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Nutraceuticals: A Potential Alternative for Pharmaceuticals

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Abstract—*The nutraceutical revolution began in the early 1980s, sparked off when the actual or potential clinical benefits of calcium, fiber, and fish oil were supported by clinical studies published in distinguished medical journals. The term "nutraceutical" was coined by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine. According to DeFelice, "a nutraceutical is any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease. Nutraceuticals may range from isolated nutrients, dietary supplements, and diets to genetically engineered ''designer'' foods, herbal products and processed products like cereals, soups and beverages. The range of products within nutraceuticals is broad and diverse including individual nutrients and biologically active phytochemicals, supplements, "functional" foods, and herbal products. Nutraceuticals have been proven to offer physiologic benefits or to reduce the risk of chronic disease, or both, beyond their basic nutritional functions. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body. Nutraceuticals create an open environment for new products that promise novel solutions to health-related issues. Nutraceuticals will play important role in future therapeutic developments. It has now progressed from being a mere concept representing an area within biomedical research, to a multibillion dollar industry with a very bright future ahead. Herbal nutraceutical is a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity, and quality of life. In the present review much effort has been devoted to provide their diseases modifying indications related to oxidative stress including allergy, Alzheimer, cardiovascular, cancer, diabetes, eye, immune, inflammatory and Parkinson's diseases as well as obesity.*

Keywords*: Herbal Nutraceuticals, therapeutic effect, antioxidants, functional foods.*

1. INTRODUCTION

Due to risk of toxicity and adverse effects of drugs, consumers are turning massively to food supplements to improve health where pharmaceuticals fails. This resulted in a worldwide nutraceuticals revolution[1]. The old proverb "an apple a day will keep the doctor away" is now replaced by "a nutraceutical a day may keep the doctor away"[2]. The term nutraceutical was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen De Felice, MD, founder and chairman of the Foundation for Innovation in Medicine(FIM), Cranford, NJ. According to De Felice, nutraceutical can be defined as, "a food (or part of food) that provides medical or health benefits including the prevention and/or treatment of a disease"[3]. However, the term nutraceutical as commonly used in marketing has no regulatory definition. Such products may range from isolated nutrients, dietary supplements, diet food, vita food, genetically engineered "designer" foods, herbal products, pharma foods, medi foods, fortified foods and processed foods such as cereals, soups and beverages etc. With recent developments in cellular-level nutraceutical agents, researchers, and medical practitioners are developing templates for integrating and assessing information from clinical studies on complementary and alternative therapies into responsible medical practice[4].

People can optimize the health-promoting capabilities of their diet by way of supplementation and by consuming foods that have been formulated or fortified to include health-promoting factors.

2. CURRENT SCENARIO.

Nutraceutical food or food components that help in treatment and prevention of diseases are made from herbal/botanical raw material. This is rapidly growing industry (7-12 % per year) with more than millions of people in the world using these natural products. The global nutraceutical market has reached $ 450 billion by 2015. According to recent analysis from Euro monitor, international global sales of health and wellness products are on track to reach a record of about $1 trillion by 2017, fueled by functional/ fortified products designed to offer specific health benefits[5]. In India, beverages and functional food are expected to witness much higher growth rates when compared to dietary supplement over the next five years[6].

In the Asia Pacific nutraceutical product market, Japan represents the largest consumer(about 47%), followed by China. India's functional food market is forecast to record moderate growth, with functional foods and beverages forecast to account for almost 71% of the dietary supplement

sector in 2017. In Middle East and Africa, dietary supplements represented the fastest growing market segment in the nutraceutical market, recording almost 31% yearly growth between 2007 and 2011.

In Eastern Europe, nutraceutical products market growth is being fueled by expansion in dietary supplements and functional food market segments. Russia represents the region's largest nutraceuticals consumer[7]. Hungary and Russia forecast to hold just over 20% and just under 24.5% of the nutraceutical market respectively in 2017.

Currently the Indian market is trying to incorporate traditional herbal ingredients (usually ayurvedic) into the nutraceutical portfolio. Key example is the chyawanprash supplements market in India, which stood at US $74.5 Million in 2012. The existence of alternative medicine in India, and the Indian consumer's belief in them, could provide a platform for the nutraceutical industry to capitalize on. India is currently a nascent market for nutraceuticals, without a concrete business model. The Indian consumer's awareness about conventional nutraceutical ingredients such as omega-3 fatty acids or lutein is severely limited, and nutraceutical manufacturers need to take up the cause and spread awareness about their products to the Indian masses[8]. Currently functional food enjoys largest share of the Indian nutraceuticals market followed by dietary supplements. This trend will drive the market for fortified foods and pro-biotic. With the rise of life style related diseases in urban India and penetration in rural India, the nutraceuticals products are going to remain in high demand.

