

Nutraceuticals with Pharmaceuticals: Its Importance and their Applications

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Abstract

In the current scenario people are deeply concerned about their health because of lifestyles have changed drastically due to increase in working hours and various psychological pressures, which have led to an increased incidence of various life-threatening diseases. In addition to this they are frustrated with the expensive, high-tech, disease-treatment and management approach. The demand for nutraceuticals and phytonutrients has increased over the past few years and they are being used by people for various therapeutic outcomes. The nutraceutical products are recognized not only for their health benefits to reduce the risk of cancer, heart diseases and other related ailments, but also to prevent or treat hypertension, high cholesterol, excessive weight, osteoporosis, diabetes, arthritis, macular degeneration, cataracts, menopausal symptoms, insomnia, diminished memory and concentration, digestive upsets and constipation. Nutraceuticals have also found considerable trust in treating headaches and migraines resulting from stress. Other related nutraceutical products are touted as cures for thinning hair, lack of confidence, poor complexion, varicose veins, alcoholism, depression, and lethargy. In this chapter we made an attempt to classify all types of nutraceuticals with examples followed by their applications in the treatment of various disorders. Furthermore, the implementation of the designing and development of dosage forms for offering better delivery carrier of the nutraceuticals, the importance and challenges have also been enumerated.

Keywords: Lifestyles; Life-threatening diseases; Disease-treatment; Nutraceuticals; Health benefits; Therapeutic outcomes.

Introduction

Nutraceuticals is derived from the amalgamation of terms nutrition and pharmaceutical and was coined by Stephen De Felice in 1989. He defined nutraceutical as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease" [1]. However the terminology is not very popular globally and mostly substituted by the term "dietary supplements" to meet the stringent regulatory requirements. But microscopically cross-sectioning of both the terms reveals some basic differences like nutraceuticals

should always aid in disease prevention or treatment rather than only supplementing the diet. US FDA do not support term nutraceutical and is generally referred as a food derived product which add some extra value to the basic nutritional component present in that specific food. Another term which is often used as a misnomer for nutraceuticals is "functional foods". It can be defined as any food which is being cooked or prepared using "scientific intelligence" with or without knowledge of how or why it is being used [2]. However when these functional food assist in prevention and/or treatment of disease(s) other than anemia, they can be classified as nutraceuticals. Nutraceuticals include a huge product bouquet ranging from isolated nutrients, plant products, diet supplements, processed cereals/ drinks to genetically modified products [3]. The worldwide life-style changes has influenced paradigm shift in the everyday dietary regime bringing into spotlight a new cascade of lifestyle disorders like obesity and type-2 diabetes. Among these cardiac dysfunctions like ischaemic heart disease and stroke stand out as the topmost mortality causes in the world. Nutraceuticals are the perfect switches to manage these lifestyle disorders and are gaining speedy global acceptance. Apart from life-style disorders nutraceuticals are used in diverse array of clinical conditions like inflammation, immuno-deficiency, allergy, arthritis, malignancies, indigestion, depression, sleep dysfunctions, hypertension and blood cholesterol control [4]. Mostly nutraceuticals are associated with more than clinically beneficent effects and this makes them more attractive to consumers. A drug traverses a series of clinical trials involving expenditure in both time and money before reaching the market but nutraceuticals are exempted from such regulatory issues. Thus it is a major attraction for many manufacturers even though they cannot assert that their product can cure/prevent a disease. Besides it is a common belief across the world that all natural products are efficacious and devoid of side effects. This built-in mindset also contributes to great extent to the expanding global market for nutraceuticals which is expected to touch USD 722.49 billion by 2027 with a CAGR of over 8%. Market for nutraceuticals has witnessed significant transformations in recent times with advent of newer technologies like nanotechnology as well as development of advanced procedures/ instruments which favour both quantitative and qualitative analysis. Although most nutraceuticals supply vital nutrients to the body, many details such as dose, drug-drug interaction, nutraceutical-drug interaction, and their effects on individuals under certain clinical

conditions remain indescribable. Besides many patients do not reveal that they are consuming nutraceuticals while in drug therapy so this enhances chances of nutraceutical-drug interactions which may significantly affect their treatment. Biotechnologists are putting lots of effort to engineer plants and crops in order to improve their nutritional value in order to maintain homeostasis. Products marketed as functional foods/ dietary supplements/ nutraceuticals may exhibit highly variability in quality and needs to pass through stringent analysis to ensure proper standards. The present work gives an overview of the history, classification, chemistry, regulations of nutraceuticals and also provides an insight to their role in drug delivery and therapy.

