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Nutraceuticals in Human Diseases: Therapeutic and Prophylactic Potentials

Review Article

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Abstract

In this era of novel technological innovations, human beings have adopted such a changed lifestyle where food intake is devoid of adequate beneficial nutrients. This problem resulted in increased risk of systemic diseases like diabetes, obesity, hypertension, cancer, cardiovascular and various other lifestyle diseases and as remedy, pharmaceutical drugs are prescribed, which, by default, come with adverse effects and complications. To overcome this, researchers have come up with the concept of nutrients as medicines that has given rise to a self-explanatory term called "nutraceuticals". The word 'nutraceutical' consists of two basic elements-"nutrition" and "pharmaceutical". Nutraceuticals, in broad sense, are food or part of food that provide medicinal or health benefits along with their basic nutritionalvalue.Itsbenefitsalsoincludethepreventionandtreatmentofdiseaseswithhardlyanyside effect or toxicity. The different food products known as nutraceuticals are dietary fibre, prebiotics, probiotics, polyunsaturated fatty acids (PUFA), antioxidants and other different types of herbal/ natural foods. Since nutraceuticals play a significant role in combating some of the major health issues, this review article is an attempt to highlight the role of nutraceuticals in modifying and maintaining normal physiological functions that maintain an overall well-being of human health.

Keywords: Nutraceuticals; Flavonoids; Systemic diseases; Functional food; ROS

Introduction

An Ayurvedic proverb says, "When diet is wrong, medicine is of no use; when diet is correct, medicine is of no need". This principle reflects in recent times. The focus of people is shifting towards positive approach for prevention of diseases as well as to stay fit and healthy. Moreover, consumers are overburdened with the expensive, advanced disease treatment approach in modern medicine. Thus, it is necessary to standardize the functional component of food for maintaining well-being, modulating immunity and protection against various diseases.

The term 'nutraceuticals' was proposed by Stephen De Felice in 1989 which is defined as a food or parts of food that provide medical or health benefits, including the prevention and treatment of diseases [1]. Another definition cited by Health Canada as a product prepared from foods but sold in form of pills or powders or in other medicinal forms, not usually associated with foods [2]. Nutraceutical is a hybrid term, combining 'nutrition' and 'pharmaceutical'. Nutrition is required by our body but it requires complex interaction of many elements to be effective in feeding our body and nutraceuticals are such compounds which help in filling the void by providing the proper balance of vitamins and other necessary components. A significant source of these nutraceutical products are phytochemicals like alkaloids, various terpenoids and polyphenols (anthocyanins, flavones, flavanols, isoflavones, ellagic acid etc.) which have therapeutic potential to cure diseases and are known to prevent many degenerative and chronic diseases [3]. Studies indicate that bioactive phytochemicals have potential to stimulate the immune system and they effectively work as antioxidants and cell protectants [4,5]. Thus, if a substance contributes towards maintenance of healthy tissues and organs, it will be considered as food ingredient, but if it has any modifying effect on the physiological process of body, it is considered to be a medicinal substance. This review consists of two major arms. The first part describes different types of nutraceuticals, classified on the basis of their chemical structures and sources. The other part focuses on its role and mode of action in common human diseases.

Classification of nutraceuticals

There are different chemical classes of nutraceuticals found in plant-derived foods. Some of them are

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quite familiar, like catechin from green tea, vitamin from lemon and resveratrol from red wine, while others are largely unknown. The chemical structures of different plant-derived antioxidants discussed here are depicted in (Figure 1). Nutraceuticals can be classified based on food sources, mechanism of action, chemical nature etc and can be broadly categorized in and in the text as follows (Figure 2):

Dietary fibre: Dietary fibre is strongly related to colonic microenvironment that prevents colorectal diseases [6,7]. Fibres impart protection by increasing fecal bulk and dilute the increased bile acid concentration. Literature suggests that some dietary fibres also lower the cholesterol synthesis [8]. Dietary fibre is basically carbohydrate in nature that cannot be digested by endogenous enzymes. Most of the plant foods like cereals, fibrous fruits, leafy vegetables, dried peas, lentils and grains are rich in dietary fibres [9].

Probiotics: Probiotics are live microbial food ingredients that provide health benefits more than any traditional nutritional food. Probiotics are effective in diarrhoeal diseases, irritable bowel syndrome, stomach infections, colic diseases in neonates, possibly by maintaining the gut microbiota and homeostasis in the pH in the intestine [10]. They do so not only by changing and re-establishing the gut microflora but also by enhancing the immune system. The foods that contain probiotics are curd, beverages, yogurt, cheese and pickles.

