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REVIEW PAPER

Nutraceuticals: The link between Foods and Pharmaceuticals

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ABSTRACT

Nutraceuticals are products which have become a link between foods and pharmaceutical supplements. They are substances which may be considered as food or an ingredient of food which will provide medical or health benefits. In a survey, conducted in the United Kingdom, Germany and France, it was shown that the diet of individuals is rated more by the consumers than exercise and hereditary factors, which are important for good health. Nutraceuticals often fill the gap between foods and drug, since they do not easily fall into the legal category of foods neither into proper pharmaceuticals. For better health management approaches it was crucial to consider the risk of toxicity of drugs and thus make use of functional foods. This resulted in the world-wide acceptance for nutraceuticals and led to a new era in medicine and health, which will have research prospectus in both food-beverages and pharmaceutical industry.

Keywords: - *Medicine, pharmaceuticals, nutraceuticals, functional foods, classification, herbal nutraceuticals, antioxidants.*

INTRODUCTION

The term nutraceutical, derived from the combination of nutrition and pharmaceutical, was coined by Dr. Stephen DeFelice, founder and chairman of Foundation for Innovation in Medicine which is an American organization which works for the domain of promoting medical health, in the year 1989. As stated by Dr. DeFelice, nutraceuticals are any substances which are either food or a part of food that can provide health benefits, including prevention and treatment for various diseases. [10] The interest in nutraceuticals was powered by the

progress in research and identifying its properties having potential application which is coupled with public interest, health benefit and consumer demand. The developing market and health trends have led to a new segment in the food and pharmaceutical industry which is now known as functional foods/nutraceuticals. These foods are being formulated and fortified in such a way that it has health-promoting capabilities and the way of supplementation can be easily optimized by the population as per their requirements.[3] Consumers demand that the food products processed now should be 'as natural as possible' which becomes parallel to one's knowledge and perception to what being healthy is. In developed countries, people are aware that the food they consume does not contain

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enough amount of nutritive value which is why they take extra vitamin supplements, but now the trends have changed. People prefer natural substitutes such as herbals, instead of pharmaceuticals. Due to increasing consumer demand in this area, pharmaceutical companies have started exploiting people's choice and have promoted benefits of natural products in the form of capsules or tablets which is known 'medicalization in nutrition.' Various terms like dietary supplements, functional foods, pharmaceuticals are often being used interchangeably, but a thin line does exist in using these terms. Functional foods are when there is 'scientific intelligence' involved while preparation of food with or without the knowledge of how or why is it used, whereas a substance is called a nutraceutical when the functional food is used in the prevention or treatment of diseases other than deficiency conditions like anaemia. The term nutraceuticals encompasses a broad range of foods which include dietary supplements, herbal products, isolated nutrients, cereals, soups and beverages. A dietary supplement, according the Dietary Supplements Health and Education Act (DSHEA) is defined as a product which intends to supplement the diet which consists of the following dietary ingredients such as a vitamin, a herb, a mineral, an amino acid, which will increase the total daily intake by combination of these ingredients. [5]

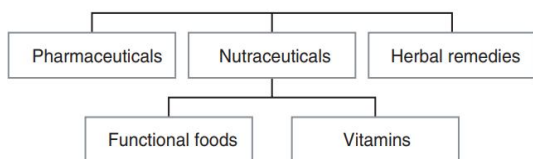


Figure 1 – Relationship between nutraceuticals and other health products [5]

Nowadays, due to the potential nutritional, safety and therapeutic effect, these nutraceuticals have been receiving a considerable interest and most of them possess multiple therapeutic properties. [1] The global nutraceutical market was estimated at USD 382.5 billion in 2019 and is expected to grow at a compound annual growth rate of 8.3% from 2020-2027 and reach USD 722.5 billion by the year 2027. [11]

The manufacturing of the nutraceuticals by the food scientist working on it will not only include physiological properties, but also the stability of the product and its cost effectiveness. To demonstrate this point, the glucoside derivative of limonin is preferable as an ingredient in foods, since it has similar anti-carcinogenic activity as that of triterpene limonin and is water soluble and virtually tasteless. The animal and plant kingdoms contain several such compounds which have therapeutic advantage or danger depending on what dose is consumed. Studies have also showed that there are no systematic follow-ups for any side-effects and fatalities while consuming any nutraceutical. Some of the ingredients which are used as nutraceuticals are being marketed as products on the basis of its use since many years as traditional medicines. A number of ingredients are now being classified as Generally Regarded As Safe (GRAS) by the Food and Drug Administration and is allowed to be a part of the human diet as food-product ingredient. [3, 6] Many pathological complications such as diabetes, neurological disorders, cancer, atherosclerosis, cardiovascular diseases involve many changes in our body which also includes alterations in redox state. Most of these

nutraceuticals, in recent studies have shown antioxidant activity with the ability to counter such situations and hence give promising results to prevent or treat such diseases and become a source of health promotion to mitigate the effects of such disorders. [1]

