

Bioactive Nutrients as Dietary Supplements and Therapeutic Agents

Bioactive Nutrients as Dietary Supplements and Therapeutic Agents:

*An Introduction to
Nutraceuticals*

By

Asma Saeed and Saeed Iqbal Zafar

**Cambridge
Scholars
Publishing**



Bioactive Nutrients as Dietary Supplements and Therapeutic Agents:
An Introduction to Nutraceuticals

By Asma Saeed and Saeed Iqbal Zafar

This book first published 2024

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

Copyright © 2024 by Asma Saeed and Saeed Iqbal Zafar

All rights for this book reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the copyright owner.

ISBN (10): 1-5275-8616-2

ISBN (13): 978-1-5275-8616-1

TABLE OF CONTENTS

List of Tables	xvii
List of Figures.....	xx
Foreword	xxiii
Preface	xxv
Keywords.....	xviii
Acknowledgements and Dedication	xxix
Chapter 1	1
Concepts to Define and Describe Nutraceuticals	
Conceptual principals.....	1
Concept of food through the evolutionary ladder	5
Ordinary food	6
Conventional food	6
Infant formulas	6
Superfood	7
Functional food	7
Food with health claims	8
Dietary supplement	9
Enteral and parenteral clinical nutrition foods	9
Medical food	9
Nutraceuticals.....	10
Complementary medicines	10
Bioactive substances	10
Biologically active food supplements	10
Why nutraceuticals to substitute pharmaceuticals	11
Categories of nutraceuticals	12
Nutrients	13
Herbals	13
Dietary supplements.....	14
Traditional and non-traditional nutraceuticals.....	14

Dietary fibers.....	15
Prebiotics.....	16
Probiotics.....	17
Essential (Polyunsaturated fibers; PUFA) fatty acids	17
Antioxidants	18
Phenolics	19
Flavonoids-anthocyanins.....	20
Orphan drug act and the growth of nutraceuticals industry	21
Carnitine, a two-in-one: a pharmaceutical and a nutraceutical	24
References.....	30
Chapter 2.....	44
Worldwide Legislation on Nutraceuticals	
Background to nutraceutical legislation.....	44
Australia and New Zealand.....	46
Brazil.....	49
Canada	50
European Union	52
India	54
Japan	56
Malaysia.....	58
Pakistan.....	59
Peoples Republic of China.....	60
Russia.....	62
Singapore	63
United States	64
References.....	71
Chapter 3.....	76
Vitamins as Bioactive Molecules	
Vitamins; A general background	77
Vitamin A	82
Chemical nature	82
Permitted health benefits claims.....	82
Physiological role.....	83
Recommended daily allowance.....	85
Deficiency symptoms.....	85
Toxicity symptoms.....	87
Natural plant and animal sources	88
Supplements	88

Vitamin B ₁ ; Thiamine	88
Chemical nature	88
Permitted health benefits claims.....	89
Physiological role	90
Recommended daily allowance.....	90
Deficiency symptoms.....	90
Toxicity symptoms.....	91
Natural plant and animal sources	91
Supplements	92
Vitamin B ₂ ; Riboflavin	92
Chemical nature	92
Permitted health benefits claims.....	92
Physiological role	92
Recommended daily allowance.....	93
Deficiency symptoms.....	94
Toxicity symptoms.....	94
Natural plant and animal sources	94
Supplements	94
Vitamin B ₃ ; Niacin.....	94
Chemical nature	94
Permitted health benefits claims.....	95
Physiological role	95
Recommended daily allowance.....	95
Deficiency symptoms.....	97
Toxicity symptoms.....	97
Natural plant and animal sources	97
Supplements	97
Vitamin B ₅ ; Pantothenic acid.....	98
Chemical nature	98
Permitted health benefits claims.....	98
Physiological role	99
Recommended daily allowance.....	99
Deficiency symptoms.....	99
Toxicity symptoms.....	99
Natural plant and animal sources	99
Supplements	100
Vitamin B ₆ ; Pyridixine.....	100
Chemical nature	100
Permitted health benefits claims.....	100
Physiological role	100
Recommended daily allowance.....	101