History of Nutraceuticals Discovery

Hippocrates (460–377 BC), the father of modern medicine paved the foundation stone for modern day nutraceuticals through his epic statement “Let food be thy medicine and medicine be thy food”. He was the pioneer to bring forward the concept that specific food can also be the solution for the prevention/ treatment of a disease apart from drug moieties.

Roman Physician Galen enforced trust in the expertise and knowledge base of his profession to design and formulate diet regimen which would maintain health standards of the entire population. Early nineteenth century marked the initiation of nutrition research by François Magendie. His research based on experimental evidences provoked the question that whether foods devoid of nitrogen do provide nutrition [5]. This modulated scientific minds to think beyond proteins, carbohydrates, fats, and minerals to achieve proper nutrition. This hypothesis was supported by experiments on mice by Nicolai Lunin which produced interesting results. He proved that certain component present in milk was essential for nutrition of mice which cannot be classified as proteins, carbohydrates, fats, and minerals [6,7]. This fact and similar research findings by several researchers ultimately led to the discovery of the vital nutrient vitamin.

From the birth of human race we are depended on offerings of Mother Nature to manage our physiological dysfunctions. One such finding presents the botanicals obtained from plants like *Vinca Rosea* and *Taxus brevifolia* which are used in cancer management till date. Ginseng has been another such traditional drug used as chemotherapeutic even today but its history as herbal medicine in China is beyond 2000 years.

Ayurveda, the bible of Indian healthcare science also provides substantial evidence of food being used for prevention/ treatment of disease [8]. Egyptians valued the medicinal importance of different spices like coriander, fennel, cumin, garlic, turmeric etc. and even considered equivalent to precious metals like gold. Honey is a popular natural antioxidant with multiple pharmacological effects like wound healing, antibacterial, anti-inflammatory, antifungal, antiviral, and antidiabetic but its reference can be traced back to Bible (Old Testament, proverb 24:13). People learned from their experiences and slowly clinical problems were provided with scientific explanations. On many occasions dietary alterations

became the remedy instead of medicines. Ship crew reported high mortality due to scurvy and this problem was solved by vitamin C rich diet. Similar findings were also observed with goitre affected patients where iodine rich salt did the trick. In a nutshell it can be concluded that with the passage of time as scientific knowledge developed, food habits were intelligently modulated for prevention/treatment of disease and this may spark which produced the modern day nutraceuticals.

Increased Demand for Nutraceuticals

Modern day work profile has led to the development of a new set of diseases popularly termed as life–style disorders. The common causative agents of these types of disorders are improper diet and dependence on fast foods, lack of physical inactivity, non-alignment with biological clock, incorrect body posture, excessive stress and inadequate rest. Nutraceuticals represent a unique blend of modern science and natural agents and perhaps the best possible solutions for management of life style diseases. Besides these lifestyle disorders are also considered responsible for the predisposition of several complex clinical conditions [9].

Diverse marketed nutraceuticals variants can also help to block the transformation of life style disorders into fatal diseases. Consumer acceptance of nutraceuticals started gaining from 1980 onwards when scientists started indulging into efficacy evaluations of such products followed by their representation in mass media [4]. Other factors like steep rise in medical management costs, increased life expectancy, increased health awareness and available scientific data confirming health benefits of nutraceuticals have also contributed to consumer acceptance of such products. Global nutraceutical market which was approximately 400 billion USD in 2019 is expected to cross 700 billion USD with a CAGR of 8.3% by 2027. Fast expansions of nutraceuticals product bouquet along with a healthy pipeline of innovative products booming the market are all contributors to the predicted growth. The entry of generic products may cause a dip in nutraceutical product costs but because of high consumer acceptance, the overall market for such products is expected to remain stable [10].

Classification of Nutraceuticals

To understand the applications, the nutraceuticals are needed to be classified. The classification into various classes counting on their uses are:

Traditional nutraceuticals

This category of nutraceuticals will be directly obtained from nature e.g. lycopene in tomatoes, omega-3 fatty acids in salmon, or saponins in soy etc.

Further, they are also classified as:

Chemical constituents

Nutrients: Primary metabolites such as amino acids, various vitamins, and fatty acids had well-defined functions in various metabolic pathways. Plant and animal products along with

vitamin have many health benefits and are helpful in curing diseases related to heart, kidney, lungs, etc.

