

Nutraceuticals: The New Generation Therapeutics

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Abstract

Nutraceutical is regarded as the bioactive substance and natural bioactive compounds include a broad diversity of structures and functionalities that provide an excellent pool of molecules for the production of therapeutic compounds. In this article, we present a review work on various nutraceuticals found naturally together with the recent progress that has been done on them. The health promoting effects of various kinds of nutraceuticals that has been claimed is also included in this article.

Keywords: Functional foods; Nutraceuticals; Bioactive compounds; Dietary supplements

Nutraceuticals is a broad term which describes any substance extracted from food sources with additional health benefits along with the basic nutritional value already present in them. They act non-specifically to promote general well-being of the individuals and also to control and prevent virulent conditions. The term “nutraceutical” combines two words – “nutrient” (a nourishing food component) and “pharmaceutical” (a medical drug) [1]. The name was coined in 1989 by Stephen DeFelic, founder and chairman of the Foundation for Innovation in Medicine, an American organization located in Cranford, New Jersey. They have remarkable role in human nutrition which has recently become one of the most important areas of investigation.

Categories of Nutraceuticals

These can be grouped into the following three broad categories:

1. Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids - Nutrients
2. Herbs or botanical products as concentrates and extracts - Herbals
3. Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements and meal replacements – Dietary supplements.

Nutrients

Nutrients are the substances that provide nourishment essential for the maintenance of life and for growth. Water and fat-soluble vitamins and antioxidants are the most commonly known nutrients and their potential health benefits have been associated with dietary intake or supplementation. Antioxidants help in the prevention of cancer and cerebrovascular diseases such as atherosclerosis. It has been found that the combination of vitamin E, C and beta carotene can be used in the reduction of low density lipoprotein oxidation and subsequent atherosclerosis [2]. Vitamin supplements stimulate the production of macrophage and T cells and thus increase antibody titre response to clinically relevant vaccines.

Herbals

Plants have been used for the treatment of numerous acute and chronic diseases since ages and such traditional medicine is still widely practiced today. Various parts of plants like seeds, berries, leaves, roots, flowers and bark are used for medicinal purposes which contain numerous nutraceuticals. The accumulation of knowledge of such

plants over hundreds of years can help in finding effective means of ensuring proper health care.

Dietary supplements

A dietary supplement is intended to provide nutrients that may otherwise not be consumed in sufficient quantities. Supplements as generally understood include vitamins, minerals, fiber, fatty acids, or amino acids, among other substances. There are more than 50,000 dietary supplements available and the most common ones are multivitamins [3].

Benefits of Nutraceuticals

Since years, nutraceuticals have played an important role in the overall well-being of humans. Several bioactive molecules are being identified to possess health benefits which continue to garner research interest so that safe and cost-effective molecules can be discovered for oral administration.

Cancer treatment

There is a tremendous need in clinics to impair cancer progression through non-invasive therapeutic approaches as all the currently available cancer therapeutic options are expensive but none of them are safe. The use of natural compounds to achieve this is of importance to improve the quality of life of young patients during their treatments. Some promising natural compounds that have shown excellent results *in vitro* and *in vivo* are: Chebulagic acid, Apigenin, Norcantharidin, Saffron/Crocin, Parthenolide, Longikaurin E, Lupeol, Spongistatin 1, and Deoxy-variolin B [4]. *Withania somnifera* (WS), commonly known as Ashwagandha, is one of the most powerful plants and is considered a major plant in ayurvedic medicine (an ancient form of medicine in Asia). The effectiveness of radiation therapy has been shown to enhance and the side effects of chemotherapeutic agents have been reduced when its extract was used in combination and moreover, the constituents do not interfere with their tumor-reducing actions [5]. Recently, it has been found that the plant contains withanolides which have anti-

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tumorigenic properties and this property has been demonstrated in experimental models [6].

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious dose-limiting side-effect. Vitamin E may help prevent CIPN. l-glutamine, goshajinkigan, and omega-3 are also promising in the prevention of the effects of CIPN [7].

Caffeic acid phenethyl ester (CAPE) is a natural bioactive compound which is derived from natural propolis and has been reported to have anti-cancer properties [8]. Metastatic cell behaviors are stimulated by the up regulation of voltage-gated channels and this ester has shown to block voltage-gated sodium channels in several cell lines from different cancers.