Deficiency symptoms.....	101
Toxicity symptoms.....	102
Natural plant and animal sources	102
Supplements	102
Vitamin B ₇ ; Biotin	102
Chemical nature	102
Permitted health benefits claims.....	102
Physiological role.....	102
Recommended daily allowance.....	103
Deficiency symptoms.....	103
Toxicity symptoms.....	103
Natural plant and animal sources	103
Supplements	103
Vitamin B ₉ ; Folic acid	104
Chemical nature	104
Permitted health benefits claims.....	104
Physiological role.....	104
Recommended daily allowance.....	105
Deficiency symptoms.....	105
Toxicity symptoms.....	106
Natural plant and animal sources	106
Supplements	106
Vitamin B ₁₂ ; Cyanocobalamin	106
Chemical nature	106
Permitted health benefits claims.....	106
Physiological role.....	106
Recommended daily allowance.....	108
Deficiency symptoms.....	108
Toxicity symptoms.....	108
Natural plant and animal sources	108
Supplements	108
Vitamin C; Ascorbic acid.....	109
Chemical nature	109
Permitted health benefits claims.....	109
Physiological role.....	109
Recommended daily allowance.....	110
Deficiency symptoms.....	110
Toxicity symptoms.....	111
Natural plant and animal sources	111
Supplements	111

Vitamin D	111
Chemical nature	111
Permitted health benefits claims.....	112
Physiological role.....	112
Recommended daily allowance.....	113
Deficiency symptoms.....	113
Toxicity symptoms.....	114
Natural plant and animal sources	114
Supplements	114
Vitamin E.....	115
Chemical nature	115
Permitted health benefits claims.....	115
Physiological role.....	115
Recommended daily allowance.....	116
Deficiency symptoms.....	116
Toxicity symptoms.....	116
Natural plant and animal sources	117
Supplements	117
Vitamin K	117
Chemical nature	117
Permitted health benefits claims.....	118
Physiological role.....	118
Recommended daily allowance.....	118
Deficiency symptoms.....	118
Toxicity symptoms.....	120
Natural plant and animal sources	120
Supplements	120
Choline.....	120
Physiological functioning.....	121
Choline deficiency symptoms	125
Sources of choline	125
Choline toxicity symptoms.....	126
Supplements	127
References.....	127
Chapter 4.....	145
Essential Minerals as Dietary Macronutrients and Micronutrients	
Calcium.....	150
Health benefits and disease risk reduction claims	150
Physiological role.....	152
Recommended daily allowance.....	153

Deficiency symptoms.....	153
Toxicity symptoms.....	154
Natural plant and animal sources	155
Supplements	155
Magnesium	155
Health benefits and disease risk reduction claims	155
Physiological role.....	156
Recommended daily allowance.....	156
Deficiency symptoms.....	157
Toxicity symptoms.....	158
Natural plant and animal sources	158
Supplements	158
Phosphorous.....	159
Health benefits and disease risk reduction claims	159
Physiological role.....	159
Recommended daily allowance.....	160
Deficiency symptoms.....	160
Toxicity symptoms.....	160
Natural plant and animal sources	161
Supplements	161
Potassium	162
Health benefits and disease risk reduction claims	162
Physiological role.....	162
Recommended daily allowance.....	163
Deficiency symptoms.....	163
Toxicity symptoms.....	164
Natural plant and animal sources	164
Supplements	164
Sodium.....	165
Health benefits and disease risk reduction claims	165
Physiological role.....	166
Recommended daily allowance.....	168
Deficiency symptoms.....	168
Toxicity symptoms.....	168
Natural plant and animal sources	169
Chromium	170
Health benefits and disease risk reduction claims	170
Physiological role.....	171
Recommended daily allowance.....	171
Deficiency symptoms.....	171
Toxicity symptoms.....	172

Natural plant and animal sources	172
Supplements	172
Copper.....	173
Health benefits and disease risk reduction claims	173
Physiological role	174
Recommended daily allowance.....	175
Deficiency symptoms	176
Toxicity symptoms.....	176
Natural plant and animal sources	176
Supplements	177
Fluoride.....	177
Health benefits and disease risk reduction claims	177
Physiological role	178
Recommended daily allowance.....	179
Deficiency symptoms	179
Toxicity symptoms.....	179
Natural plant and animal sources	180
Supplements	180
Iodine	181
Health benefits and disease risk reduction claims	181
Physiological role	181
Recommended daily allowance.....	183
Deficiency symptoms	183
Toxicity symptoms.....	184
Natural plant and animal sources	184
Supplements	184
Iron.....	185
Health benefits and disease risk reduction claims	185
Physiological role	185
Recommended daily allowance.....	186
Deficiency symptoms	187
Toxicity symptoms.....	187
Natural plant and animal sources	188
Supplements	188
Manganese	189
Health benefits and disease risk reduction claims	189
Physiological role	189
Recommended daily allowance.....	190
Deficiency symptoms	191
Toxicity symptoms.....	191
Natural plant and animal sources	192

