

ROLE OF NUTRACEUTICALS IN VARIOUS DISEASES: A COMPREHENSIVE REVIEW

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ABSTRACT

Nutraceuticals have received considerable interest because of their presumed safety and potential nutritional and therapeutic effects". The concept of nutraceuticals was started from the survey in U.K., Germany and France which concluded that diet is rated more highly by consumers than exercise or hereditary factors for achieving good health. In recent years there is a growing interest in nutraceuticals which provide health benefits and are alternative to modern medicine. By using nutraceuticals, it may be possible to reduce or eliminate the need for conventional medications, reducing the chances of any adverse effect. Nutraceuticals often possess unique chemical actions that are unavailable in pharmaceuticals. The entire world is fighting diseases characteristic of the modern age such as obesity, osteoporosis, cancer, diabetes, allergies, and dental problems. With a global increase in the prevalence of obesity, both nutrition and exercise play key roles in its prevention and treatment. Nutrients, herbals and dietary supplements are major constituents of nutraceuticals which make them instrumental in maintaining health, act against various disease conditions and thus promote the quality of life. Using food products to promote health and cure disease is renowned. Currently most of the drug molecules available in the formulations were anciently used in their crude form.

Keywords: Nutrient, Disease and treatments, Future food, Medicine.

INTRODUCTION^{1,8}

Today the exploration and exploitation of the disease fighting properties of a multitude of photochemical found in both food and nonfood plants have created a renaissance in human health and nutrition research. At the same time, many opportunities for the development of novel dietary products have been created. With all new fields of study come new term knew as "Nutraceuticals"¹. A term combining the words "nutrition" (a nourishing food or food component) and "pharmaceutical" (a medical drug), is a food or food product that provides health and medical benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and specific diets to

genetically engineered foods, herbal products and processed foods such as cereals, soups and beverages. ^[2]Hippocrates, the father of Western medicine, said that people should "Let food be thy medicine." The Indians, Egyptians, Chinese, and Sumerians are just a few civilizations that have provided evidence suggesting that food can be effectively used as medicine to treat and prevent disease this fact was supported by Ayurveda, the five thousand year old ancient Indian health science. In Japan during the 1980s the modern nutraceutical market began to develop and now days the nutraceutical industry has grown alongside the expansion and exploration of modern Technologies^{3,4}.

Foods and nutrients play a vital role in normal functioning of the body. They are helpful in maintaining the health of the individual and in reducing the risk of various diseases. Nutraceuticals are medicinal foods that play a role in maintaining well being, enhancing health, modulating immunity and thereby preventing as well as treating specific diseases. Thus the field of nutraceutical can be envisioned as one of the missing blocks in the health benefit of an individual. It has been scientifically proved and supported by various research articles that nutraceutical are efficacious to treat and prevent various disease conditions⁵.

About 2000 years ago, Hippocrates correctly emphasized "Let food be your medicine and medicine be your food".

In the past five years, the world has witnessed the explosive growth of a multibillion dollar industry known as nutraceutical. The term "nutraceutical" combines the word "nutrient" (a nourishing food or food component) with "pharmaceutical" (a medical drug).^[6]

"Nutraceutical" is a term coined in 1979 by Stephen De Felice.^[7] It is defined "as a food or parts of food that provide 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" food, herbal products, and processed products such as cereals, soups, and beverages. A nutraceutical is any nontoxic food extract supplement that has scientifically proven health benefits for both the treatment and prevention of disease⁸.

CONCEPTS OF NUTRACEUTICALS⁹

In the pharmaceutical development process, it is a requirement to have clinical test results from animal tests and studies, for verification of the effects. On the other hand, in the case of nutrition, there was no verification method for foods in preventing diseases in the past. In recent years however, as food composition has been scientifically proven to cause

lifestyle-related diseases, and has become a social issue.

