Bioactive Nutrients as Dietary Supplements and Therapeutic Agents

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An Introduction to Nutraceuticals

By

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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 **nutr**ition and pharma**ceutical** 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.

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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 – *nūtrīre*, to nourish) and pharmaceutic (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".

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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

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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