Supplements	192
Molybdenum	192
Health benefits and disease risk reduction claims	192
Physiological role	193
Recommended daily allowance	194
Deficiency symptoms	194
Toxicity symptoms	194
Natural plant and animal sources	195
Supplements	195
Selenium	195
Health benefits and disease risk reduction claims	195
Physiological role	196
Recommended daily allowance	197
Deficiency symptoms	197
Toxicity symptoms	198
Natural plant and animal sources	198
Supplements	199
Zinc	199
Health benefits and disease risk reduction claims	199
Physiological role	200
Recommended daily allowance	201
Deficiency symptoms	201
Toxicity symptoms	202
Natural plant and animal sources	202
Supplements	203
References	203
Chapter 5	236
Functional Foods, Nutraceuticals, and Dietary Supplements:	
Dietary Fiber with Health Claims	
Dietary fiber in the food	236
Definitions and the physiological role of dietary fiber	236
Types of dietary fibers	241
Viscous dietary fiber	242
Functional dietary fiber	242
Health benefits of dietary fiber	244
Immunity and inflammation	245
Gastrointestinal functions	245
Cardiovascular disease	247
Glycemic control and diabetes type-2	248
Management of obesity and body weight	248

Fibers available in the market as dietary supplements	249
Inulins and fructooligosaccharides	249
Chitosan (= Quitosane).....	251
Vegetable gum fiber supplements	251
β -Glucans	253
Pectins	254
Psyllium husk	255
Wheat/resistant dextrin.....	256
Methylcellulose	257
Calcium polycarbophil	257
Polydextrose.....	259
References.....	260
Chapter 6.....	271
Prebiotics, Probiotics, and Synbiotics as Nutraceuticals	
Intestinal microbiota	271
Gut environment for the microbiota life	272
Stomach.....	273
Small intestine.....	274
Large intestine.....	276
Conditions imposing change in the microbiota profile in the gut environment.....	277
Role of gut microbiota in maintaining human health.....	277
Protective.....	277
Structural and histological.....	278
Metabolic.....	279
Dysbiosis	279
“...biotics”: different manifestations	280
Antibiotics	280
Prebiotics.....	281
Probiotics.....	282
Synbiotics	282
Prebiotics	283
Fermentable fibers as prebiotics.....	284
The nature and production of prebiotics.....	288
Health benefits of prebiotics.....	291
Colonic microbiota and fermentation of prebiotics	291
Physiologic effects of short-chain fatty acids.....	293
Probiotics	295
Probiotic microbes, and food products.....	296
Probiotics in health and disease.....	297
Mechanism of probiotic action.....	301

Synbiotics	306
References.....	310
Chapter 7.....	330
Essential Fatty Acids, Vegetable Oils, and Bioactive Phytochemicals	
Essential fatty acids.....	330
Linoleic acid.....	334
Linolenic acid.....	335
Gamma (γ)-linolenic acid.....	335
Alpha (α)-linolenic acid	336
Docosahexaenoic acid	337
Eicosapentaenoic acid	338
Arachidonic acid	338
Vegetable oils with health benefits	340
Olive oil.....	341
Corn oil	342
Sunflower oil	343
Canola oil	344
“Bad fats”	346
<i>Trans</i> fats (technically correct nomenclature: fatty acids)	347
Triglycerdides	349
Saturated fats.....	350
Cholesterol	352
Phytosterols and phytostanols	356
Phospholipids – phosphatidylcholine.....	360
Phosphatidylserine	364
References.....	366
Chapter 8.....	391
Bioactive Phytochemicals in Fruits and Vegetables	
Carotenoids; fruit and vegetable pigments.....	392
Lutein and zeaxanthin in drak green leafy vegetables	399
Lycopene and tomatoes.....	403
Resveratrol from grapes and small berries.....	409
Organosulphur compounds in vegetables	412
Organosulphur compounds of garlic	413
Isothiocyanates of cruciferous vegetables	417
Indole-3-carbinol and 3,3'-diindolylmetane of cruciferous vegetables	420
Curcumin in turmeric.....	423
Soy protein and isoflavones (phytoestrogens)	429