3. FUTURE PROSPECTS.

Faced with technological, regulatory and logistical challenges, food and pharmaceuticals companies are taking advantage of the growth of nutraceuticals in different ways. WHO estimates that 60 % of the cardiac patients in the world will be Indians by 2030. Asia is expected to have 190 million diabetes cases, more than half of them are in India and China[9]. Scientists say that the percentage of overweight/ obese people in India is on track to rise from 9% in 1995 to 24% in 2025. The annual global nutraceuticals market is expected to be worth US$250 billion by 2018. Implementation of regulatory body is necessary to standardize the nutraceutical industry and use them in an efficient way to prevent from various diseases.

4. SOME IMPORTANT NUTRACEUTICALS.

Carnitine. Carnitine is an amino acid derivative that is found in all cells of the body, especially in striated muscles(heart muscles). It is synthesized in the liver, kidneys and brain from the amino acids lysine and methionine. Two analogs of carnitine, acetyl-L-carnitine and propionyl-L-carnitine, have been used clinically[10]. During myocardial ischaemia, blood flow to the heart is reduced, and carnitine levels in myocardial muscle decrease by as much as 40%[11]. This results in an increase of free fatty acids and their metabolites within the cell cytoplasm, and a reduction of the oxidative processes necessary for energy production[12]. Supplementation with carnitine may be of use in patients with ischaemic heart disease. Carnitine will lower, to a variable extent, plasma triglycerides and elevate high-density lipoprotein cholesterol levels. Carnitine can also be obtained from the diet,predominantly from food of animal origin, such as meat and dairy produce. In humans, 100–200 _mol carnitine is synthesised daily and an omnivorous diet supplies approximately 300–400 μ- mol daily[13]. The main function of carnitine is in fatty acid metabolism. The biochemical reactions of this nutrient are based on the reversible reaction between carnitine and long-chain fatty acyl groups:

Carnitine + Acyl-coA ↔Acyl-L-carnitine + Coenzyme A

Carnitine is therefore involved with many coenzyme A-dependent pathways[14]. The acetyl form of carnitine can easily cross the blood–brain barrier and it appears to be well tolerated and safe in humans[15]. Acetyl-L-carnitine is a very promising agent for the treatment of patients with mild Alzheimer's disease. It is thought to have many actions on brain cells and to increase the availability of acetylcholine to neurons, possibly by providing acetyl groups to conjugate with choline. It is also believed to be a partial cholinergic agonist, working in a similar way to the current pharmacological treatments for Alzheimer's disease[16]. Acetyl-L-carnitine has also been shown to increase the levels of nerve growth factor (NGF)[17] ,one of a group of substances known as neurotrophins. NGF is involved in the formation of neurons in the developing brain, and has been recently discovered to be implicated in the repair and maintenance of neurons and the formation of new connections between them[18].

With ageing there is gradual decline in the ability to efficiently generate energy necessary for anabolic processes, including the protein synthesizing activity of osteoblasts. L-Carnitine is necessary as a carrier molecule for the transport of acyl and acetyl groups from fatty acids across the mitochondrial membrane to enhance the bone health during old age.

Glucosamine and Chondroitin. Glucosamine is an amino monosaccharide, consisting of glucose and the amino acid glutamic acid[19]. It is found naturally in the body and is present in almost all human tissue, especially in cartilage, tendons and ligament tissues. It is a precursor of the disaccharide units of articular cartilage glycoaminoglycan (GAG), which forms most of the cartilage tissue[19-20]. The sulfate, hydrochloride and *N*-acetyl forms are usually used for therapeutic purposes. Chondroitin sulfate is a GAG made up from alternate sequences of differently sulfated units of uronic acid and *N*-acetylgalactosamine[21]. It is commercially obtained from bovine or calf cartilage[21].

Glucosamine is produced in the body by the addition of an amino group to glucose[22]. This ability declines with age and predisposes the body to arthritis. *In vitro* experiments have shown a dose-dependent increase in proteoglycan after

administering glucosamine, and increased synthesis of collagen[22]. Glucosamine is perhaps the most widely marketed supplement for degenerative joint disease, and is available from most pharmacies and health food stores, usually as the hydrochloride or sulfate salt. It is sometimes combined in supplements with the compound chondroitin sulfate, a GAG derived from bovine or calf cartilage. Both these compounds are reported to improve cartilage metabolism and to have anti-inflammatory effects[22]. The absorption of chondroitin would be expected to be less than that of glucosamine, due to its high molecular weight. Glucosamine has been linked with the skin enhancement also. Oral glucosamine has been shown to improve skin dryness and smoothness[23], and a significant reduction in wrinkles and fine lines was reported in one group of women[24].