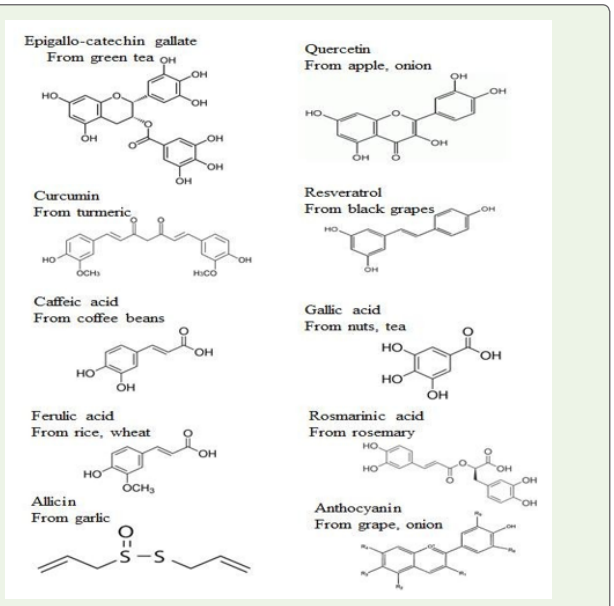

Figure 1: The chemical structures and sources of different nutraceuticals.

Figure 2: Classification of nutraceuticals based on their nature, chemical structure and mechanism of action.

Prebiotics: They are basically short carbohydrate chains, non-digestable by the enzymes present in our upper digestive tract and are not absorbed in any segment of gastrointestinal system through normal physiological process. Instead, they get fermented by some bacteria (bifidobacteria and lactobacilli) present in the small intestine [11]. Some examples include inulin, fructo-oligosaccharides and galacto-oligosaccharides

Polyunsaturated Fatty Acids (PUFA): Dietary PUFA affect a wide variety of physiological processes. PUFAs, that contain omega-3 and omega-6 fatty acids are beneficial to human health and their role in various systemic and inflammatory diseases are well documented [12]. Cold water fishes, fish oils, nuts, salmon, tuna, groundnuts, oysters, flaxseeds are rich sources of essential fattyacids. The major omega-3-fattyacids, also called as essential fatty acids because of their indispensible benefits, are α-linolenic acid, eicosapentanoic acid, and docosahexanoic acid which have several nutraceutical properties [13].

Antioxidant Vitamins: Vitamins like vitamin C, vitamin E and carotenoids are collectively known as antioxidant vitamins. These vitamins act both independently as well as synergistically to prevent oxidation of cellular organelles, membranes, biochemical pathways leading to several degenerative diseases including cancer, cardiovascular diseases, cataracts etc.[14].

Spices: Spices are used for thousands of years as food supplements to enhance the quality of foods. They impart characteristic flavour, aroma, zest and colour to foods, stimulating our appetite as well as modify the texture of food. Recent research reveals that Indian dietary spices not only enhance the taste of the foods but they have antioxidative, chemo preventive, anti mutagenic, anti-inflammatory, immune modulatory effects for the benefit of human health [15]. They contain essential oils, phytochemicals and vitamins.

Terpenes: Terpenes are also known as isoprenoids, are most abundant in green foods, soy plants and grains, have a unique anti-oxidant activity as they react with free radicals by partitioning themselves into lipid bilayer of the cell membrane because of the presence of their hydrophobic carbon tail [16].

Polyphenols: These are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens. There are approximately 8,000 different classes of polyphenols, the most important being flavonols, flavones, flavan-3-ols, flavanones and anthocyanin [17,18]. These will be discussed in detail in the following section.

The flavonoid polyphenols

Flavonoids are plant secondary metabolites having low molecular weight with significant antioxidant and chelating properties. They are widely found in fruits, vegetables, wines, teas and cocoa as glycosides, dimers, polymers and in conjugation with other compounds also [18]. These have beneficial effects in several diseases including cancer, cardiovascular disease, myocardial damage and neurodegenerative

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disorders [19,20]. Flavonoids are extensively metabolized in the digestive tract and exert modulatory action in cells by interaction with protein kinase and lipid kinase signaling pathways [21]. Also, by virtue of their capacity to inhibit low density lipoprotein (LDL) oxidation, they protect from diseases, resulting in a significant alteration in their redox status. The main representatives of flavonoids polyphenols are quercetin, catechin and kaempferol. The richest sources are onions, apple, curly kale, leeks, broccoli, berries and leafy vegetables like cabbage and lettuce [17].

• Tea catechin

Green tea is by far the richest source of catechin and epicatechin but they are also found in many types of fruits like apricot, beans, cherry, grape, peach [22]. Enzymatic oxidation of green tea leaves (*Camellia sinensis*) during fermentation/heating to black tea results in polymerization of catechins into more complex condensed polyphenols theaflavins (dimers) and thearubigins (polymers) [23,24]. Other than the major flavanols catechin and epicatechin, other isomers like gallocatechin, epigallocatechin, and epigallocatechin gallate (EGCG) also have proven antioxidant properties. Tea catechins and polyphenols are effective scavengers of reactive oxygen species (ROS) *in vitro* and function as antioxidants through their effects on cytokines and transcription factors. Cell culture and animal studies provide experimental evidences that catechin and its derivatives possess the bioactivity to affect the pathogenesis of several chronic and systemic diseases. Catechins inhibit the invasion and proliferation of the smooth muscle cells in the arterial wall, which reduce the formation of the atheromatous lesion [25]. Literature suggests that theaflavins and thearubigins of black tea possess strong anticancer, antibacterial and antiviral properties and help in mineral absorption in intestine [26]. A recent study demonstrates that the catechins carry strong anti-aging activity also [27]. EGCG also protects neurons by activating several signaling pathways, involving Mitogen-Activated Protein (MAP) kinases [28].

