatment and prevention of obesity premature? *Nutr Res Rev.* 2009;22(2):111–7.

van Rossem L, Wijga AH, de Jongste JC, Koppelman GH, Oldenwening M, Postma DS, Abrahamse-Berkeveld M, van de Heijning B, Brunekreef B, Smit HA. Blood pressure in 12-year-old children is associated with fatty acid composition of human milk: the prevention and incidence of asthma and mite allergy birth cohort. *Hypertension.* 2012;60(4):1055–60.

Vidakovic AJ, Gishti O, Voortman T, Felix JF, Williams MA, Hofman A, Demmelmair H, Koletzko B, Tiemeier H, Jaddoe VW, Gaillard R. Maternal plasma PUFA concentrations during pregnancy and childhood adiposity: the Generation R Study. *Am J Clin Nutr.* 2016;103(4):1017–25.

Vieira ML, Fonseca FL, Costa LG, Beltrame RL, Chaves CM, Cartum J, Alves SI, Azzalis LA, Junqueira VB, Pereria EC, Rocha KC. Supplementation with selenium can influence nausea, fatigue, physical, renal, and liver function of children and adolescents with cancer. *J Med Food.* 2015;18(1):109–17.

Visuthranukul C, Sirimongkol P, Prachansuwan A, Pruksananonda C, Chomtho S. Low-glycemic index diet may improve insulin sensitivity in obese children. *Pediatr Res.* 2015;78(5):567–73.

Wada M, Nagata S, Saito M, Shimizu T, Yamashiro Y, Matsuki T, Asahara T, Nomoto K. Effects of the enteral administration of Bifidobacterium breve on patients undergoing chemotherapy for pediatric malignancies. *Support Care Cancer.* 2010;18(6):751–9.

Wang H, Yu XD, Huang LS, Chen Q, Ouyang FX, Wang X, Zhang J. Fetal vitamin D concentration and growth, adiposity and neurodevelopment during infancy. *Eur J Clin Nutr.* 2018;72(10):1396–1403.

Wang W, Wu Y, Zhang D. Association of dairy products consumption with risk of obesity in children and adults: a meta-analysis of mainly cross-sectional studies. *Ann Epidemiol.* 2016;26(12):87082.e2.

Wei W, Liu Q, Tan Y, Liu L, Li X, Cai L. Oxidative stress, diabetes, and diabetic complications. *Hemoglobin.* 2009;33(5):370–7.

Wen J, Hong Q, Wang X, Zhu L, Wu T, Xu P, Fu Z, You L, Wang X, Ji C, Guo X. The effect of maternal vitamin D deficiency during pregnancy on body fat and adipogenesis in rat offspring. *Sci Rep.* 2018;8(1):365.

Winzenberg T, Shaw K, Fryer J, Jones G. Calcium supplements in healthy children do not affect weight gain, height, or body composition. *Obesity (Silver Spring).* 2007;15(7):1789–98.

Xu P, Wang H, Kayoumu A, Wang M, Huang W, Liu G. Diet rich in Docosahexaenoic Acid/Eicosapentaenoic Acid robustly ameliorates hepatic steatosis and insulin resistance in seipin deficient lipodystrophy mice. *Nutr Metab (Lond).* 2015;12:58.

Zhao Y, Chen B, Shen J, Wan L, Zhu Y, Yi T, Xiao Z. The beneficial effects of quercetin, curcumin, and resveratrol in obesity. *Oxid Med Cell Longev.* 2017;2017:1459497.

Zheng S, Steenhout P, Kuiran D, Qihong W, Weiping W, Hager C, Haschke F, Clemens RA. Nutritional support of pediatric patients with cancer consuming an enteral formula with fructooligosaccharides. *Nutr Res.* 2006;26(4):154–62.

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19

Respiratory Tract Function and Nutraceuticals

Kavita Joshi, Vineet Jain, Kunal Dhankhar, Harvinder Popli,* and Keerti Jain*

Contents

* Corresponding author.

19.1 Introduction of Nutraceuticals

The term "nutraceutical" was coined by Stephen DeFelice in 1989 from the words "nutrition" and "pharmaceutical" and it has gigantic possibilities for development and extension with regard to medical advantages (Ruchi et al. 2017). Nutraceuticals are characterized as dietary/nourishment supplements that convey a concentrated form of an assumed bioactive operator from sustenance, displayed in a non-food lattice and utilized in measurements with the intent of improving a person's well-being (Mukherjee et al. 2017). A nutraceutical can likewise be characterized as "sustenance (or part of nourishment) that gives medicinal or medical advantages, including the counteractive action or potential treatment of a malady" (Kalra 2003). This term is connected to items that can be disengaged from natural items, dietary enhancements (supplements), explicit weight control plans and handled nourishments (like homemade food), for example, oats, soups and drinks that other than sustenance are additionally utilized as prescription (Nasri et al. 2014). Recently, nutraceuticals have emerged as beneficial health products obtained from many industries such as food, herbal and pharmaceutical manufacturing industries (Dillard & German 2000). Natural medication are becoming increasingly popular as they are transformed into edible items and people recognize the side effects and toxicity issues of conventional medicines. With the modernized, aggressive way of life, increased levels of stress and the lack of physical activity, all types of diseases are having a field day (Nethathe & Russell 2014). Nutraceuticals provide non-specific biological therapy for treatment and prophylaxis of various types of disease (Wong 2001). So the significance of such products has been linked with the treatment of numerous disorders, for example, malignancy, metabolic issues, cold and cough, depression, coronary illness, postponed gastrointestinal purging and many other conditions that need particular consideration (Lachance & Das 2007).

Well before the advancement of the particular logical control of nourishment, rationalists and later doctors paid close attention to the job of the day-by-day diet in individual and general well-being. Strikingly, over the last 2,000 years, from the time of Hippocrates (460–377 BC) to the beginning of present-day medicine (Andlauer & Fürst 2018), the act of medication itself comprised the most piece of the insightful decision of characteristic nourishment items. Hippocrates obviously recognized the imperative connection between nourishment and well-being and underlined that distinctions of illnesses rely upon nutriment (Hippocrates, Jones & Potter 1923). Only a clinician can commit murder with complete exemption (Pliny & Rackham 1938). In contrast, Galen (131–201 AD), a doctor, reflected trust in the information and capacity of doctors to set up sound weight control plans that would improve general well-being (Goss 1958). Casimir Funk found in the shell of a grain of rice a nitrogen-containing amine-base (amine); since he felt that this substance was "life-basic" for the individual, he characterized the phrase "Vitamine" from "Vita = life" and "amine = chemical amine" (Casmir 1975). To be sure, it is very entrancing that

the power we today credit to nutrients resembles that one portrayed to "mixture vitae" (Bitensky 1973) which was portrayed as a mixture of life in old days.

Any well-being useful impact of nutraceuticals is identified with the way that they are obtained from sustenance or part of nourishment, and therefore, they can be viewed as protected or, by and large, perceived as sheltered (generally recognized as safe, GRAS) (Santini, Tenore & Novellino 2017). Conventional drugs are also gaining a legitimate spot in the present medicinal services framework as home grown dietary enhancements. Some notable and furthermore some novel bioactive phytochemicals have been separated from different herbal plants which were utilized in traditional Chinese medicine and Ayurvedic medicine (Misra 2013). Numerous phytochemicals present in consumable plant materials and plant extricates utilized in conventional medication or in dietary enhancements are unreservedly accessible to the general population. Another are which has received significant attention recently is that of prebiotics and polyunsaturated fats (PUFAs) (Ansari & Inamdar 2010). Prebiotics are non-absorbable nourishment supplements, which positively influence the host by invigorating development, movement, or both, of explicit intestinal bacteria (Das et al. 2012).

The reasons for a shift towards nutraceuticals are (Chaudhari et al. 2017) as follows:

1. Expansion of the number of buyers who are worried about human services costs.
2. Disappointment with pharmaceutical operators in advancing well-being, people are moving to nutraceuticals to improve their well-being and avert ceaseless sickness.
3. Health care providers recognize the way that our strongly prepared nourishment supply, originating from harvests developed with synthetic composts, pesticides, herbicides and often genetically modified seeds, need adequate supplements that are fundamental to perfect health.
4. Individuals who are currently trusting more in avoidance than fix.
5. Individuals with constant sicknesses who have discovered no arrangement in allopathic meds.
6. Economically challenged patients.