Lignans	435
Flavonoids.....	438
Anthocyanins	447
Ellagic acid	455
Green tea; epigallocatechin-3-gallate (EGCG).....	460
References.....	465
Chapter 9.....	531
Fruits and Vegetables: “Nature’s Multinutraceutical Capsules”	
How fruits and vegetables impact on health	533
Dietary phytochemicals and cardiovascular disease.....	534
Dietary phytochemicals and cancer.....	537
Role of dietary fiber in several diseases	537
Consumption of fruits and vegetables reduces the risk of mortality and lowers the risk of multimorbidity	541
Lower risk of mortality as associated with the consumption of fruits and vegetables.....	542
Lower risk of multimorbidity as associated with the consumption of fruits and vegetables.....	543
Campaigns on health benefits of fruits and vegetables	545
Australia: “Go for 2&5”	546
Canada: “Eating well with Canada’s food guide”	548
European Union	552
United Kingdom: “Five a Day Eatwell Plate”	556
United States: “ChooseMyPlate”	558
WHO-FAO: Fruit and vegetable promotion initiative.....	563
Fruits and vegetables in the prevention of disease	567
Cardiovascular disease	568
Stroke	571
Hypertension; high blood pressure.....	573
Diabetes mellitus type 2	574
Bone health, osteoporosis, and osteoarthritis	575
Rheumatoid arthritis.....	578
Eye diseases: cataracts, glaucoma, and macular degeneration	578
Bowel health and diverticulitis.....	581
Chronic obstructive pulmonary disease.....	582
Asthma	583
Neurodegenerative diseases	584
Cancer	585

Strength of fruit and vegetable linked reduction of chronic diseases.	590
Coronary heart disease	590
Hypertension	590
Stroke	590
Cancer	591
Type 2 diabetes mellitus.....	591
Osteoporosis.....	591
Chronic obstructive pulmonary disease (COPD)	591
Asthma	591
Rheumatoid arthritis.....	591
Eye diseases	591
Obesity	591
Chronic inflammatory bowel diseases (CIBD)	592
Dementia	592
Nuts: rich sources of “good” fats and bioactive nutrients	592
Walnuts	598
References.....	600
Chapter 10.....	636
Proposed Extended Definition of Nutraceuticals	
Extended definition of nutraceuticals.....	638

LIST OF TABLES

Table 2.1. Comparative summary of the legal status of nutraceuticals in different countries.....	67
Table 3.1. Vitamins with their health benefits claims and disease reduction claims in different countries	79
Table 3.2. Natural sources known to be rich in vitamins	81
Table 3.3. Recommended dietary allowance (RDAs) of different vitamins by age-group stages	86
Table 4.1. Recommended dietary allowance (RDAs) of different minerals by age-group stages	146
Table 4.2. Natural sources known to be rich in minerals	148
Table 4.3. Minerals with health benefits claims and disease-reduction claims as permitted in different countries.....	150
Table 5.1. Classification of fiber as food ingredients	237
Table 5.2. Some natural sources of soluble and insoluble dietary fibers.....	240
Table 5.3. Dietary fiber with their health benefits claims and disease-reduction claims as permitted in different countries.....	244
Table 6.1. Prebiotic fiber content, their natural sources, and the amount required to meet the recommended daily need of prebiotics	285
Table 6.2. Natural sources, branded products, and chemical nature of some fermentable fibers.....	286
Table 6.3. Some probiotic food products	296

Table 6.4. Some probiotic microorganisms, their branded names, and commercial producers.....	299
Table 6.5. Some clinical applications of probiotic bacteria	302
Table 6.6. Some prebiotic-probiotic combinations in synbiotic relationships.....	307
Table 7.1. Essential fatty acids, vegetable oils, and lipids-related bioactive compounds with their health benefits claims and disease-reduction claims as permitted in different countries	333
Table 7.2. Comparative fatty acids profile of vegetable oils most used as dietary constituents (percent by weight of total fat)	340
Table 8.1. Phytochemicals and natural resources rich in phytochemicals with their health benefits claims and disease-reduction claims as permitted in different countries.....	392
Table 8.2. Various diseases against which curcumin may have therapeutic effects	426
Table 8.3. Physiological functions performed in the human body by different constituents of soybeans	430
Table 8.4. Approval status of health claims for soy protein in different Countries	434
Table 8.5. Classification of flavonoids into their major sub-classes, principal dietary flavonoids, and their rich sources	442
Table 9.1. Phytochemicals present in fruits and vegetables with their functions in promoting health and preventing disease.....	535
Table 9.2. Types of dietary fiber, their sources, and beneficial effects on health	540
Table 9.3. Average nutrient energy, and saturated, monounsaturated, polyunsaturated, linoleic and α -linolenic fatty acid contents of different kinds of nuts (g per 100 g fresh weight of nuts unless noted otherwise)....	595