• Quercetin

Quercetin is an integral component of human diet. It is an abundant flavonoid, exhibits abroad spectrum of properties i.e. antioxidant, anti-inflammatory, anti-thrombotic, anti-hypertensive, anti-carcinogenic, vasodilatory and immunomodulatory actions having potential to prevent many diseases. Quercetin is commonly present as glycoside and is converted to glucuronide/sulfate conjugates during intestinal absorption and only conjugated metabolites are found in circulating blood [29]. The anti-carcinogenic property of quercetin is deciphered by inducing apoptosis in tumor cells at relatively higher concentration and acts as potential chemotherapeutic drug [30]. Quercetin shows favorable effects on a variety of antioxidant biomarkers, such as antioxidant enzymes, plasma antioxidant capacity, resistance to LDL oxidation and reduced lymphocyte DNA damage [31]. Studies indicated that quercetin helps to regenerate, inactivate the harmful effects of metalions and improves memory [32]. Quercetin is also known to possess strong anti-diabetic activity by reducing induced alterations and lipid peroxidation in patients. In addition, quercetin is neuroprotective against colchicine, which causes cognitive impairments [33]. So, quercetin is a promising agent for disease prevention.

¬ **Non-flavonoid polyphenols:**

Plant-derived non-flavonoid phenolic compounds like resveratrol, caffeic acid, curcumin are widespread in various foodstuffs and beverages such as coffee beans, potatoes, fruits like apples and their juices, tobacco leaves, olive oil and wines [34]. There is growing interest in biological and pharmacological properties of non-flavonoid phenolic compounds. They have been reported to have antioxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic activities [18].

• **Resveratrol**

Resveratrol is the non-flavonoid polyphenol which has received much attention and currently the focus of intense research. It is present in grapes and red wine. The biological effects of this polyphenol includes as an inducer of cell differentiation, anti-inflammatory actions, scavenging free radicals and anti-aging properties which has been documented in disease models [35]. Current research suggests that resveratrol may enhance prognosis of neurodegenerative disorders such as, Parkinson's, Huntington's, Alzheimer's diseases and stroke [36]. Resveratrol decreases nuclear factor kappa B (NFκB) activation which, in turn, suppresses induced nitric oxide synthase (iNOS), cyclooxygenases (COX)-1 and 2 expression, as well as many other genes including multiple cell adhesion molecules, thus reduces inflammation [37]. Chronic activation of NFκB and tumor necrosis factor (TNF)-α is also associated with cancer and other systemic diseases, such as diabetes [38]. Resveratrol stimulates cellular mechanisms of oxidative resistance by inducing mitochondrial superoxide dismutase (SOD) in cultured mammalian cells [39]. The cardioprotective effects of resveratrol may be in part to their ability to decrease LDL cholesterol oxidation [40].

• **Caffeic acid**

Caffeic acid is a hydroxycinnamic acid widely present in coffee beans, wine, cidar, olive oil and in several fruits in chlorogenic acid form. Experimental evidences suggest that caffeic acid is a potent antioxidant. Caffeic acid has several biological and pharmacological properties, such as antiviral, antioxidants, anti-inflammatory, anticarcinogenic, antimutagenic and immunomodulatory activites [41]. Caffeic acid inhibits lipoxygenase activity and suppresses lipid peroxidation and LDL oxidation [42]. Caffeic acid completely blocks the production of ROS and xanthine/xanthine oxidase system and inhibits DNA damage *in-vitro* [43]. It selectively blocks the biosynthesis of leukotrienes, components involved in immunoregulatory diseases, asthma, and allergic reactions. Caffeic acid and its derivatives have been shown to sequester nitric oxide (NO) radical and protects human skin from UVA and UVB of sunlight [44].

• Curcumin

Curcumin is a diferulolylmethane, possesses two phenol moieties and is therefore a polyphenol, found in turmeric, the Indian spice which is derived from the rhizomes of the plant *Curcuma longa*, a perennial herb. Curcumin has gained much attention as a drug due to its ubiquitous presence and use from ancient ages. Number of preclinical and clinical trials has confirmed its non-toxic and safe nature, even if it is orally administered. Curcumin has been shown

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to have antioxidant, anti-infective, anti-diabetic, wound healing and anticancer properties, and its use has been investigated in various diseases like diabetes, Alzheimer's disease, hepatitis, rheumatoid arthritis and cancer [45]. Curcumin mitigates inflammatory responses by suppressing numerous signaling pathways, e.g. COX-2, lipoxygenase, STAT-3, Nrf2, suppression of pro-inflammatory cytokines such as NFκB, interlukins (IL) -1, -6, -8, inducible nitric oxide synthase, and NO production in lipopolysaccharide -, interferon (IFN)-γ, or TNF-α-activated macrophages and natural killer (NK) cells [46,47]. It is a strong antimicrobial agent too. Combinational therapy of curcumin with other chemotherapeutic drugs may prove superior because of their ability to reduce the size of tumor. Recently, new mechanisms like liposomal and subiquitous presence are emerging to increase the efficacy and bioavailability of curcumin. Nanoencapsulated curcumin is also very effective as a preventive drug against glioblastoma multiforme in experimental animals [48]. In addition to suppressing inflammation in many *in vitro* and *in vivo* models, curcumin also shares the function of regulating adenosine Monophosphate-Activated Protein Kinase (AMPK) and mechanistic target of rapamycin (mTOR) [49]. It also appears to regulate mitochondrial function when the compound induces apoptosis of tumor cells.

