DIETARY SUPPLEMENTS AND NUTRACEUTICALS

A TEXTBOOK

Editors:
Mukesh Singh Sikarwar
Arunachalam Muthuraman
Sohrab A. Shaikh

Bentham Books

Dietary Supplements and Nutraceuticals: A Textbook

Edited by

Mukesh Singh Sikarwar
Amity Institute of Pharmacy
Amity University, Gwalior
Madhya Pradesh
India

Arunachalam Muthuraman
& Sohrab A. Shaikh
Pharmacology, Toxicology and
Basic Health Sciences Unit
Faculty of Pharmacy
AIMST University
Semeling, Bedong, Kedah
Malaysia

Dietary Supplements and Nutraceuticals: A Textbook

Editors: Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh

ISBN (Online): 979-8-89881-399-4

ISBN (Print): 979-8-89881-400-7

ISBN (Paperback): 979-8-89881-401-4

Published by Bentham Science Publishers Pte. Ltd. Singapore, in collaboration with Eureka Conferences, USA.

First published in 2026.

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
No. 9 Raffles Place
Office No. 26-01
Singapore 048619
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

FOREWORD

In today's world, the spectrum of medicine is wide, and innovations are the driving force for the pharmaceutical industry. Nutrition and lifestyle are now equally important as medicine, especially in the case of non-communicable and lifestyle-related diseases. Due to a sedentary lifestyle and its related obesity, chronic conditions like hypertension, cardiovascular disease, and diabetes are on the rise. Nutraceuticals can provide a promising solution to prevent and manage these conditions by combining traditional wisdom with modern science. Nutraceuticals bridge the gap between nutrition and medicine, offering innovative solutions for enhancing well-being.

This book explores the diverse realm of dietary supplements and nutraceuticals, which includes water and fat soluble vitamins, carbohydrates, proteins, micronutrients including zinc, chromium, CoQ10, iodine, selenium, good fat including DHA and EPA, prebiotics, probiotics, various phytochemicals like carotenoids, resveratrol, diallyl sulfides, flavonoids, isoflavones, and rice bran. This book highlights the source, chemistry, applications, and benefits of different nutraceuticals while emphasizing the importance of rigorous standards according to WHO guidelines for assessing the quality of herbal medicines.

Whether you are a healthcare professional, researcher, curious reader, or student, the insights shared by the authors in this book will deepen your understanding of the role of nutraceuticals and dietary supplements in holistic health. May this book inspire you to embrace the potential of nutraceuticals for a healthier future.

SNR. ASSOC. PROF. DR. Sundram M. Karupiah
B.Sc (Hons), MSc (Pharmacy), Ph.D (USM)
AIMST University DU010(K)
Batu 3 1/2, Bukit Air Nasi
Jalan Bedong Semeling, 08100 Bedong
Kedah, Malaysia

Preface

The beginning of an AI and data analytics-driven society is around the corner, and personalized medicine is being revolutionized with innovations. Science-supported health solutions and tailored medicine are on the rise. Before the Human Genome Project, the field of personalized medicine was limited due to the lack of comprehensive genetic information. Changes in gene expressions by environmental factors, including behaviour and food, play key roles in disease development; hence, epigenetics influenced by diet and nutrition shall be considered and addressed in health clinics. Genomic and metabolic profiling can identify individual needs for micronutrient optimization in personalized nutrition. Nutrigenomics is an emerging area that is grounded in molecular biology and studies the interaction of dietary components with the genome; however, in India, Ayurgenomics, originating from the ancient Indian system of medicine Ayurveda, combines the traditional wisdom with genomic insight, recommending key interventions based on diet, lifestyle, and herbal drugs.

Dietary supplements and nutraceuticals play a key role in the management of various diseases. Non-Communicable Diseases (NCDs) are burdened with high oxidative stress due to chronic low-grade inflammation, and such interconnected biological processes are central to the pathogenesis and progression of many NCDs, including cardiovascular diseases, diabetes, cancer, and neurodegenerative disorders. Therapeutic strategies to combat oxidative stress and inflammation include dietary antioxidants and dietary supplements in an anti-inflammatory diet. Micronutrients are the cofactors of enzymes essential for various biochemical pathways. For example, in Cardiovascular Diseases (CVDs), magnesium regulates blood pressure by modulating calcium channels, and selenium is a cofactor for glutathione peroxidase, protecting from oxidative stress and atherosclerosis. Chromium improves insulin action, and zinc supports insulin synthesis in the management of impaired glucose tolerance, insulin resistance, and inflammation. In bone health, calcium and vitamin D are essential for bone mineralization, and magnesium is a cofactor for enzymes regulating bone metabolism.

Vitamin-based nutraceuticals prevent oxidative damage and modulate inflammation, especially in Non-Communicable Diseases (NCDs) and age-related conditions. Vitamins also act as cofactors for enzymes and antioxidants. Short-chain fatty acids produced by gut bacteria play a key role in neuro-immunoendocrine regulation, and these fatty acids can also prevent the growth of pathogenic microorganisms. Modulation of neurochemical pathways through the highly interconnected gut-brain axis has also recently been recognized. Prebiotics may influence the metabolism of minerals by increasing their solubility and absorption. Nutraceuticals for prophylactic and therapeutic purposes are often developed with rigorous clinical research to ensure efficacy and safety in addressing specific health conditions.

Combining dietary supplements through a synergistic approach maximizes their potential to enhance health and manage or prevent diseases. The synergistic approach focuses on bioactive compound interaction to amplify their combined effects rather than individual effects. Ingredients like Shatavari root and ashwagandha are highly regarded in traditional medicine for their adaptogenic properties to help manage stress, reduce hot flashes and night sweats, and maintain hormonal balance. The amino acid L-theanine promotes relaxation, calming, and better sleep, addressing anxiety-driven menopause symptoms. A combination of such products could bring greater relief in menopause symptoms than individual products.

This textbook aims to equip students and researchers with updated information in the field of nutraceuticals. As implied in the title, the dietary supplements, and nutraceuticals, this

textbook gives comprehensive knowledge on different dietary supplements and nutraceuticals. This book displays the description of antioxidants, vitamins, macro & micronutrients, essential fatty acids, pre & probiotics, phytochemicals, herbal drugs, and synergistic & clinical nutraceuticals. It focuses on detailed descriptions of selected crude drugs potentially used as dietary supplements and nutraceuticals. This textbook is an easy guide for students and scholars from different domains of health sciences.

As we progress toward precision wellness and the concept of personalized nutrition, this book can be handy in dealing with plant proteins, microalgae-based supplements, probiotics, omega-3, and fermented ingredients to support gut health, cognitive function, and heart health supplements. Challenges such as supply chain transparency, digital health integration, and regulatory compliance will remain areas for further discussion.

Editors would like to extend their heartfelt appreciation to all the authors and contributors who have contributed their time and wisdom in completing this book.

Special thanks to Humaira Hashmi, editorial manager of publications, Bentham Books, for her generous assistance in coordinating throughout the book publication.

Editors are open to suggestions for improvement of this work.

Mukesh Singh Sikarwar
Amity Institute of Pharmacy
Amity University, Gwalior
Madhya Pradesh
India

&

Arunachalam Muthuraman & Sohrab A. Shaikh
Pharmacology, Toxicology and
Basic Health Sciences Unit
Faculty of Pharmacy
AIMST University
Semeling, Bedong, Kedah
Malaysia

Dedication

Thank you to all co-authors for their valuable contributions & support in making this book product for undergraduates & research students, and educators. We are also thankful to Faculty members of Pharmacy, AIMST University, Malaysia, and Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India for their unconditional support. This book is dedicated to Pharmacy students, budding researchers & scientists who are working in this field of research.

List of Contributors

Arunachalam Muthuraman	Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia
Khian Giap Lim	Clinical Pharmacy and Pharmacy Practice Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia
Muthusamy Ramesh	Department of Pharmaceutical Analysis and Quality Assurance, Institute of Pharmaceutical Sciences, Sandip Foundation, Nashik 422213, India
Maulshree Bhandari	Invertis Institute of Pharmacy, Invertis University, Bareilly, Uttar Pradesh, India
Mukesh Singh Sikarwar	Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India
Nallupillai Paramakrishnan	Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru 570015, Karnataka, India
Nazmun Nahar Alam	Faculty of Medicine, AIMST University, Bedong 08100, Kedah, Malaysia
Sumitha Elayaperumal	Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education and Research, Mysore, Karnataka, India
Sohrab A. Shaikh	Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia
Vaibhav Kumar Rathi	Department of Pharmacy, Quantum University, Roorkee (Haridwar), Uttarakhand, India
Yamunna Paramaswaran	Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia
Venkata Rathina Kumar Thigarajan	Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai, 625020, India
Yuvaraj Sivamani	Department of Pharmaceutical Chemistry, Crescent School of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, 600048, Chennai, Tamil Nadu, India

CHAPTER 1

Introduction of Dietary Supplements and Nutraceuticals for the Healthcare System

Arunachalam Muthuraman[1,*] and **Sohrab A. Shaikh**[1]

[1] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia*

Abstract: Dietary supplements like vitamins, minerals, and herbs, and other products (macronutrients, essential fatty acids, prebiotics, and probiotics) are widely used for various ailments and to improve health status. The evidence of these dietary supplements' action in health benefits is not clear. Hence, the acceptance of these agents as medicine is not recognized in various countries. Moreover, cellular oxidative stress is very common in metabolic and other chronic disorders. However, the common actions of dietary supplements, *i.e.*, free radical scavengers, energy production, and regulation of cellular functions, are well known and reported. Besides, it is identified as safer, has beneficial effects, and has minimal side-effect-causing agents. However, a clear correlation between dietary supplements and nutraceuticals in the clinical Healthcare system. Hence, this book chapter reveals the beneficial effect of dietary supplements in the management of metabolic and inflammatory disorders, along with the correlation of their antioxidant potential.

Keywords: Amino acids, Free radical scavenger, Growth hormone, Non-enzymatic antioxidants, Oil supplements.

INTRODUCTION

Dietary Supplements are essential to maintain the Healthcare system. It is added to conventional food to improve the healthy physiological system [1]. It also reduces the health risks of various diseases. However, the U.S.A. Food and Drug Administration (FDA) is not authorized to review dietary supplement products for safe and effective use in the Healthcare system [2]. Before the intake of dietary supplements, it is necessary to consult healthcare consultants because sometimes dietary supplements can cause potentially unwanted effects [3]. Crucially, a healthy balance between foods and nutrients is needed to consider better health

[*] **Corresponding author Arunachalam Muthuraman:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia; E-mail: muthuraman.a@aimst.edu.my

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

benefits and maintain the healthcare system [4]. Dietary supplements cover minerals, vitamins, herbs, and amino acids, including enzymes [5]. Worldwide, dietary supplements are widely used for ingestible products, and they are distinguishable from conventional foods and drugs. Further, the United States defined that dietary supplements (except tobacco) are products intended to be dietary supplements with one or more of the additional ingredients like minerals, vitamins, herbs, herbal extracts, amino acids, and metabolites [6, 7]. Besides, dietary products like multivitamins, garlic tablets, fish oil capsules, probiotics, natural weight-loss aids, and some kinds of energy drinks are also considered dietary supplements. Further, the dietary supplements are mostly for oral administration [8, 9].

Dietary Supplements

The dietary supplements of marketed products are available in the form of powders, liquids, capsules, tablets, gel caps, and soft gels. Further, dietary supplements should not include chemical compounds like approved drugs or licensed biological products [10]. Mostly, dietary supplements are not intended to be used for the treatment, cure, mitigation, and prevention of any type of disease [7, 11]. In addition, it is not to be viewed as a substitute for conventional medications for any disease. Regulatory bodies outline that dietary supplements are any food products that differ from conventional foods. However, the supplementary products exhibit health benefits and rarely have undesirable side effects [12]. Of course, the side effects are reversible and tolerable [13]. Paradoxically, drugs can cause potential adverse effects, which can be irreversible [14]. Moreover, the dietary supplements must be safe and effective for health and physiological action. Other than in the USA and some other countries, dietary supplements are considered botanical formulations and drugs [15]; and they are proven safe and sold without any prescriptions, like extracts of the Eastern purple coneflower (*Echinacea purpurea*). It is commonly used for the improvement of the healthy immune system [16].