19.2 The Significance of Nutraceuticals in the Present Era (Ashwini, Vaishali & Digambar 2018)

- Higher trust in item quality and adequacy.
- The improved market for nutraceutical items.
- Increased open mindfulness.
- Increased social insurance industry mindfulness.
- Establishment of a self-overseeing motivation.

- Have a psychological benefit by accomplishing something for oneself.
- Be seen to be more "normal" than conventional natural drugs and considerably less liable to cause unsavoury side effects.
- May present nourishment for populaces with exceptional requirements (for example supplement heavy sustenance for the elderly).

19.3 Categorization of Nutraceuticals According to Disease

The approach of nutraceuticals matters because of the power it holds to treat diseases through diet only. They are proposed to prevent diseases (Singh 1992; Ruchi, Amanjot, Sourav, & Keerti 2017). The classification of nutraceuticals is given in Table 19.1 and Figure 19.1.

Table 19.1 Classification of Nutraceuticals and Their Uses

S.No	Class of Nutraceuticals	Definition	Uses
1	**Functional Foods**	Also called the tertiary function of foods, It was supposed to be directly involved in modifying physiological systems, such as the immune, endocrine, nervous, circulatory and digestive systems.	Omega-3 enriched foods, oats, tomatoes and nuts.
2	**Fortified Foods**	Foodstuffs to which compounds of proven therapeutic or preventive efficacy have been added.	Gold kiwifruit is genetically modified for a high level of ascorbic acid, carotenoids, and lutein and zeaxanthin.
3	**Medicinal Products**	A product that contains a compound with proven pharmacological and beneficial therapeutic effects, a drug, prodrug or a cellular element, plus excipients, or excipient.	Tablet, capsule, elixir, solution for injection, transdermal formulation, cream or ointment.
4	**Dietary Supplements**	A substance added to the diet, often taken as a pharmaceutical formulation, to treat or prevent a deficiency.	Inulin which on further hydrolysis gives oligofructose and galactooligosaccharide.
5	**Recombinant Products**	It involves the application of biotechnology and genetic engineering in the production of energy providing foods such as yogurt and cheese or extraction of bioactive components by enzymatic or fermentation technology.	Yogurt, cheese, vinegar and other products produced with the help of recombinant biotechnology.
6	**Herbal Products**	Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations.	Concentrates and extracts e.g., aloe vera, wheat grass,ginger, garlic etc.
7	**Natural Products**	These are the chemical constituents of plants with distinct biological activities. These are been reported to have active components which exert their effects toward the metabolism and biochemical reactions in living beings and thus, provide health benefits.	Carotenoids, flavanoids, glycosides, carbohydrates and other natural products.

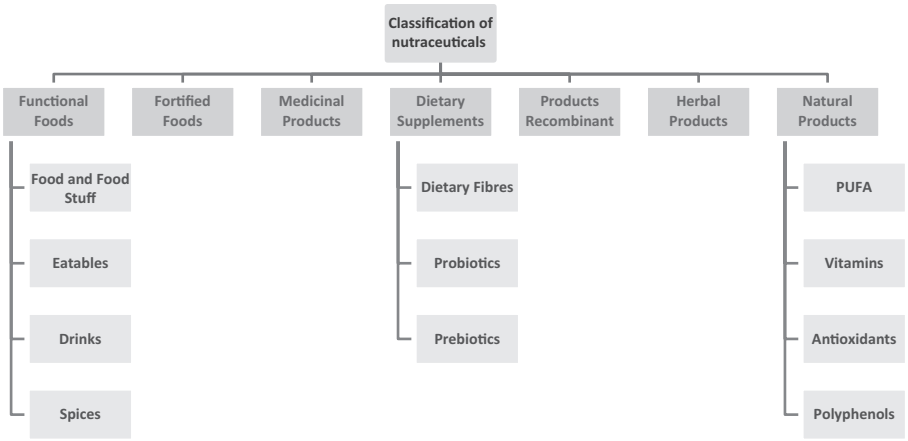

Figure 19.1 *Classification of nutraceuticals (Hathcock 2001, Kaur et al. 2015).*

19.4 Respiratory Function and Disorders

The lungs depend on separated air through the nose (with cilia and bodily fluid endeavouring to channel/trap undesirable particles) or unfiltered air by means of the mouth. Anatomically, the respiratory tract has been partitioned into the upper (organ outside thorax – nose, pharynx and larynx) and lower respiratory tract (organ inside thorax – trachea, bronchi, bronchioles, alveolar pipe and alveoli (DeVries, Kriebel & Sama 2016). Our lungs are one of the biggest essential organs. The oxygen we take in goes into our lungs and goes into the blood from that point. It is then transported to all the cells in our body through our circulatory system. The lungs are situated in the area of the chest in the body, secured by the ribs in the rib confine. Their structure can be contrasted with that of a topsy turvy tree. The windpipe separates into two airways called bronchi, which lead to the lungs. Inside the lungs, the airways continue stretching into smaller airways until the air sacs otherwise called alveoli are reached ("Respiratory System" 2018).

The elements of the human respiratory framework are:

- To transport air into the lungs and to encourage the dispersion of oxygen into the circulatory system.
- To remove carbon dioxide from the blood and breathe it out from the body.
- To eliminate some toxic waste from the body.
- To maintain the acid-base balance of the body through various mechanisms like bicarbonate ion system and help in regulating the temperature of the body (Walden 2018).

Respiratory diseases are the most commonly reported medical health issues in the world. Millions of people are suffering from different kinds of respiratory

diseases. Pollution is the major factor responsible for these respiratory disorders. Polluted air contributes to Chronic Obstructive Pulmonary Disease (COPD) prevalence and symptom onset (Kampa & Castanas 2008). WHO evaluates that in 2012, some 14% of deaths were expected to be caused by COPD or intense lower respiratory diseases, and 14% of deaths caused by lung tumor growth (Kumar 2018).

19.4.1 Causes

The common causes behind respiratory disorders are:

- Genetic Issues
- Toxic agents
- Accidents
- Harmful lifestyle
- Low immune functioning
- Adverse climatic conditions and intolerable air pollution
- Excessive exposure to smoke and other toxic materials present in the environment
- Inappropriate development of lungs during childhood/before birth
- Presence of fungal, viral and bacterial infections (Philips 2018).

19.4.2 Disorders of the Respiratory Framework Is Characterized into Four General Territories

- **Obstructive conditions:** e.g., emphysema, bronchitis, COPD, asthma assaults.
- **Restrictive conditions:** e.g., sarcoidosis, alveolar harm, fibrosis, pleural emanation.
- **Vascular ailments:** e.g., aspiratory embolism, pneumonic edema, aspiratory hypertension.
- **Infectious, ecological and other "ailments":** e.g., pneumonia, tuberculosis, asbestosis, particulate contaminations, coughing is of a noteworthy issue.

Disorders of the respiratory system are classified into four general areas:

- **Obstructive conditions:** e.g., emphysema, bronchitis, COPD, asthma attacks.
- **Restrictive conditions:** e.g., sarcoidosis, alveolar damage, fibrosis, pleural effusion.
- **Vascular diseases:** e.g., pulmonary embolism, pulmonary edema, pulmonary hypertension.

- **Infectious, environmental and other "diseases":** e.g., pneumonia, tuberculosis, asbestosis, particulate pollutants, Coughing is of a major issue (Dasaraju & Liu 1996).

19.4.3 Current Therapeutic Regimen for Respiratory Disorders

- **Traditional Therapy:** In the general public, herb salves, including air-dried herbs, homemade soups and other natural items have had a long history of combining plant supplements with local cooking.
- **Modern Therapy:** In spite of the fact that the utilization of herbs and characteristic items from plants (natural products from plants, NPFPs) and normal items from creatures (natural products from animals, NPFAs) have been basically referred to in audits dependent on ebb and flow respiratory infections e.g., vitamin, mineral and organic mixes, with and without cancer prevention agent properties will be discussed (Steinemann et al. 2018).

19.5 Role of Nutraceuticals in the Suppression of Respiratory Tract Disorders

The role of nutraceuticals in respiratory diseases is given in Table 19.2.