¬ **Phenolic acids**

Phenolic acids are derivatives of benzoic and cinnamic acids and aromatic secondary plant metabolites, widely distributed among medicinal herbs [50]. Among the others, sorghum and millet have the widest variety of phenolic acids. They are associated with color, sensory qualities, nutritional and antioxidant properties of foods. Recent literature suggests that phenolic acids behave as antioxidants, due to the reactivity of the phenol moiety [51]. They have antimicrobial, anti-inflammatory and hepatoprotective properties also [52]. Humans consume phenolic acids on a daily basis. The total dietary intake is approximately 1g per day depending on the composition of the diet. Phenolic acids are often available in the market as dietary supplements, such as grape seed extract or green tea extract. The following phenolic acids are worth mentioning as neutraceuticals:

• **Gallic acid**

Gallic acidis found in a variety of herbs like gallnuts, grapes, berries, walnuts, apples, flaxseed coffee, wine and tea. Besides its antioxidative property, literature says that gallic acid have anti-fungal and anti- viral properties contribute towards a stronger immune system [53]. Gallic acid acts as a potent antioxidant and defends the cells against oxidative damage [54]. Gallic acid has been reported to induce apoptosis selectively in cancer cells, without harming healthy cells and inhibit proliferation of metastatic tumor cells [55] has been useful to rejuvenate brain nerves and neuronal disorders, thus protects the tissues from further deterioration. Gallic acid is used as tring entasit helps to constrict tissues and stop bleeding and is effective in the treatment of internal hemorrhages [56]. Presently, gallic acid is readily available as purified supplement as well as with vitamin and other nutritional supplement containing gallic acid.

• **Ferulic acid**

Ferulic acid is one of the abundantly found plant constituent which occur from the metabolism of phenylalanine and tyrosine via Shikimate path ways in plants [57]. Ferulic acid is found conjugated with mono and polysaccharides, lipids as it never occur free in plants and are particularly found in the cell walls of several plants. It is commonly found in cereals, fruits, some vegetables and sweet corn and is easily metabolized in the liver. It acts as antioxidant in response to free radicals by donating hydrogen from its phenolic hydroxyl group, which has been reported similar to that of SOD. It is more bioavailable than other dietary flavonoids and monophenolics, although its bioavailability depends on subsequent interaction with target tissues [58]. Ferulic acid stays in blood for longer period of time than other antioxidants such as ascorbic acid. Recent studies reveal that ferulic acid and related ester derivatives decrease the levels of some inflammatory mediators, e.g., prostaglandin E2 and TNFα and iNOS expression and function in cells stimulated by the bacterial endotoxin lipopolysaccharide [59]. The derivative of this phenolics, alkyl ferulate has an anti-carcinogenic potential. In addition, there are reports which say that blood glucose level in streptozotocin-induced diabetic animals is reduced by the administration of ferulic acid [60]. This works well in all herbal antioxidant formula, vitamin and herbal health supplements. Thus our body's immune system can be benefited from ferulic acid. Besides its nutritional value, it is widely used as food additive and in food industries for vanillin production.

• **Rosmarinic acid**

Rosmarinic acid is a diphenolic compound, found in Rosemary, lemon, oregano, some higher plants, some fern and hornwort species. It is anester of caffeic acid and 3,4 dihydroxyphenyllactic acid. It is regarded as a potential pharmaceutical plant product and is noted for its anti oxidant properties and having significantly low toxicity [61]. Various rosmarinic acid containing extracts from the leaves of herbs and spices have been reported to possess antioxidant, antimutagenic, anti-tumorigenic, anti-HIV, anti-proliferative, and anti-cyclooxygenase, anti-lipooxygenase properties [62]. It gets absorbed in the gastrointestinal tract and skin easily. So, pills and ointments containing rosamarinic acid a real ready available in pharmaceutical sector.

¬ **Organosulfur compounds**

Organosulfur compounds contain sulfur as one of the functional groups. Organosulfur compounds possess a variety of useful properties like synthetic reagents, intermediates and solvents; as drugs, biochemicals, natural compounds. These are readily available in nature, inexpensive and of great utility [63]. A wide variety of organosulfur compounds are found in living system, including the sulfur containing amino acids cysteine and methionine, peptides such as glutathione, antibiotics like penicillin, cephalosporin, bacitracin, co-factors and vitamins like thiamine, biotin, lipoic acid, co-enzyme A, S-adenosylmethionine etc [64]. Plants and vegetables with sulfur content are onion, garlic, asparagus, cabbage, turnip, radish, horseradish, mustard, pineapple and many others. Some organosulfur compounds having health importance are discussed below.