Dietary supplements also provide measurable health benefits. However, clinical usage remains a scientific debate. In conclusion, the general public receives mixed forms of information from the dietary supplement industry and the scientific community of the healthcare system [17]. Significant scientific evidence is still valid for the support, *i.e.*, the role vitamins and minerals play in maintaining a good healthcare system. Moreover, the major questions are the safety and efficacy of vitamins [18]. However, vitamin E and vitamin D are shown to possess remarkable therapeutic actions for the prevention of a variety of chronic diseases [13, 19]. The health claims of botanical dietary supplements remain less convincing. The additional issue of dietary supplement efficacy is the

inconsistency and variability of product quality [1]. Furthermore, dietary supplements are often subject to adulteration, and prescribed products may be contaminated with heavy metals and/or pathogenic microbes [20 - 22].

Even though some of the botanical dietary products are strongly considered for the treatment of medicine, such as Saint-John's wort used for depression, anxiety, tiredness, trouble sleeping, and loss of appetite [23, 24]. Hormones like ghrelin are secreted by adipose tissue and influence the hunger and appetite process of the gastrointestinal system [25]. The neuropeptide Y is produced in the brain and used as an appetite stimulant. Besides, melanocyte-stimulating hormones, insulin, and leptin are also used as appetite suppressants by acting on the hypothalamus region of the brain [26, 27]. Some dietary supplements have adequate amounts of essential nutrients and it is important for the improvement of overall health benefits like calcium and vitamin D produce strong bones and reduce bone loss; folic acid decreases the risk of certain birth defects; omega-3 fatty acids of fish oils help to treat the heart disease; and combination of vitamins C and E, zinc, copper, lutein, and zeaxanthin improve the age-related macular degeneration associated vision loss [28, 29]. The class of dietary supplements, examples, and health benefits are tabulated in Table **1**.

Table 1. Class of dietary supplements, examples, and their health benefits.

Class	Example	Health Benefits
Amino acids	Growth hormone and other hormones	Growth activation. Gaining weight [30].
Carbohydrate	Dextrose	Electrolyte balance. Cell growth. Enhance the natural anabolic effect [31].
Food and Foodstuff	Fish oils, carrots, garlic, royal jelly, and yeast (contain minerals and vitamins).	Improves neurovascular health and immune functions [32].
Herbals	Ginseng, Fiber (Contains amino acids, Chicoric acid, and alkylamides) *Allium sativum* (contains Allicin, adenosine *Ginkgo biloba* (contains ginkgolides)	Improves cellular amino acid and protein synthesis. Imuno-stimulants Anti-hypertension. Memory improvements [33].
Minerals	Selenium, multi-mineral.	Enhance the metabolic activity *via* catalytic actions [34].
Multivitamins and Multi-minerals	Vitamin D, calcium.	Improves the visual function. Enhance bone strength [35].

CHAPTER 2

Water-Soluble Vitamins Antioxidant Potential

Sohrab A. Shaikh[1,*]

[1] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia*

Abstract: Water-soluble vitamins are essential for the development, growth, and bodily functions. These vitamins are dissolved in water and are not stored in the body; a regular dietary supply is necessary. The key members of this group are vitamin C and the B-complex vitamins. Ascorbic acid (vitamin C) is primarily obtained from fresh fruits and vegetables and acts as a powerful antioxidant, detoxifying free radicals within the body. Thiamin (vitamin B1) plays a crucial role in energy metabolism and exhibits antioxidant activity by inhibiting lipid peroxidation and interacting with free radicals, converting them into less harmful compounds. Riboflavin (vitamin B2), found mainly in milk, is an important yet often overlooked antioxidant that contributes either independently or as part of the glutathione redox cycle, protecting against oxidative damage, particularly during reperfusion. Niacin (vitamin B3), comprising nicotinic acid and nicotinamide, forms the coenzymes Nicotinamide Adenine Dinucleotide (NAD) and Nicotinamide Adenine Dinucleotide Phosphate (NADP), essential for cellular redox processes and energy production. Niacin also functions as an independent antioxidant, enhancing the glutathione cycle and reducing oxidative stress. Coenzyme acid (vitamin B5), as a precursor to coenzyme A (CoA), is vital for metabolic processes involving proteins, lipids, and carbohydrates. Pantothenic acid derivatives panthenol and pantetheine have shown neuroprotective effects by enhancing the glutathione system in preclinical studies, revealing their antioxidant effects. Furthermore, pyridoxine (vitamin B6), biotin (vitamin B7), folic acid (vitamin B9), and cobalamins (vitamin B12) also play significant roles in antioxidant defense, protecting against oxidative stress either by maintaining glutathione levels or reducing reactive oxygen species (ROS) through different pathways. These vitamins collectively contribute to the body's antioxidant mechanisms, highlighting their importance in maintaining overall health and preventing oxidative damage.

Keywords: Antioxidant, B-complex vitamins, Dietary supplements, Oxidative stress, Vitamin C.

[*] **Corresponding author Sohrab A. Shaikh:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia; E-mail: shaikh.sohrab@aimst.edu.my

INTRODUCTION

Water-soluble vitamins are a group of vitamins that dissolve in water and are not stored in the body [1], hence need to be supplied through a regular diet for body development, growth, and function [2]. Vitamin C and B complex vitamins are soluble in water [1]. The B vitamins, namely B1, B2, B3, B5, B6, B7, B9, and B12, are recognized, and they are also known as thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, and cobalamin, respectively. These vitamins are naturally present in the same foods and share the characteristic of being water-soluble. Since the body does not produce B vitamins independently, it is crucial to obtain enough from the diet. Additionally, indirect ingestion through animal sources such as meat, eggs, and dairy is possible. Notably, vitamin B12 is not synthesized by plants but by bacteria, and it is exclusively found in various animal products. The entire spectrum of B vitamins plays essential roles as coenzymes in enzymatic reactions. Some B vitamins have neuro-specific functions and are termed "neurotropic," contributing to both the central and peripheral nervous systems [3]. Moreover, vitamin C is reported to have antioxidant activity by neutralizing free radicals, while B vitamins support antioxidant defenses through their role in metabolic pathways. Regular intake of these vitamins is essential for protecting against oxidative stress, which may help in reducing the risk of various pathological conditions. Hence, the subsequent topics of this chapter provide the information of individual water soluble vitamins along with their antioxidant potential.

VITAMIN C (ASCORBIC ACID)

Ascorbic acid (Fig. **1**), a vital water-soluble vitamin necessary for various bodily functions, is obtained primarily from fresh vegetables and fruits, which serve as key dietary sources [4]. Vitamin C can be obtained from a variety of dietary sources such as asparagus, beet greens, bell peppers, berries, bok choy, broccoli, Brussels sprouts, cabbage, cantaloupe, cauliflower, citrus fruits, collard greens, fennel, grapefruit, green leafy vegetables, kale, kiwifruit, lemons and limes, mustard greens, oranges, papaya, parsley, pineapple, potatoes, raspberries, sea vegetables, spinach, strawberries, sweet potatoes, Swiss chard, tomatoes, and turnip greens [5, 6].

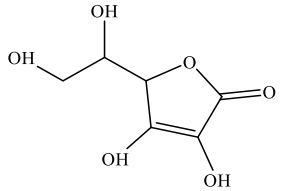

Fig. (1). Chemical structure of ascorbic acid.

The ascorbic acid acts as an antioxidant that detoxifies the free radicals produced within the body [4, 7]. Moreover, recent studies indicate that vitamin C may reduce vulnerability to viral respiratory infections and pneumonia [8]. Biologically, vitamin C plays a role in the metabolic processes of folic acid, tyrosine, and tryptophan. Additionally, it plays a role in synthesizing carnitine and catecholamines. Vitamin C aids in iron absorption and the breakdown of histamine. It also helps form neurotransmitters and is involved in the synthesis and maintenance of collagen. Furthermore, it increases the level of procollagen messenger RNA, acts as a coenzyme, and promotes the growth, development, and maintenance of osteoblasts, delaying the onset of osteoporosis. Vitamin C also protects sperm from oxidative damage, enhances lymphocyte function while reducing bacteriological activity. Additionally, it plays a role in neuronal modulation and the regulation of central nervous system homeostasis.

Additionally, clinical trial findings indicate that increased doses of vitamin C can reduce microvascular complications in type 2 diabetes, lower glycosylated hemoglobin levels, and decrease low-density lipoproteins. This highlights the important role of vitamin C as an adjunct treatment for both type 2 diabetes and atherosclerosis [6, 9, 10]. In another scenario, acute vitamin C deficiency can lead to scurvy [11], hence emphasizing its crucial role in preventing and treating scurvy [5].

Ascorbic Acid Antioxidant Potential

The importance of administering exogenous micronutrients to patients with severe disease to reestablish antioxidant levels has been known for decades [4]. As a potent antioxidant, ascorbic acid functions by contributing electrons to neutralize free radicals. It inhibits the generation of new free radicals through the suppression of the NADPH oxidase pathway. Additionally, it plays a crucial role in the recycling of other antioxidants [12]. This versatile compound is involved in controlling the lipid peroxidation of cellular membranes and nuclear materials within the cell. It mitigates DNA damage by reducing reactive oxygen species and safeguards proteins crucial for DNA repair. Moreover, it acts as a preventive measure against the formation of nitrosamine, a compound that gives rise to reactive nitrogen species. When combined with L-carnitine, it is reported to enhance the antioxidant and anti-inflammatory properties, thereby improving cisplatin-induced nephrotoxicity. High doses of vitamin C have been documented to elevate the production of reactive oxygen species within cells, disrupting the mitochondrial membrane potential. Additionally, at pharmacological doses, vitamin C can generate both ascorbate radicals and hydrogen peroxide. Consequently, the pro-oxidant effects induced by high doses of ascorbic acid have been proposed as a selective mechanism for killing cancer cells. The potential

CHAPTER 3

Fat-Soluble Vitamins Antioxidant Potential

Sohrab A. Shaikh[1,*]

[1] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia*

Abstract: The fat-soluble vitamins A, D, E, and K play important roles in maintaining overall health. These vitamins are stored in the body for future use and are mostly found in fruits, vegetables, nuts, and animal products. Vitamin A is essential for various physiological functions, including vision, epithelial integrity, red blood cell synthesis, growth, development, immune response, and reproduction. Moreover, vitamin A, along with carotenoids, can engage in electron transfer and quench singlet oxygen, suggesting their potential role in a biological antioxidant network. Furthermore, another fat-soluble vitamin, vitamin D, known as the "sunshine vitamin" due to its production in the skin upon sunlight exposure, is vital for musculoskeletal health and maintaining serum calcium levels. Additionally, vitamin D is reported to reduce the generation of Reactive Oxygen Species (ROS) through NADPH oxidase and enhance the antioxidant defenses by increasing the activity of enzymes like superoxide dismutase. Another vitamin in this group is Vitamin E, a potent fat-soluble antioxidant, which comprises eight isomers: four tocopherols and four tocotrienols. Each isoform has distinct biological effects and acts as a powerful scavenger of free radicals, contributing to the body's antioxidant defense. Vitamin K is another fat-soluble vitamin obtained from certain foods and dietary supplements, and is integral to the body's coagulation pathways. Additionally, vitamin K plays a role in preventing oxidative damage by inhibiting the activation of 12-lipoxygenase, an enzyme involved in arachidonic acid metabolism, thereby reducing ROS production. Collectively, these fat-soluble vitamins contribute to antioxidant defense and overall health, supporting various physiological functions and protecting against oxidative stress.

Keywords: Antioxidants, Dietary supplements, Oxidative stress, Vitamin A, Vitamin D, Vitamin E, Vitamin K.