Resveratrol. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced naturally by several plants in response to injury or when the plant is under attack by pathogens such as bacteria orfungi[25].Resveratrol has been identified in the leaves, skins and petals of *Vitis vinifera*, and also in wines and grape juice, but is also in other foods, such as peanut butter. In grape products, levels are higher after infection of the vine with *Botrytis cinerea*, and in red wines manufactured with extended time in contact with the skins[26]. There is evidence to suggest that resveratrol acts as an antioxidant and inhibits LDL oxidative susceptibility *in vivo*, by both chelating and free radical scavenging mechanisms. Cardioprotection is thought to result from its ability to inhibit platelet aggregation. At a physiological concentration of 1.2 g/L, resveratrol was shown to reduce platelet aggregation by ~41% in healthy subjects, and this was raised to 78.5% by increasing the dose[27].Cardioprotective effects of resveratrol may also be contributed to by inhibition of endogenous cholesterol biosynthesis, by inhibition of squalene monooxygenase, which is the rate-limiting enzyme in cholesterol biosynthesis[28]. This may explain the protective effects on CVD.

Conjugated linoleic acid. Conjugated linoleic acid (CLA) is a collective term used to describe the mixture of positional and geometric isomers of linoleic acid with conjugated double bonds. The two bioactive isomers of CLA are *cis*-9, *trans*-11 and *trans*-10,*cis*-12, and these two isomers usually predominate in commercial mixtures. The main dietary sources of CLA are the meat and dairy products of grazing animals in whose stomachs bacteria are able to modify dietary linoleic acid. CLA concentrations in dairy products are usually of the order of 3–9 mg/g, and are formed as a result of rumen gut microbial isomerisation of dietary linoleic acid. The levels of CLA in human plasma are directly related to milk fat intake; no isomerisation from linoleic acid occurs in the human gut[29].

There is a 40–50% reduction in colorectal cancer relative risk in those who use non-steroidal anti-inflammatory drugs (NSAIDs) continuously; this has led to the suggestion that inhibition of eicosanoid synthesis (NSAIDs block production of prostaglandins (PG) – eicosanoids) may have anticancer effects[30]. Arachidonic acid leads to eicosanoid production; it has been shown that eicosanoid products such as prostaglandin E2 (PGE2) are involved in carcinogenesis and that they can influence cell proliferation and tissue differentiation[31]. Enzymes involved in eicosanoid manufacture include cyclooxygenase (COX) and lipoxygenase (LOX)[32]. It is known that CLA is incorporated into phospholipids and competes with arachidonic acid, possibly thus displacing it from cell membranes. This would alter subsequent eicosanoid production[33]. For example, CLA has been shown to reduce arachidonic acid-derived PGE2, and this correlates with a reduction in tumorigenesis[34].

Soy isoflavones. The soybean in North America, also called the soya bean (*Glycine max*), is a species of legume native to East Asia, widely grown for its edible bean which has numerous uses. The plant is classed as an oilseed rather than a pulse by the UN Food and Agriculture Organization (FAO). Soy is available in a wide variety of different food forms, for example whole soybeans, soy sauce, tofu, tempeh, soymilk, miso (fermented soybean paste) and natto (fermented soybeans)[35]. Soy isoflavones have various properties like anti- cancerous, lowering the blood pressure, reducing the risk of CVDs etc. The major isoflavones present in soybeans are genistein, daidzein and, to a lesser extent glycitein. Genistein is found in the highest proportion. This conjugates to form its β-glycoside genistin in biological fluids. Daidzein and its β-glycoside daidzin are less abundant in soy foods but still present in significant quantity[36]. A third isoflavone, glycitin (and its aglycone glycitein), is found in soy but this has been much less researched as it is only found in relatively small amounts.These isoflavones are available as extracted compounds, in a range of foods, in traditional and modern commercial products, and in soy protein. The structural similarity between the isoflavones and oestradiol is the basis for the proposition that the isoflavones may be able to replace human oestrogenic activity.17β-Oestradiol is one of the most potent endogenous oestrogens in humans. The structures of isoflavones are similar to the structure of 17β-oestradiol in two ways: (1) Both have an aromatic ring with a hydroxyl group attached to it; (2) A nearly identical distance exists between the two hydroxyl groups in both[37].