Classification of nutraceutical factors

There are hundreds of substances reported as nutraceuticals and some of the recognizable substances include fibre, carotenoids, allyl sulphur compounds, isoflavones and tocotrienols. Depending upon an individual's interest or background, the organizational scheme for nutraceutical compounds can vary. Taking an example of a cardiologist, the most interested nutraceutical substances would be for reducing the risk factors of heart disease. Their interest may lie in substances which positively influence hypercholesterolemia and hypertension and to reduce platelet-dependent thrombotic activity or free radical-dependent thrombotic activity. *n*-3 fatty acids, grape flavonoids, quercetin and phytosterols are some of the nutraceutical substances which would be of particular interest. Similarly for oncologists those substances would be favourable that are associated with targeting anti-carcinogenic activities. The nutraceuticals in this case would be associated with amplification of microsomal detoxification systems and antioxidant defences and also they may slow the progression of the existing cancer or tumour mass. Nutraceuticals can be separated into groups of plants, animals and microbes which include bacteria and yeasts. This classification or separation of nutraceutical substances is important for the ease of diet planning

and can be an effective tool for classroom and seminar construction. The food source may not necessarily be the point of origin for one or more substances, which is an interesting consideration with this classification scheme. One example to justify this is the conjugated linoleic acid (CLA), which is originally made by bacteria in the rumen of the cow and is actually a part of human diet, as a component of beef and dairy products. Another example is of choline and phosphatidylcholine which is present in plants, animals as well as in microbes because of their fairly conserved biochemical aspects. Table 1 contains the nutraceutical substances which are grouped on the basis of their food-source providers.

Also there are amino acids and their derivative which are produced by bacteria in fermentation systems and they become a non-food source of the nutraceutical factors sourced by development of modern fermentation techniques. These nutraceutical molecules can be produced into organisms which are economically feasible by using recombinant-genetic engineering techniques and enable new avenues for obtaining nutraceutical compounds. An example of this is the production of eicosapentaenoic acid (EPA) by bacteria. It is a fatty acid which is produced in bacteria and some algae. The EPA obtained from salmon is produced by algae and later incorporated in the salmon that consume those algae. Using recombinant techniques, the appropriate DNA is imported in non-EPA producing bacteria.

Table 1-Examples of nutraceutical substance classified by food source

PLANTS	ANIMALS	MICROBIAL
Pectin	Eicosapentaenoic acid	<i>Saccharomyces boulardii</i>
Cellulose	Creatine	<i>Bifidobacterium bifidum</i>
Quercetin	Conjugated linoleic acid	<i>Lactobacillus acidophilus</i>
Ascorbic acid	Calcium	<i>Streptococcus salivarius</i>
β-glucan	Coenzyme Q ₁₀	<i>Bifidobacterium longum</i>
Lycopene	Choline	<i>Bifidobacterium infantis</i>
Proanthocyanidins	Lecithin	
Lignin		
Geraniol		
Hemicellulose		
α-tocopherol		

In relation to the above mentioned classification, nutraceuticals can also be classified or grouped on the basis of relatively concentrated foods. This classification is appropriate when the interest is related to a particular nutraceutic or when there is interest in a specific food for geographical reasons or for the purpose of developing functional foods. An example where the interest is may be in the local crop or ones which are traditionally used in some countries include pepper in south western

United States, red wine in Western Europe and Northern California, olive oil in Mediterranean regions. Many of these nutraceutical compounds are usually found in higher concentrations in particular foods for example capsaicinoids in pepper fruits, and allyl sulphur usually present in onions and garlic. Following table (Table 2) gives a list of some nutraceuticals that are considered unique to specific foods.