INTRODUCTION

The fat-soluble vitamins A, D, E, and K possess unique properties that enhance overall health. These vitamins are commonly found in fruits, vegetables, nuts, and

[*] **Corresponding author Sohrab A. Shaikh:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia; E-mail: shaikh.sohrab@aimst.edu.my

animal products. After being consumed and metabolized, they are stored in the body for later use [1]. The main fat-soluble microconstituents in the human diet consist of carotenoids and phytosterols [2]. Fat-soluble vitamins are essential for various physiological functions, including supporting vision, maintaining bone health, enhancing immune function, and aiding in blood coagulation [3]. Vitamin A aids in vision, while vitamin D assists in regulating calcium and phosphate balance, vitamin E helps with antioxidant activity, and vitamin K helps with blood coagulation. Although vitamin D was once regarded as merely a vitamin, it is now also recognized to be a prohormone [4]. In the past two decades, a lack of these vitamins has been associated with elevated risks of cancer, type 2 diabetes, and various issues with the immune system [5].

VITAMIN A

Vitamin A is made up of fat-soluble retinoids such as retinal (Fig. **1A**), retinol (Fig. **1B**), and retinyl esters [6]. Vitamin A is a necessary vitamin for the body's healthy functioning, including the visual system, epithelial integrity, red cell synthesis, growth and development, immunological and reproductive function, and so on. However, because the human body does not synthesize this vitamin, appropriate daily consumption is required to avoid micronutrient deficit and impairment of the body's proper functioning [7].

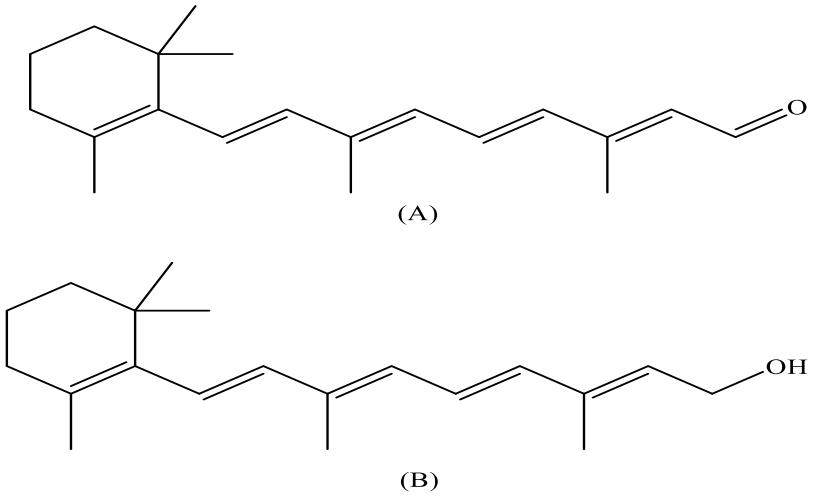

Fig. (1). Chemical structure of retinal (**A**) and retinol (**B**).

Dietary sources provide vitamin A in two forms. Preformed vitamin A, found as retinol and retinyl ester, can be obtained from foods like meat, whole milk, yogurt, cheese, margarine, butter, eggs, chicken, chicken liver, processed meats, pizza, and fish oils. Provitamin A, or beta-carotene, is found in colorful fruits and

vegetables such as carrots, pumpkins, papayas, sweet potatoes, and red palm oil. Both forms of ingested vitamin A must be converted into retinal and retinoic acid after absorption to support biological functions [8 - 10]. A deficiency in vitamin A leads to the replacement of normal epithelial tissue with stratified, keratinizing epithelium in the eyes, periocular glands, respiratory system, digestive tract, and genitourinary tract. Vitamin A is required for gene regulation because of its role in cell morphogenesis, differentiation, and proliferation [8]. Vitamin A is essential for regenerating visual pigments, maintaining the integrity of mucosal membranes, and supporting the immune system. A deficiency in vitamin A can hinder the regeneration of visual pigment in retinal rods, leading to night blindness. If untreated, this deficiency can cause the deterioration of rods, resulting in xerophthalmia and potentially leading to blindness. Additionally, deficiencies may manifest as xerosis and breakdown of mucosal membranes in the intestines and lungs, along with compromised immune function, leading to frequent infections [9, 11].

Vitamin A supplements are used to treat xerophthalmia, severe malnutrition, measles, and to prevent deficiency among pregnant women living in regions where vitamin A deficiency is prevalent. Notably, the treatment of xerophthalmia holds significance as it stands out among vitamin-deficient illnesses that have escalated to epidemic levels. Administering vitamin A supplements has proven efficacy in addressing xerophthalmia, effectively averting night blindness, a significant issue in developing nations [8].

Vitamin A Antioxidant Potential

Vitamin A and carotenoids can receive and transfer electrons under certain conditions, and carotenoids can also quench singlet oxygen. As a result, both sets of chemicals have the potential to be part of a biological antioxidant network [12]. Although vitamin A is not widely recognized as an antioxidant, some research suggests it may have an indirect antioxidant role. Studies have shown that all-trans retinoic acid can inhibit thioredoxin-interacting protein, which reduces the activation of hepatic stellate cells (linked to liver cancer) and lowers oxidative stress. Additionally, retinoic acid, a metabolite of vitamin A, has been found to increase the expression of antioxidant genes in mature buffalo oocytes *in vitro*. Furthermore, in both normal and varicocele sperm, all-trans retinoic acid has been shown to enhance superoxide dismutase and glutathione transferase activity, while decreasing levels of malondialdehyde and reactive oxygen species. These findings suggest that retinol may boost the activity of antioxidant enzymes. As a result, growing evidence indicates that vitamin A might help protect the body from oxidative stress [13]. In addition to providing a metabolic source of retinol, beta-carotene and other dietary carotenoids act as antioxidants, reducing the

CHAPTER 4

Therapeutic Uses of Macronutrients in the Healthcare System

Arunachalam Muthuraman[1,*], Yuvaraj Sivamani[2] and **Sumitha Elayaperumal[3]**

[1] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia*

[2] *Department of Pharmaceutical Chemistry, Crescent School of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur – 600048, Chennai, Tamil Nadu, India*

[3] *Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education and Research, Mysore, Karnataka, India*

Abstract: The macronutrients, such as carbohydrates, proteins, fats, and lipids, act as nutritive components of food, and they supply the energy for the body's demands. Macronutrients help in maintaining the body's structure and functions of various systems. Large amounts of macronutrients are required for day-to-day life functions. Furthermore, it is an essential nutrient for a healthy lifestyle and body homeostasis functions. Besides, it plays a vital role in various body functions with multiple biological and pharmacological actions. The outcomes of macronutrients vary with age, sex, fitness goals, pre-existing health conditions, and the daily intake amount of macronutrients. The role of these essential macronutrients in the Healthcare system for various ailments needs to be addressed to achieve better outcomes. However, the clear correlation of macronutrients in the clinical Healthcare system remains to be explored. Hence, this book chapter discusses the functional actions, mechanisms, and beneficial effects of macronutrients.

Keywords: Aerobic metabolism, Body-building elements, Macronutrient deficiency, Mediterranean diet, Tissue repair.

INTRODUCTION

Macronutrients are the types of nutrients that are used in the largest amounts, like carbohydrates, protein, and fats [1]. The nutritive components of food in macronutrients are essential for the body's energy demand and maintenance of

* **Corresponding author Arunachalam Muthuraman:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia;
E-mail: muthuraman.a@aimst.edu.my

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

body structure and system functions [2]. They are also involved in body growth, metabolism, and other body functions [3, 4]. The metabolism process is a major part of energy production, and it processes the body's building blocks (nutrients) that are required for day-to-day life. [5]. Macronutrients support the abundant calories, whereas they vary depending on the source of food and the person's condition. One gram of carbohydrates or proteins is supposed to make four calories; moreover, one gram of fat provides nine calories of energy [6, 7]. The details of macronutrients about carbohydrates, protein, and fats are described in the following sections.

CARBOHYDRATES AS MACRONUTRIENTS

Carbohydrates are the primary source of body energy. It is utilized by muscles and provides abundant energy to muscles and the central nervous system with the influence of movement and exercise [8, 9]. The energy production from carbohydrates is 45-65% of calories per day. Moreover, the amount depends upon the individual's health status and conditions [9]. The carbohydrate-based energy is produced in the form of glucose and enters all tissues and cells. Further, it undergoes multiple steps in the metabolism process, leading to the production of energy in the form of Adenosine Triphosphate (ATP). This metabolism process undergoes the aerobic and anaerobic processes [8, 10]. In metabolic pathways, it is entered into the glycolysis, the Krebs cycle, and the electron transport chain pathways [11, 12]. However, the production of energy is also raised with hexose monophosphate (HMP) shunt pathways. The HMP shunt is also referred to as the pentose phosphate pathway. It is a unique pathway involved in the production of essential energy-producing bio-compounds, *i.e.*, Ribose-5-phosphate (R5P) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) [13, 14]. In addition, these glucose metabolic products are shunted off the process and can support the production of energy compounds (glucose) from amino acids (protein) and fats (gluconeogenesis pathway). These gluconeogenesis and HMP pathways are also known as anabolic pathways [15]. Carbohydrate-derived energy mainly occurs in high-energy-utilizing tissues like the brain, kidneys, central nervous system, and muscles [16, 17]. Furthermore, the excess carbohydrates are stored in the muscles and liver in the form of glycogen [18, 19]. The primary sources of carbohydrates (macronutrients) are wheat, bread, maize, rice, potatoes, sugar cane, banana, honey, beans, nuts, and seeds [20].

Furthermore, carbohydrates are classified into three major categories based on their sugar group arrangements: monosaccharides, disaccharides, and polysaccharides [21]. Both mono- and disaccharides are known as simple sugars and are easily utilized by the body tissue, which elevates the blood sugar level rapidly [13]. Hence, diabetic patients are recommended to avoid this kind of

carbohydrate. Examples include sugar, honey, sweet fruits, and sugar cane [22]. However, polysaccharides are a complex form of carbohydrates. It is broken down into simple sugar forms in the body. Examples are starch and cellulose [21]. It is commonly consumed by diabetic patients without dietary restrictions [23]. Thus, appropriate intake of carbohydrate macronutrients contributes to a healthy body condition, aids in the regulation of blood glucose content in individuals with diabetes, and supports overall metabolic health [24, 25].

Carbohydrate abnormalities also affect the Healthcare system, like lactose intolerance, sucrase deficiency, fructose malabsorption, and congenital carbohydrate intolerances [26, 27]. Lactose intolerance is a kind of carbohydrate macronutrient deficiency disorder. Lactase enzymes are present in the jejunum and cleave the milk sugar, *i.e.*, lactose. Sometimes it disappears in the weaning age [28]. The disappearance effects occur gradually, whereas the process is faster in age-onset conditions. Rarely do these enzymes disappear in early childhood and late adulthood. The absence of lactase leads to abnormal conditions in the body, and it is referred to as lactose intolerance [29]. These changes are mostly identified in white people due to biological abnormalities. Furthermore, this lactase intolerance effect persists throughout life, and it is also known as lactase persistence. In this case, the consumption of milk and lactose-containing products causes diarrhea, cramping, bloating, and flatulence-like gastrointestinal disorders [30]. Moreover, these problems are overcome with the consumption of small amounts of lactose-containing products in a day, plant-based non-dairy beverages, and lactase-treated dairy products [31, 32]. Similarly, sucrase deficiency is a carbohydrate macronutrient-related problem [33]. It is rare in the Healthcare system, and it is documented in adult patients with renal calculi [34, 35].

Further, these sucrase deficiency conditions are common in Human Immunodeficiency Virus (HIV) affected patients, *i.e.*, 31% of the HIV-infected population has a sucrase deficiency problem [36]. Fructose malabsorption also causes gastrointestinal problems like cramps, bloating, and osmotic diarrhea [27]. Further, they are not responding to medications and surgical interventions [37, 38]. The malabsorption of fructose-like problems is similar to the problem of consuming concentrated amounts of sugar, *i.e.*, beverages with high-fructose corn syrup, whereas these problematic effects do not occur when eating sufficient quantities of fruits [39]. Fructose malabsorption appears with fructose intake exceeding 25 grams per meal. These levels were reduced to around 15 grams in those who already have functional bowel disease [40]. Congenital carbohydrate intolerances are also rare, but they can cause life-threatening effects. In this case, all kinds of malnutrition problems, like alactasia (total absence of lactase), glucose-galactose malabsorption, and sucrase-maltase deficiency [41].