19.5.1 Nutraceuticals Used to Treat Respiratory Disorders

A summary of nutraceuticals is given in Table 19.3.

19.6 The Emerging Role of Nutraceuticals in Respiratory Function Maintenance

- The way of eating will help fight the impacts of pollution and counteract the effects of contamination on asthma and other respiratory disorders.
- The significance of such products has been related to the treatment and treatment of numerous disarranges, for example, malignant growth, metabolic issues, colds and coughs.
- A mix of supplements, botanicals and basic oils can address the general well-being of the respiratory framework and give additional help to the immune system.
- Antioxidants are the lungs' first line of defense against free radicals. A number of natural supplements can provide explicit help to the various portions of the lungs against pollution and free radicals.
- Nutrigenomics is noteworthy in the activity of nutraceuticals against developing and various contaminations by providing genetic information.

Table 19.2 Summary of Nutraceuticals According to Their Use in Various Respiratory Disorders

S. No.	Category	Examples	Uses
1	Herbs	• Eucalyptus • Lungwort • Oregano • Plantain leaf • Lobelia • Peppermint • Osha root • Elecampane	Respiratory spasms, which can be beneficial for dry, irritating coughs and asthma.
2	NPFAs	• Fish oil • Heparin • PUFA	Anti-inflammatory. Asthma and idiopathic pulmonary fibrosis.
3	NPFPs	• Green tea	Type 2 diabetes and lung cancer. Strong antioxidant and anti-inflammatory effects.
4	Vitamin	• Vitamin C • Vitamin D • Vitamin E • Flavonoids • Carotenoids • Antioxidants	Anti-asthmatic. COPD. Antioxidants and they show anti-inflammatory as well as anti-allergic properties. Reducing the expression of ECM genes.
5	Minerals	• Magnesium • Calcium • Potassium	Anti-asthmatic.
6	Diet	• Fruits and vegetables • Bread and cereals • Beans, nuts and seeds • Dairy products, fish, poultry, wine, red meat and olive oil	Reduces the risk of developing lung diseases, particularly asthma and COPD.
7	Chinese Drugs	• Phlegm • Reishi mushroom • Ginger root	Normal inflammatory response. Support a healthy histamine response. Immune balancing.
8	Ayurvedic Medicine	• Adhatodavasica • Tylophoraindica • Holy basil • Ivy leaf • Stinging nettle	Anti-spasmodic activity in the lungs. Respiratory health. Anti-inflammatory. Immune balancing.
9	Aroma Therapy	• Oils of cypress • Sweet marjoram • Niaouli • Red Mandarin • Asian ginseng	Antispasmodic activity. Promote clear airways within the lungs. Antimicrobial activity. Promotes healthy inflammatory.

(Baybutt et al. 2002, Gayan-Ramirez 2018, Zhao et al. 2014, Kubo et al. 2005, Hu & Cassano 2000, Jinno et al. 2006, Sriram, Kalayarasan & Sudhandiran 2009, Berthon & Wood 2015, Littlefield 2015).

Table 19.3 Summary of Various Nutraceuticals and Their Sources

Sr. No	Nutraceutical to Be Used	Source	Used to Treat Disease
1.	Dietary fibers (beta-glucan)	Fruits and vegetables	Asthma
2.	Probiotics and prebiotics	Bacteria like lactobacillus and bifidobacteria	Asthma
3.	Fructo-oligosaccharides (FOS)	Fruits (banana, chicory, tomato)	Bronchitis
4.	Vitamin C	Citrus fruits	Asthma
5.	Vitamin E	Vegetables	Asthma
6.	Carotenoids	Carrot and raddish	Asthma
7.	Vitamin A	Fruits & Vegetables	Lungs Inflammation
8.	Alpha tocopherols	Soya, Sesame & Nuts	Lung Edema
9.	Prostaglandins and cytokines		COPD
10.	PUFA (poly unsaturated fatty acids)	Fish oils, soybean oils and nuts	Nuts
11.	Adhotavasaka	Shrub	Bronchoconstriction and cough
12.	Albizialebbeck	Bark	Cough, cold, asthma, bronchitis
13.	*Boswellia serrata*	Whole plant	Chronic Lungs Inflammation
14.	*Curcuma longa*	Dried flower buds	Ova asthma
15.	*Glycyrrhiza glabra*	Dried ttems	COPD, cough
16.	*Piper longum*	Riped Fruits	Tuberculosis and respiratory tract infection
17.	*Zingiber officinale*	Rhizomes	Asthma, bronchitis cold
18.	*Kalanchoe Integra*	Boiled eaf extract	Acute and chronic bronchitis, ronchial asthma
19.	*Hedychium spycatum*	Rhizomes	Cough, asthma and other respiratory disorder
20.	*Tylophora indica*	Leaves	Bronchial asthma, bronchitis, whooping cough
21.	*Ocimum sanctum*	Leaves	Cough, cold, asthma and bronchitis
22.	*Solanum xanthocarpum*	Juice of berries	Bronchitis & Asthma
23.	Quercetin (flavanoids)	Onions, Apples, Tea, Berries&Broccoli	Asthma and bronchial inflammation
24.	Colchicine (alkaloid)	Plant of *Colchicum autumnale*	Pulmonary fibrosis and bronchial asthma
25.	Warifteine (alkaloid)	*Cissampelos sympodialis*	Airway-Hyperresponsiveness & Lung Remodeling
26.	Resveratrol (dietary polyphenol)	Seeds of grapes	Asthma, allergic airway disease

(Yadav et al. 2012, Biol et al. 2018, Gulati et al. 2016, Hwang & Ho 2018, Prabu et al. 2012).

- Nutraceuticals have received significant attention because of potential in supporting wellbeing and aiding in recovery for different health issues (Lachance and Das 2007, Nasri et al. 2014).
- Foods and supplements have a key role in the typical workings of the body. They have turned out to be exceptionally useful in keeping up the strength of an individual and in decreasing the danger of different sicknesses.
- Nutraceuticals are part of a curative diet that has a fundamental role in taking care of well-being, improving health and modulating immunity, and thereby preventing various infections (Ahmad et al. 2013).

19.7 Advantages of Nutraceutical Therapy in Respiratory Tract Functions

- Increase the well-being of our diet.
- Help us to live longer.
- Help us to avoid particular medical conditions.
- Useful for treating nourishment inadequacies.
- Usually, they do not require prescriptions.
- Nutraceuticals do not need clinical trials to determine their effectiveness.
- They are the substrates for numerous biochemical reactions.
- They are ligands that can act as agonists or antagonists of cell surface or intracellular receptors.
- In some cases, they can act as the scavengers of highly reactive species or toxic chemicals.
- They are compounds that enhance the absorption and/ or stability of essential nutrients.
- Side effects might be less common than from general pharmaceuticals (Das et al. 2012b, Nasri et al. 2014, Dillard & German 2000).

19.8 Advanced Research on Respiratory Function Based on Nutraceuticals

A number of chronic respiratory diseases are caused by air pollution and other environmental factors. For the treatment of these chronic respiratory diseases, a number of drugs are available but none of them cure these disorders, and they have a lot of side effects. So nowadays research on nutraceuticals has been increasing to find better treatment options (Whyand et al. 2018, DeVries, Kriebel & Sama 2016).

Currently, many research studies are being carried out on nutraceuticals to find their efficacy in respiratory disorders. Quercetin, a flavonoid, has been found to be very beneficial in the case of pulmonary fibrosis. It generally acts by disturbing the redox balance of the lungs in cases of pulmonary fibrosis (Veith et al. 2017). Like quercetin, epigallocatechin gallate obtained from green tea has also shown promising results with pulmonary fibrosis (Sriram,

Kalayarasan & Sudhandiran 2009). Vitamins are of crucial importance as nutraceuticals. Consumption of vitamin A might have beneficial effects on asthma by the downregulation of oxidative stress (Paiva & Russell 1999) or by directly affecting the immune system (Mora, Iwata & von Andrian 2008). It has been observed that a low dietary intake of ascorbic acid and tocopherols is associated with a higher prevalence of asthma and other respiratory disorders (Tricon et al. 2006). Animal studies have shown that curcumin, obtained from *Curcuma longa*, has potent anti-inflammatory activity in lungs and it may also protect from pulmonary fibrosis (Yang et al. 2017, Chauhan, Dash & Singh 2017). Fats like PUFA and omega-3 oils have also shown to reduce inflammation. For mild and acute forms of asthma LCPUFAs, like fish oil, have shown to be more effective.