Table-2 Examples Of Foods With Higher Content Of Specific Nutraceutical Compounds

Nutraceutical Compounds	Foods Of Remarkably High Concentration
Isoflavones	Soybeans, legumes, apios
Allyl sulphur compounds	Onions, garlic
Lycopene	Tomatoes and tomato products
Lignans	Flax, rye
Catechins	Tea, cocoa, apples, grapes
Lactobacilli and Bifidobacterium	Yogurt and other dairy products
Anthocyanates	Red wine
Curcumin	Turmeric
Quercetin	Onions, red grapes, broccoli, citrus fruits
β-carotene	Carrots, squash, pumpkin, citrus fruits
β-glucan	Oat bran

Another means of grouping the nutraceuticals is by their mechanism of action. The classes for differentiation are antioxidant activity, antibacterial, antihypertensive, anti-aggregate, anti-inflammatory, anti-carcinogenic, anti-hypercholesterolemic, osteoprotective and so on. Examples are listed in Table-3. This classification is easier when in diet planning, also helpful for individuals who are genetically predisposed to a particular medical

condition or for scientists who want to develop powerful functional foods. A product developer would also benefit from these as he might consider the ingredients which are categorized to develop a new product that would be effective against several disorders like inflammation, high blood pressures and high cholesterol levels.

Table-3. Nutraceuticals Classified on the Basis of Mechanism of Action

Anticancer	Antioxidant Activity	Anti-Inflammatory	Osteogenetic Or Bone Protective	Positive Influence On Blood Lipid Profile
Capsaicin Genestin Limonene	Ascorbic acid β-carotene Tocopherols	Linoleic acid Eicosapentaenoic acid γ-linolenic acid	Soy protein Genestin Fructo-oligosaccharide	β-glucan Quercetin Tannins
Curcumin	Catechins	Curcumin	Casein phosphopeptides	Pectin
α-Tocopherol <i>L. acidophilus</i> <i>L. bulagricus</i>	Gingerol Tannins Lycopene	Quercetin	Inulin Calcium	Resveratrol Saponins α-Tocotrienol

Health Benefits Of Nutraceuticals

There are plenty of benefits of nutraceuticals and also everyday new uses are being discovered. Nutraceuticals have the potential to treat a wide array of diseases, disorders and illnesses which range from physiological to psychological health. Nutraceuticals have been used to enhance immunity, boost energy, prevent chronic diseases, reduce drug cravings, relieve anxiety and improve overall health. Besides these substances used a nutraceuticals have shown promising results in treating disorders due to oxidative stress including allergic reactions, cardiovascular disorders, neurological disorders like Alzheimer's disease, inflammatory diseases, obesity and Parkinson's disease. There are various nutraceuticals which have been shown to treat or prevent more than one disease. [9]

Lycopene

Lycopene is a red colour natural pigment synthesized by plants and microbes but not animals. Lycopene contained vegetables and fruits exhibit cancer-protective effect by decreasing the oxidative stress and damage to DNA and are found exclusively in guavas, tomatoes, watermelon, pink

grapefruit and papaya. They are particularly found in red fruits for example, tomato and is one of 600 carotenoids which function as pigments in photosynthesis and photoprotection. Out of these, around 24 of them are present in foods, for example β-carotene which is present in carrots, green-leafed vegetables, broccoli and lutein found in green peas, spinach and watercress. Since lycopene is not synthesized by humans, there are extra dietary supplements which are necessary such as processed tomato ketchups, tomato juice, paste which are good sources of lycopene. A lipid rich diet also increases the bioavailability of lycopene and once it is ingested, it is found concentrated in adrenal glands, liver, testes and prostate. Since it is concentrated in various tissues, it protects against cancer. The link between carotenoids and prevention of cancer and coronary artery disease (CAD) has increased the importance of vegetables and fruits in human diet.(ncbi) There are evidences that lycopene is also beneficial in the prevention or symptom reduction of coronary heart disease (CHD). β-carotene also has antioxidant activity, prevents chronic inflammation that is associated with cancer as well as which is associated with immune-suppression. It is available in formulations

like oral gel, tablets and capsules and the recommended dose is 10-40mg/day. [1, 2, 4]