Herbals: Nutraceuticals along with herbs had an excellent impact on prevention of various chronic diseases to make life better. Salicin present in the willow bark (*Salix nigra*) had been proved for anti-inflammatory, analgesic, antipyretic, astringent, and antiarthritic response clinically [11].

Phytochemicals: They are mainly classified on the basis of phytochemicals. Flavonoids, a class of secondary metabolites, which are present in most of the plants, having more than 4000 varieties had been proven clinically for preventing various diseases such as cancer, diabetes, heart diseases, and kidney problem through its antioxidant properties and their bioactive components[12].

Probiotic microorganisms: Probiotics are very important to make life smoother by removing the toxic flora of the intestine and maintaining a friendly environment, for example, useful consumption of *Bacillus bulgaricus*. Currently various probiotic products are available in the market with adequate nutrients to counter various pathogens so that a number of ailments related to human body can be treated [13].

Nutraceutical enzymes: Enzymes are proteinous in structure, are produced by the cell, and act as a biocatalyst. It eases the metabolic rate and fastens the life process. The medical problem mainly related to the GIT whether GERD (Gastroesophageal Reflux Disease) or constipation or diarrhoea or ulcerative colitis could be treated with enzyme supplements. The enzyme could be a better option for diabetic patients.

Nontraditional nutraceuticals they are foods enriched with supplements or biotechnologically designed crops to boost the nutrients; for example, rice and broccoli are rich in β -carotene and vitamins, respectively. They are mainly of two types-

Fortified Nutraceuticals: These types of nutraceuticals include breeding at the agriculture level or addition of compatible nutrients to the main ingredients such as minerals added to cereals, flour fortified with calcium, iron, and folic acid, and milk fortified with cholecalciferol commonly used for vitamin D deficiency [14].

Recombinant nutraceuticals represent the category of energy providing foods prepared by applying genetic engineering. Example: Production of yoghurt and cheese.

Chemistry of Nutraceuticals

Nutraceuticals are found in both natural and processed foods, including carotenoids, flavonoids, curcuminoids, phytosterols, and certain fatty acids (Figure 1). Many of these nutraceuticals have the potential to act as therapeutic agents, and may therefore be suitable for incorporation into functional or medical foods as a means of preventing or treating certain types of cancer. Nutraceuticals vary considerably in their chemical structures, physiochemical properties, and biological effects. For example, nutraceuticals vary in their molar mass, structure, polarity, charge, and functional groups, which influence their chemical reactivity, physical state, solubility characteristics, and

biological fate and functions[15]. Some nutraceuticals are naturally present in whole foods, such as fruits, vegetables, and cereals, and are therefore often consumed in this form. Conversely, other nutraceuticals are isolated from their natural states and converted into additives that can be incorporated into functional foods, dietary supplements, or pharmaceuticals. Based on chemical nature the nutraceuticals are classified as follows-

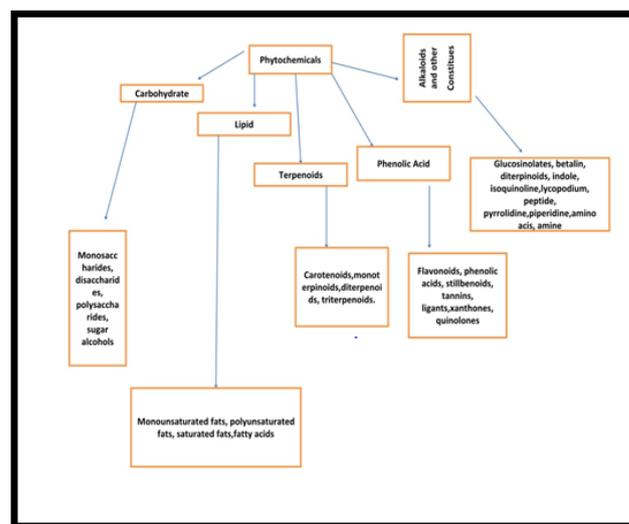


Figure 1: Chemical components of nutraceuticals.