Table 9.4. Average nutrient content of protein, fiber, folate, polyphenols, calcium, magnesium, and potassium in different kinds of nuts per 100 g fresh weight of nuts) 596

LIST OF FIGURES

Figure 1.1. (a) The concept of nutraceuticals; (b-f) some nutraceutical bioactive molecules and their natural sources	5
Figure 1.2. Structure of L-carnitine and acetyl-L-carnitine	26
Figure 3.1. Structure of retinol, retinal, retinoic acid and β -carotene	84
Figure 3.2. Structure of vitamin B ₁ or thiamine and thiamine pyrophosphate.....	89
Figure 3.3. Structure of vitamin B ₂ or riboflavin.....	93
Figure 3.4. Structure of nicotinamide adenine dinucleotide (NAD) and vitamin B ₃ or niacin.....	96
Figure 3.5. Structure of vitamin B ₅ or pantothenic acid and coenzyme A	87
Figure 3.6. Structure of pyridoxal 5'-phosphate and vitamin B ₆ or pyridoxine.....	101
Figure 3.7. Structure of vitamin B ₇ or biotin	103
Figure 3.8. Structure of vitamin B ₉ or folic acid.....	104
Figure 3.9. Structure of vitamin B ₁₂ or cyanocobalamin	107
Figure 3.10. Structure of vitamin C or ascorbic acid	109
Figure 3.11. Structure of vitamin D ₂ or ergocalciferol and vitamin D ₃ or cholecalciferol.....	113
Figure. 3.12. Structure of vitamin E; α -tocopherol and vitamin E; γ -tocopherol.....	115
Figure 3.13. Comparative structural forms of vitamins K1 and K2 (MK-4 and MK-7)	119

Figure 3.14. Structure of (a) Choline; (b) Acetylcholine and (c) Lecithin.....	122
Figure 5.1. Structure of inulin and fructooligosaccharide.....	250
Figure 5.2. Structure of chitosan (classified as a biopolymer).....	252
Figure 5.3. Structure of β -Glucan	254
Figure 5.4. Structure of pectin	255
Figure 5.5. Structure of dextrin.....	257
Figure 5.6. Structure of methylcellulose.....	258
Figure 5.7. Structure of calcium polycarbophil	258
Figure 5.8. Structure of polydextrose	259
Figure 7.1. Structure of linoleic acid and oleic acid	334
Figure 7.2. Structure of docosahexaenoic acid, eicosapentaenoic acid, alpha-linolenic acid and gamma-linolenic acid	336
Figure 7.3. Structure of arachidonic acid.....	339
Figure 7.4. General structural formula of vegetable oils	341
Figure 7.5. Structure of cholesterol	352
Figure 7.6. Structure of cholesterol and phytosterol: pampesterol	357
Figure 7.7. Structure of phosphatidylcholine.....	361
Figure 7.8. Structure of phosphatidylserine.....	364
Figure 8.1. Structure of β -carotene ($C_{40}H_{56}$).....	394
Figure 8.2. Structure of β -cryptoxanthin ($C_{40}H_{56}O_2$).....	395
Figure 8.3. Structure of lycopene ($C_{40}H_{56}$)	404
Figure 8.4. Structure of resveratrol ($C_{14}H_{12}O_3$)	410
Figure 8.5. Structure of alliin, allicin and ajoene.....	414

Figure 8.6. Structure of phenyl isothiocyanate and sulphoraphane	418
Figure 8.7. Structure of indole-3-carbinol (C_9H_9NO)	421
Figure 8.8. Structure of curcumin ($C_{21}H_{20}O_6$)	424
Figure 8.9. Mammalian lignans (1) enterodiol, and (2) enterolactone....	437
Figure 8.10. Structure of flavons, flavonols, flavonones, flavanols, isoflavones, and anthocyanidins	439
Figure 8.11. Structure of delphinidin, malvidin, cyanidin-3-glucoside and Pelargonidin	447
Figure 8.12. Structure of ellagic acid ($C_{14}H_6O_8$) and gallic acid ($C_7H_6O_5$)	456
Figure 8.13. Structure of ellagitannin (phyllanthin) of <i>Phyllanthus amarus</i>	458
Figure 8.14. Structure of epigallocatechin gallate ($C_{22}H_{18}O_{11}$).....	461