Medicinal plants used in respiratory diseases as nutraceuticals:

1. ***Adhatodavasica*:** The roots, leaves and flower of this plant are used as a bronchodilator in case of asthma. Vasicine is known to have a major role in the activity of the drug (Rachana et al. 2011).
2. ***Bryophyllum pinnatum*:** This plant has shown so many different uses such as immunosuppressant, anti-inflammatory, antioxidant and wound healing. Leaves of this plant have proven to be effective in bronchial asthma in some recent studies. However, anti-allergic effects of this drug also have been demonstrated by researchers (Julius et al. 2014).
3. ***Albizialebbeck*:** The aqueous extract of this drug has shown to be useful asthma and anaphylaxis in experimental studies (Biol et al. 2018).
4. ***Boswellia serrata* and *Curcuma longa*:** Extract of *Boswellia serrata* has been used for asthma in traditional medicine. This extract contains resins, amino acids, terpenes, polyphenols and β-boswellic acid, which is the main active component (Khajuria et al. 2008). *Curcuma longa*, on the other hand, has curcumin, which is the main active component (Zhang et al. 2011).
5. ***Glycyrrhiza glabra* and *Hedychium spicatum*:** Glycyrrhiza has been used to treat cough since ancient days. Glycyrrhizin and Glycyrrhizinic acid are the main active constituents of this drug responsible for this use (Ram et al. 2011, Park et al. 2004). A study has evaluated the effectiveness of aqueous and ethanolic extract of Hedychium as an anti-inflammatory agent. The result of this study supports the use of this drug in respiratory disorders (Ghildiyal et al. 2012).
6. ***Ocimum sanctum* and *Piper longum*:** Recent animal data has shown the immunomodulatory effects of *Ocimum sanctum*. But the leaves of this plant have been used for cough and asthma in the past (Mediratta et al. 1988). On the other hand, *Piper longum* has been reported to be a good nutraceutical remedy for respiratory disorders and tuberculoses (Singh 1992).
7. ***Zingiber Officinalis*:** It is also known as ginger. It has been shown that this drug can be used in cough and asthma. Recently it was found

Table 19.4 List of Marketed Nutraceuticals

S. No.	Marketed Formulation (Brand Name)	Generic Name	Use to Treat Disease	Manufacturer
1.	Omacor	Omega-3 polyunsaturated fatty acids	Asthma & Bronchial Inflammation	Aurobindo pharma
2.	B.Colostrum	Bovine colostrum	Asthma	FinecurePharma
3.	Immuno Boost C+	Vit. C, colostrum, *Echinacea purpurea*	Broncho constriction, Cold	FinecurePharma
4.	Oxi Grape-50	Dicalcium Phosphate	Cold, Broncial Inflammation	FinecurePharma
5.	KO-Q-10 Plus	Ginger and Ggeen tea extract	Cold, Inflammation of Lungs	FinecurePharma
6.	Appocarotenal	Precursor of vitamin A	Asthma	DSM Nutraceuticals
7.	Elavida	Polyphenols	Broncial Inflammation	DSM Nutraceuticals
8.	Nutritional Lipids	LC-PUFA	Cold & Asthma	DSM Nutraceuticals
9.	ALL-Q	Coenzyme 10	Bronchial inflammation	DSM Nutraceuticals
10.	Life sARA	Omega-6-fatty acids	Asthma	DSM Nutraceuticals

(Drugs.com, n.d., Chauhan et al., 2013, "Pharmaceutical Manufacturing and Exports, Research and Development in Pharma" 2018, DSM, n.d.).

that fresh ginger extract has antiviral use against human respiratory syncytial virus-induced plaque formation on airway epithelium (Ram et al. 2011).

19.8.1 Marketed Products

A list of marketed nutraceuticals is given in Table 19.4.

19.9 Challenges/Limitations in the Use of Nutraceuticals

Due to the increase in consumption of nutraceuticals, nowadays consumers worry about food sanitation and the nature of the crude materials used to make nutraceutical supplements has received intense scrutiny (Dahiya 2013). Unlike pharmaceutical preparations, nutraceutical preparations do not need to fulfil many requirements. Generally, it may be easy to develop a pharmaceutical form (tablets, powders, capsules, suppositories, etc.) containing bioactive food for a formulator (Keservani et al. 2017), but:

- It is often challenging to obtain excellent bioavailability for such products.
- Selection of suitable raw materials for the preparation of the formulation is a great challenge.

- Selection of the drug delivery system (Dillard & German 2000) for the nutraceuticals is also a challenge.
- Nutraceuticals consist of biological products that have a higher tendency to degrade easily e.g., probiotics (Ernst 2001) so this limits their shelf life and the stability of the formulation is a factor which cannot be compromised (Chang 2000).
- Active ingredients of the product should be released only when triggered by an external stimulus (Ruchi et al. 2017). But this is quite difficult to achieve in the case of nutraceuticals.
- Due to insufficient awareness about nutraceuticals; manufacturing processes in several firms give negligible consideration to product extraction, enhancement of the shelf life, storage of the crude and prepared materials, meeting the quality standards of the ingredients and prevention from contamination (Crandell & Duren 2001).
- The bioavailability of any product is usually affected by the low stability, solubility and/or permeability of the bioactive constituent in the gastrointestinal tract. For example, in the case of curcumin (Gbassi & Vandamme 2012).
- Probiotics encapsulation technology (PET), which has recently emerged as an approach for the delivery of probiotics, is under investigation to overcome challenges of probiotics delivery.
- Conditions that maintain cell viability like solvent type, biomaterial selection and toxicity and choice of proper technology are of main concern in formulating probiotics (Bagchi & Nair 2016).
- Nutraceuticals include dietary supplements, functional foods, etc., and the components used in the formulation must be of food grade.
- Many widely used medicinal plants still lack extensive physiological characterization. This limits the choice for researchers and decreases the scope of innovations in the nutraceutical domain.
- A major concern for the use of nutraceuticals is the lack of quality control that results in adulteration or contamination of nutraceuticals (Patil 2011).
- The cost of nutraceuticals is another major concern (Briskin 2000).

19.9.1 Approaches to Overcome Challenges

Manufacturers in industries can't add a nutraceutical to a supplement, even if they have a very good effect and advantages. The use of nanotechnology for pharmaceutical applications has created other options for decreasing the side effects of potentially risky nutraceuticals (Keservani et al. 2014). Advances in micro- and nanoscale encapsulation for producing fit-for-purpose delivery systems have shown promise for adjustment, taste veiling, controlled discharge and targeted delivery of bioactive compounds and nutraceuticals (Augustin & Sanguansri 2015). Encapsulation includes entanglement of a bioactive part (e.g., a nutraceutical) inside an auxiliary material, which might be

Table 19.5 Showing the Selected Materials Used Encapsulation of Neutraceuticals

Class	Examples
Proteins	Milk proteins, gelatins and plant proteins
Carbohydrates	Starch and starch derivatives, non-starch polysaccharides, cyclodextrins and sugars
Lipids & Waxes	Waxes, milk fats, vegetable fats and oils
Surfactants	Natural surfactants, synthetic surfactants, mono and diglycerides

alluded to as the framework or wall material or encapsulant. The encapsulated bioactive part is shielded from the outside environment until it is discharged by a trigger at an ideal site and time. Materials used to embody nutraceuticals are given in Table 19.5.

The use of novel drug delivery systems to deal with their formulation problems have drawn more and more the attention of researchers by introducing nano-carriers like:

Nanoemulsion: It is a nanoformulation in which two immiscible liquids are mixed to get one single phase in the size range of 20 nm to 200 nm. Resveratrol is a natural product with poor bioavailability. It is a stilbenoid, a type of natural phenol and a phytoalexin produced by several plants in response to injury, or when the plant is under attack by pathogens such as bacteria or fungi. It has been encapsulated with a nanoemulsion to enhance its bioavailability (Ruchi et al. 2017).