• **Allicin from garlic**

Garlic is one of the important dietary constituents having

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medicinal properties. Allicin, the major bioactive component produced from allicin by the action of allinase, a thiosulfinate from raw garlic, scavenges superoxide by suppression of the formation of superoxide by the xanthine/xanthine oxidase system, via a thiol exchange mechanism [65,66]. In addition, allicin demonstrated hypolipidemic, anti platelet, antibacterial, anticancer, chemo preventive and procirculatory activities [67]. Some reports suggest that they get decomposed to give a sulfenic acid that reduces free radicals and inhibits oxidation of cellular bio molecules [68]. It is also well-known for its potent anti microbial activity. The therapeutic efficacy of garlicen compasses a wide variety of ailments, including cardio vascular, cancer, hepatic and microbial infections to name but a few.

- **Anthocyanins**

Anthocyanins, are water soluble pigments, distributed in colored fruits such as berries, grapes, flowers, grains, black soy beans etc. They impart the vibrant colours in fruits, vegetables and flowers, thus help in pollination, and they have potent antioxidant/anti-inflammatory, antiviral, neuroprotective activities [69]. They scavenge lipophilic radicals, inhibits lipid peroxidation and the inflammatory mediators COX-1 and -2. Besides, they are the natural food colorant widely used in food and beverage industries. Several studies have summarized its anti-diabetic and anti-obesity activities via modulation of adipocytokine expression [70].

Role of Nutraceuticals in human health

A free radical is defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. Although oxygen is a crucial element for life, under certain conditions, it becomes detrimental on human body. Most of the potential damage is caused by the formation and activity of ROS and Reactive Nitrogen Species (RNS). These species are mainly regulated by endogenous systems, but due to over production of these chemical moieties which are induced by exposure to external oxidants or failure indefense mechanism, many human diseases are triggered. Free radicals adversely damage lipids, proteins, DNA, cell structure leading to loss of form and function. For this reason, many chronic and degenerative human diseases like cancer, autoimmune diseases, atherosclerosis inflammatory diseases, aging, cataract, rheumatoid arthritis, asthma, cardiovascular and neurodegenerative diseases arise [71,72]. The problem arises when the body's antioxidant defense system cannot overcome the production of free radicals which results in oxidative stress. Thus, a balance between free radical production and antioxidant defenses must be established for proper physiological function of human body as described in [73] (Figure 3). Human body is enriched with (Figure 3): The critical balance of ROS in the ellis responsible for normal physiological functions and antioxidants play a very crucial role in it. Accumulation of ROS beyond a threshold level, under various endogenous and exogenous stimuli induces lethal damage in cell organelles and macromolecules which may lead to various diseases.

Antioxidant defence against ROS and RNS. These free radical scavengers include ascorbic acid (Vitamin C), α tocoferol (vitamin E), β-carotene, enzymes such as catalase and Superoxide Dismutase (SOD), and trace elements including selenium and zinc. Based on

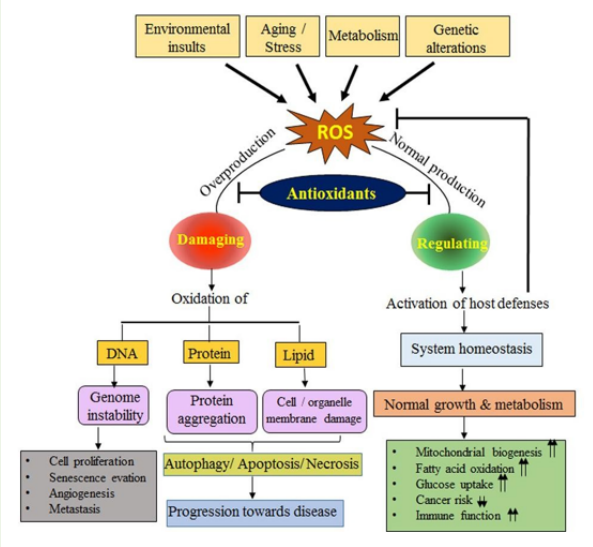

Figure 3: The critical balance of ROS in the cell is responsible for normal physiological functions and antioxidants play a very crucial role in it. Accumulation of ROS beyond a threshold level, under various endogenous and exogenous stimuli induces lethal damage in cell organelles and macromolecules which may lead to various diseases.

the premise of oxidative stress, phytochemicals and nutraceuticals are becoming a great source of interest which is paving the way for biomedical research [2,3]. With the increase in life's pan of human, many chronic, age related diseases known as lifestyle diseases such as neurodegenerative diseases, type II diabetes, and several types of cancers are in rise which encouraged many health organizations to recommend plant derived food to improve our health status.

A. Nutraceuticals and obesity management: Obesity is one of the major global health epidemic of the 21st century, affecting virtually all ages and socioeconomic groups caused mainly due to unhealthy eating habits and improper lifestyle. The widespread presence of obesity is associated with significant metabolic complications like type 2 diabetes, hyperlipidaemia, hypertension, and cardiovascular disease where nutrition and physical activity play significant role in its prevention and treatment. Treatment with natural products is currently in practice to develop effective strategy to control obesity having lesser side effects [74]. Functional foods like curcumin regulate adipocyte differentiation by inducing cell cycle arrest and cause an increase in apoptosis [75,76]. Literature says that polyphenols, anthocyanins, tannins displayed inhibitory effect on several digestive enzymes (maltase, sucrase and lipase) thus helping in postprandial hyperglycemic and hyper-insulinemia [77]. Conjugated linolenic acid found in flax seeds, nut oil and fish oil reduces overall fat mass of the body [78].