Nutraceuticals in Drug Delivery

With the steep rise in global market for nutraceuticals delivery approaches for such products are gaining scientific spotlight. A perfect nutraceuticals should be biologically active and for that it should be well absorbed in human body. As nutraceuticals are mostly absorbed by oral route the major concern is that the absorption of nutraceutical product by the gastrointestinal tract and also its fate after fast pass metabolism. Therefore the absorption kinetics and the pharmacokinetics of these products are still in a mist. This presents a unique challenge to many nutraceuticals products and so research thrust in their delivery approaches is now gaining momentum [16]. A very common example is the marketed nutraceutical containing Milk thistle plant extract recommended for hepatoprotection [17]. The main bioactive component of the extract silymarin suffers from degradation in the GIT which is a major setback to the efficacy of the nutraceuticals. Similar problems are also observed in different bioactives like alpha-tocopherol, ascorbic acid, curcumin, green tree extract, lycopene used in various nutraceuticals formulations. So, researchers are trying to solve the issue by using modern drug delivery approaches to improve upon the efficacy of nutraceuticals [18].

The most promising and widely explored approach in nutraceutical drug delivery is based on nanotechnological interventions [19]. Nano-scale delivery of nutraceuticals has a definite impact on the absorption and distribution kinetics of the nutraceuticals leading to product efficacy enhancements. Another positive aspect of using nanocarriers is that they not only enhance their absorption and bioavailability but also

provide protection to the nutraceuticals against GIT degradation and first pass effect [20]. Nanoemulsion based drug delivery systems and nano-micelles are often explored to improve oral bioavailability of nutraceuticals as these products are mostly given by oral route. In case of pleiotropic plant bioactives like curcumin which forms an integral part of several nutraceuticals products, different delivery approaches like nanoparticles, liposomes, micelles, phospholipid complexes are designed to achieve bioavailability enhancements[21].

Besides these nano-devices provide site-directed delivery of nutraceuticals which significantly reduce chances of residual toxicity. As per different research reports and marketed products various types of delivery devices like reverse micelles, nano emulsion, nano suspension, liposome, phytosome, surfactant micelles etc. are investigated [22] for efficacy enhancements of nutraceuticals. Some new technological advancements in nutraceuticals delivery is nano-sized self-assembled structured liquid (NSSL) technology[23]. This technology protects the nutraceuticals products from the acidic behavior of gastro intestinal tract in addition to bioavailability enhancements. Surface geometry of delivery devices formed using NSSL technology reveals micellar structure which enlarges into fortifying nano-vehicles (FNVs) after association with targeting ligands [24]. But in spite of several advantages of such products their impact on the cost of nutraceuticals would actually play a vital role in consumer acceptance and their future use (Table 1).

SI No.	Delivery Approach	Nutraceutical	Intended Effect	Reference
1	Nano-complex	β -carotene, folic acid, curcumin and ergocalciferol	Nutraceutical Delivery	[25]
2	Phytosome	Silymarin	Oral delivery	[26]
3	Nutraceutical conjugated gold nanoparticle	Quercetin, Andrographolide	Leishmaniasis	[27,28]
4	Nanospheres and Nanocapsules	Curcumin	Oral delivery	[29]
5	Metal Nanoparticle	Garlic, cayenne pepper	Antibacterial activities	[30]
6	Colloidal nanoparticles	Curcumin	Anticancer oral delivery	[31]
7	Nano hydrogel	Curcumin, Caffeine	Oral delivery	[32]
8	Liposome delivery	Ginseng extract, Curcumin	Oral delivery	[33]
9	Solid Lipid Nanoparticles (SLNs)	α -Lipoic acid	Topical Delivery	[34]

10	Nanostructure Lipid Carriers (NLCs)	Resveratrol	Oral delivery	[35]
11	Dendrimers	Green tea extract, ginseng	Oral delivery, Nasal delivery	[36]
12	Biopolymer Nanoparticles	Casein, Zein, zein-quercetin	Oral delivery	[37]
13	Nano suspension	Curcumin	Oral delivery	[26,38,39]
14	Nano-complexes	B-lactoglobulin	Oral delivery	[40]
15	Phytosome	Silymarin	Oral delivery	[26, 41]
16	Gold nanoparticle	Quercetin	Antileishmanial efficiency	[42-44]

Table 1: Different delivery approaches for nutraceuticals.

Though there are several delivery methods available for the nutraceutical delivery. But the nutraceutical therapy has a lacking in the market till. Some of the products are under trial. There are some problems with the market related also. These nutraceutical products are more active than the other synthetic medicine. It also takes a part to treat against some deadly disease like cancer, diabetes. It also works with the conjugation with nano particles and treat some neuro degenerative disease like Alzheimer's, Parkinson's etc. So, with in some upcoming years nutraceuticals can lead in the market.