Liposomes: These are the spherical vesicles made of phospholipids that consist of the lipid bilayer. Liposomal preparation of anti-gout drug colchicine has been proven very effective in the treatment of gout (Priprem et al. 2008).

Phytosomes: These are the complex of phospholipids and active pharmaceutical ingredients (APIs). These can be used to overcome low solubility problems of drugs like ginseng (Bhattacharya 2009).

Microspheres: These are the spherical vesicles like particles having a size in the range of 1–1000 μm. They are used to achieve the desired release or used in the site-specific delivery of API. Parenteral preparation of camptothecin has been loaded in microspheres which shows prolonged anticancer effect than conventional intravenous preparation (You et al. 2006).

Transferosomes: They consist of an aqueous phase surrounded by a lipid bilayer. They have been successfully used for improving penetration of drugs like vincristine, curcumin and colchicine (Patel et al. 2009).

19.9.2 Safety and Efficacy

Numerous nutraceuticals are being utilized as an option for both sustenances and medication. An expansive number of these items make unlawful medical

claims with no guidelines or appropriate information to support their viability. All things considered, purchasers/patients need confirmation that an item is protected and ideally ready to do what it says (Crandell & Duren 2001). Nutraceuticals do not have major toxic effects in this regard. The stock ought not to be taken in the familiar sayings, "if little is great, a ton is better" since "it can hurt". Nutraceuticals, in the same way as other substances, may cause issues because of some unwanted impacts, or by delaying the progress of proper treatment. It is much simpler to set up the security of a nutraceutical than setting up its viability. Studies demonstrate that test portions of nutraceuticals are a few-fold greater than the proposed doses helping to build up to toxic date. These investigations must test the animal's reactions in both the short and long term. The absence of information regarding risks related to nutraceuticals should not to be interpreted as proof of trustworthiness (Oh & Jun 2014). Proof of viability is given by studies that report the pharmaceutical, pharmacokinetics and pharmacodynamics properties of a compound. Pharmaceuticals date is an assessment of the nature of assembling, virtue of item and precision of labelling. Pharmacokinetics information comprises of absorption, distribution, metabolism, excretion and toxicity (ADMET) of the medication, which essentially summarises the passage of the medication through the body. It likewise responds to the inquiry regarding the ingestion, distribution, digestion, and discharge. Pharmacodynamics assessment depicts how APIs act in the body (de Whalley et al. 1990).

19.10 Regulatory Aspects

19.10.1 India

The essential arrangement of tenets administering the nutraceutical showcase is the Dietary Supplement Health and Education Act (DSHEA) of 1994 (Ahad, Nissar & Rather 2017). In contrast to pharmaceuticals, nutraceuticals are commonly not under the administrative control of the Drugs and Cosmetic Act of 1940. In this way, different acts have been passed to provide guidance for the use of nutraceuticals. The Prevention of Food Adulteration Act 1954 came into power on June 1, 1955, and the Fruit Product Order was likewise passed in 1955. Furthermore, the Meat Food Products Order was passed in 1973; the Edible Oils Packaging (Regulation) Order was passed in 1998; the Solvent Extracted Oil, De-Oiled Meal and Edible Flour (Control) Order were passed in 1967; the Milk and Milk Products Order was passed in 1990; and the Essential Commodities Act was passed in 1955 relating to where food is made. To bring all the acts under one umbrella and bind them together, approving strategies, basic application structures and methodology for the enrolment of nourishment organizations, centralised permissions, security, and sterile and clean conditions, the Prime Minister's gathering on the industry established a single food regulatory authority in 1998 that provides a unified set of rules on food and farming enterprises (Ray, Joshi & Gulati 2016). The Indian Food Safety and Standards Bill (FSSB) was passed

in 2005 and was marked by the president on August 23, 2006. Lastly, the legislature of India executed the Food Safety and Standards Authority of India (FSSAI) in 2006. The Food Safety and Standards Act (FSSA) intends to coordinate sanitation laws in the nation to deliberately and logically build up the sustenance handling industry and to make a change in outlook from an administrative routine to self-compliance. The demonstration accompanied two fundamental targets: (1) to acquaint a solitary resolution relating with nourishment and (2) to accommodate logical improvement of the sustenance handling industry. Manufacture, capacity, appropriation and deal and import of nutraceuticals in India are directed under the Food Safety and Standards Act of 2006 (Keservani et al. 2014, Ahmad et al. 2011)

19.10.2 USA

In the USA, watershed enactment was passed in 1994 to control the assembling and showcasing of nutraceuticals. This law, known as the Dietary Supplement Health and Education Act (DSHEA) 1994, replaced 45 years of expanding FDA guidelines on well-being related items. The FDA may build up good manufacturing practices for nutraceuticals as long as these guidelines follow the less stringent guidelines for food instead of those for medications (Kaushik, Dureja & Kumar 2003, Tutelyan et al. 2016).

19.11 Future Perspectives on Nutraceuticals

Businesses increasingly look at how supplements influence individuals from a medicinal services viewpoint. Thus they looking at ways both medical treatment and nutrition can be incorporated into the medical field to guarantee that holistic medical care is provided. Interest in new innovation and the use of hereditarily altered innovation inside the sustenance business for restorative and medical advantages is set to drive a further increment in market incomes inside the nutraceuticals industry. Extending the collection of logical research which approves the viability and security of these new items will animate further interest in the innovation and application of nutraceuticals (Daliri & Lee 2015). Promising innovations, for example, nutrigenomics, imaging procedures and combining advances, are dynamically being utilized in nutrition research. New ideas in sustenance innovation may likewise add to some further advances in creating nourishment items that can bolster the great strength of society. The expanded purchaser mindfulness on utilitarian nourishments and nutraceuticals will, in any case, drive further income development, throughout the globe. Increased consumer awareness of functional foods and nutraceuticals will, however, drive further growth in revenue globally. Domestic growth in nutraceutical consumption is expected to continue as novel products and new target segments are introduced by domestic producers, including specialty goods focused on probiotics and heart health. An aging global population and rising social insurance costs have shifted consumer focus to more

advantageous living, insurance care and helper source finding or medication. Continuing concerns over "expectation," expanded worldwide guidelines, and security because of overseas production could stifle development (van der Zanden et al. 2014).

19.12 Conclusion

Nutraceuticals can play an important role in the prevention and treatment of respiratory tract disorders like COPD, asthma and cough. They are generally nutritionally supplemented and can be added to the treatment regimen to get better results or to reduce side effects during main pharmacotherapy. Currently many nutraceuticals are in use for various upper and lower respiratory tract infections, and many are yet to be introduced to the market. Medicinal herbs, such as a nutraceutical, are the potential source of therapeutic agents for respiratory tract disorders and they are widely used for various types of other disorders like chronic heart disease, gastrointestinal tract disorders, and cancer. Respiratory disorders are generally related to inflammation so nutraceuticals lowering inflammation are also a potential source of therapeutic agents. Nowadays, research has been not only focused on the search of new potential nutraceuticals but also on the drug delivery systems by which a nutraceutical can be delivered to consumers. Research in this field is under progress for some novel approaches that can treat respiratory disorders.

References

Ahad, Tehmeena, Jasia Nissar, and A.H. Rather. 2017. "Nutraceuticals-Health Benefits: A Review." *International Journal of Engineering Technology Science and Research* 4 (12): 262–267.

Ahmad, Faruque, Fakhruddin Ali Ahmad, Z.R. Azaz, Ahmad Azad, Sarfaraz Alam, and Syed Amir Ashraf. 2013. "Nutraceutical Is the Need of Hour." *World Journal of Pharmacy and Pharmaceutical Sciences* 4 (3): 2516–2525.

Ahmad, Md. Faruque, Syed Amir Ashraf, Fakhruddin Ali Ahmad, Javed Akhtar Ansari, and Md. Rizwan Ahmad Siddiquee. 2011. "Nutraceutical Market and Its Regulation." *American Journal of Food Technology* 6 (5): 342–347. doi:10.3923/ajft.2011.342.347.

Andlauer, Wilfried, and Peter Fürst. 2018. "Nutraceuticals: A Piece of History, Present Status and Outlook." *Food Research International* 35 (2–3): 171–176.