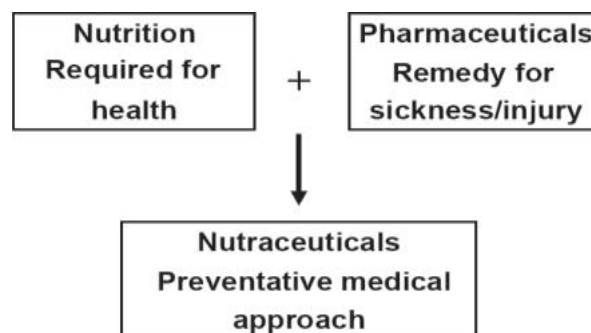


Fig: 1: concept of nutraceuticals
Benefits Of Nutraceuticals¹⁰

From the consumers' point of view, functional foods and nutraceuticals may offer many benefits:

1. May increase the health value of our diet.
2. May help us live longer.
3. May help us to avoid particular medical conditions.
4. May have a psychological benefit from doing something for one self.
5. May be perceived to be more "natural" than traditional medicine and less likely to produce unpleasant side-effects.
6. May present food for populations with special needs (e.g. nutrient-dense foods for the elderly).

CATEGORIES OF NUTRACEUTICALS¹¹

Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. They are categorized as follows.

(a) Nutrients

Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids, Common nutrients and their associated health benefits.

Table 1: List of nutrients and their relevance¹²

Nutrients	Health benefit
Vitamin A	Antioxidant, essential, for growth and development and in the treatment of certain skin disorders.
Vitamin E	Antioxidant, helps form blood cells, muscles, lung and nerve tissue, boosts the immune system.
Vitamin K	Essential for blood clotting
Vitamin C	Antioxidant, for healthy bones, gums, teeth and skin, in wound healing, prevent common cold and attenuate its symptoms.
Vitamin B1	Helps to convert food in to energy, essential in neurologic functions.
Vitamin B2	Helps in energy production and other chemical processes in the body, helps maintain healthy eyes, skin and nerve function.
Vitamin B3	Helps to convert food in to energy and maintain proper brain function.
Folic acid	Produce the genetic materials of cells, in pregnancy for preventing birth defects, RBCs formation, protects against heartdisease.

Calcium	Bones and teeth and maintaining bone strength important in nerve, muscle and glandular functions.
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(b) Herbals

Herbs or botanical products as concentrates and extracts. Common herbs and their therapeutic relevance.

Table 2: Herbals used and their therapeutic relevance¹³

Herbals (Botanicalsource)	Therapeutic activity
Aloe Vera gel (Aloe Vera L. N.L.Burm.)	Dilates capillaries, anti-inflammatory, emollient, wound healing properties.
Ephedra (Ephedra sinica Stapf.)	Bronchodilator, vasoconstrictor, reduces bronchial Edema.
Garlic (Allium sativum L.)	Antibacterial, antifungal, antithrombotic, hypotensive anti-inflammatory
Licorice (Glycyrrhiza glabra L.)	Expectorant, secretolytic, treatment of peptic ulcer.
Ginger (Zingiber officinale Rosc.)	Carminative, antiemetic, cholagogue, positive inotropic.

(c) Dietary Supplement¹⁴

Dietary supplements are products administered through mouth that contain a dietary ingredient intended to add something to the foods you eat. Examples of dietary supplements are black cohosh for menopausal symptoms, ginkgo biloba for memory loss, and glucosamine/chondroitin for arthritis. They also serve specific functions such as sports nutrition, weight-loss supplements and meal replacements.

Supplement ingredients may contain vitamins, minerals, herbs or other botanicals, amino acids, enzymes, organ tissues, gland extracts, or other dietary substances. They are available in different dosage forms, including tablets, capsules, liquids, powders, extracts, and concentrates.

Traditional and Non- Traditional nutraceuticals

Wide variety of nutraceutical foods are available in the market which falls in the category of traditional foods and non traditional foods.

a) Traditional Nutraceuticals

Under the category of traditional Nutraceuticals comes food in which no change to the food are made; It is simply natural, whole foods with new information about their potential health qualities. There has been no change to the actual foods, other than the way the consumer perceives them. Many fruits, vegetables, grains, fish; dairy and meat products contain several natural components that deliver benefits beyond basic nutrition, such as lycopene in tomatoes, omega-3 fatty acids in salmon or saponins in soy. Even tea

and chocolate have been noted in some studies to contain health-benefiting attributes. Tomatoes and salmon are two types of food that researchers have found to contain benefits beyond basic nutrition - in this case, lycopene and omega-3 fatty acids, respectively.

b) Non traditional Nutraceuticals¹⁵

They are the outcome from agricultural breeding or added nutrients and/or ingredients such as orange juice fortified with calcium, cereals with added vitamins or minerals and flour with added folic acid are non traditional nutraceutical. Agricultural scientists successfully have come up with the techniques to boost the nutritional content of certain crops. Research currently is being conducted to improve the nutritional quality of many other crops¹⁵.