B. Nutraceuticals and Cardiovascular diseases: It is the most common health-related concern worldwide, especially in elderly people. It accounts for 17.3 million deaths annually which represent 30% of all mortalities since 2008 [79]. In addition to the lifestyle conditions and environmental factors, 'unhealthy diet' is considered as one of the culprits for cardio vascular risk. Epidemiology data strongly suggest that a diet rich in fruits, vegetables, natural products, low fat dairy products prevents the risk of cardiovascular diseases

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significantly [80]. Nutraceuticals not only prevents the risk but also reduces its progression. Table 1 summarises the source of various nutraceuticals and their action in cardiovascular diseases.

C. Nutraceuticals and Diabetes: Several studies have highlighted the beneficial role of functional foods and nutraceuticals in various metabolic disorders including type-2 diabetes mellitus. Beside the determinants like obesity, poor diet, physical inactivity, hypertension, genetic predisposition etc., systemic inflammation and oxidative stress play pivotal role in pathogenesis of diabetes [87]. ROS generated from oxidative stress, leads to β-cell dysfunction of pancreas and creates insulin resistance and accelerates other systemic complications like nephropathy, retinopathy neuropathy and other long-term pathogenic conditions [88].

Lifestyle interventions and nutritional medicinal strategies are the primary determinants to prevent diabetic complications in pre-diabetic and high-risk individuals. A balanced nutritional management, consists of nutraceuticals and abundance of bioactive components like phenolic compounds, sulphur compounds, herbs, natural antioxidants are involved in glucose metabolism which may prevent progression of diabetes and other associated complications. Some of the nutritional supplements are already available in markets which are extensively prescribed by the clinicians, e. g. L-carnitine, α- lipoic acid, omega-3 fatty acids, berberine, chromium, soy and phytoestrogens. Further investigations using phytochemicals and other bioactive components are needed as supplementary treatment for diabetic patients.

D. Nutraceuticals and neurodegenerative disease: Nutraceuticals prove to be a more "safer" option for the treatment of Alzheimer's disease as well as Parkinson's disease as opposed to current pharmacological strategies which by default come with more side effects. They have shown promising results in preliminary studies of regulation of brain physiology. The mechanism of action of nutraceuticals includes regulation of signaling pathways, inhibition of oxidative stress, neuro inflammation and reduction of vascular dementia [89]. Examples of some nutraceuticals along with their proposed mode of action are as follows:

Apart from these, nutraceuticals are useful for headache and chronic migraine also. Studies have revealed the preventive action of nutraceuticals in migraine [93]. The commonly prescribed vitamin and mineral supplements used are magnesium, riboflavin, co-enzyme Q10 etc [94]. Essential oils from some aromatic plants like lavender, sandalwood, eucalyptus etc. are mood enhancers and anti-depressants.

E. Nutraceuticals and Cancer: Other than the environmental factors, oxidative stress and redox signaling play pivotal role in the genesis as well as metastasis of cancer and ROS also affects the responsiveness of cancer cells to therapeutic interventions. Oxidative damage leads to permanent changes in the DNA which favours oncogenic transformation followed by uncontrolled proliferation and angiogenesis as depicted in [95] (Figure 4). The importance of nutraceuticals as anticancer agents is increasingly being recognized. However, some challenges, particularly their bioavailability, have restricted their progress through clinical trials.

Nutraceuticals, mostly phytochemicals, have well documented role in treatment of cancer, as suggested by epidemiologic and animal model studies. They hold a great promise, as proven by multiple reports on their ability to modulate key signaling pathways/ molecules that influence tumorigenicity [96]. Majority of cancer drugs discovered till date are derived from natural sources. Literature says that simple food with low carbohydrate content and moderate amounts of protein, dietary fibres and fat are suitable for cancer patients. Chemotherapy and radiotherapy are the major treatment modalities for cancer patients. However, drug related side effects are common for chemotherapy which causes significant mortality and morbidity. To minimize this, instead of other pharmacological drugs, natural products or antioxidants (e. g. microbial and plant secondary metabolites) are used as adjuvants along with the chemotherapeutic drugs to increase its efficacy. As majority of nutraceuticals are rich in antioxidants, they participate in the signaling pathways related to redox mediated cytokines and proteins which directly modulate endocrine system, immunological cascade, inflammatory cascade and inflammatory pathways [97]. *In vitro* studies have documented the role of nutraceuticals in anti-carcinogenic actions of chemicals by blocking their mutagenic activity and suppressing cell proliferation. Dietary antioxidants possess a wide range of prophylactic as well as therapeutic actions on cells by promoting cell-cycle stasis, senescence, promoting apoptosis and necrosis and inhibiting angiogenesis, thus prevent metastasis [98].

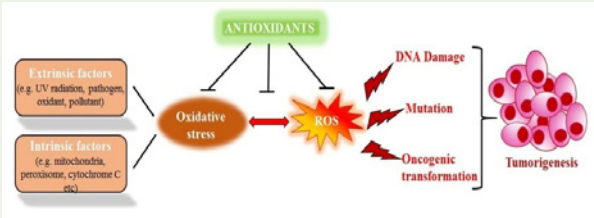

Figure 4: Molecular mechanism of oxidative stress and ROS-induced carcinogenesis and prevention by nutraceuticals/ dietary antioxidants.