FOREWORD

As many as 24 centuries hence, the Greek physician Hippocrates, regarded as the father of modern medicine, commenced telling his patients circa 400 BC to “let food be thy medicine and medicine thy food”. This concept, only three decades ago, was given a scientific term by DeFelice in 1989 as “*Nutraceuticals*”, having been partly derived from two words **nutrition** and **pharmaceutical** with a prefix and a suffix, respectively, borrowed from each. The term has since found a place in English language and scientific dictionaries, such as the Oxford Dictionary as “another term for functional food” noting the year 1990 as its origin, and in Merriam-Webster Dictionary as “a specially treated food, vitamin, mineral, herb, etc., that you eat or drink to improve your health”. In substance, nutraceuticals refer to such natural materials and sources that as bioactive nutrients function as dietary supplements and therapeutic agents.

Since its emergence as a new term, interest of researchers in nutraceuticals has continued unabated as evident from the huge pile-up of research literature and review articles on new nutraceutical substances and resources, their health benefits, and result of epidemiological studies, and clinical trials. As a result, an array of popular products, such as probiotics, dietary fibers and prebiotic, herbal and non-herbal extracts, vitamins and minerals, phytochemicals, fruits and vegetables ingredients, and bioactive phyto-lipids have remained the focus of considerable research. Indeed, nutraceuticals and functional foods have gained considerable merit in terms of human health and global business. The worldwide demand of nutraceuticals has touched US \$ 205 billion during 2017 with the projected annual growth rate of 6.4%. Likewise, the global market in probiotics, as subsector of nutraceuticals, has reached to US \$ 40 billion during 2018. An important factor in the market growth of nutraceuticals is the upward trend of aging population. Anti-aging and age-defying properties, perceived gentleness, and health promoting effects are major key drivers of the phenomenal growth in nutraceutical industry, and their popularity.

An increase in the global healthcare costs are also expected to attract more attention on preventive and prophylactic healthcare, self-diagnosis, and self-medication. Furthermore, here is a tendency in human beings to place more trust on natural products, evident from the fact that over 74% of Americans believe that “natural” means healthier. An increasing interest

in nutraceuticals also stems as consumers learn more about epidemiological studies indicating a specific diet, such as Mediterranean diet, or certain dietary components, such as polyphenols, are associated with lower risk of certain diseases. Another, factor for the market upsurge of dietary supplements containing vitamins and minerals is greater awareness of their essential needs, following the post-1997 charting of their dietary reference intake allowance in different age groups by the US Academy of Sciences. Information disseminated through the social media are also leading to a greater use of health foods, and nutraceuticals.

Despite rich cultural uses, unbroken ethnomedicinal knowledge of herbs and plants, as well as an availability of a large variety of medicinal and dietary herbs, the contribution of the Pakistani industry towards international nutraceutical market is not more than 1% and thus there is huge potential yet to be untapped in terms of development of evidence-based food and beverages, pharmaceuticals and nutrition products for the global market.

Within the foregoing context, it needs to be emphasized that while much scientific literature is available, there is a serious dearth of general knowledge literature on nutraceuticals from which a common man may benefit and which is easily accessible to the common people. The presented book is an excellent effort to fill this void. The book sufficiently covers the whole spectrum of nutraceutical-related topics in easy-to-understand language, but without losing the scholarly finesse. It is hoped that this introductory book will provide a genesis to more comprehensive books on subject.

In brief, the book entitled, *“Bioactive Nutrients as Dietary Supplements and Therapeutic Agents: An Introduction to Nutraceuticals”*, by Dr. Seed Iqbal Zafar and Dr. Asma Seed is certainly a welcome addition in world’s literature on nutraceuticals. I am confident that the book will receive a wide appreciation both from novice, as well as professionals.

Prof. Dr. M. Iqbal Choudhary

Mustafa (PBUH) Laureate, *H. I., S. I., T. I.*

Coordinator General COMSTECH /

Director ICCBS / Distinguished National Professor

UNESCO CHAIR on Medicinal and Bio-Organic Natural Product

Chemistry

PREFACE

Nutraceutical, during recent decades, has emerged as a new term in scientific literature. The term has a fascinating background. Though it has no etymologically referable base relevant to a standard etymon, its genesis is traceable to two words routinely used in our daily lives: nutrient (Latin – *nūtīre*, to nourish) and pharmaceutical (Greek – *pharmakeutikos*, *pharmakon*, a drug). Within the multidimensional scope of these two words, a nutraceutical is defined as food or part of a food that not only provides health benefits as a “nutrient” but also acts as a “pharmaceutical” substance in the prevention and treatment of disease. The term was coined by Stephen DeFelice in 1989. Forerunning the first use of the term was DeFelice’s obsession with a wonder substance called L-carnitine on which he had already spent his lifetime investigating the wide range of its pharmacological activities, including decades of research and development work followed by clinical trials. He regarded L-carnitine not only as a pharmaceutical preparation but also a substance that belonged to a new category of bioactive nutrients, thus preferring it to term as a nutraceutical.