CHAPTER 5

Therapeutic Uses of Micronutrients in the Healthcare System

Khian Giap Lim[1], Venkata Rathina Kumar Thigarajan[2] and **Arunachalam Muthuraman[3,*]**

[1] *Clinical Pharmacy and Pharmacy Practice Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong, 08100, Kedah, Malaysia*

[2] *Department of Pharmacognosy, College of Pharmacy, Madurai Medical College, Madurai - 625020, India*

[3] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia*

Abstract: Micronutrients are considered vitamins and minerals that are needed for the body to function in smaller amounts. The impact of micronutrients on the body's health and homeostasis is very critical. The deficiencies of micronutrients readily cause severe health impairments and even cause life-threatening conditions. The requirement for micronutrients depends upon the various influencing factors, such as absorption and excretion of nutrients. Micronutrient deficiency is associated with various disorders, and the requirements of micronutrients are variable based on the person's disease conditions and health status. Furthermore, pre-existing health conditions like sex, age, and fitness are also major factors in micronutrient requirements for essential body functions. The common principles of micronutrient actions are free radical scavenging and regulation of natural killer cells to prevent various disease progressions like cancer, Alzheimer's, and heart disease. However, the strong relationship between micronutrients and their uses in clinical conditions needs to be explored. Hence, this book chapter is focused on discussing the beneficial effects of micronutrients in the management of various ailments in patients.

Keywords: Amino acids, Free radical scavenger, Neurodegenerative disorders, Non-enzymatic antioxidants, Oil supplements.

INTRODUCTION

Micronutrients are an essential part of a healthy life after the use of macronutrients. Micronutrients are needed in very small quantities daily in our

[*] **Corresponding author Arunachalam Muthuraman:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia.; E-mail: muthuraman.a@aimst.edu.my

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

diet. It covers vitamins and minerals [1]. The major vitamins and their functions in the Healthcare process are described in chapters 2 and 3. This chapter is focused on essential minerals as micronutrients for a better Healthcare process. Micronutrients play a role in healthy body development, the prevention of disease, and maintaining well-being [2]. Moreover, these micronutrients are not produced in the body except for vitamin D. Hence, the supplements of micronutrients are essential in the diet. Worldwide, half of the younger children (< 5 years of age) are suffering from vitamin and mineral deficiencies [3]. The deficiencies of micronutrients are playing a role in devastating consequences. The details of various micronutrients like calcium, potassium, sodium, iron, zinc, magnesium, cobalt, chromium, coenzyme Q10 (CoQ10), iodine, and selenium are discussed in the following sections [4].

CALCIUM IN THE HEALTHCARE SYSTEM

Calcium is one of the essential micronutrients. In a cellular system, it acts as a secondary messenger for the cell signaling process. The abundant quantity is present in bones and teeth [5]. Furthermore, it also enhances the functions of the nervous system, cardiovascular system, and other organ functions. The recommended calcium levels for adults are 1,000 milligrams per day, and post-menopausal women need 1,200 mg per day [6]. Good sources of calcium are dairy products, legumes, and green and leafy vegetables. Moreover, calcium is important for maintaining the structure of bones and teeth. It also supports making normal body movements with tissue that is strong, rigid, and flexible [7]. Calcium nutrients are available in different forms, as free ions and bound forms. The free ion forms of calcium are present in the extracellular fluid, cell cytosol, and circulatory system [8]. Besides, it helps to make the constriction and dilation of blood vessels, muscular functions, blood clotting, neuronal impulse transmission, and hormone secretion [9, 10]. The transport of calcium ions occurs with active transport and passive diffusion in the intestinal mucosa [11]. In lower concentrations of calcium, it undergoes active transport, whereas passive diffusion occurs when the calcium ion concentration is raised [12]. In addition, the calcium reservoir, *i.e.*, bone, releases the calcium to maintain the cellular and circulatory calcium homeostasis process [13]. Calcium in bone and teeth is stored in the form of calcium hydroxyapatite and calcium phosphate [14]. It also helps to cure the bone *via* bone remodeling with bone growth, and repair [15].

The lower amount of calcium causes the weakening of bones and teeth. The deficiency of calcium leads to tingling and abnormal cardiac rhythm, and sometimes causes life-threatening conditions, whereas a large quantity of calcium leads to kidney stones, reduced absorption of other minerals, and constipation [16, 17]. The altered levels of calcium affect the various levels of the health system.

Calcium deficiency can raise bone weakness, the fragility of bones, and osteoporosis [18]. In addition to that, calcium deficiency is also responsible for rickets in children and multiple bone disorders in adults. In rickets conditions, the growth of cartilage bones is not mineralized and leads to the irreversible modification of the skeletal structure [19]. Chronic calcium deficiency leads to osteomalacia with defects of bone mineralization [4]. Normally, the symptoms of hypocalcemia are rising neuromuscular irritability, perioral numbness, tingling of hands and feet, and muscle spasms [20]. In severe conditions, calcium deficiency shows renal calcification, tissue injury, brain calcification, cataracts, congestive heart failure, paresthesia, seizures, coma, and neurological behavioural abnormalities like depression and bipolar disorders [2]. Hence, the balanced micronutrient calcium is needed from an individual's birth to the end of their life.

POTASSIUM IN THE HEALTHCARE SYSTEM

Potassium ions are essential for a variety of body functions. It is mainly involved in the healthy functions of the kidneys, heart, muscles, and nervous system [21]. It is also involved in the cellular membrane potential and structural regulatory functions. The recommended dose of potassium for adults is 4,700 milligrams per day [22]. The sources of potassium are bananas, coconut water, dried fruit, avocados, beans, and lentils [23]. The lower amount of potassium causes high blood pressure, stroke, and kidney stones, whereas a large amount of potassium produces harmful effects in patients with kidney disease [21]. The altered levels of these micronutrients, *i.e.*, potassium, affect the body's health. Besides, potassium helps to regulate body fluid, impulse transmission, and muscular contractions [24]. In a healthy body, about 98% of potassium is present in cells. Further, 80% is present in muscular cells, and 20% is present in bones, liver, and red blood cells [25]. Normally, potassium is present in the body in the form of electrolytes (positive charge) [26]. Furthermore, the lower and/or higher levels of potassium electrolytes affect many crucial functions [27].

Potassium deficiency causes hypertension, risk of kidney stones, altered bone turnover, excretion of urinary calcium ions, and changes in salt sensitivity. In severe conditions, potassium deficiency causes hypokalemia with the use of diuretics and other medications [28]. The symptoms of mild hypokalemia are constipation, muscle weakness, fatigue, and malaise, whereas moderate to severe hypokalemia conditions are shown as polyuria, encephalopathy with renal disease, glucose intolerance, paralysis of muscular tissue, respiratory dysfunction, and cardiac arrhythmias [29 - 31]. Moreover, chronic high hypokalemia can cause life-threatening problems like muscular contractions and cardiac dysfunctions. In addition, hypokalemia also contributes to magnesium depletion, which leads to the risk of cardiac arrhythmias *via* reduction of intracellular potassium ion

CHAPTER 6

Essential Fatty Acids Benefits in the Healthcare System

Nallupillai Paramakrishnan[1], Yuvaraj Sivamani[2], Sumitha Elayaperumal[3] and **Arunachalam Muthuraman[4,*]**

[1] *Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru - 570015, Karnataka, India*

[2] *Department of Pharmaceutical Chemistry, Crescent School of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur – 600048, Chennai, Tamil Nadu, India*

[3] *Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education and Research, Mysore, Karnataka, India*

[4] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia*

Abstract: The dietary Essential Fatty Acids (EFA), also referred to as Polyunsaturated Fatty Acids (PUFA), include alpha-linolenic acid, Docosahexaenoic Acid (DHA), Eicosapentaenoic Acid (EPA), and linoleic acid. It regulates the immune and central nervous system functions, and also produces various hormones. It is also correlated positively to infant development; reduction of cardiovascular morbidity and mortality; prevention of cancer progression; optimal functioning of the brain and eyes; arthritis; hypertension; and diabetes mellitus. It shows the multiple pharmacological actions *via* β-oxidation for the production of cellular energy currency, *i.e.*, Adenosine Triphosphate (ATP); esterification of cellular lipids into phospholipids, triglycerides, and cholesterol esters; and conversion of the longer chain fatty acids to unsaturated fatty acid products. The clear correlation of dietary EFA for the management of various ailments in multiple clinical conditions remains to be explored. Hence, this book chapter reveals the beneficial effects of dietary EFA in the management of various metabolic and inflammatory disorders, along with the correlation of their mechanism of action.

Keywords: Cytokines, Eicosanoids, Nuclear factor kappa-activated B cells, Peroxisome proliferator-activated receptors, Retinal degeneration, Visual pigments.

[*] **Corresponding author Arunachalam Muthuraman:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia; E-mail: muthuraman.a@aimst.edu.my

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

INTRODUCTION

Essential Fatty Acids (EFAs) are essential for healthy body functions. It is synthesized in the body. EFAs are alpha-linolenic acid, Docosahexaenoic Acid (DHA), Eicosapentaenoic Acid (EPA), and linoleic acid [1]. Generally, EFA is also referred to as Polyunsaturated Fatty Acids (PUFA). EFA is also categorized as two families of omega-3 (ω-3) and omega-6 (ω-6) fatty acids [2]. Omega-3 fatty acids, *i.e.*, alpha-linolenic acid, DHA, and EPA, are composed of a final carbon-carbon double bond in the ω-3 position, whereas ω-6 fatty acids, *i.e.*, linoleic acid, have a carbon-carbon double bond in the ω-6 position [3]. Both ω-3 and ω-6 fatty acids possess physiological transformation in the human body and produce stable energy [1, 4]. The EFA is called a functional food, as it plays a significant role in the improvement of healthy physiological functions. The EFA is important for maintaining the membrane structure and functions. Membranes are mainly incorporated with phospholipids associated with EFA [5, 6]. It is also involved in the regulation of membrane flexibility, fluidity, and permeability with active membrane-bound enzymes and cell-signaling actions [7]. Furthermore, it also regulates the endogenous metabolism and composition of cellular membranes. Thus, increasing ω-3 fatty acids raises the ω-3 fatty acids content in the red blood cells, immune cells, atherosclerotic plaques, and cardiac myocytes [8]. The details of alpha-linolenic acid, DHA, EPA, and linoleic acid have been described in the following sections [9].

PHYSIOLOGICAL FUNCTIONS OF EFA

EFA has pleiotropic actions on cellular functions. Further, it regulates gene expression *via* interactions of transcriptional factors and influences membrane lipid compositions [10]. In addition, both ω-3 and ω-6 fatty acids modulate the expression of fatty acid metabolic and inflammatory proteins *via* interactions of specific transcription factors like Peroxisome Proliferator-activated Receptors (PPARs) and poly(ADP-ribose) glycohydrolase (PARG) actions [11]. It also acts as a hydrophobic hormone-like steroid hormone, and it controls the gene expression and binds directly to PPARs, leading to activation of the transcription factors, *i.e.*, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and sterol regulatory element-binding transcription factor 1 (SREBP-1) [12, 13]. Both are responsible for the transcription of inflammatory proteins. Besides, ω-3 fatty acids suppress the NFκB nuclear content and inhibit the production of eicosanoids and cytokines [14]. It also alters the conservation and recycling of DHA and regulates the retinal degeneration and impairment of visual pigment [15]. In the nervous system, brain phospholipids alter the glucose uptake process *via* cortical astrocytes and enhance synaptic plasticity and memory functions [16].

The details of ω-3 essential fatty acids (alpha-linolenic acid, DHA, and EPA) have been described in the following sections.