Ansari, J.A., and N.N. Inamdar. 2010. "The Promise of Traditional Medicines." *International Journal of Pharmacology* 6 (6): 808–812. doi:10.3923/ijp.2010.808.812.

Ashwini, Chintale, Kadam Vaishali, and Nalwad Digambar. 2018. "Role of Nutraceuticals in Various Diseases: A Comprehensive Review." *International Journal of Research in Pharmacy and Chemistry* 3 (2): 290–299.

Augustin, Mary Ann, and Luz Sanguansri. 2015. "Challenges and Solutions to Incorporation of Nutraceuticals in Foods." *Annual Review of Food Science and Technology* 6 (1): 463–477. doi:10.1146/annurev-food-022814-015507.

Bagchi, Debasis, and Sreejayan Nair. 2016. *Developing New Functional Food and Nutraceutical Products*. Academic Press.

Baybutt, Richard C., Cecilia Rosales, Heather Brady, and Agostino Molteni. 2002. "Dietary Fish Oil Protects against Lung and Liver Inflammation and Fibrosis in Monocrotaline Treated Rats." *Toxicology* 175 (1–3): 1–13. doi:10.1016/S0300-483X(02)00063-X.

Bhattacharya, S. 2009. "Phytosomes: Emerging Strategy in Delivery of Herbal Drugs and Nutraceuticals." *Pharma Times*. https://www.researchgate.net/publication/282417895_Phytosomes_Emerging_strategy_in_delivery_of_herbal_drugs_and_nutraceuticals.

Biol, Turk J, Muhammad Zia-Ul-Haq, Shakeel Ahmad, Mughal Qayum, and Sezai Ercişli. 2018. "Compositional Studies and Antioxidant Potential of *Albizia lebbeck* (L.) Benth. Pods and Seeds." *Turkish Journal of Biology* 37 (1): 25–32. doi:10.3906/biy-1204-38.

Bitensky, R. 1973. "The Road to Shangri-La Is Paved with Vitamins." *American Journal of Psychiatry* 130(11): 1253–1256.

Briskin, D.P. 2000. "Medicinal Plants and Phytomedicines. Linking Plant Biochemistry and Physiology to Human Health." *Plant Physiology* 124 (2): 507–514. http://www.ncbi.nlm.nih.gov/pubmed/11027701.

Chang, J. 2000. "Medicinal Herbs: Drugs or Dietary Supplements?" *Biochemical Pharmacology* 59 (3): 211–219. http://www.ncbi.nlm.nih.gov/pubmed/10609549.

Chaudhari, Shilpa P., Priyatama V. Powar, and Mahesh N. Pratapwar. 2017. "Nutraceuticals: A Review." *World Journal of Pharmacy and Pharmaceutical Sciences*. 6 (8): 681–739.

Chauhan, Preeti S., D. Dash, and Rashmi Singh. 2017. "Intranasal Curcumin Inhibits Pulmonary Fibrosis by Modulating Matrix Metalloproteinase-9 (MMP-9) in Ovalbumin-Induced Chronic Asthma." *Inflammation* 40 (1): 248–258. doi:10.1007/s10753-016-0475-3.

Chauhan, B., G. Kumar, N. Kalam, and S.H. Ansari. 2013. "Current Concepts and Prospects of Herbal Nutraceutical: A Review." *Journal of Advanced Pharmaceutical Technology & Research* 4 (1): 4–8.

Crandell K.M., and S.E. Duren. 2001. "Nutraceuticals: What Are They And Do They Work?" In: J.D. Pagan (ed.), *Advances in Equine Nutrition II*, Nottingham University Press, Nottingham, pp. 29–36.

Dahiya, Kiran. 2013. "Nutraceuticals and Their Impact on Human Health." *Journal of Plant Biochemistry & Physiology* 1 (4). doi:10.4172/2329-9029.1000e111.

Daliri, Eric, and Byong Lee. 2015. "Current Trends and Future Perspectives on Functional Foods and Nutraceuticals." In: M.-T. Liong (ed.), Beneficial Microorganisms in Food and Nutraceuticals, Springer, Cham, pp. 221–244. doi:10.1007/978-3-319-23177-8_10.

Das, Lipi, Eshani Bhaumik, Utpal Raychaudhuri, and Runu Chakraborty. 2012. "Role of Nutraceuticals in Human Health." *Journal of Food Science and Technology* 49 (2): 173–183. Springer. doi:10.1007/s13197-011-0269-4.

Dasaraju, Purushothama V., and Chien Liu. 1996. "Infections of the Respiratory System." In: S. Baron (ed.), *Medical Microbiology*, 4th edn., University of Texas Medical Branch at Galveston. http://www.ncbi.nlm.nih.gov/pubmed/21413304.

de Whalley, Catherine V., Sara M. Rankin, J. Robin S. Hoult, Wendy Jessup, and David S. Leake. 1990. "Flavonoids Inhibit the Oxidative Modification of Low Density Lipoproteins by Macrophages." *Biochemical Pharmacology* 39 (11): 1743–1750. doi:10.1016/0006-2952(90)90120-A.

DeVries, Rebecca, David Kriebel, and Susan Sama. 2016. "Low Level Air Pollution and Exacerbation of Existing COPD: A Case Crossover Analysis." *Environmental Health: A Global Access Science Source* 15 (1): 98. doi:10.1186/s12940-016-0179-z.

Dillard, Cora J., and J Bruce German. 2000. "Phytochemicals: Nutraceuticals and Human Health." *Journal of the Science of Food and Agriculture* 80 (12): 1744–1756. Drugs.com. n.d. "Nutraceutical Products." Drugs.com. doi:10.1002/1097-0010(20000915)80:12<1744::AID-JSFA725>3.0.CO;2-W.

DSM. n.d. "Nutraceuticals." https://www.dsm.com/markets/human-nutrition/en/products/nutraceuticals.html

Ernst, E. 2001. "Functional Foods, Neutraceuticals, Designer Foods: Innocent Fad or Counterproductive Marketing Ploy?" *European Journal of Clinical Pharmacology* 57 (5): 353–355. doi:10.1007/s002280100327.

Funk, Casmir. 1975. "The Journal of State Medicine. Volume XX: 341–368, 1912. The Etiology of the Deficiency Diseases. Beri-Beri, Polyneuritis in Birds, Epidemic Deopsy, Scurvy, Experimental Scurvy in Animals, Infantile Scurvy, Ship Beri-Beri, Pellagra." *Analytica Chimica Acta* 76 (2): 176–177. http://www.ncbi.nlm.nih.gov/pubmed/1094860.

Gayan-Ramirez, Ghislaine. 2018. "Relevance of Nutritional Support and Early Rehabilitation in Hospitalized Patients with COPD." *Journal of Thoracic Disease* 10 (S12): S1400–S1414. doi:10.21037/jtd.2018.03.167.

Gbassi, Gildas K., and Thierry Vandamme. 2012. "Probiotic Encapsulation Technology: From Microencapsulation to Release into the Gut." *Pharmaceutics* 4 (1): 149–163. doi:10.3390/pharmaceutics4010149.

Ghildiyal, Shivani, Manish K. Gautam, Vinod K. Joshi, and Raj K. Goel. 2012. "Pharmacological Evaluation of Extracts of *Hedychium spicatum* (Ham-Ex-Smith) Rhizome." *Ancient Science of Life* 31 (3): 117–122. doi:10.4103/0257-7941.103189.

Goss, Charles Mayo. 1958. "A Translation of Galen's Hygiene (De Sanitate Tuenda?) By Robert Montraville Green, 1951. XXVII + 277 Pages. $5.75. Charles C. Thomas, Publisher, Springfield." *The Anatomical Record* 131 (2): 257–259. doi:10.1002/ar.1091310209.

Gulati, Kavita, Nishant Rai, Sulekha Chaudhary, and Arunabha Ray. 2016. "Nutraceuticals in Respiratory Disorders." In: Ramesh C. Gupta (ed.), *Nutraceuticals: Efficacy, Safety and Toxicity*, Academic Press, London, pp. 75–86. doi:10.1016/B978-0-12-802147-7.00006-1.

Hathcock, John. 2001. "Dietary Supplements: How They Are Used and Regulated." *The Journal of Nutrition* 131 (3): 1114S–1117S. doi:10.1093/jn/131.3.1114S.