Contribution of Nutraceuticals in Therapeutics

Nutraceutical products provide several pharmacological benefits (Figure 2) like anti aging, protection against some chronic diseases, maintaining body homeostasis, cardiovascular diseases, neurodegenerative diseases, metabolic disorders like diabetes, degenerative diseases like cancer, protein deficiency, ophthalmic complications, allergic problems and Parkinsonism [45]. This part of this chapter will provide an insight to the contribution of nutraceuticals for management of diverse clinical conditions.

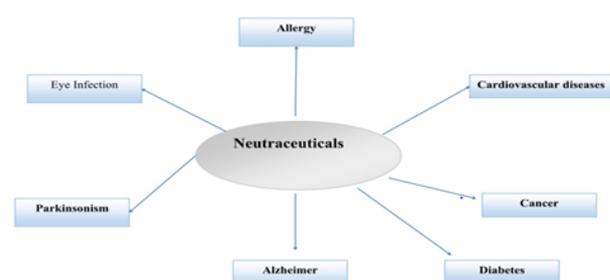


Figure 2: Nutraceuticals in disease management

Nutraceuticals in Allergic Disorders

Allergy is a common disorder due to the hypersensitivity in human immune system. The clinical management is complex as most of the allergy causes are either unknown or difficult to trace. Allergy produces several effects in the body ranging from irritation to some fatal ones like acute respiratory distress [46]. Allergic condition is associated with hematological changes like enhancement of white blood cell and basophil count. Quercetin is a plant bioactive often used in nutraceutical for management of allergy due to its effect on low density lipoprotein [47]. Eucalyptus essential oil is another plant derivative mostly used in nutraceuticals for management of allergy [48].

Nutraceuticals in Cardiovascular Disease

Cardiovascular problems top the list of global mortality causes according to World Health Organization. This disease presents itself in different forms like cardiac failure, vesicular blockage, hypertension, stroke etc. and any of them may result in death or warrant immediate surgical intervention like angioplasty and bypass surgery. But at least 50% cardio vascular disease can be prevented with timely precautions. Vitamins, anti oxidants, omega 3 fatty acids, dietary fibers and minerals are the formulated as nutraceuticals supported by physical exercise is recommended for cardiovascular disease management [49,50]. Flavonoid compounds abundantly found in vegetables/ fruits are often designed as nutraceuticals for cardiovascular problems. These plant bioactives block the angiotensin-converting enzyme and also prevent the platelet aggregation by blocking the cyclooxygenase enzyme. Other substances like melatonin, serotonin, dietary indoleamines, tannis etc are explored as nutraceuticals for minimizing cardiovascular risk [51]. Omega 3 fatty acids found in fish lower the lipid and bad cholesterol levels so are used as nutraceuticals for treatment of cardiac arrhythmia. Consumer acceptance for nutraceuticals in heart diseases is related to the belief that these products do not associate any residual effect [52].

Nutraceuticals used in Cancer Therapy

Complexity in cancer treatment today is mainly due to side effects of existing therapeutics and emergence of drug resistance. A world wide survey reports that in 2020, 15 million new cancer incidences would be found leading to about 50 % rise in cancer population [53]. Cancer treatment till date mostly revolves round chemotherapy, radiation therapy and surgery. But a healthy life style with an antioxidant rich diet can be the best precautionary measure against cancer. Nutraceuticals can be the perfect candidates to fill the existing gap in cancer treatment as they have limited side effects and are often enriched with compounds/ plant extracts which can evade resistance [54].

Recent research has shown that carotenoids like lycopene has reported potency in different cancers and so is an essential component of many nutraceuticals formulations [55]. Nutraceuticals of plant extracts rich in biochanin, isoflavones, tannins and plant bioactives like curcumin, gallic acid, caffiec

acid portray remarkable potency against diverse cancers [56,57]. β carotene & pectin containing nutraceuticals are found to be effective in prostate cancers linked to their free radical scavenging activity [58].

Regular consumption of fruits can serve the body with different types of neutraceuticals like cysteine, Vitamin C, Vitamin E, lycopene and it can prevent from different types of cancer. Some biotransformed products from glucosinolates are effective against in colon, lung breast and liver cancer [58]. A large scale clinical trial is reported to be in progress for the management of prostate cancer with some active neutraceuticals specially lycopene, green tea, Vitamin D and E [59].