ALPHA-LINOLENIC ACID IN THE HEALTHCARE SYSTEM

Alpha-linolenic acid is a type of omega-3 fatty acid, and it is present in various plants like chia seeds, flaxseeds, flaxseed oil, canola oil, mustard oil, tofu, perilla, soy, soybean oil, walnuts, and walnut oils [17]. It is similar to omega-3 fatty acids like DHA and EPA. The recommended intake of alpha-linolenic acid for men is 1.8 to 2.0 g per day and for women 1.4 to 1.5 g per day [18]. It is necessary for growth and development. The intake of alpha-linolenic acid reduces the risk of cardiac disease *via* the reduction of various risk factors like antiplatelet and anti-thrombotic actions [19]. Dietary omega-3 fatty acids like alpha-linolenic acid also prevent the risk of type-2 diabetes mellitus, atherosclerotic events, stroke, and peripheral vascular disease [20 - 22]. Besides, alpha-linolenic acid reduces blood pressure, asthma, and dry eye *via* reduction of inflammation and improves physiological functions [23 - 25]. The benefits of alpha-linolenic acid are improved cognitive and brain health, supporting mood balance, and reducing joint inflammation and pain [26]. Furthermore, the deficiency of alpha-linolenic acid causes reduced vision, inability to walk, pain and weakness in the legs, scaliness of the skin, excessive cholesterol, and inflammation [27, 28].

Moreover, alpha-linolenic acid has interaction properties with various medications like blood-thinning medications (warfarin, clopidogrel, and aspirin) and cholesterol-lowering medications (atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin) [29, 30]. Experimentally, alpha-linolenic acid is used for the treatment of rheumatoid arthritis, pneumonia, multiple sclerosis, systemic lupus erythematosus, diabetes, renal disease, ulcerative colitis, and Crohn's disease [31, 32]. It also treats skin cancer, chronic obstructive pulmonary disease, migraine, depression, psoriasis, and eczema [33, 34]. The oral dosing of alpha-linolenic acid, *i.e.*, 1.2 to 2 grams per day, prevents coronary heart disease-associated chest pain, heart attack, and heart failure [35, 36].

DHA in the Healthcare System

DHA is one of the major ω-3 fatty acids, and it is found with EPA in cold-water fish like tuna and salmon. It is also present in sardines and herring fish; walnuts, flaxseed, flaxseed oil, canola oil, soy beverages, milk, and yogurt [37]. Physiologically, DHA supports the development of eye and neuronal tissues and leads to the prevention of visual disturbance and attention deficit hyperactivity disorders [38, 39]. Further, it reduces the risk of cardiovascular disease *via* reduction of blood thickness, tissue swelling, and lowering triglycerides in blood levels [40, 41]. Moreover, the DHA reduces the cholesterol and fat deposition in

CHAPTER 7

Prebiotics / Probiotics as Therapeutic Agents in the Healthcare System

Yamunna Paramaswaran[1], Muthusamy Ramesh[2], Nallupillai Paramakrishnan[3] and **Arunachalam Muthuraman[4,*]**

[1] *Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia*

[2] *Department of Pharmaceutical Analysis and Quality Assurance, Institute of Pharmaceutical Sciences, Sandip Foundation, Nashik - 422213, India*

[3] *Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru - 570015, Karnataka, India*

[4] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Jalan Bedong-Semeling, Bedong 08100, Kedah, Malaysia*

Abstract: Probiotics are live microorganisms found in foods or supplements that benefit the host, whereas prebiotics are non-digestible food ingredients that nourish beneficial gut bacteria. Typically, probiotics contain live microorganisms that help to maintain and improve the normal intestinal microflora, *i.e.*, "good" bacteria in the body. Prebiotics are mainly high-fiber-containing foods, and they act as food for human intestinal microflora. Both prebiotics and probiotics are useful for the healthy functions of human organ systems. The health benefits of these products are significantly shown in the regulatory mechanism at the cellular and molecular levels. The major physiological functions of these products are enhancing the metabolic alteration of good bacteria (microflora) and host cell secretion of mucus proteins. Besides, it also enhances calcium absorption, regulates mucosal barrier functions, and supports gut-endothelial barrier actions *via* the prevention of bad bacteria invasion and survival in the digestive system. The metabolite of probiotics also stimulates the host immune cell functions. Moreover, prebiotics act either directly or indirectly to support the microbiota for the development of healthy neurovascular, cardiovascular, renal, hepatic, and lung functions. However, the therapeutic actions and mechanisms of these products remain to be explored in various pathological conditions. Hence, this book chapter is focused on the exploration of prebiotics and probiotics in the management of various disorders in patients, besides foods and/or supplementary actions.

Keywords: Alpha-glucan, Galacto-oligosaccharides, Gut microbiota, Immune function, Inulin.

[*] **Corresponding author Arunachalam Muthuraman:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia.; E-mail: muthuraman.a@aimst.edu.my

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

INTRODUCTION

The term "prebiotics" was first introduced by Glenn Gibson and Marcel Roberfroid in 1995. Prebiotics are substances obtained from certain types of carbohydrates, primarily non-digestible fiber, that serve as food for beneficial gut bacteria [1]. Further, these fibers are eaten by beneficial gut bacteria. Besides, the gut bacteria are collectively called gut flora or gut microbiota, which is essential for various important body functions [2]. The beneficial bacteria are good and help to protect the gut from harmful bacteria and fungi organisms [3]. In addition, these bacteria enhance immune functions; minimize the symptoms of depression, and help reduce obesity complications [4]. Some of the gut bacteria are formed from vitamin K and short-chain fatty acids [5]. Prebiotics are types of fiber present in vegetables, fruits, and legumes [6]. Some fibers are not digested by human enzymes and hormones, whereas good gut bacteria are easily digested for feed consumption [2]. The probiotic fiber-containing foods are beans, peas, oats, bananas, berries, asparagus, dandelion greens, garlic, leeks, and onions [7]. Gut bacteria convert the prebiotic fiber to short-chain fatty acids, *i.e.*, butyrate. Butyrate also regulates the natural movement of food in the gut compartment and boosts the blood flow into the colon tissue [8]. Further, a short-chain fatty acid also possesses anti-inflammatory and anti-cancer properties. Besides, these short-chain fatty acids are essential nutrients for colon cell linings and promote efficient gut-barrier functions *via* filtering the entry of harmful substances, bacteria, and viruses [9]. Overall, prebiotics are reduces gut inflammation, risk of cancer and improves healthy gastrointestinal functions [10].

Probiotics are live bacteria and provide various healthy body functions. Probiotics are beneficial bacteria found in various foods or supplements. The natural probiotic food is yogurt [11]. Beneficial bacteria (probiotics) are commonly found in fermented foods like sauerkraut, kimchi, kombucha tea, kefir, and pickled vegetables, where they are grown using naturally occurring sugars or fiber. Conversely, the pasteurization process is used to heat-treat foods, which kills all beneficial bacteria [12, 13]. Eating balanced amounts of prebiotics and probiotics helps to maintain healthy gut microbiota functions. Moreover, some foods have both beneficial bacteria and digestible fiber feed for gut-beneficial bacteria [14]. It is also known as symbiotic products like cheese, sauerkraut, and kefir [15]. The role of prebiotics and probiotics in the Healthcare system has been described in the following sections [16].

Physiological Functions of Prebiotics and Probiotics

Multiple types of microorganisms are present in the gut region. Normally, 10^{10} to 10^{12} live microorganisms per gram of tissue are present in the human colon [17].

These residual microorganisms are essential for the healthy functions of the stomach and small and large intestines [9]. Most of the microorganisms are anaerobic organisms and survive in the large intestine. It needs digestible fibers as food, and it is called prebiotics [11]. The imbalance of microbes will be developed with the influence of endogenous factors like mucin secretions [18]. Human dietary fibers, like non-digestible carbohydrates, are the chief source of microbial growth and energy development [19]. Prebiotics are influenced by gut microbial growth and functions; subsequently, they affect intestinal functions, such as the lack of human intestinal metabolism and integrity [20]. In addition, the suppression of gut pathogens (Bifidobacterium and Lactobacillus species) with lactic acid formation can modulate immune functions (antagonistic effects against pathogens) [21].

Normally, probiotics are carbohydrate fibers, and fermented products enhance the selective specific gut microbiota functions. Overall, prebiotics are categorized as carbohydrates (oligosaccharides) and non-carbohydrate products [22]. Various compounds like fructo-oligosaccharides, galacto-oligosaccharides, trans-galacto-oligosaccharides, alpha-glucan oligosaccharides, and inulin are the most common prebiotics [23]. The fermented products also act as prebiotics for gut microbiota for the production of short-chain fatty acids, lactic acid, butyric acid, and propionic acid [24]. All these compounds possess various beneficial effects on the body. Propionic acid helps the healthy functions of T-helper-2 cells in human airway tissue, macrophages, and dendritic cells of bone marrow. Fatty acids also reduce the colon's pH [24]. The peptidoglycan of fermentation products also acts as an immune stimulator for the prevention of pathogenic microorganisms-associated infections [18]. The beneficial effects of prebiotics are mainly due to the byproducts of microbial digestion, like butyrate, influencing the development of intestinal epithelial tissue, and fatty acids supporting blood circulation [25]. The primary properties of prebiotics are a) resistant to the stomach's acidic pH with lack of hydrolysis by digestive enzymes; b) unabsorbed in the gastrointestinal tract; c) fermented by intestinal microbiota; d) intestinal bacteria are selectively stimulated by this compound; e) improves the host’s health. The details of prebiotics are explained in the following sections [18, 26].

Host Cell Functions of Prebiotics

Galacto-oligosaccharides are an extension product of lactose. It is categorized into two subgroups, *i.e.*, 1) excess galactose attachment in C3, C4, and C6; and 2) the trans-glycosylation of lactose [27]. These end products are a mixture of tri- to pentasaccharides with galactose, and they are also named trans-galacto-oligosaccharides. In infants, it potentially stimulates the Bifidobacteria and Lactobacilli [18]. Further, it also stimulates the Enterobacteria, Firmicutes, and

CHAPTER 8

Phytochemicals as Nutraceuticals

Mukesh Singh Sikarwar[1,*] and **Vaibhav Kumar Rathi**[2]

[1] *Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India*

[2] *Department of Pharmacy, Quantum University, Roorkee (Haridwar), Uttarakhand, India*

Abstract: Phytochemicals serve as essential components in nutraceuticals derived from plants and in functional food products. Plants are designed to generate phytochemicals as protective responses when faced with environmental stressors. The complexity of these phytochemicals suggests they possess significant potential for various physiological actions. A significant number of secondary metabolites generated by plants find applications in the field of medicine. Nutraceuticals are products sourced from food that offer both nutritional and medicinal benefits, typically taken in forms similar to pharmaceuticals, such as capsules, pills, or tablets. Functional foods are typically consumed like regular foods, which clearly differentiates them from nutraceuticals. Nutraceuticals differ from functional foods in that they are not classified as food. Instead, they consist of extracts or dosage forms derived from food, aimed at enhancing health outcomes. Phytochemicals like alkaloids, glycosides, carotenoids, phenolics, sulfides, flavonoids, phytoestrogens, and many other phytochemicals are used as nutraceuticals. Recently, the traditional system of medicines started launching nutraceuticals, for example, Ayurveda nutraceutical products range from beauty products to Non-Communicable Disease (NCD) management like diabetes, hypertension, and cancer management. Nutraceuticals reduce oxidative stress by quenching the free radicals in NCD, hence have the value of appropriate therapeutic nutritional interventions. This chapter is an attempt to compile the background, source, chemistry, and clinical studies of different classes of phytochemicals having the potential of nutraceuticals.

Keywords: Chemical structure, Clinical trials, Nutraceutical, Phytochemical.

INTRODUCTION

Phytochemicals are the microchemicals that are produced inside the cells of plants, and secondary metabolites are the phytochemicals that are produced due to defense mechanisms in plants and various other reasons, including environmental

[*] **Corresponding author Mukesh Singh Sikarwar:** Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India; E-mail: mukeshsikarwar@gmail.com

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

stress and adverse environments for the survival of the plant. Secondary metabolites produced from these plants could be utilized as nutraceuticals. To be a nutraceutical plant, it should have medicinal value apart from its nutritional value [1]. Phytochemicals as a nutraceutical could be classified based on chemical class and their action. Nutraceutical products for eye care, skin care, hair care, energy boosters, antihypertensives, anti-obesity, antidiabetic, hormone regulators, stimulants, anti-ageing, and rejuvenators are widely available in the market [2]. In this chapter, some of the important nutraceuticals are discussed.