Hippocrates, W.H.S. Jones, and P. Potter. 1923. *Hippocrates*. Heinemann, London.

Hu, G., and P.A. Cassano. 2000. "Antioxidant Nutrients and Pulmonary Function: The Third National Health and Nutrition Examination Survey (NHANES III)." *American Journal of Epidemiology* 151 (10): 975–981. doi:10.1093/oxfordjournals.aje.a010141.

Hwang, Yu-Ya, and Yuan-Soon Ho. 2018. "Nutraceutical Support for Respiratory Diseases." *Food Science and Human Wellness* 7 (3): 205–208. doi:10.1016/J.FSHW.2018.09.001.

Kaushik, D., H. Dureja, and V. Kumar. 2003. "Developments in Nutraceuticals." *Indian Journal of Pharmacology* 35 (6): 363–372. http://www.ijp-online.com/article.asp?issn=0253-7613;year=2003;volume=35;issue=6;spage=363;epage=372;aulast=Kaushik;type=0.

Jinno, Jun-ichi, Naoki Kamada, Masateru Miyake, Keigo Yamada, Tadashi Mukai, Masaaki Odomi, Hajime Toguchi, Gary G. Liversidge, Kazutaka Higaki, and Toshikiro Kimura. 2006. "Effect of Particle Size Reduction on Dissolution and Oral Absorption of a Poorly Water-Soluble Drug, Cilostazol, in Beagle Dogs." *Journal of Controlled Release* 111 (1–2): 56–64. doi:10.1016/j.jconrel.2005.11.013.

Julius, Asiedu-Gyekye Isaac, Awortwe Charles, Nyamekye Effah Samuel, Antwi Daniel Ansong, Seidu Mahmood, Adjei Samuel, Banga N'guessan Benoit Kwame, Amoateng Patrick, and Nkansah Edwin. 2014. "Nutraceutical with Anti-Inflammatory Activity for the Management of Airway Remodeling in Bronchial Asthma: *Kalanchoe integra* Var. Crenata (Andr.) Cuf Leaf Extract." *Pharmacology & Pharmacy* 05 (03): 250–261. doi:10.4236/pp.2014.53032.

Kalra, Ekta K. 2003. "Nutraceutical: Definition and Introduction." *AAPS PharmSci* 5 (3): E25. doi:10.1208/ps050325.

Kampa, Marilena, and Elias Castanas. 2008. "Human Health Effects of Air Pollution." *Environmental Pollution* 151 (2): 362–367. doi:10.1016/J.ENVPOL.2007.06.012.

Kaur, Ginpreet, Simi Mukundan, Vaidehi Wani, and Maushmi Skumar. 2015. "Nutraceuticals in the Management and Prevention of Metabolic Syndrome." *Austin Journal of Pharmacology and Therapeutics* 3 (1): 1–6.

Keservani, Raj K., Rajesh K. Kesharwani, Anil K. Sharma, Surya P. Gautam, and Santosh K. Verma. 2017. "Nutraceutical Formulations and Challenges." In: D. Bagchi and S. Nair (eds), *Developing New Functional Food and Nutraceutical Products*, Academic Press, London, pp. 161–177. doi:10.1016/B978-0-12-802780-6.00009-2.

Keservani, Raj K., Anil K. Sharma, F. Ahmad, and Mirza E. Baig. 2014. "Nutraceutical and Functional Food Regulations in India." In: D. Bagchi (ed.), *Nutraceutical and Functional Food Regulations in the United States and Around the World*, Academic Press, Burlington, MA, pp. 327–342. Elsevier. doi:10.1016/B978-0-12-405870-5.00019-0.

Khajuria, Anamika, Amit Gupta, Pankaj Suden, Surjeet Singh, Fayaz Malik, Jaswant Singh, B. D. Gupta, et al. 2008. "Immunomodulatory Activity of Biopolymeric Fraction BOS 2000 FromBoswellia Serrata." *Phytotherapy Research* 22 (3): 340–348. doi:10.1002/ptr.2320.

Kubo, Hiroshi, Katsutoshi Nakayama, Masaru Yanai, Tomoko Suzuki, Mutsuo Yamaya, Mika Watanabe, and Hidetada Sasaki. 2005. "Anticoagulant Therapy for Idiopathic Pulmonary Fibrosis." *Chest* 128 (3): 1475–1482. doi:10.1378/CHEST.128.3.1475.

Kumar, Pramod. 2018. "Role of Plastics on Human Health." *The Indian Journal of Pediatrics* 85 (5): 384–389. doi:10.1007/s12098-017-2595-7.

Lachance, P.A., and Y.T. Das. 2007. "Nutraceuticals." In: J.B. Taylor and D.J. Triggle (eds), *Comprehensive Medicinal Chemistry* II, Elsevier, pp. 449–461. doi:10.1016/B0-08-045044-X/00014-6.

Littlefield, S. 2015. "Natural Support for Respiratory Health." Redd Remedies. 2018. Accessed September 9. https://reddremedies.com/natural-support-for-respiratory-health/.

Mediratta, P.K., V. Dewan, S.K. Bhattacharya, V.S. Gupta, P.C. Maiti, and P. Sen. 1988. "Effect of *Ocimum sanctum* Linn. on Humoral Immune Responses." *The Indian Journal of Medical Research* 87 (April): 384–386.

Misra, Laxminarain. 2013. "Traditional Phytomedicinal Systems, Scientific Validations and Current Popularity as Nutraceuticals." *International Journal of Traditional and Natural Medicines* 2 (1): 27–75.

Mora, J. Rodrigo, Makoto Iwata, and Ulrich H. von Andrian. 2008. "Vitamin Effects on the Immune System: Vitamins A and D Take Centre Stage." *Nature Reviews Immunology* 8 (9): 685–698. doi:10.1038/nri2378.

Mukherjee, P.K., R.K. Harwansh, S. Bahadur, V. Duraipandiyan, and N.A. Al-Dhabi. 2017. "Factors to Consider in Development of Nutraceutical and Dietary Supplements." In: S. Badal and R. Delgoda (eds), *Pharmacognosy: Fundamental, Applications and Strategy,* Academic Press, London, pp. 653–661. doi:10.1016/B978-0-12-802104-0.00034-2.

Nasri, Hamid, Azar Baradaran, Hedayatollah Shirzad, and Mahmoud Rafieian-Kopaei. 2014. "New Concepts in Nutraceuticals as Alternative for Pharmaceuticals." *International Journal of Preventive Medicine* 5 (12): 1487–1499. http://www.ncbi.nlm.nih.gov/pubmed/25709784.

Nethathe, G.D., and S.L. Russell. 2014. "Traditional Medicine Use and the Anaesthetist." doi:10.1080/22201181.2014.983711.

Oh, Yoon Sin, and Hee-Sook Jun. 2014. "Role of Bioactive Food Components in Diabetes Prevention: Effects on Beta-Cell Function and Preservation." *Nutrition and Metabolic Insights* 7: 51–59. doi:10.4137/NMI.S13589.

Paiva, S.A., and R.M. Russell. 1999. "Beta-Carotene and Other Carotenoids as Antioxidants." *Journal of the American College of Nutrition* 18 (5): 426–433. http://www.ncbi.nlm.nih.gov/pubmed/10511324.

Park, Hae-Young, Sung-Hwan Park, Hae-Kyung Yoon, Myung Joo Han, and Dong-Hyun Kim. 2004. "Anti-Allergic Activity of 18beta-Glycyrrhetinic Acid-3-O-Beta-D-Glucuronide." *Archives of Pharmacal Research* 27 (1): 57–60. http://www.ncbi.nlm.nih.gov/pubmed/14969340.

Patel, R., S.K. Singh, S. Singh, N.R. Sheth, and R. Gendle. 2009. "Development and Characterization of Curcumin Loaded Transfersome for Transdermal Delivery." *Journal of Pharmaceutical Sciences and Research* 1 (4): 71–80. https://pdfs.semanticscholar.org/6677/5854f0f3cb2048a107438d68ddda52c96f63.pdf.

Patil, C.S. 2011. "Current Trends and Future Prospective of Nutraceuticals in Health Promotion." *Bioinfo Pharmaceutical Biotechnology* 1 (1): 1–7. http://www.bioinfo.in/contents.php?id=341.