Sulforaphane (SFN) is a metabolic by product of cruciferous vegetables and in broccoli, it is present in very high concentrations. Its anticancer potency and the underlying mechanisms have been studied extensively using various cell cultures and experimental models [9].

Beta-sitosterol (BS) is a plant derived nutrient and is found to possess anticancer properties against breast cancer, prostate cancer, colon cancer, lung cancer, stomach cancer, ovarian cancer, and leukemia [10]. It interferes with multiple cell signaling pathways, including cell cycle, apoptosis, proliferation, survival, invasion, angiogenesis, metastasis and inflammation.

Synergistic effects of various combinations of dietary natural products including curcumin, quercetin, soybean isoflavones and silibinin have been described that have potential for the treatment of prostate cancer [11]. Various factors have been suggested which help in the decrease of cancer cell replication and increase in the chance of remission. For the prevention and successful treatment of cancers, it is necessary that dietary supplements with high doses of vitamin C are consumed in at-risk populations along with some changes in lifestyle.

Antioxidant properties

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells [12]. Certain groups of substances such as vitamins, carotenoids, flavonoids and minerals possess antioxidant characteristics. These substances help to boost immune and digestive systems and modulate inflammatory and degenerative processes in the body [13]. According to a recent study, dietary modification through the intake of antioxidants can help in the prevention of skin cancer [14].

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene), a type of natural phenol, is produced naturally by several plants in response to injury or when the plant is under attack by pathogens such as bacteria or fungi. Food sources of resveratrol include the skin of grapes, blueberries, raspberries, and mulberries [15]. It has been shown to be a scavenger of a number of free radicals. Its antioxidant property is mainly due to its effect as a gene regulator. Downregulation of the expression and activity of the oxidase enzyme helps in the inhibition of the production of reactive oxygen species. The polyphenolic compound stimulates mitochondrial biogenesis and thus reduces superoxide generation in mitochondria. Upregulation of the tetrahydrobiopterin-synthesizing enzyme GTP cyclohydrolase I prevents superoxide production from uncoupled endothelial nitric oxide synthase. Moreover, the expressions of a variety of antioxidant enzymes are also increased by resveratrol [16].

Treatment for osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis, affecting

millions of people worldwide. It occurs when the protective cartilage on the ends of the bones wears down over time. Although osteoarthritis can damage any joint in the body, the disorder most commonly affects joints in hands, knees, hips and spine. There's no known cure for osteoarthritis, but treatments can help reduce pain and maintain joint movement.

Some substances appear to display anti-inflammatory activity primarily through the inhibition of COX-2, an enzyme which is responsible for inflammation and pain. The C-phycoyanin (CPC)-based nutraceutical and constituents may be able to mediate 3 primary pathogenic mechanisms of osteoarthritis: inflammation, chondral degeneration, and oxidative stress in vitro [17]. Oral supplementation of chondroitin sulphate plus glucosamine helps repair the articular surface in osteoarthritis. Chondroitin-S reduces the concentration of the pro-inflammatory cytokines and transcription factor involved in inflammation. GlcN.S enhances cartilage specific matrix components and prevents collagen degeneration in chondrocytes by inhibiting hydrolytic enzymes, and preventing the oxidation of lipids and proteins. Chondroitin-S and GlcN.S are slow-acting drugs that alleviate pain and partly restore joint function in OA patients [18]. Recently, Methylsulfonylmethane (MSM) and boswellic acids (BA) have proved to be effective supplements for the management of inflammation and degeneration of joints [19]. Nowadays, glucosamine is becoming a popular OA supplement. It is an endogenous monosaccharide which is an important precursor in the biosynthesis of glycosylated proteins and lipids. Most glucosamine dietary supplements are derived from a polymer, chitin, found in the exoskeleton of shellfish and crabs. Several varieties of glucosamine supplements which include sulfate, hydrochloride and n-acetyl salts are sold in pharmacies, supermarkets and health food-stores [20].

Maintenance of cardiovascular health

Cardiovascular problems, or problems that affect the heart and blood vessels, are some of the greatest overall health problems worldwide.