In non-fermented soy products the conjugated isoflavones predominate, whereas in fermented products such as soy sauce and miso, the aglycone forms are more abundant. Fermented soy foods therefore already contain the aglycone form of genistein, theoretically allowing this to be absorbed straight into the blood.Cooking also generates this absorbable form by degrading the heat-labile malonyl glucosides of daidzein and genistein to the non-acylated form[38], allowing absorption in the gut.

Over the last 30 years, numerous animal and human studies have indicated that ingestion of isoflavone-rich soy protein is

associated with decreased LDL and unchanged or increased HDL-C plasma concentrations[39]. Consumption of soy products containing isoflavones may improve vascular function via a variety of mechanisms. Due to their structural similarities to oestrogen, it is thought that they may cause an effect by binding to oestrogen receptor (ER) β-receptors present in the vasculature, and protect against atherosclerosis[40].

Soy also has positive effect on blood pressure. A trial involving normotensive men and women concluded that soy protein supplementation, involving 40 g protein and 118 mg isoflavonoids daily for three months, resulted in a significant reduction in the systolic, diastolic and mean blood pressures[41].

Genistein is able to interfere with cell processes by inhibiting DNA topoisomerase and protein tyrosine kinase (PTK) [42]. Genistein is thought to target specific PTKs, particularly the epidermal growth factor receptor, and blocks the EGF-mediated pathway by preventing phosphorylation of tyrosine receptors, thereby causing cell death[43].This may result in apoptosis of cancerous cells.

Polyunsaturated fatty acids. Fatty acids derive from triglycerides (animal fats and plant oils) in the diet, and many can also be synthesised *de novo*. There is, however, a group that can only be obtained from the diet as the body lacks the ability to synthesise them, and these are known as essential fatty acids. Many of those of interest are derived from fish and plant oils and include linoleic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), α-linolenic acid (ALA) and γ-linolenic acid (GLA).

n-3 PUFA. The *n*-3 PUFA ALA is converted to EPA and then DHA which can compete with and inhibit the action of COX-2, and reduce PGE2 formation.

Flaxseed/ α-linolenic acid: Flaxseed oil contains more than 50% ALA, which is an essential *n*-3 fatty acid. Other sources of ALA include candlenut, hemp seed, pumpkin seed, canola, walnut and soybean[44]. Flaxseed provides the richest plant source precursor, ALA, which is converted to these long-chain fatty acids, and provides a way to correct deficiency and prevent diseases associated with decreased *n*-3 fatty acids.

Docosahexaenoic acid (DHA): is one of the major components of grey matter in the brain, and is important in the retina, testes, and present at high levels in fish oil. The major source is marine algae, consequently the largest commercial source is fish feeding off the algae. Many of the important body functions are thought to require adequate tissue levels of DHA, particularly brain and eye functions, and there is a growing trend to enrich a large number of foods with DHA, the virtues of which are widely extolled in the media. DHA is produced in the body from EPA by desaturation and elongation reactions[45].

n-6 PUFA. The *n*-6 PUFA linoleic acid is converted to GLA, then dihomo γ-linolenic acid (DGLA) and finally arachidonic acid (AA) through the action of a series of enzymes. Cyclooxygenase-2 (COX-2) then converts AA to prostaglandin E2 (PGE2). DGLA also forms the precursor of prostaglandin E1 (PGE1) through the action of cyclooxygenase-1 (COX-1) enzymes.

γ-Linolenic acid (GLA): γ-Linolenic acid (GLA) is an *n*-6 PUFA found in evening primrose oil and borage oil, which is metabolised in the body to dihomo γ-linolenic acid (DGLA)[46]. DGLA is the precursor of the 1-series of prostaglandins, which, although they are able to induce signs of inflammation, may actually decrease the activity of inflammatory cells. Ingestion of GLA, and its subsequent metabolism to DGLA, may also suppress inflammation through competitive inhibition of the production of leukotrienes and the 2-series prostaglandins[46] and may therefore be of benefit to those with arthritic conditions.