Grape Seed Proanthocyanidin Extract

These substances occur naturally in vegetables, fruits, nuts, seeds, flowers and bark. Proanthocyanidins which are present in grape seed extract are based on either catechins or epicatechin, these monomers join together and form dimers, trimers, oligomers and many other different structures. These are available in formulations like tablets, capsules, patch, gel, sustained release tablet and effervescent tablet. These compounds are poorly absorbed by the small intestine and are thought that ingestion results in metabolism by bacteria present in the colon. Proanthocyanidins are said to be anti-angiogenic compounds. Angiogenesis is an enzymatic process while involves the down-regulation in healthy individuals and anti-angiogenic compounds are selective against newly formed blood vessels while they spare the existing ones not leading to any side effects even after prolonged exposure. They prevent diseases which involve degenerative process such as Parkinson's disease, multiple sclerosis, cancer, diabetes, arthritis, and osteoporosis. According to research it was suggested that Grape seed proanthocyanidin extract (GSPE) could be used as an adjuvant for skin protection from sunlight damage. 1% of GSPE containing formulations into a skin cream and applied 30 minutes prior to UVA/UVB radiation exposure has been reported to produce a 9% increase in sun protection as it resulted in scavenging the oxygen free radical. It was found to be effective in mitigating the

hyperpigmentation problem in women with chloasma. [1, 4]

Probiotics

Scientific interest in this area augmented from the work Metchnikoff did to transform toxic flora of the large intestine into a host friendly colony of *Bacillus bulgaricus*. Probiotics are generally defined as live microbial feed supplement which is beneficial to the host when given in an adequate amount as it improves the intestinal microbiota and maintains a proper balance. Following are the categories which are included as probiotics: Lactobacilli such as *L. acidophilus*, *L. brevis*, *L. casei*, *L. delbrueckii subsp. bulgaricus*; Gram positive cocci such as *Enterococcus*, *Lactococcus lactis*, *Streptococcus salivarius subsp. thermophilus* and Bifidobacteria such as *B. infantis*, *B. bifidum*, *B. longum*, *B. thermophilum*. Probiotics are available in formulations such as powder form, liquid, gel, or paste or granules form and capsule form. There are evidences that probiotics are beneficial in treating infections of the ear, urinary tract, decrease the risk of systemic conditions like allergy, asthma and cancer. Specific probiotics are also used to treat gastrointestinal conditions which include lactose intolerance, acute diarrhoea and side effects associated with antibiotics. They have properties of non-toxic, non-pathogenic, resistance to gastric acid and adherence to the epithelial tissues which produce antibacterial substances.

Prebiotics

Prebiotics are generally defined as dietary ingredients which are beneficial to the host as they selectively alter the composition and metabolism of

the gut microbiota. These are particularly fructose-based oligosaccharides which have unique chemical structures and are not digested by humans. The consumption of prebiotics promotes the growth of *Lactobacillus* and *Bifidobacteria* in the gut and thus improves metabolism. Foods like bananas, tomatoes, chicory roots and alliums are a rich source of fructo-oligosaccharides. Some oligosaccharides like stachyose and raffinose are present in beans and peas. Prebiotics have health benefits which include lactose tolerance, neutralization of toxins, anti-tumour properties, and reduction of constipation, blood lipids and blood cholesterol levels and stimulate intestinal immune system. [1, 2]

Flax seeds and other spices

Flaxseed, also known as linseed is produced from *Linum usitatissimum* has been used for number of medical and non-medical application since many years. Recent research studies have shown new health benefits which are now promoted by producers. It contains 50% α -linolenic acid (ALA) which is an essential *n*-3 fatty acid. ALA is an important fatty acid and it should be a part of the human diet. Other sources of ALA include pumpkin seeds, canola, walnut, soybean and candlenut. Studies have recommended the replacement of *n*-3 polyunsaturated fatty acids (PUFAs) by *n*-6 fatty acids, but ideally the ratio should be equal. Both *n*-6 and *n*-3 are precursors of eicosanoids which include thromboxanes, prostaglandins and leukotrienes. A balance is required in the diet as those derived from *n*-6 fatty acids have opposing properties to those derived from *n*-3. If a diet is rich in *n*-6 and lacks *n*-3 fatty acids, it can lead to

allergies, inflammation, blood aggregation, cardiovascular diseases and diabetes. Flaxseed provide the richest source precursor, ALA, which is then converted to long chain fatty acids and a proper way to correct/prevent the deficiency and diseases associated with decreased *n*-3 fatty acids. The therapeutic areas which are covered when using flaxseed as nutraceuticals, include cancer prevention and improve respiratory health as it also have antioxidant properties. They are available as soft capsule formulations. Flaxseed contains lignans which include matairesinol, pinoresinol and the major one is secoisolariciresinol diglucoside (SDG). Recent studies have shown the activity of flaxseed and lignans against metastasis. In an experiment, different groups of mice with oestrogen receptor – negative breast cancer were supplemented with flaxseed oil and SDG; there was a reduced tumour growth and metastasis in all cases and there was no significant difference in effect of SDG and flaxseed oil, proving both have anti-cancer properties. [4]