Nutraceuticals in Management of Diabetes

Diabetes is a common metabolic disease and is one of the top ten mortality cause as per World Health Organization. Most of the cases it is related with the obesity. More than 50 % of the global population are suffering in diabetes mainly type 2 (non-insulin-dependent diabetes mellitus) due to lifestyle changes [60]. Available anti-diabetic medicines suffer from diverse adverse effects so there is huge demand for alternatives in this area. In recent years in some scientific reports has shown that some herbal medicine and herbal dietary supplements are in preclinical trial level in the management of diabetes [61]. Isoflavones is a phytoestrogen using in type 2 diabetes treatment producing a steep decline in the mortality rate [62]. Omega-3 fatty acid and Ethyl esters of n-3 fatty acid are also used in diabetes management. Lipoic acid and some dietary fibers like psyllium is incorporated in nutraceuticals to mitigate diabetic neuropathy, hyperlipidemia and control of blood sugar level [63]. Other than this diverse medicinal plants are reported to be active in type 2 diabetes control [64].

Nutraceuticals in Alzheimer's Disease

Alzheimer is a neurodegenerative disease which affects more than 26 million people all over the world. It starts with dementia and turns to Alzheimer's and lastly death. Most of the cases it happens in older age that is more than 60 and till date it is non curable. As per scientific reports woman are more affected by this disease than the men may be linked to exposure to the stress conditions [65]. Some of the nutraceutical products like β carotene, lycopene, curcumin, lutein are useful in the management of Alzheimer. There are some research reports which claim that some extracts of plants like *Lavandula officinalis*, *Zizyphus jujube* are useful in treatment of Alzheimer's as they contribute in memory enhancemets [66].

Nutraceuticals in Ophthalmic Disorders

Age related Macular Degeneration (A.M.D) may lead to fatal effects like blindness which can be prevented by the use of vitamins and other components like lutein, n-3 fatty acid and zeaxanthin. Apart from this certain polyphenolic flavonoids, carotenoids are strong antioxidants can prevent the age related

macular degeneration [35]. are also very effective against the A.M.D. Astaxanthin a carotenoid found in sea animals like from shrimps, salmons, and sea bream has potent activity in ophthalmic problems. It finds from the marine [65]. Lutein is another carotenoid found in sweet potatoes, carrots, mangoes, corn etc. used to visual disturbances [67]. Some marketed nutraceuticals is tabulated in **Table 2**.

SI no	Disease Condition	Active Ingredients of Nutraceuticals
1	Cardiovascular disease	n-3 PUFAs, Tannins, Anthocyanins, Octacosanol [68]
2	Eye disorder	Lycopene, β Carotene, Green tea, Vitamin C, Vitamin E, Astaxanthin [69].
3	Alzheimer's	Curcumin, Lutein, lycopene, Turmerin [70].
4	Diabetes	Isoflavones, Omega-3 fatty acid, Psyllium [54].
5	Cancer	Lycopene, Biochanin, Daidzein, β Carotene [71].
6	Allergy	Quercetin [72].
7	Immunity problems	Astragalus, Garlic, Echinacea angustifolia [73].
8	Inflammation	Glucosamine, Chondroitin, Vitamin C [74].
9	Obesity	Capsaicin, Psyllium fiber, green tea, ma-huang guarana [75].
10	Miscellaneous	B-carotene, kaempferol, Moringa oleifera Lam, Saponins, Terpenes, Chitosan, Curcumin [76].
11	Toxicity	Most of the medicinal plant extracts [Cynara scolymus] [77].

Table 2: List of nutraceuticals for management of different diseases.

Marketed Nutraceuticals

Currently nutraceuticals are gaining importance in global market. Nearly 85 % of the nutraceuticals are devoted to vitamins and minerals product while 10% are anti-oxidants and the rest around 5 % belong to botanical products [78]. Though China and India also present a huge market for nutraceuticals, U.S.A heads the list of global sales as US dollars are miles ahead than Indian/ Chinese currency [79].

Globally the demand of nutraceuticals is increased about 5.8% more than \$ 15.5 billion from 2010- 2019 [80]. Which definitely would have positive impact on nutraceuticals manufactured company. At present nutraceuticals products are the largest category products as per the reports[81]. Globally

the demand of vitamin products increases around 5% . Along with vitamins there are carotenoids, anti oxidants, calcium supplements, immune supplements, energy drinks, neurotonic, and nutritional supplements which dominate the global nutraceutical market [82-86]. Currently global nutraceutical market is estimated at 117 billion USD 2019-2020 [87]. The USA is the largest nutraceutical market in the world and India is slowly catching up with an expanding market of 21% per year Some popular nutraceuticals in the global market are listed in **Table 3**.