CAROTENOIDS: A AND B-CAROTENE, LYCOPENE, XANTHOPHYLLS, LEUTIN

Carotenoids are largely present in photosynthetic plants and nonphotosynthetic tissues within the unique cells called xanthophores. Different hues of meals, including fruits and vegetables, are attributable to the presence of carotenoids. The trans form of carotenoids isomerizes to the cis form during the digestion of food. Carotenoids mainly exist in fruits and vegetables, and their composition is determined by climate variables and geographic areas. α and β-Carotene, lycopene, xanthophylls, and leutin are some of the main carotenoids frequently exploited as nutraceuticals. Carotenoids are more abundant in the peel than pulp of the fruits and are efficient synergistically in polyherbal form. Certain carotenoids, like zeaxanthin and lutein, have a tremendous role in the protection of macula lutea against photooxidative damage and reduce the risk of age-related macular degeneration [3, 4]. Lycopene and beta carotenes provide protection by their antioxidant potential.

Carotenoids and terpenoids are made up of isoprene units, with each unit having five carbons; therefore, carotenoids can be classified in the chemical class of terpenoids. Carotenoids are mostly tetraterpenoids and are made up of 40 carbon skeletons with a conjugated polyene chain. Condensation of isoprenyl units could synthesize the carotenes (hydrocarbons) or xanthophylls (hydrocarbons containing oxygen). Various colors in fruits and vegetables are due to carotenoid pigments, and these colors are due to the absorption of light by different chain lengths. Carotenoids are isolated from natural resources and synthesized in the laboratory [5]. More than 600 naturally occurring carotenoids are known; however, very few are commercialized. Humans do not have the mechanism to synthesize the carotenoids *de novo*; hence, carotenoids are a required part of the diet and supplements since they perform a huge number of essential biological tasks. Carotenoids are mainly stored in the liver and adipose tissues. However, at greater concentrations, it could accumulate in the adrenal gland, lungs, corpus luteum, and testes. Human plasma and tissue were also found to have an increased number of carotenoids such as phtoene and phytofluene, a colorless substance [6].

α-Carotene

α-carotene is found in dark green foods such as green beans, spinach, and broccoli [7]. After central cleavage, α-carotene converts to one molecule of physiologically active retinol. The conversion effectiveness of β-carotene to vitamin A (retinol) is theoretically higher than that of α-carotene (Fig. **1**). Alpha carotene includes only one retinyl group, whereas beta carotene contains two. Alpha carotene is an equally significant carotene since it has potential antioxidants, anti-cancer, and immunomodulatory properties. Although α-carotene contains provitamin A activity, clinical trials on it are limited due to its connection with β-carotene and the difficulty of isolating it. Carrots have significant levels of α-carotene, which have been linked to increased blood concentrations [8]. It is also found in certain types of squash and pumpkin [9]. One study demonstrated that α-carotene is more effective than β-carotene in reducing the proliferation of human malignant tumour cells [10].

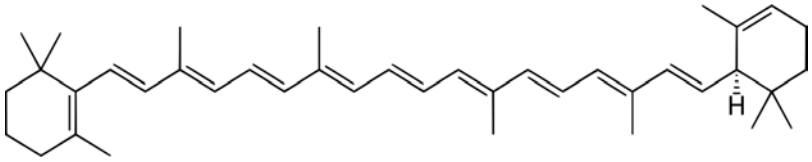

Fig. (1). Chemical structure of α-carotene.

α-carotene has a β-ionone ring at one end and an α-ionone ring at the other end. A study found that greater amounts of α-carotene, all-trans-beta-carotene, and total lycopene were linked to improved cardiac autonomic function. The CVD-stratified research revealed that increasing blood concentrations of alpha-carotene had positive effects on cardiac autonomic dysfunction [11].

β-Carotene

The term β-carotene comes from the Greek word “beta” (β) and the Latin word carota, which means carrot. Beta carotene is a prominent component of the carotenoid family that occurs naturally as a pigment in plants. β-carotene 15, 15′-monooxygenase produces two retinol molecules in the presence of oxygen, making it a significant precursor of vitamin A found in fruits and vegetables [12]. β-carotene is a provitamin that converts into vitamin A through metabolism (Fig. **2**). Apricots, asparagus, carrots, broccoli, Chinese cabbage, grapefruits, beetroot, cantaloupe, pumpkin, sweet potato, pink grapefruit, tomatoes, watermelon, mango, papaya, peaches, prunes, oranges, lettuce, peas, spinach, chilli powder, and paprika are the most common natural sources. β-Carotene has the greatest provitamin A activity, and deficiency can cause xerophthalmia, blindness, and early death [13]. Because of its antioxidant qualities, this nutraceutical has the

CHAPTER 9

Herbs as Nutraceuticals

Mukesh Singh Sikarwar[1,*], Vaibhav Kumar Rathi[2] and **Maulshree Bhandari[3]**

[1] *Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India*

[2] *Department of Pharmacy, Quantum University, Roorkee (Haridwar), Uttarakhand, India*

[3] *Invertis Institute of Pharmacy, Invertis University, Bareilly, Uttar Pradesh, India*

Abstract: Herbal drugs are best utilized as nutraceuticals due to the presence of a variety of phytochemicals. Nutraceuticals are gaining popularity due to their pivotal role in the management of chronic diseases, especially noncommunicable diseases. Inflammation and oxidative stress are the underlying causes for multiple diseases, including diabetes, cardiovascular disease, cancer, and liver diseases. Most of the herbs contain pigments like chlorophyll in leaves, flavonoids in fruits and flowers, tannins in bark (stem and roots), carbohydrates in exudates like gum and mucilage, and alkaloids in different parts of the plants. These phytochemicals are extensively studied for their reactive oxygen species quenching potential and prevention of low-grade inflammation, hence used as nutraceuticals in the prevention and management of diseases as an adjuvant to the primary treatment. This chapter compiles the pharmacognostical and chemical background, including pharmacological and clinical studies on these herbs. Popular herbal drugs like Andrographis, Ashwagandha, Bramhi, Boswellia, fenugreek, garlic, ginger, gingko, ginseng, kelp, milk thistle, psyllium husk, St. John's Wort, turmeric, valerian, spirulina, wheatgrass, chlorella, and Lingzhi mushroom, along with other herbs, are covered in this chapter. Most of these herbs are used as Ayurveda and clinical nutraceuticals; however, the dosage form and dose are key factors for the successful outcome of these nutraceuticals. The marker compounds of the herbs and their percentages in standardized dosage form contribute to their possible role in prevention and treatment.

Keywords: Clinical studies, Drug interaction, Nutraceuticals, Pharmacological use.

INTRODUCTION

Herbal nutraceuticals are plant-derived supplements that enhance well-being and treat illnesses caused by bad dietary choices. Nutraceuticals are extracted from

[*] **Corresponding author Mukesh Singh Sikarwar:** Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India; E-mail: mukeshsikarwar@gmail.com

oils, roots, seeds, berries, or flowers. Herbal nutraceuticals come in many forms, such as capsules, tablets, powders, liquids, and gels. Prebiotics, probiotics, herbal formulations, dietary fiber, proteins, and other natural resources are readily accessible and have a large commercial value. Nutraceuticals are of increasing interest due to their potential nutritional, safety, and therapeutic advantages, potentially altering gene expression, antioxidant defenses, cell proliferation, and mitochondrial integrity [1]. Herbal bioactive components, including flavonoids, terpenoids, saponins, and polyphenols, are vital nutraceuticals with health-promoting therapeutic qualities, typically utilised as dietary supplements in traditional healthcare. The following plants are examined in as much detail as possible as nutraceuticals.

HAWTHORN

Hawthorn, a fragile plant from the Rosaceae family and Crataegus genus, originated from the Mediterranean, North Africa, Europe, and Central Asia. With approximately 200 species worldwide, few, such as C. *oxycantha, C. laevigata, C. monogyna, C. orientalis, and C. pinnatifida*, are well studied or used medicinally (Fig. **1**). Since ancient times, its leaves, flowers, and fruits have been employed in extracts or tinctures. Today, hawthorn is legally acknowledged as an herbal medication in pharmacopoeias of nations including China, England, Germany, and France [2]. Hawthorn preparations are standardized according to the number of flavonoids and oligomeric proanthocyanidins they contain. These compounds have important diuretic, inotropic, and vasodilator properties. Numerous Crataegus species have demonstrated encouraging benefits in treating peripheral vascular disease, hypertension, angina, congestive heart failure, hyperlipidemia, and diabetes mellitus, according to extensive research on both humans and animals [3].

Fig. (1). Hawthorn berries.

Ethnopharmacology of Hawthorn

The hawthorn has been used as a medicine for many years. The berries and leaves were thought to have medicinal properties in the thirteenth century, when they were used to cure digestive disorders like vomiting and diarrhoea. Hawthorn was utilized by the Chinese to treat dyspnoea, regulate hyperlipidaemia, reduce "fullness of the stomach," and enhance digestion by reducing food stasis. Utilization for kidney stones and as a diuretic dates back to the eighteenth century. In Europe, use for a range of cardiovascular conditions was first documented in the late 1800s. Hawthorn was not widely used in American medicine until 1896. These days, hawthorn is mostly utilized as an alternative treatment for several cardiovascular conditions, including hypertension, arrhythmias, angina, the New York Heart Association's (NYHA) functional class II Congestive Heart Failure (CHF), and hyperlipidaemia. The berries, blossoms, and leaves of hawthorn have been considered the plant's most active parts since the 1800s [4].

Chemical Constituents

Hawthorn includes catechins, amines, triterpene saponins, oligomeric procyanidins, and flavonoids (*e.g.*, hyperoside, quercetin, quercitrin, hyperine) as well as flavon-C-glycosides (*e.g.*, vitexin, isovitexin, orientin, isoorientin). Crataegus acid, a triterpene carboxylic acid prevalent in hawthorn berries, is considered to contribute to its coronary vasodilator properties. Amines are presumably inactive after consumption owing to fast breakdown in the stomach. The flavonoids and oligomeric procyanidins are regarded as the key drivers of hawthorn's pharmacological actions. In animal studies, hawthorn increases oxygen consumption, demonstrates positive inotropic action, strengthens blood vessel walls, and promotes coronary blood flow, with flavonoids predominantly responsible for these cardiovascular effects. Human studies imply that increased flavonoid consumption decreases coronary heart disease risk. Additionally, oligomeric procyanidins in hawthorn's leaves and blossoms may inhibit Human Neutrophil Elastase (HNE) and scavenge free radicals, thus minimizing myocardial damage during ischemia and lowering the risk of cardiac failure [5].

Clinical Trials of Hawthorn

Congestive heart failure: Hawthorn has shown potential in treating congestive heart failure in both controlled and uncontrolled clinical investigations. The largest trial to date was an uncontrolled, multicenter, observational investigation of the therapeutic benefits of hawthorn extract WS 1442 (Crataegutt novo 450, Willmar Schwabe) in 1011 patients with NYHA functional class II CHF [6 - 8]. Each individual got one tablet with 84.3 mg of procyanidin twice a day for 24

CHAPTER 10

Synergistic Effects of Dietary Supplements and Nutraceuticals

Mukesh Singh Sikarwar[1,*]

[1] *Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India*

Abstract: Synergism means the interaction of two or more elements that produce a combined effect greater than the sum of their individual effects. In traditional medicine, the concept of holistic medicine utilizes the synergy of phytochemicals in treating mild to complex health conditions. The polyherbal nature of traditional medicine is also deeply rooted in the key concept of synergism. Nutraceuticals are mostly natural products that exhibit medicinal values along with nutritional values, for example, isolated nutrients, herbal products, and processed foods, whereas dietary supplements are specific dietary ingredients such as vitamins, minerals, herbs, amino acids, and enzymes with the goal of providing essential nutrients like vitamins and minerals to support general health. Synergism in nutraceuticals is the interaction of multiple bioactive compounds, ingredients, or nutrients that work together to produce enhanced health benefits compared to their individual effects. The benefits of synergism in nutraceuticals include enhanced therapeutic efficacy, targeted health support, and a broader spectrum of health benefits. The present chapter includes the description of the synergistic effects of fatty acids and antioxidants, vitamin D and vitamin K, vitamin C and zinc, the synergistic effects of piperine, and the synergistic effects of probiotics. Synergistic nutraceuticals pave the way for personalized nutrition *via* advances in nutrigenomics, innovative delivery systems due to nanoencapsulation and liposomal technologies, and holistic approaches due to integrating traditional medicine knowledge with modern research to design synergistic nutraceuticals.