Hypertension (HTN or HT), also known as high blood pressure or arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is persistently elevated. It is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults [21]. There are several nutraceuticals having lowering effect on blood pressure which include minerals, lipids, whole proteins, peptides, amino acids, probiotics, and vitamins. It has been shown that the use of potassium, L-arginine, vitamins C and D, cocoa flavonoids, beetroot juice, some probiotics, coenzyme Q10, controlled-release melatonin, aged garlic extract, and coffee helps in controlling hypertension [22]. When hypertension is associated with elevated levels of homocysteine (Hcy), it is known as hyperhomocysteinemia. Endoplasmic reticulum (ER) stress is induced by homocysteine in endothelial cells which lead to inflammation in the blood vessels and can ultimately result in ischemic injury. Black tea (BT) protects against hypertension-associated endothelial dysfunction through alleviation of ER stress. Therefore, BT supplements can prove to be beneficial for hypertensive patients [23].

Stroke is a worldwide major cause of mortality and morbidity. Ischemic stroke occurs when an artery to the brain is blocked. The brain depends on its arteries to bring fresh blood from the heart and lungs. The blood carries oxygen and nutrients to the brain, and takes away carbon dioxide and cellular waste. If an artery is blocked, the brain cells (neurons) cannot make enough energy and eventually stops working.

Alpha-linolenic acid (ALA) is an essential omega-3 polyunsaturated fatty acid found in seeds like canola, walnut, chia and flax. According to a recent study, ALA may be an efficient brain preconditioned against stroke [24]. If daily diet is enriched in ALA, then devastating damage caused by stroke can be prevented.

Other common food nutraceuticals

Regular consumption of fruit and vegetables helps in the prevention of cancer, stroke, cardiovascular disease, Alzheimer disease, cataracts, and age-related problems. There are several functional foods that contain significant amounts of bioactive components which may provide desirable health benefits [25].

Lycopene is the natural substance (part of the carotenoid group) responsible for the deep red color in many foods, most particularly in tomatoes. Dietary intakes of tomatoes and tomato products have demonstrated to reduce risks of cancer and cardiovascular diseases [26]. Apart from antioxidant properties of lycopene, there are several other mechanisms which are responsible for its beneficial properties. These include regulation of intercellular gap junction communication, hormonal and immune system and modulation of metabolic pathways [27]. Lycopene supplements have shown to improve body functioning in the individuals diagnosed with metabolic syndrome. There was a significant change in the inflammation status, insulin resistance also improved and the cholesterol levels were also controlled in such individuals [28].

Spices are aromatic or pungent vegetable substances used to flavour foods and have been used as preservatives for thousands of years. Spices have also been recognized to possess medicinal properties like digestive stimulant action, hypolipidemic effect, antidiabetic influence, antilithogenic property, antioxidant potential, anti-inflammatory property, antimutagenic, and anticarcinogenic potential of spices [29].

Curcumin (diferuloylmethane) is a yellow pigment which is derived from the rhizomes of *Curcuma longa* and is the major active ingredient in turmeric. Since years it has been used extensively in Ayurvedic medicine. It is non-toxic and exhibits a variety of therapeutic properties, including antioxidant, analgesic, anti-inflammatory and antiseptic activities. It has also shown to have positive effect in the treatment of arthritis [30]. Curcumin acts as an epigenetic regulator in various diseases and disorders. It inhibits DNA methyltransferases (DNMTs) which functions as a DNA hypomethylating agent; modulates histone modifications via regulation of histone acetyltransferases (HATs) and histone deacetylases (HDACs); and regulates of micro RNAs (miRNA) [31]. The clinical implication of native curcumin is hindered due to low solubility, physico-chemical instability, poor bioavailability, rapid metabolism, and poor pharmacokinetics. Therefore, there is a need to improve curcumin's pharmacokinetics, systemic bioavailability, and biological activity which can be done by encapsulation curcumin or by loading into nanoform(s) [32].

Quercetin is a one of a broad group of natural polyphenolic flavonoid substances found in many fruits, vegetables, leaves and grains, particularly abundant in onions and apples. It acts as a strong reducing agent and protects body tissue against oxidative stress. It acts as antioxidant by improving normal cell survival and as pro-oxidant induces apoptosis in cancerous cells whereby prevents tumor proliferation. Quercetin has been associated with numerous important properties like anti-viral, anti-inflammatory, antibacterial and muscle relaxing properties. It also acts as modulator of genes which are related to cell cycle, signal transduction, and xenobiotic metabolism [33].