Other spices such as turmeric/curcumin, fenugreek, onion, garlic, pepper/capsaicin, and eugenol have different health benefits like lowering of blood cholesterol level, protection and dissolution of cholesterol gallstones, antioxidant activity, and hypoglycaemic potential. Spices and herbs are almost non-toxic in all cases when used as food and are traditionally used in our daily diet in optimum amounts. But again, if the doses of these spices or medicinal herbs increase than the required level, can cause kidney toxicity, anaemia, weight loss, liver toxicity and other dermatological problems. [2]

Melatonin

Melatonin is a hormone which is secreted by the pineal gland. It is biosynthesized from tryptophan and the intermediate in this process is serotonin. Melatonin has been called a drug since it is regarded as a hormone. Its production varies with age. Young adults secrete about 5-25 micrograms of melatonin daily and this is decreased with advancing age. Foods such as bananas, tomatoes, cucumbers and beetroots have been identified to contain melatonin. It is rapidly metabolized by the liver and more than 85% of it is excreted as 6-sulfatoxymelatonin in the urine. The recommended dose of melatonin is 0.3-2.5 mg/day and the therapeutic advantages of this are in the areas of cardiovascular health, cancer prevention, sport enhancement, sleep improvement and bone health as it also has antioxidant activity. It is available as tablets, patches and in liquid formulations. Research has shown that melatonin overcomes cardiac injury after arterial occlusion followed by reperfusion. Melatonin is a powerful antioxidant in terms of ameliorating hypoxia and re-oxygenation damage. Intraperitoneal dose of 150µg/kg was found to be the most effective. Melatonin plays an important role in the control of circadian rhythms and is being widely researched as an aid to shift-work adaptation, jet lag and for problems of insomnia. The hypothesis of 'melatonin replacement' states that decline in melatonin due to age contributes to insomnia and its replacement with physiological doses improves sleep. It is also a powerful free-radical scavenger and is used as an antioxidant in ageing and related problems. Melatonin is proapoptotic as well as it inhibits

apoptosis in immune cells and neurons, which is why is it considered for cancer therapy as its activity in relation to apoptosis may depend on both type of the cell and functional state of cell. It not only reverses the metabolic changes and enhances lymphocyte and macrophage response to tumours, but also acts at G-protein membrane receptors and help in stimulating cytokines thus mounts an immune response. An example is when melatonin is administered with interleukin-2; it synergistically acts to prolong survival of cancer patients. There are also evidences that melatonin has health benefits in bone health as bone formation or resorption cycles are thought to follow a circadian pattern which in part is modulated by the cyclical secretion of melatonin. For skin health, topical application of melatonin either alone or combined with vitamins C and E has shown to reduce UV-induced skin erythema. [1, 2, 4]

Ornithine

Ornithine is one of the nutraceuticals in combination with others which is believed to increase performance either by renewing or increasing energy stores in the body or modify the biochemical changes contributing to fatigue. Ornithine α -ketoglutarate (OKG) is a salt formed from one molecule of α -ketoglutarate and two molecules of ornithine which is a precursor of many metabolites which are involved in cell propagation and tissue repair and thus is widely promoted as supplement for athletes and bodybuilders. It is involved in synthesis of amino acids in muscles, liver and lung tissue and is also used for treatment of burns and trauma from post-surgery. Beneficial

effects have been observed at 170mg/kg dosage level of ornithine. [1, 2, 4]

CONCLUSION

With the ever-changing lifestyles of human beings, a healthy diet is very important. Nutraceuticals have proven health benefits and their consumption will be an advantage as it will prevent number of disease and disorders and allow humans to maintain an overall good health. Nutraceuticals provide physiological benefits and is used to improve health, delay aging, prevent chronic diseases, maintain structure and function of the body and increases life expectancy. The present review has efforts devoted to provide an overall insight of different substances used as nutraceuticals and are nowadays more preferred over other complementary therapies, particularly those with antioxidant activities. When formulating nutraceuticals, consumer-friendly terms must be used and should be provided with scientifically correct and proven information and instruction to patients.

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