Keywords: Dietary supplements, Holistic medicine, Polyherbal, Synergism.

INTRODUCTION

Synergism is a phenomenon where multiple agents interact to produce a combined effect greater than their individual effects, a concept widely used in fields like medicine, pharmacology, biology, ecology, and technology. In Herbal drugs, the

* **Corresponding author Mukesh Singh Sikarwar:** Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India; E-mail: mukeshsikarwar@gmail.com

polyherbal therapy involves combining multiple compounds to improve therapeutic effects on the same physiological target, like piperine in black pepper, which enhances the bioavailability of curcumin in turmeric. Compounds, like valerian root and hops, work together to enhance the sedative effects *via* additive synergism. Synergistic effects may allow lower dosages of each herb, reducing side effects. Herb synergy emphasizes the significance of holistic approaches in herbal medicine, where the whole is often greater than its parts.

SYNERGISTIC NUTRACEUTICALS

Synergistic nutraceuticals are natural bioactive compounds that work together through pharmacokinetic or pharmacodynamic synergy to enhance their health benefits by acting on similar or complementary biological targets (Fig. **1**).

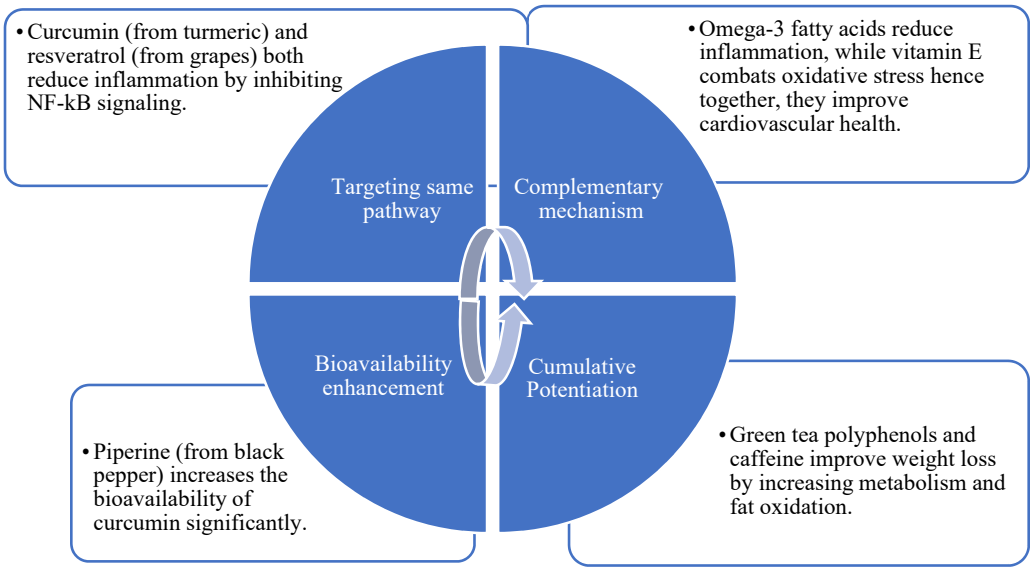

Fig. (1). A general diagram showing different principles of pharmacodynamic synergism in nutraceuticals.

Fatty Acids and Antioxidants

ω-6 Polyunsaturated fatty acids (PUFAs) are essential fatty acids involved in various cellular metabolism. Studies show their antistress activity, including reducing oxidative stress, regulating cyclooxygenase activity, and altering membrane phospholipid composition and receptor function [1]. One of the most important problems with unsaturated lipids is lipid oxidation, which causes radical-initiated oxidative degradation in unsaturated lipids. Off-flavors, harmful aldehydes, and the co-oxidation of proteins and colourants are formed during lipid oxidation. The food industry faces a significant challenge in controlling lipid oxidation due to the complexity of food products and the influence of multiple

elements. This process produces volatile chemicals like aldehydes, ketones, and alcohols, leading to rancidity [2]. Antioxidants are molecules that prevent food product deterioration by minimizing lipid oxidation, scavenging free radicals, chelating metal ions, and quenching singlet oxygen [2]. A study reported that combining Astaxanthin and omega-3 fatty acids individually and in combination protects against oxidative stress *via* the Nrf2-ARE pathway. It is shown that lower concentrations of Astaxanthin show synergistic effects when combined with Docosahexaenoic Acid (DHA) or Eicosapentaenoic Acid (EPA) [3].

Research on synergism was carried out on fatty acid, carotenoid, and tocopherol compositions of 20 Canadian lentil cultivars. Results showed that Carotenoids and tocopherols showed weak correlation with DPPH activity; however, their combination showed good correlation, suggesting they may act synergistically [4]. There have been reports of both synergistic and non-synergistic effects of omega-3 fatty acids and salmon calcitonin on haematological, anti-inflammatory, and antioxidant indices in diabetic rats. The combination of salmon calcitonin and omega-3 fatty acids showed synergistic effects on total bilirubin and antioxidant capacity, but non-synergistic effects on malondialdehyde, uric acid, interleukin-6, lactate dehydrogenase, superoxide dismutase, catalase, glutathione peroxidase, and haematological parameters, comparable to metformin's therapeutic action, which was more or less than that of omega-3 fatty acids [5]. Edible oils lose their qualities and nutritional value as a result of oxidation during production and storage. In order to prevent this oxidation and preserve the nutritional value and biological activity of edible oils, lipophilic antioxidants are essential [6]. A study showed that the oxidative stability of blended oils high in unsaturated fatty acids is improved by combining the natural antioxidants β-carotene, sesamol, and caffeic acid. The primary antioxidant in the early phases of oxidation is β-carotene. The primary antioxidants in the middle and late phases of oxidation are sesamol and caffeic acid [7].

Vitamin D and Vitamin K

Vitamin D, also known as calciferol, is a fat-soluble vitamin found in some foods and supplements. It is produced endogenously when sunlight hits the skin, triggering vitamin D synthesis [8]. Vitamin D, obtained from sun exposure, foods, and supplements, undergoes two hydroxylations in the body for activation. The first hydroxylation occurs in the liver, converting vitamin D to 25-hydroxyvitamin D, or calcidiol, and the second hydroxylation occurs primarily in the kidney, forming the physiologically active 1,25-dihydroxyvitamin D, or calcitriol [9]. Vitamin K is a lipid-soluble vitamin found in two forms: K1 (phylloquinone) and K2 (menaquinones). The derivative without the side chain, called menadione or K3, lacks vitamin K activity. K1, the main form in the liver, is crucial for the

CHAPTER 11

Standardization and Quality Control of Nutraceuticals

Mukesh Singh Sikarwar[1,*] and **Vaibhav Kumar Rathi**[2]

[1] *Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India*

[2] *Department of Pharmacy, Quantum University, Roorkee (Haridwar), Uttarakhand, India*

Abstract: Standardization in nutraceuticals is essential due to biochemical variation in crude drugs influenced by environmental factors, adulteration, substitution, and other factors affecting the quality of crude drugs used in the preparation of nutraceuticals. Standardization is crucial for the safety, efficacy, quality, and consistency of nutraceuticals, which are derived from natural sources and can vary significantly depending on source, processing, and storage. Standardization of nutraceuticals is a regulatory requirement in different countries covered under different guidelines. The European Food Safety Authority (EFSA) controls the nutraceutical sector in Europe; the Dietary Supplement Health and Education Act (DSHEA) 1994 governs it in the United States; the Food for Specified Health Uses (FOSHU) governs it in Japan; and the Food Safety and Standards Authority of India (FSSAI) oversees it in India. This chapter includes the profiles of a few chosen nutraceuticals, including their names and chemical contents. Therapeutic uses, dosages, and forms. The topic also includes WHO recommendations for standardisation and quality control of plant preparations, completed products, and crude pharmaceuticals for their efficacy, safety, and quality.

Keywords: FSSAI, Functional food, Quality control, Standardization, Specified health uses.

INTRODUCTION

Nutraceuticals are naturally derived, bioactive compounds with health benefits. To ensure quality, a systems approach is needed from farm gate to plate, starting with optimizing the agricultural crop and ensuring the quality of functional food products containing nutraceuticals. Phytochemical fingerprinting, employing botanical, farm-site, biodata, and agronomic approaches to identify crops, is the key to standardisation. For ascertaining real-time compliance, standardisation,

[*] **Corresponding author Mukesh Singh Sikarwar:** Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India; E-mail: mukeshsikarwar@gmail.com

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

documentation, and change monitoring in handling, harvesting, processing, and manufacturing, such knowledge requires the establishment of rapid assay methods. Quick tests can also ensure chemical and microbiological safety throughout the shelf life of the product.

Bigger vitamin/mineral companies scaled up their herb business during and after the passage of the 1994 Dietary Supplement Health and Education Act (DSHEA). Due to this, the business from health food stores shifted towards the pharmacies and dollar stores through partnering and buying acquisitions. People in the USA purchased natural medication with the structuring-function assurance, causing dietary supplement consumption in the US to rise from $8 billion in 1993 to $14 billion in 1999. Standardized biomarker products lack pre-market safety testing and FDA approval, causing consumer value issues. Consumers are becoming more educated about these products' differences in market forms [1].

Nutraceuticals' efficacy and safety assessment depend on their raw materials, with traditional foods requiring a toxicity study, while non-traditional ones require a genotoxicity, carcinogenicity, teratogenicity, and 90-day toxicity study [2]. Nutraceutical regulations worldwide are diverse and often unclear, leading to potential danger. Manufacturers and consumers should be aware of their country's regulations to make informed decisions, as information and expectations can be misleading and potentially dangerous [3]. The European Food Safety Authority (EFSA) defines nutraceuticals as food supplements containing vitamins, minerals, and amino acids. They must adhere to Good Manufacturing Practices for quality assurance. In the USA, nutraceuticals are regulated by the Dietary Supplement Health and Education Act (DSHEA), which includes specific regulations for finished supplements and dietary ingredients.

FOOD FOR SPECIFIED HEALTH USES (FOSHU)

By FOSHU, foods are ingredients with health-giving attributes that are officially recognized to have physiological effects in individuals.

Types of FOSHU

Qualified FOSHU: Foods with health benefits but which have not been demonstrated at the FOSHU level, or for which there is some efficacy but no action mechanism for the beneficial ingredient, will be permitted to qualify as qualified FOSHU. Standardised FOSHU: Foods having sufficient FOSHU certification and accumulated evidence are subject to standards and specs. Standardised FOSHU that meets standards and requirements is authorized.

The reducing the risk of disease FOSHU: If there is clinical and nutritional evidence to support an ingredient's disease risk-reducing claim, then it is granted approval [4]. In India, the Food Safety and Standards Authority of India regulates the nutraceutical industry, with proposed 2022 regulations aiming to enhance safety, labelling, and quality control. To comply with FSSAI regulations, manufacturers must obtain approval before marketing their products. Consumer confidence can be strengthened by requesting independent testing in third-party laboratories. Transparency is also crucial, with easy-to-understand labelling about nutraceuticals' composition and effects [3].