NUTRACEUTICALS AND DISEASES

1) Nutraceuticals against Alzheimer's disease (AD)¹⁶

Alzheimer's disease (AD), also called senile dementia of the Alzheimer type (SDAT), primary degenerative dementia of the Alzheimer's type (PDDAT), or simply Alzheimer's, is the most common form of dementia. The various nutraceuticals which are used to cure Alzheimer's disease is as follow:-

Antioxidants

Antioxidants are very essential in the treatment of almost all diseases because most chronic diseases carry with them a great pact of oxidative stress. Oxidative stress plays a chief job in neurodegenerative diseases such as

Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Oxidative stress is accelerated by the ageing process along with lack of dietary antioxidants. A huge number of studies have found an association between high dietary antioxidant intake and a decreased risk of AD which is very imperative because preventing a disease is significantly easier than treating it. So prevention is key and researches suggest that preventing AD is actually not that complex. Treatment with antioxidants is a hopeful loom for slowing disease progression.

There is an ongoing study with vitamin E to see if it really slows AD progression. An assessment was done by isolating the patients into two groups one is treated with 1000 IU of vitamin E and at least 5 mg of donepezil (Aricept) and the other who did not take any vitamin E. Consequences showed that those taking the permutation therapy declined at a drastically lower rate. Food utilization studies have had similar outcomes. There are plentiful antioxidants in food, you get a surplus of them – everything from flavonoids to well known antioxidants like vitamin E and vitamin C.

Alpha-lipoic acid¹⁷

Alpha-lipoic acid (ALA) also plays a responsibility in brain function. Oxidative stress and energy diminutions are biochemical characteristics and brand of AD. Alpha lipoic acid is potent antioxidant, which also progress glucose metabolism and consumption in the brain. Hager et al gave 600 mg ALA day by day to nine patients with AD and related dementia, who were already getting standard acetyl cholinesterase inhibitors, in an open study lasting about 337 days. Results showed that those receiving the ALA had a stabilization of cognitive function demonstrated by stable scores on the MMSE scale and AD assessment scales.

Phosphatidylserine¹⁸

Phosphatidylserine is a very interesting complex. Phosphatidylserine is the key phospholipids in the brain and it makes up the basic configuration of the cell membrane. Membrane phosphatidylserine and phospholipids play a vital role in cell-to-cell announcement and transfer of biochemical letters to the cell. Phosphatidylserine boost cellular metabolism and communication, and oral supplemental outcomes neuronal membranes, cell metabolism and specific neurotransmitters: acetylcholine, nor epinephrine, serotonin, and dopamine. Numerous double-blind placebo-controlled studies have been carried out on

phosphatidylserine and they show that it can lead to very noteworthy improvements in early dementia, early AD, and age-related cognitive decline.

2) Cardiovascular diseases¹⁹⁻²⁶

Worldwide, the burdens of chronic diseases like cardiovascular diseases, cancers, diabetes and obesity is rapidly increasing. In 2001, chronic diseases contributed approximately 59% of the 56.5 million total reported deaths in the world and 46% of the global burden of disease. Cardiovascular diseases (CVD) is the name for the group of disorders of the heart and blood vessels and include hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease (stroke), heart failure, peripheral vascular disease, etc. In 1999 CVD alone contributed to a third of global deaths and by 2010 it would be the leading cause of death in developing countries. Majority of the CVD are preventable and controllable. It was reported that low intake of fruits and vegetables is associated with a high mortality in cardiovascular disease.^[19,20] Many research studies have identified a protective role for diet rich in fruits and vegetables against CVD²¹.

This apart, nutraceuticals in the form of antioxidants, dietary fibers, omega-3 polyunsaturated fatty acids (n-3 PUFAs), vitamins, and minerals are recommended together with physical exercise for prevention and treatment of CVD. It has been demonstrated that the molecules like polyphenols present in grapes and in wine alter cellular metabolism and signalling, which is consistent with reducing arterial disease²².