What was labeled as a nutraceutical in 1989, L-carnitine commenced its journey to this term in 1964 when DeFelice initiated clinical trials on it as a pharmaceutical product possibly having antihyperthyroid activity, which it showed by making the subjects euthyroid within a week, further associated with markedly reduced pulse rate. Over the years, L-carnitine has been shown to have pharmacological activities in several kinds of cardiovascular disorders that include myocardial ischemia and apparently non-ischemic conditions. As a nutraceutical, L-carnitine is an essential ingredient of a variety of dietary supplements consumed worldwide for weight management, energy foods for sportsmen, alleviation of cardiovascular conditions, for making-up carnitine losses during the renal hemodialysis procedure, as an essential external nutrient for infants since they are unable to biosynthesize it in their bodies at their early stage in life, and in carnitine deficiency cases falling within such categories as primary systemic, secondary and myopathic carnitine deficiencies resulting in muscle weakness and fatigue, plasma lipid abnormalities and refractory anemia. The United States Food and Drug Administration (US FDA) has approved the use of L-carnitine in the prevention and treatment of its deficiency syndromes. US FDA has further approved L-carnitine as

an orphan drug for the rare disease condition of fatal carnitine deficiency in children. US FDA, however, has not todate extended the nutraceutical status to L-carnitine, as it has yet to recognize the term nutraceutical within a specific legal regulatory framework. Insufficiency of L-carnitine has been claimed to be an important factor in aging. Included in other likely health-related benefits associated with this miracle substance are in the treatment of Alzheimer's dementia, depression in the elderly, HIV infection, peripheral neuropathies, ischemia and perfusion of the brain, chronic diabetic neuropathy, and cognitive impairment associated with various conditions. A greater brief on the role of L-carnitine as a nutraceutical is given in the relevant section in the first chapter of the text that is also devoted to the concepts to define and describe nutraceuticals. A rather longish foregoing note on the origin of the term and the underlying story behind the definition of nutraceuticals was considered necessary for building-up the preface to the present book.

It is significant to note that nutraceuticals are yet to receive a universally recognized legal regulatory statute. Different countries refer to substances that may be typically included under the term nutraceutical differently as regards their legal status for marketing and general public access are concerned, such as: complementary medicines (Australia); bioactive substances (Brazil); nutraceutical (Canada, Japan); dietary supplements (China, New Zealand); food supplements (European Union); health supplements, functional foods and special dietetic products (India); neither defined nor recognized (Malaysia); health supplements (Pakistan); biologically active food supplements (Russia); and no legal definition (Singapore, United States). In consideration of the diversity of opinions and treatment as to their legal regulatory status in different countries, a full chapter is devoted to worldwide legislation on nutraceuticals.

Never mind the lack of a universally recognized legal regulatory statute, the market stakes in the nutraceuticals trade are huge; Bourne Partners – a US-based company of investment professionals and healthcare executives – in their 2013 sector report on nutraceuticals industry noted that the global market of nutraceuticals was US \$ 142 billion, which was projected to reach US \$ 250 billion in 2018. As such, the trade in nutraceutical-like products has assumed a new dimension wherein usage of the term nutraceuticals has become synonymous with dietary supplements, functional foods, dietary fibers, probiotics, prebiotics, bioactive substances, biologically active food supplements, and their ingredients. This trend also reflects the multifaceted nature of nutraceuticals. In consideration thereof, separate chapters in the present book are devoted to vitamins as bioactive molecules, essential minerals as dietary macro- and micronutrients, dietary

fibers with health claims as constituents of functional foods, nutraceuticals and dietary supplements, prebiotics and probiotics as nutraceuticals, bioactive phytolipids, and a wide variety of both phenolic and non-phenolic phytochemicals. A chapter is devoted to the nutraceutical potential that fruits and vegetables are endowed with as the “Nature’s multinutraceutical capsules”. A final chapter proposes to extend the current definition of nutraceuticals to also include fruits and vegetables as an idea for debate and discussion among experts for giving it a proper language and adoption.