Indian food business operators are allowed to declare flavour additions on the label of a product in accordance with the Food Safety and Standards (Labelling and Packaging) Regulations, 2011, by virtue of the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food, and Novel Food) Regulations, 2016. Tablets, capsules, and syrups should comply with the general quality requirements and regulations as provided in the Indian Pharmacopoeia, British Pharmacopoeia, or United States Pharmacopoeia. As per the Indian Council of Medical Research, the level of nutrients added to foods cannot exceed the daily recommended intake. International food standard bodies like the Codex Alimentarius Commission use it if no standards are available. The highest nutritional value for any health supplement category is 15% of a day's intake. Food business operators are authorized to use food colouring, but with some restrictions. Articles intended for the correct age groups, sexes, and physiological phases must supply the necessary number of calories, protein, vitamins, minerals, and other essential elements for standard nutrient or nutritionally complete formulations for the correct age groups, sexes, and physiological phases. Purity standards for food ingredients to be used in food articles should be established and notified by the Food Authority. The permissible limit of variation in food articles covered under these regulations is not more than 10% from the value declared on the label of nutrients or nutritional ingredients. Production of ingredients and products should be in accordance with good manufacturing practices established [5].

Nutraceuticals' yearly growth rate in India was determined to be 25%, comparable to that of the developed nation of Japan. According to this perspective, a large number of new businesses have started producing nutraceuticals in India. The growing demand for nutraceuticals in India suggests their potential for disease prevention and treatment. Therefore, regulatory authorities must ensure product quality and safety to minimize adverse events like toxicity, adulteration, misuse, and overdose. As food products are transported across borders, maintaining safety and quality standards is crucial. New and existing companies should follow FSSAI's regulatory guidance to ensure the best use of nutraceuticals [6]. Quality

CHAPTER 12

Current Regulations and Clinical Applications of Nutraceuticals

Khian Giap Lim[1], Nazmun Nahar Alam[2] and **Arunachalam Muthuraman[3,*]**

[1] *Clinical Pharmacy and Pharmacy Practice Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia*

[2] *Faculty of Medicine, AIMST University, Bedong 08100, Kedah, Malaysia*

[3] *Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia*

Abstract: The global nutraceutical market has a higher impact, and in the coming decades, it will become a multibillion-dollar business. Nutraceuticals are comprised of multiple diverse food product categories, including vitamins (water and fat-soluble); micro and macronutrients, essential fatty acids, prebiotics and probiotics, phytochemicals, and herbs. Pharmacological aspects, nutraceuticals, and dietary supplements possess synergistic effects. However, standardization and quality control checking of nutraceuticals can be useful for the safe and effective management of illness in clinical settings. The key driving forces of nutraceutical usage in clinical applications are wider due to its possible usage over a longer period, ease of administration to aged populations, compatibility with consumer lifestyle, and a higher rate of cost-benefits. However, the major challenges regarding safety and efficacy concern the scientific evidence and rationality-based therapy in clinical trials. This kind of study may reach out to the patient with consistent and well-defined regulatory clearance, and it provides greater opportunities for growth and expansion, and encourages nutraceutical applications in a clinical setup. Hence, this book chapter focused on expressing the possibilities and current perspectives of nutraceuticals for clinical applications.

Keywords: Chelation, Fenton reactions, Mammalian target of rapamycin, Mitochondrial protection, Natural health products, Nuclear factor kappa B.

INTRODUCTION

Nutraceuticals like dietary supplements and their isolated products are commercialized for medicinal use, and it is claimed that they produce physio-

* **Corresponding author Arunachalam Muthuraman:** Pharmacology, Toxicology, and Basic Health Sciences Unit, Faculty of Pharmacy, AIMST University, Bedong 08100, Kedah, Malaysia; E-mail: muthuraman.a@aimst.edu.my

Mukesh Singh Sikarwar, Arunachalam Muthuraman & Sohrab A. Shaikh (Eds.)

logical benefits and also support chronic disorders [1]. However, the major questions raised by the scientific community are about the evidence of the molecular mechanism and chemical structure of the responsible compounds. Sometimes, nutraceuticals fail to address the scientific evidence for the management of chronic disorders due to their multi-functional (pleiotropic) physiological/pharmacological actions, mechanisms of action, and safety and efficacy in clinical conditions [2]. Hence, numerous studies are required to establish the use of nutraceuticals in various chronic disorders in clinical conditions. Therefore, the challenges and therapeutic action of nutraceuticals in chronic disorders and the use of nutraceuticals with evidence-based clinical applications in various disorders can be warranted [3]. The basic approaches of clinical applications of nutraceuticals are categorized into nutrition, pharmaceuticals, and nutraceutical products [4]. Nutrition products provide support for essential physiological functions, and they are required daily. Pharmaceutical products provide the mitigation/treatment of abnormal physiological functions, and they are required in pathological conditions. Nutraceutical products play both functions and also produce the enhancement of physiological function and fight against the progression of the disease [5]. Hence, the net effects are producing the maximal benefits and more safety and efficacious action in clinical conditions.

The classification of nutraceuticals is wider, *i.e.*, vitamins (water and lipid-soluble vitamins); micro/macronutrients; essential fatty acids; pre- and probiotics; and phytochemicals (herbs). The broader definition of nutraceuticals is known as optimized food products with health benefits and treats chronic disorders [6, 7]. More precisely nutraceuticals are also considered non-nutrient secondary metabolites type of nutraceuticals *i.e.*, such as terpenoids, polyphenols, and glucosinolates, illustrated in Fig. (**1**). It has synergistic, agonistic, and antagonist actions. The standardization, quality control, and clinical benefits of nutraceuticals are well established [8]. However, the approval and recognition of the use of nutraceuticals in clinical conditions remains to be established with more scientific evidence. However, the regulatory process to approve the nutraceuticals in clinical conditions remains delayed and questionable. Certain regulatory bodies have started to approve nutraceuticals in various clinical conditions for the management of various disorders [9].

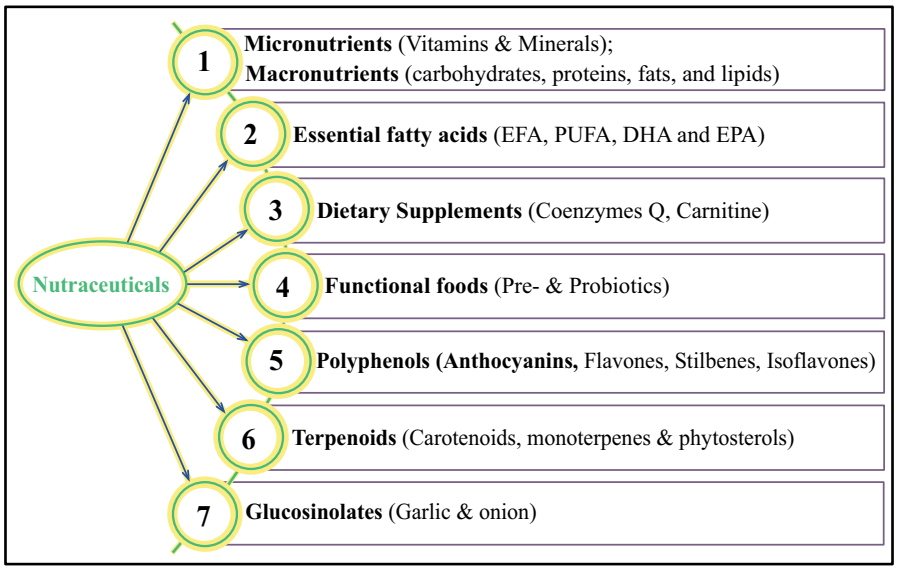

Fig. (1). Classification of nutraceuticals (Nutrient and non-nutrient types). *Abbreviations:* DHA, Docosahexaenoic Acid; EFA, Essential Fatty Acids; EPA, Eicosapentaenoic Acid; and PUFA, Polyunsaturated Fatty Acids.

Nutraceuticals have organ-protective roles in various disorders like cardiovascular diseases (hypertension, atherosclerosis), metabolic disorders (diabetes mellitus), arthritis, obesity, and cancer. Hence, it is also known as preventive medicine [10, 11]. Nevertheless, the legislation for the sales, marketing, safety, and efficacy of nutraceuticals in various regions around the world with cultural influence is a challenge [12]. This chapter discussed and summarized the use of nutraceuticals with regulatory requirements in various regions of the world. From the regulatory perspective, nutraceuticals are classified according to the regulatory framework and nutraceutical policy of the specific country [13]. Canada considers Natural Health Products (NHPs) and supplemented foods to be nutraceuticals. However, the European Food Safety Authority, the USA Food and Drug Administration (FDA), and Health Canada agencies allow use in clinical conditions based on the strength of scientific evidence and evaluation reports [9, 14]. Evidence-based medicines are integrated based on the available evidence for the decision-making process with Randomized Clinical Trials (RCTs). RCT permits a strong correlation between the interventions and outcomes [15].

Furthermore, RCT plays a central role in the regulatory process for the approval of drugs and health claims of nutraceuticals. However, the limitation of this RCT method of drug evaluation model is either sensitive or not relevant to nutraceuticals due to i) the inability of true placebos applications; ii) the effect size of healthy populations are often modest conditions; iii) the analysis with

SUBJECT INDEX

F

G

H

I

K

L

M

N

O

P

Q

R

S

T

V

X

Z

Mukesh Singh Sikarwar

Dr. Mukesh Singh Sikarwar is currently working as Professor and Deputy Director at Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India. He received his PhD in Pharmacy from KLE University, Belgaum, India, in 2011. He served as a Senior Lecturer and Associate Professor at AIMST University, Malaysia, from 2013 to 2021. His current areas of research are herbal antioxidants, antidiabetics and antihyperlipidemics, novel drug delivery in herbal drugs, formulation and evaluation of herbal drugs, and food safety. He has published 76 research and review papers in various peer-reviewed international and national journals and also serves as a reviewer for many international journals. He has presented 36 research papers at various national and international conferences. He is a life member of APTI, a Board of Director member of the Asian Society of Pharmacognosy, a member of the Asian Council of Science Editors, and is registered as a pharmacist with the M.P. State Pharmacy Council, India.

Arunachalam Muthuraman

Dr. Arunachalam Muthuraman is currently working as an Associate Professor at AIMST University, Malaysia. He received his PhD in Pharmacy from Punjabi University, Patiala, India, in 2012. His current area of research is the screening of various lead compounds and newer herbal medicines for the management of diabetic retinopathy, vascular dementia, Alzheimer's disease, Parkinson's disorders, stroke, and neuropathic pain disorders. He has published 85 international research papers and 18 review papers in various peer-reviewed international and national journals and also serves as a reviewer for many international journals. He has also published 02 books and 24 international book chapters. He is also a recipient of various prestigious awards, including World Top 1% Neuroscientist ("Expert in Neuralgia-2021"); Outstanding Scientist Award (2021); Best Faculty Award (2019); Dr. APJ Abdul Kalam Teaching Excellence Award (2019); Dr. APJ Abdul Kalam Research Excellence Award (2018); Dr. APJ Abdul Kalam Young Scientist Award (2017); Sushruta Best Young Scientist Award for Medicine (2018); and Young Scientist Award (2013). He received the "Extramural Research Project" grant (Rs. 20 lakhs) from the Council of Scientific and Industrial Research, New Delhi, India. He received the Malaysian FRGS project grant (RM 189,800) in 2019 from the Ministry of Education, Malaysia. Currently, he has received another FRGS grant (RM 163,500) in 2021 from the Ministry of Education, Malaysia. He is a life member of the Indian Pharmacological Society, Association of Pharmacy Professionals, Association of Pharmaceutical Teachers of India, ACS Network, and Vice President of the International Association of Pharmaceutical Scientists and Educators (APSE). He is a registered pharmacist in the Tamil Nadu State Pharmacy Council (9764 A1), India.

Sohrab A. Shaikh

Dr. Sohrab A. Shaikh is an Assistant Professor at the Faculty of Pharmacy, AIMST University, Bedong, Kedah, Malaysia. He received his Ph.D. in Pharmacy from AIMST University, Malaysia, in 2024. With over 17 years of academic experience, he specializes in teaching Pharmacology and pharmacy-related courses. His current research focuses on the pharmacological evaluation of natural antioxidants in animal models of neurological disorders, including vascular dementia, depression, and anxiety. His scholarly contributions include publications in national and international journals, presentations at prestigious conferences, and authorship of book chapters and review articles. He has successfully secured internal research grants from AIMST University, Malaysia, and has served as a project leader for a Malaysian FRGS grant. He is a registered pharmacist with the Maharashtra State Pharmacy Council, India, and a life member of the Association of Pharmaceutical Teachers of India.