Table 1: Source of different nutraceuticals and their role in various cardiovascular diseases.

Nutraceuticals	Source	Function(s)
Phytosterols	Vegetables, cereals, seeds, Nuts	Improves serum lipid profile, lowers LDL [81]
Polyphenols	Fruits, vegetables, legumes, tea, coffee, wine cocoa	Improves HDL level, decrease LDL oxidation, Anti-atherosclerotic, prevents myocardial ischemia and platelet aggregation [82]
Flavonoids	Fruits, vegetables, wine, tea, dietary fibres, oilseeds	Enhances vascular reactivity, lipoprotein metabolism, inhibits platelet aggregation [83]
Spirulina	*Cyanobacteria* sp.	Improves blood lipid profiles, decrease risk of atherosclerosis [84,85]
Probiotics	Curd, yogurts, cheese, fermented rice products	Reduce hypertension, decrease miscellar content [85]
Soy proteins	Oats, flaxseeds, barley	Lowers cholesterol absorption, increases LDL clearance and intraluminal viscosity [86]

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Functional foods also help in increasing function of NK cells and TNFα in patients with advanced stage of cancer. The major nutraceuticals involved in cancer care are represented below:

Humans are constantly exposed to intrinsic and extrinsic carcinogens and free radicals. Such oxidants can also arise either during routine metabolism or from the drugs that are administered for any purpose. Cellular antioxidant systems resist the damage. The critical balance of oxidation-reduction (redox) in the system is maintained by various factors including intrinsic antioxidant enzymes like SOD, glutathione peroxidase, catalase and continues a balance [99]. When the pool of free radicals exceeds the threshold level, it creates an imbalance and favours oxidation of various macromolecules and organelles. Warburg et al. first described the role of oxygen in cancer [100]. Later, it was described that nascent oxygen is connected with various systemic diseases including cancer through two possible mechanisms: induction of gene mutations and the effects on signal transduction and transcription factors.

Despite intensive research, antioxidant strategies are not yet been established as clinically effective, as there are few clinical trials and tested efficacies for most of them. Further investigation is needed to elucidate its role and impact on disease progression, angiogenesis and metastasis.

F. Nutraceuticals and Other Diseases: Apart from the major lifestyle diseases, nutraceuticals play a beneficial role in the prevention and treatment of various other diseases as mentioned below:

Arthritis: It is a chronic, disabling and a multifactorial disease that is prevalent within our aging population and ultimate solution is joint replacement surgery. Examples of nutraceuticals for the treatment of arthritis are glucosamine, chondroitin, fish oil, gamma linolenic acid [101]. Glucosamine is an endogenous a monosaccharide which maintains the cartilage integrity. It is a widely prescribed supplement for osteoarthritis patients. Often, it is prescribed in combination with chondroitin. The use of fish oils (e.g. cod liver oil) in diet and its active ingredient n-6 fatty acid has shown its effectiveness in reducing inflammation in the cartilages in several clinical trials and *in vitro* animal models [102].

Cataract: Flavonoids like quercetin, morin, catechin, and flavones obtained from fruits, green leafy vegetables help in the prevention of cataract due to their ability to scavenge free radical [103]. Some vitamin supplements, dietary carotenoids lutein and zeaxanthin are also useful to prevent cataract. They have potential to filter harmful short wave length blue light and decrease H_2O_2 mediated damage of lens protein [104].

Constipation: A fibre rich diet can relieve constipation. Herbal medicines and certain phytochemicals are very useful to treat constipation. Botanical laxatives such as senna, frangula, aloe, rhubarb and cascara are used in the treatment of constipation. Some natural fibers present in skin of vegetables and fruits, leafy vegetables, buckwheat seed proteins have beneficial role in constipation [105].

Diarrhoea: The discomfort caused from diarrhea is due to excessive fluid loss followed by dehydration. Affected individuals are advised to take herbal drinks like peppermint tea, rosemary, lemon, orange, and catnip to get relief. They can be beneficial in stopping diarrhea due to the presence of tannin which plays an important role in contracting the human tissue which results in fluid retention in the body [106].

Menstrual pain: Dysmenorrhea is mainly triggered by higher levels of prostaglandins. Foods like beans, almonds, spinach that are rich in calcium and fruits like blueberries, cherries, vegetables like bell pepper that have high antioxidant and mineral content can also be beneficial. Studies reveal that a gluten-free diet, omega-3 fatty acids, calcium supplement helped to decrease painful symptoms of menstrual pain as well as endometriosis by reducing inflammation [107].

Gastritis: Certain flavonoids show anti-ulcer activity and help in prevention of gastric mucosal lesions. The bioactive component of aloe vera is reported to help in prevention of stress-induced gastric ulceration in the rats [108]. Similarly, curcumin has proven to be effective in improving endoscopic healing of pepticulcers.