SI no	Product name	Category	Use	Company Name
1	Omega women	Antioxidant, Vitamins	Immune supplement	Wassen, U.K
2	Calcirol D-3®	Calcium and vitamins	Calcium supplement	Cadilla healthcare limited, Ahmedabad, India.
3	EFAGold™ Super Lignan capsule	Vitamin D and Lignan	Cardiovascular agents	Nature's Way, USA
4	Proteinex®	Predigested proteins	Protein supplement	Pfizer Limited
5	5-Hour energy	Taurine, caffeine	Energy drink	Living essentials, USA
6	Revital®	Vitamins and minerals	Daily health supplement	Ranbaxy Lab Ltd
7	Muscle Optimeal®	Protein, Vitamins, dietary fibre	Meal replacement drink mix	Jarrow formulas, USA
8	Weight smart™	Vitamins and trace elements	Nutritional supplement	Bayer corporation, USA
9	Wellife®	Granulated-L-glutamine	Amino acid supplement	Daesang America Inc., Hackensack, NJ, USA
10	GRD®	Proteins, vitamins	Nutritional supplement	Zydus Cadilla Ltd. Ahmedabad, India
11	Rox®	Taurine, caffeine	Energy drink	Rox America, Spartanburg, SA, USA
12	Coral calcium	Calcium and trace minerals	Calcium supplement	Nature's answer, Hauppauge, NY, USA
13	Chaser™	Activated calcium carbonate	Hangover supplement	Living essentials, Walled lake MI, USA
14	Proplus®	Soy proteins	Nutritional supplement	Campbell soup company, Camden, NJ, USA

15	Pner plusTM	Vitamin	Neuropathic pain suoolement	NeuroHelp, San Antonio, Texas, USA
16	OlivenoITM	Natural antioxidant	Dietary supplement	Cre Agri, Hayward, CA, USA
17	Snapple-a-dayTM	Vitamins and Minerals	Meal replacement beverage	Snapple beverage group, USA
18	TOZAL Eye Health Formula	omega 3 fatty acids, zinc, antioxidants and lutein	improved vision	AmeriSciences, USA,
19	Ferradol Food® powder	Carbohydrate, Protein, Niacinamide	Nutritional supplement for children and adults	Pfizer Limited, India
20	BrainSpeed Memory®	Vitamins, Minerals	Improve Brain health	Natrol, USA

Table 3: List of some market friendly nutraceuticals.

Note:- There are also a lot of marketed products are available in the world only some of the products are enlisted in this list (Table 3).

Regulatory Perspectives of Nutraceuticals

The regulatory framework of nutraceuticals especially in Indian subcontinent is in the growing stage. With increased acceptance of nutraceuticals as alternative therapeutics in modern world, there is a need to ensure the quality standards for such products. The Food Safety and Standards Authority of India (FSSAI) under the aegis of Food Safety and Security ACT is the main regulator for the manufacture, storage, distribution, sales, import and quality maintenance of nutraceuticals in order to make them safe for human use [88]. It also provides a clear guideline regarding the basic standards these products should attain to enter the Indian market. This act covers nutraceuticals, dietary supplements, functional food, organic food, unprocessed food, can food, novel foods, irradiated foods and benchmarks the criteria for import, production, manufacturing, distribution, selling, packaging, labeling and advertisement restrictions of such products by any company [89]. The claim of nutraceuticals regarding cure or prevention any clinical dysfunctions which can be permitted for Indian market are lucidly described under the provisions of this act. Diverse formulations like powders, granules, tablets, capsules, liquids orals, jellies are allowed for nutraceuticals with the exception of injectables. As per the act nutraceuticals cannot be loaded with any narcotic or psychotropic substance listed in the Schedule of Narcotic Drugs and Psychotropic Substances Act or in Schedules E and E(I) of the Drugs and Cosmetics Act[90]. The act states the registration and licensing procedure for nutraceuticals including import, manufacturing, marketing and other necessary permissions for the product to be launched in India. The evaluations that nutraceuticals should pass through is covered in every detail in the Act starting from the raw material source. Different FSSAI officials like food safety officer, food analyst etc. act at different

in process checkpoints to ascertain that the product quality & standards fall in accordance with the norms specified by the act.