Coconut, *Cocos nucifera*, is cultivated to provide a large number of products which have nutritional and medicinal values. Coconut oil comprises medium-chain fatty acids (MCFA) which are easily absorbed and metabolised by the liver, and can be converted to ketones. Ketone bodies may be beneficial to people with memory impairment, as in Alzheimer's disease (AD) as they can be used as an alternative energy source in the brain [34].

Milk proteins are precursors of many different biologically active peptides which are inactive within the sequence of the precursor proteins but can be released by gastro-intestinal digestion of milk, fermentation of milk with proteolytic starter cultures or enzymatic proteolysis [35]. These peptides are claimed to be health enhancing nutraceuticals for food and pharmaceutical functions. Whey, the liquid which remains after milk has been curdled and strained is an excellent source of bioactive compounds. Whey protein comprises 20% of total milk protein and it is rich in branched and essential amino acids, functional peptides, antioxidants and immunoglobulins. It gives benefits against a wide range of metabolic diseases such as cardiovascular complications, hypertension, obesity, diabetes, cancer and phenylketonuria. Whey proteins have shown to enhance recovery rate from and protect skin against detrimental radiations [36]. Angiotensin converting enzyme (ACE) inhibitor peptides can exert an antihypertensive effect. Immunomodulating casein peptides have been found to stimulate the proliferation of human lymphocytes and the phagocytic activities of macrophages. Antimicrobial peptides have been shown to kill sensitive microorganisms [37]. Antithrombotic peptides inhibit the fibrinogen binding to a specific receptor region on the platelet surface and also inhibit aggregation of platelets. Casein phosphopeptides can form soluble organophosphate salts and may function as carriers for different minerals especially calcium [38].

Buckwheat (*Fagopyrum esculentum*) is a plant cultivated for its grain-like seeds, and also used as a cover crop. Flour obtained from buckwheat is of great nutritional value as it contains high levels of proteins, polyphenols and minerals. Its antioxidant property is due to high levels of quercetin present. It has been shown to reduce risks of hyperlipidaemia and blood pressure and improve weight regulation [39].

Litchi chinensis belongs to the Sapindaceae family and is well-known in the Indian traditional system for its traditional uses. All parts of the plant are rich sources of phytochemicals--epicatechin; procyanidin A2 and procyanidin B2; leucocyanidin; cyanidin glycoside, malvidin glycoside, and saponins; butylated hydroxytoluene; isolariciresinol; kaempferol; rutin; and stigmasterol [40]. It is a rich source of antioxidants, so it protects from degenerative diseases and prevents arthritis. It is also effective to protect from asthma.

Wild apple fruit (*Malus sylvestris*) is a good source of polyphenolic compounds which have therapeutic effects on many diseases caused by reactive oxygen species and oxidative stress (e.g. cardiovascular or degenerative diseases, atherosclerosis, diabetes, osteoporosis, cancer, dermatitis, phototoxicity) [41]. It has been indicated that wild apple fruit might be taken into consideration as a source of antioxidant substances for food, dermocosmetic and cosmetic industry.

Seaweeds belong to a group of marine plants known as algae which consumed as sea vegetables in several Asian countries. Fucosterol (24-ethylidene cholesterol) is a sterol that can be isolated from algae, seaweed, and diatoms. It exhibits various biological therapeutics, including anti-cancer, anti-diabetic, anti-oxidant, hepatoprotective, anti-hyperlipidemic, anti-fungal, anti-histaminic, anti-cholinergic,

anti-adipogenic, anti-photodamaging, anti-osteoporotic, blood cholesterol reducing, blood vessel thrombosis preventive, and butyrylcholinesterase inhibitory activities [42].

Grape is a natural source of polyphenols with exceptional biological activities which has led to the development of several new grape-based food additives, dietary supplements, and bulk nutraceuticals which include grape seed oil, grape seed and skin powders, and pomace extracts. Grape-derived nutraceuticals also have a wide range of biological activities, which includes antioxidant, anti-inflammatory, and antimicrobial properties [43]. Special attention is paid to the role of biotechnology in producing a “new generation” of grape nutraceuticals by using plant cell technology and metabolite and genetic engineering techniques.