Nutraceutical Scenario in India

There is growing acceptance of the potential role of nutraceuticals and functional foods to minimize health risks, lifestyle diseases and improve health quality among the Indian population. People are becoming more aware of their nutritional needs and taking progressive steps to prevent chronic lifestyle diseases for well-being. The youngsters are now actively pursuing fitness practices to prevent obesity, cardiovascular diseases, diabetes and other secondary complications derived from that. The Indian nutraceuticals industry is rapidly growing despite the economic down turn and rising inflation rates. Literature suggests that there is a huge scope of growth of nutraceuticals market in India and is concentrated in the southern part followed by the eastern part of the country [109]. This market is majorly dominated by some pharmaceutical companies like Dabur, Himalaya Drugs etc. Previously, production of functional foods or nutraceuticals was limited to food companies only, but pharmaceutical companies are now diversifying their product line due to earn revenue on this. Simultaneously, extensive research is going onto utilize the large pool of natural resources having minimal side effects and to move into less expensive drugs [110,111]. The

Table 2: Nutraceuticals and their mode of actions.

Nutraceuticals	Proposed mode of action
Antioxidant and vitamin supplements	Reduce oxidative stress
Polyunsaturated fatty acids (n-3 PUFA) of Fish oil	Modulates dopamine producing neurons in the basal ganglia in case of Parkinson's disease [90]
Quercetin	Antioxidant, anti-neuro inflammatory as well as anti-carcinogenic agent [91]
Ginkgo biloba	Treats mental ill-health, fatigue, boosts memory, overall performance of brain [92]
Huperzine alpha or huperzine A	Used to treat Alzheimer's disease [93]
Moss or Huperzia serrate	Reversible inhibitor of acetyl cholinesterase [92]

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Table 3: Classes, key components and sources of different classes of functional foods.

Class	Component	Source
Polyphenols	Epigallocatechin-3-gallate	Green tea
	Resveratrol	Red wine, grapes
	Quercetin	Fruits, vegetables
	Caffeic acid	Coffee
Vitamins	Vit A, C, E	Fruits, supplements
Carotinoids	Lycopene	Tomato
Allylsulfur compounds	Diallyl sulfide and Diallyl disulfide	Garlic

dietary supplements, such as vitamins, antioxidants, purified extracts and spot medicines have been captured by pharmaceutical giants and nutraceuticals along with beverage are now majorly produced by Fast Moving Consumer Goods (FMCG) companies like Amway, Sami Labs, Zandu Pharmaceuticals etc. It is predicted by extensive market research by www.bccresearch.com that global nutraceutical market should touch $336.1 billion by 2023 from $230.9 billion in 2018 at a Compound Annual Growth Rate (CAGR) of 7.8%, from 2018 to 2023 [112]. According to the Assocham Report [113], the nutraceuticals market in India is estimated at around $ 4 billion in 2017 and is expected to grow at a significant 21% CAGR to $ 10 billion in 2022. For accelerated growth, production companies along with researchers and scientists must educate common people for their better understanding and to adopt effective communication strategies without harming the interest of chemists and druggists for the target consumers.

Future Directions

Nature is a vast reservoir of active compounds which canasta against several diseases. The incidence of lifestyle diseases is rising steeply. Parallel to it, the demand of natural products or medicines derived from it is growing because they are in expensive and having very less toxicity. There is growing interest for the role of nutraceuticals in reducing health problems as well as systemic diseases. Nutraceuticals are available in several forms, like, dietary supplements, purified extracts, genetically modified foods, fermented or processed foods, beverages which provide all the necessary components that should be present in diet to maintain optimal health [114].

In gist, it has led to the new era of preventive and therapeutic solution, in which food and pharmaceutical industry may merge to produce functional foods, as suggested by the report of www.kpmg.org [115].

This review focuses on the positive aspects of nutraceuticals that have the potential of being included into foods. Although there is a growing interest for the role of nutraceuticals in reducing health problems, there are regulatory bindings for the safety and toxicity for the products. Besides their beneficial effects, there are some limitations for using nutraceuticals. Poor bioavailability is the major constraint for their uses as nutraceuticals get eliminated from the body very easily and fail to provide significant medicinal benefit [116]. Moreover, lack of regulation is another limitation about the safety and efficacy of nutraceuticals. There is nothing mentioned regarding their doses, possible side effects, nutraceutical-drug interaction, allergic responses and their effect on individuals under certain health conditions. However, a person's susceptibility to any disease depends on genetic make-up, environmental factors, habit and lifestyle. So, the response to nutraceuticals may vary. Beyond their effective doses, nutraceuticals may pose toxicity and can be harmful to health also [117]. The success of using nutraceuticals can only be achieved with good marketing, lesser cost and consume reduction.

For new ingredients to be included in dietary supplements or nutraceuticals, manufacturers are responsible to perform all the related pre-clinical toxicity and safety studies. Local and international regulatory bodies need to judge the confirmation that supports manufacturer's conclusion that the ingredient is non-toxic [118]. As most of the nutraceuticals are of plant or microbiological origin, more research is required from different angles to streamline purity, dosage requirements, preclinical trials for disease prevention and treatment. The signaling pathways and receptor binding studies are needed to perform to customize studies.

Increasing awareness levels about fitness and health will encourage people to lead healthier lifestyles. This is the opportunity for food and pharmaceutical companies to make their products more consumer friendly if they merge natural products and nutraceuticals with medicines.

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