"Pharmaceutical Manufacturing and Exports, Research and Development in Pharma – Aurobindo Pharma." 2018. Accessed October 3. http://www.aurobindo.com/.

Philips. 2018. "What Are the Causes of Respiratory Diseases." Healthcare@home. Accessed September 9. https://www.philips.co.in/healthcare/philipshealthcareathome/blog/what-are-the-causes-of-respiratory-diseases.

Pliny, the Elder, and H. Rackham. 1938. *Natural History*. Harvard University Press. http://www.hup.harvard.edu/catalog.php?isbn=9780674993891.

Prabu, Sakthivel Lakshmana, Timmakondu Narasimman Kuppusami Suriyaprakash, Chellappan Dinesh Kumar, and Subramaniam Suresh Kumar. 2012. "Nutraceuticals and Their Medicinal Importance." *International Journal of Health & Allied Sciences* 1 (2): 47–53. doi:10.4103/2278-344X.101661.

Priprem, Aroonsri, Jintanaporn Watanatorn, Saengrawee Sutthiparinyanont, Wathita Phachonpai, and Supaporn Muchimapura. 2008. "Anxiety and Cognitive Effects of Quercetin Liposomes in Rats." *Nanomedicine : Nanotechnology, Biology, and Medicine* 4 (1): 70–78. doi:10.1016/j.nano.2007.12.001.

Rachana R. S. Basu, M. Pant, K. Priyanka and S. Sonam. 2011. "Review & Future Perspectives of Using Vasicine, and Related Compounds." Indo Global Journal of Pharmaceutical Sciences 1: 85–98. https://www.researchgate.net/publication/260156399_Review:Future_Perspectives_of_Using_Vasicine_and_Related_Compounds.

Ram, Arjun, Selvakumar Balachandar, Pavadai Vijayananth, and Vijay Pal Singh. 2011. "Medicinal Plants Useful for Treating Chronic Obstructive Pulmonary Disease (COPD): Current Status and Future Perspectives." *Fitoterapia* 82 (2): 141–151. doi:10.1016/j.fitote.2010.09.005.

Ray, Arunabha, Jagdish Joshi, and Kavita Gulati. 2016. "Regulatory Aspects of Nutraceuticals: An Indian Perspective." *Nutraceuticals* January: 941–946. doi:10.1016/B978-0-12-802147-7.00066-8.

"Respiratory System – National Library of Medicine – PubMed Health." 2018. Accessed September 6. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022181/.

Ruchi, Sharma, Kaur Amanjot, Thakur Sourav, Bhardwaj Keerti, Bose Sujit. 2017. "Role of Nutraceuticals in Health Care: A Review." *International Journal of Green Chemistry* 11 (3): 385–394. doi:10.22377/ijgp.v11i03.1146.

Santini, Antonello, Gian Carlo Tenore, and Ettore Novellino. 2017. "Nutraceuticals: A Paradigm of Proactive Medicine." *European Journal of Pharmaceutical Sciences* 96 (January): 53–61. doi:10.1016/j.ejps.2016.09.003.

Singh, Jagtar, and Shweta Sinha. 1992. "Classification, Regulatory Acts and Applications of Nutraceuticals for Health." *International Journal of Pharmacy and Biological Sciences* 37: 13–45.

Singh, Y.N. 1992. "Kava: An Overview." *Journal of Ethnopharmacology* 37 (1): 13–45. http://www.ncbi.nlm.nih.gov/pubmed/1453702.

Sriram, Narayanan, Srinivasan Kalayarasan, and Ganapasam Sudhandiran. 2009. "Epigallocatechin-3-Gallate Exhibits Anti-Fibrotic Effect by Attenuating Bleomycin-Induced Glycoconjugates, Lysosomal Hydrolases and Ultrastructural Changes in Rat Model Pulmonary Fibrosis." *Chemico-Biological Interactions* 180 (2): 271–280. doi:10.1016/j.cbi.2009.02.017.

Steinemann, Nina, Leticia Grize, Marco Pons, Thomas Rothe, Daiana Stolz, Alexander Turk, Christian Schindler, Christine Brombach, and Nicole Probst-Hensch. 2018. "Associations between Dietary Patterns and Post-Bronchodilation Lung Function in the SAPALDIA Cohort." *Respiration* 95 (6): 454–463. doi:10.1159/000488148.

Tricon, S., S. Willers, H.A. Smit, P.G. Burney, G. Devereux, A.J. Frew, S. Halken, et al. 2006. "Nutrition and Allergic Disease." *Clinical & Experimental Allergy Reviews* 6 (5): 117–188. doi:10.1111/j.1365-2222.2006.00114.x.

Tutelyan, Victor A., Alexey S. Petrenko, Elena A. Smirnova, Boris P. Sukhanov, and Anatoliy V. Kutyshenko. 2016. "Regulatory Aspects of Nutraceuticals." *Nutraceuticals*, 959–970. doi:10.1016/B978-0-12-802147-7.00068-1.

van der Zanden, Lotte D.T., Ellen van Kleef, René A. de Wijk, and Hans C.M. van Trijp. 2014. "Knowledge, Perceptions and Preferences of Elderly Regarding Protein-Enriched Functional Food." *Appetite* 80 (September): 16–22. doi:10.1016/j.appet.2014.04.025.

Veith, C., M. Drent, A. Bast, F.J. van Schooten, and A.W. Boots. 2017. "The Disturbed Redox-Balance in Pulmonary Fibrosis Is Modulated by the Plant Flavonoid Quercetin." *Toxicology and Applied Pharmacology* 336 (December): 40–48. doi:10.1016/j.taap.2017.10.001.

Whyand, T., J.R. Hurst, M. Beckles, and M.E. Caplin. 2018. "Pollution and Respiratory Disease: Can Diet or Supplements Help? A Review." *Respiratory Research* 19 (1): 79. doi:10.1186/s12931-018-0785-0.

Walden, M. 2018. "Respiratory System and Breathing." TeachingPE.com. Accessed September 6. http://www.teachpe.com/anatomy/respiratory_system.php.

Wong, Elyssa. 2001. "Regulation of Health Food in the United States." Research and Library Services Division Legislative Council Secretariat, Hong Kong.

Yadav, Shyamlal Singh, Biswajyoti Patgiri Galib, and Pradeep Kumar Prajapati. 2012. "Clinical Efficacy of Two Different Samples of Shirishavaleha in Tamaka Shwasa (Bronchial Asthma)." *Ayu* 33 (2). 255–260. doi:10.4103/0974-8520.105247.

Yang, Xia, Jian-Ning Lv, Hui Li, Bo Jiao, Qiu-Hong Zhang, Yong Zhang, Jie Zhang, et al. 2017. "Curcumin Reduces Lung Inflammation via Wnt/β-Catenin Signaling in Mouse Model of Asthma." *Journal of Asthma* 54 (4): 335–340. doi:10.1080/02770903.2016.1218018.

You, Jian, Fu-de Cui, Xu Han, Yong-sheng Wang, Lei Yang, Ying-wei Yu, and Qing-po Li. 2006. "Study of the Preparation of Sustained-Release Microspheres Containing Zedoary Turmeric Oil by the Emulsion–solvent-Diffusion Method and Evaluation of the Self-Emulsification and Bioavailability of the Oil." *Colloids and Surfaces B: Biointerfaces* 48 (1): 35–41. doi:10.1016/j.colsurfb.2005.12.011.

Zhang, Dongwei, Chuangfang Huang, Changfu Yang, Renzuo J Liu, Jifeng Wang, Jianzhao Niu, and Dieter Brömme. 2011. "Antifibrotic Effects of Curcumin Are Associated with Overexpression of Cathepsins K and L in Bleomycin Treated Mice and Human Fibroblasts." *Respiratory Research* 12 (1): 154. doi:10.1186/1465-9921-12-154.

Zhao, Hongyun, Yee Chan-Li, Samuel L. Collins, Yuan Zhang, Robert W. Hallowell, Wayne Mitzner, and Maureen R. Horton. 2014. "Pulmonary Delivery of Docosahexaenoic Acid Mitigates Bleomycin-Induced Pulmonary Fibrosis." *BMC Pulmonary Medicine* 14 (1): 64. doi:10.1186/1471-2466-14-64.

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