Oryzanol is present in rice bran oil which possesses a variety of health benefits which include reduction of cholesterol in blood, improvement of capillary action of blood vessels, anti-aging effect and others. Biscuit is a widely utilized cereal based processed food and the fortification of oryzanol into the biscuits can be used to provide antioxidant rich, highly stable and acceptable functional food to the consumers [44].

The intake of fiber in the diet helps in the reducing the risk and lowering the incidence of numerous diseases. It has been found that dietary fiber from whole foods or supplements may reduce the risk of cardiovascular disease by improving serum lipids and reducing serum total and low-density lipoprotein (LDL) cholesterol concentrations in adults and children. High fiber intake is also associated with reduced risk of colorectal and breast cancer [45]. Fibre consumption is associated with high nutritional value and antioxidant status of the diet, enhancing the effects on human health.

Chronic exposure to solar UV radiation damages skin, increasing its thickness and reducing its elasticity, and causes skin cancer. It has been shown that olive leaf extract helps in the prevention of UVB-induced skin damage and tumor growth [46]. Red Ginseng (the roots of *Panax ginseng* C.A. Meyer) is used clinically in China, Korea and Japan for various diseases, including atherosclerosis, hypertension and stress etc. The oral administration of Red Ginseng extract may be useful as a health supplement for protection against photoageing [47].

Ginger root/rhizomes (*Zingiber officinale* Roscoe) is well known as a remedy for travel sickness, nausea and indigestion and is used for wind, colic, irritable bowel, loss of appetite, chills, cold, flu, poor circulation, menstrual cramps, dyspepsia (bloating, heartburn, flatulence), indigestion and gastrointestinal problems such as gas and stomach cramps. Dietary supplements containing preparations of these roots are being used by consumers, and clinical trials are being carried out to evaluate their anti-inflammatory or antiemetic properties [48]. The exact mechanism responsible for the anti-emetic effects of ginger is unknown; however, the ginger phytochemicals, especially 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol, may function as a 5-hydroxytryptamine (5-HT₃) antagonist, NK₁ antagonist, antihistaminic, and possess prokinetic effects [49]. It has been shown that 6-gingerol can be a safe and potent chemotherapeutic/chemopreventive compound which acts through cell cycle arrest and induction of apoptosis in human oral and cervical tumor cells [50,51].

Future Prospects

The production of nutraceuticals is emerging as one of the major global food industries as it gives rise to improved healthcare and increased life expectancy. Since large number of medicinal herbs, spices

and trees are found in India, it is becoming a major producer and exporter of functional foods and nutraceuticals. Currently, research is being focused on traditional herbal extracts which were earlier linked with prevention of chronic diseases and health enhancement along with the establishment of their safety and efficacy.

The role of nutraceuticals in the prevention of various diseases is not necessarily due to a single compound, but due to the cumulative effect of several components present in the product. Therefore, it is important to conduct biomarker research for the comparison of preventative effects for different kinds of food. Moreover, standards should also be established to assess the prevention of diseases. New products can be developed by the recognition of variation in functional food and nutraceuticals composition for specialized markets which can lead to the production of plants with biochemically uniform produce having highly predictable health and nutritional properties. Measures should be taken to decrease the costs of the functional foods to the industry by finding new methods to isolate, characterize and purify them from various sources. Better characterization of the products is needed to optimize the benefits to human and animal health by the application of modern approaches in genomics, proteomics and metabolomics. Public awareness about the health promoting effects and value added properties of food products can help in the expansion of the global market.

Conclusion

Under nutrition and micronutrient deficiencies contribute substantially to the global burden of disease, especially, developing countries where rates of under nutrition and increased exposure to infectious diseases caused by crowding and inadequate sanitation are very high. The worldwide nutraceuticals market is growing day by day in the form of dietary supplements and functional foods and beverages. But dietary supplements are not as effective as their natural sources. Therefore, there is a need for the development of methods to increase the nutritional value of the foods and this can be achieved by the use of biotechnology. Biotechnological methods can be used for studying and cloning of various genes which can help to induce the expression of bioactive compounds. Development of nutraceuticals for novel health benefits, elucidating mechanisms of action of these products, development of study systems such as *in vitro* co-culture cell models can help in the elimination of various health issues. Modeling new eating habits using the existing knowledge is needed for the eventual ideal of ‘health for all’ vision.

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