The authors concede forthright that as a new book on the hitherto unexplored frontiers that nutraceuticals may have the potential but may not have received the due consolidated consideration, there may be many aspects of omissions, commissions, and even errors, which are regretted. All suggestions to remove these for improving the present text will be gratefully accepted and incorporated in any subsequent edition.

As with most books, the text in this monographic work is also not based on the original work of the authors but is rather a compilation of facts, data and opinions reported in research papers or reviews already published in literature. Efforts of all these researchers, reviewers, editors, and correspondents in their respective publications are duly listed under the heading “References” at the end of each chapter. All these authors are, accordingly, acknowledged as *de facto* contributors to the present book on introduction to nutraceuticals. Nevertheless, special mention in this acknowledgement is further due to several publications, which have been extensively relied upon, most specifically of the Linus Pauling Institute Micronutrient Information Centre of the Oregon State University, Corvallis, USA; the legal status publication on nutraceuticals by Malla *et al.*, Canadian Agricultural Innovation and Regulation Network of the University of Saskatchewan, Saskatoon, Canada; dietary reference intake publications of the National Academy of Sciences, Washington DC, USA; and the national nutrient database for standard reference of the National Data Laboratory, USDA-ARS, Beltsville, USA.

Conflict of interest. The authors declare no conflict of interest as related with the publication titled, “Introduction to Nutraceuticals: Bioactive Nutrients as Dietary Supplements and Therapeutic Agents”.

Saeed Iqbal Zafar
Asma Saeed
January, 2023

KEYWORDS

Nutraceutical, nutraceutical legislation, antioxidant, bioactive nutrient, bioactive phytochemical, bioactive substance, dietary fiber, dietary supplement, essential fatty acids, essential minerals, flavonoid-anthocyanin, functional food, L-carnitine, phenolics, phytolipid, prebiotic, probiotic, therapeutic agent, traditional and non-traditional nutraceutical, vitamin, vitamin supplement

ACKNOWLEDGEMENTS AND DEDICATION

The senior author (Saeed Iqbal Zafar) acknowledges that the manuscript draft was written by him during his association with the School of Biological Sciences, University of the Punjab, Lahore, Pakistan in various capacities including member of its board of governors, HEC (Higher Education Commission) eminent professor, HEC research project principal investigator, and trainer scientist. He further acknowledges that he first became aware of the term “Nutraceuticals” from Dr. Asma Saeed, a researcher principally in the domain of environmental biotechnology, who on a fringe interest had earlier published her findings on the biosynthetic pathways of anthocyanins in Saskatoon berries acclaimed to have nutraceutical attributes in the *Canadian J Plant Sci* **86**: 193-197, 2006 and the *J Agric Food Chem* **55**: 10414-24, 2007, and later having also researched on biosynthetic pathways of anthocyanins in small tropical fruits (*Syzygium cumini*, vern. jaman; mulberry; and *Grewia asiatica* vern. falsa— all known to have therapeutic attributes in the traditional Eastern herbal system of medicines) in a Pakistan Science Foundation funded project. In consideration of her interest in phenolics, anthocyanins and flavonoids as relevant with the concept of nutraceuticals, the senior author requested her to join in as a collaborating author, particularly by making inputs in chapters 1 and 3-4, on bioactive phytochemicals in chapters 7-8, and wherever else she could make useful contributions. Her acceptance of associating as the second author is thankfully acknowledged. The senior author is further deeply indebted to Dr. Javed Iqbal, Professor and Director, School of Biological Sciences, University of the Punjab, Lahore, Pakistan, for making available the infrastructure facilities and the enabling financial support to conduct the present effort of writing on “Nutraceuticals”. The authors also extend sincere gratefulness to Dr. Adil Hussain, Senior Research Officer, FBRC, Pakistan Council of Scientific and Industrial Research (PCSIR), Laboratories Complex Lahore Pakistan, for his help in arranging the references at the end of each chapter.

It is indeed relevant to note that the mention of any brand name of a particular product or of the manufacturing company in the text is only intended as an illustrative example, which is neither to the exclusion of other products available in the market nor as the recommended product and the manufacturing company.

The senior author takes this opportunity to dedicating his present writing effort to Eram, his wife, the soul and spirit in motivating him to write the present book on “Nutraceuticals” primarily to educate the general public on the potential aspects of a natural alternative in a prophylactic approach to avoid pharmaceutical preparations as much as possible.

Dr. Saeed Iqbal Zafar