Lycopene. Lycopene is a natural red pigment synthesised by plants and microorganisms, but not by animals. High levels of lycopene are present in tomato juice, sauce and other concentrated extracts, plus a number of red fruits and vegetables, for example watermelons, pink grapefruit and pink guava[47].As humans are unable to synthesise carotenoids such as lycopene, they must be obtained from dietary intake. Processed tomato products such as tomato ketchup, tomato paste and tomato juice are all good sources of lycopene and, unlike some other nutrients, lycopene is not lost through cooking or food processing. Indeed, the lycopene bioavailability increases with heat processing and therefore tomato-based products are a better source than raw tomatoes[48]. After ingestion, lycopene is metabolised to a series of epoxides and diols[49]. Lycopene is one of the best dietary antioxidants and may therefore help to prevent CVS. The mechanisms of action of lycopene that have been proposed include inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase and thereby inhibition of cholesterol synthesis, LDL degradation, alterations in the size and composition of LDL particles, plaque ruptures and altered endothelial functions[50].

A recent study of the effects of supplementation with 250 mg daily of tomato extract (containing 15 mg of lycopene) demonstrated a reduction in blood pressure in patients with type 1 hypertension over the eight-week treatment period[51].

Herbal Spices. Spices such as turmeric, red pepper, black pepper, licorice, clove, ginger, garlic, coriander, and cinnamon target inflammatory pathways, thereby may prevent neurodegenerative diseases. The yellow curry spice, curcumin, has both antioxidant and anti-inflammatory activities that confer significant protection against neurotoxic and genotoxic agents. Curcumin has been shown to affect Alzheimer's disease through numerous mechanisms. In the neurons, a 75-kDa neurotrophin receptor (p75NTR) has been described as a receptor for Abeta. Abeta binds to p75NTR, activates NF-κB,

and induces cell death. Curcumin inhibited the activation of NF-κB and prevented Abeta-induced cell death in a human neuroblastoma cell line, suggesting a possible treatment for *Alzheimer's Disease*[52]. It has also shown positive effect in patients with *Parkinson's Disease.*

Piperine, an active alkaloid in *Piper nigrum*, is another nutraceutical that has shown potential against Alzheimer's disease. Chonpathompikunlert et al. investigated the effect of piperine on memory performance and neurodegeneration in an animal model of *Alzheimer's Disease.*

Brain Tumor: A brain tumor is considered as an abnormal growth of cells within the brain or the central spinal canal. Curcumin has been studied for its in vitro and in vivo antitumor activity against various types of brain tumors[53]. Medulloblastoma, an aggressive cancer and the most common malignant brain tumor in children, usually arises in the cerebellum. Bcl-2 and MMP-9, which play major roles in the pathogenesis and progression of medulloblastoma, are regulated by the transcription factor NF-κB. Bangaru et al. investigated the effect of curcumin on medulloblastoma cell proliferation, apoptosis, and migration. They found that curcumin inhibited cell proliferation and blocked clonogenicity of medulloblastoma cells. Furthermore, curcumin downregulated Bcl-2 and Bcl-xL, leading to caspase-mediated medulloblastoma cell death. Additionally, curcumin also blocked migration of medulloblastoma cells[53].

Epilepsy: Dietary modifications and nutraceuticals can benefit patients with epilepsy. Such spice-derived nutraceuticals include anethole[54], apigenin[55], kaempferol[55], capsaicin[56], curcumin[57], eugenol[58], limonene[59], myrcene[59], piperine[60], and quercetin[61].

Meningitis: Inflammation of the protective membranes covering the brain and spinal cord is called meningitis. This inflammation may be due to infection with viruses, bacteria, or other microorganisms. Meningitis is considered a life-threatening disease owing to the inflammation's proximity to the brain and spinal cord[62]. In Asia, garlic-derived preparations are used to treat human systemic fungal infections and cryptococcal meningitis. Concentrated garlic extracts could be used to treat cryptococcal infections[63]. Later, they showed that the commercial preparation allitridium, which contains diallyltrisulfide, also possesses potent in vitro fungicidal effects, with activity synergistic with amphotericin B[64].

5. CONCLUSION

At present, nutraceuticals represents the fastest growing segment of today's food industry. The hectic and stressful lifestyle and unhealthy diet leads to various kinds of diseases. Nutraceuticals which are rich in anti-oxidants and other health enhancing compounds can play a major role in preventing life threatening diseases. The use of nutraceuticals as an attempt to accomplish desirable therapeutic outcomes with reduced side effects, as compared with other therapeutic agents has met with great monetary success. The nutraceuticals market is growing rapidly at a very fast pace. Many nutraceuticals rich food items have been discovered with their potential benefits and doses. Research strategy is currently focusing on common spices and herbs for their nutraceutical benefits at the genome level. Study of effect of nutraceuticals at the genome level will help alleviate various diseases at the molecular level thus providing overwhelming benefits to the consumers.

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