In United States, nutraceuticals are regulated as per Dietary Supplement Health and Education (DSHEA) Act and monitored by US Food and Drug Administration. But the regulatory evaluation of the total phase of nutraceuticals product development initiating from its raw material procurement to manufacture and finally sales is different from those applicable to pharmaceutical products. FDA intervention is directed to confirm safety of nutraceuticals but the entry of the product to the market does not warrant FDA approval or registration [91]. In case of dietary supplements designed and formulated in line with DSHEA act can avail registration in US. All companies associated with nutraceuticals need to monitor the effects of their products and intimate FDA of any instances of unwanted effects [92]. Within the European frontiers, European Food Safety Authority monitors the safety of plant derived products which are constituents of different nutraceuticals. Nutraceutical consumers globally are increasing day by day but these products needs to be supported by substantial experimental data regarding their safety window and biological efficacy.

The Future of Nutraceuticals

A majority of the world population is focused towards maintenance of proper health and in this context nutraceuticals play a vital role. Additionally the adverse effects related to drugs available in the market have increased their inclination to such products [93]. In global market presently a large number of nutraceuticals formulations are available with diverse bioactives ranging from vitamins to plant bioactives. With time the list of nutraceuticals products are enhancing based on supportive research where their consumption is linked to prevention of complex clinical conditions like cancer, diabetes, cardiovascular disease etc [94]. The high consumer acceptance can be traced back to low health risks compared to synthetic drugs.

Customers are showing keen interest in different types of nutraceuticals for relieving stress, boosting energies, mental alertness, preventative metabolic disorders, combating oxidative stress etc. To compete & sustain in the global market nutraceuticals companies are targeting to innovate new products aided by advertisement in print and web media to attract the customer pool [95]. Countries like U.S.A, Germany, China, and U.K. are making huge investments in nutraceutical research as they eye high profits in future years which would be dominated by critical issues like antibiotic resistance where these products may only stand out as facile solutions. Currently in developed countries like U.S.A over 50% of the population depend on nutraceuticals for maintenance of day to day health . Technological advancements like neutrigenomics, real time cellular imaging techniques are now being extensively studied to develop newer nutraceuticals. Such technological interventions in nutraceutical formulation development and allied food industry would have a definite positive impact in health care management. Progress in encapsulation technology has made provisions for multiple ingredients to be encapsulated in a single capsule.

Liquid Encapsulation Technology in nutraceutical formulations allows pellets, oils, granules and powders to be incorporated in hard gelatin capsule. This technology also has the potential to be extended for isolation and purification of nutraceuticals. Different new delivery strategies like nanoparticles, phytosomes, liposomes, lipid nanoparticles are now gradually emerging to shape the future of next-gen nutraceuticals with high degree of efficacy. Enzymes represent a unique domain of nutraceuticals with immense potential for future use. Enzyme oriented nutraceuticals supported by newer technologies like nanotechnology would definitely occupy a considerable market share in times ahead. Unique and advanced characterization methods with the application of the genomics, proteomics and the metabolomics are to be explored for betterment of nutraceuticals products. However detailed pharmacokinetics studies and pre-clinical/ clinical evaluations of such products need to be done to ensure their biological efficacy, predict their mechanism of action and confirm their health-care related claims. Besides toxicity profile of all nutraceuticals needs to be extensively evaluated which would help the manufacturing companies meet the regulatory requirements as well as ensure product safety. In a nutshell we can conclude that though nutraceuticals products have high acceptance rate, newer technological interventions and supportive scientific evidences are highly warranted to secure the future of such products and introduce them in healthcare practice.

Conclusion

Though a common myth is available that age is just a number but with the age the defense mechanism of our body becomes weak. It increases the risk of neurodegenerative diseases as well as age related disorder. Nutraceuticals products are natural products contains different ingredients which can prevent different diseases. Continuous research focuses on nutraceuticals to get success in treatment and natural therapies. Presently a wide range of nutraceuticals products are marketed successfully due to their excellent therapeutic activities against different diseases and presently there is a high demand on natural products in the market also. Nutraceutical industries are continuing with a faster rate in food as well as pharma industry. The nutraceuticals market is growing gradually worldwide day by day with dietary supplement, food or beverages. Future development of nutraceutical products in different aspects can give better out come to fight against deadly disease. Though there is still lacuna in the concept of nutraceuticals. People have to change their mind set and adopt to take a new style of healthy living and taking food to make a new concept " Health for All".

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