Flavonoids are widely distributed in onion, endives, cruciferous vegetables, black grapes, red wine, grapefruits, apples, cherries and berries.^[23] Flavonoids in plants available as flavones (containing the flavonoid apigenin found in chamomile); flavanones (hesperidins - citrus fruits; silybin- milk thistle flavonols (tea: quercetin, kaempferol and rutin grapefruit; rutin buckwheat; ginkgo flavonglycosides - ginkgo)²⁴ play a major role in curing the cardiovascular diseases^{25,26}. Flavonoids block the angiotensin-converting enzyme (ACE) that raises blood pressure; by blocking the "suicide" enzyme cyclooxygenase that breaks down prostaglandins, they prevent platelet stickiness and hence platelet aggregation. Flavonoids also protect the vascular system and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells. Flavonoids block the enzymes that produce

estrogens, thus reducing the risk of estrogens-induced cancers.

3) Parkinson's disease²⁷⁻²⁹

Parkinson's disease is a brain disorder that results from nerve damage in certain regions of the brain causing muscle rigidity, shaking, and difficult walking^[27], usually occurring in mid to late adult life. Canadian researchers indicated that vitamin E in food may be protective against Parkinson's disease.^[28] Creatine appeared to modify Parkinson's disease features as measured by a decline in the clinical signs.^[29] Researchers have also studied glutathione to determine its effect on nerve and its power as an antioxidant. The appropriate long-term dosing, side-effects and the most effective method of administration are not yet clear. Nutritional supplements have shown some promising results in preliminary studies, it is important to remember that there is not sufficient scientific data to recommend them for Parkinson's disease at present. The patients should be cautioned that over-the-counter medications do have side effects and interactions with other drugs and are also expensive.

4) Obesity³⁰⁻³²

Obesity is a complex condition, with serious social and psychological dimensions, affecting virtually all ages and socioeconomic groups. The worldwide existence of obesity nearly doubled between 1980 and 2008.^[30] According to country estimates for 2008, over 50% of both men and women in the WHO European Region were overweight, and roughly 23% of women and 20% of men were obese.^[30] Given the worldwide increase in obesity and its health consequences, efficient strategies for its prevention and treatment are important. It has been recommended that weight reduction programs focus on achieving a modest weight loss of 7–10% of the initial weight³¹.

Obesity arises from an energy imbalance whereby energy intake exceeds energy expenditure. Dealing with obesity — by either

prevention or treatment — requires modification of one or both components of energy balance. Approaches to weight management (including a functional food approach) therefore can target multiple aspects of the energy balance systems: food intake, energy expenditure, and energy storage. All of these approaches are currently being taken by pharmaceutical companies; however, developing functional foods designed for weight management may be a more attractive approach for dealing with the 61% of the population that is currently overweight or obese³².

Current status of nutraceuticals in obesity^{33,34}

There is a very high prevalence of obesity globally; hence nutrition and exercise play key roles in its prevention and treatment. Nutraceuticals like conjugated linoleic acid (CLA), capsaicin, Momordica Charantia (MC), and Psyllium fiber possess potential antiobese properties³³. A blend of glucomannan, chitosan, fenugreek, G Sylvester, and vitamin C in the dietary supplement significantly reduced body weight and promoted fat loss in obese individuals. Further studies are needed to establish long term efficacy and adverse effect potential³⁴.

5) In Apoptosis and Disease Prevention³⁵

It has been suggested by various epidemiological and animal model studies that nutraceuticals, mostly photochemical derived from nutritional or medicinal plants such as tea, garlic, ginger, soya bean and others may have chemo preventive activity. Their mechanism of reducing cancer incidence in these studies is closely related to apoptosis. There is a vast amount of information in the literatures, which supports the effects of nutraceuticals in cultured human cells, specifically in apoptosis. In this section, we review effects of some selected photochemical that belong with the following structural classes: carotenoids, flavonoids, stilbenes, or other sulphur-containing compounds³⁵.

Table 3:

S No	Phytochemicals	Source and content	Action
1	Carotenoids	Genistein, quercetin, rutin Obtain from tomato Lycopene and β -carotene.	Inhibit carcinogenesis in tumour cells. Induce apoptosis in prostate cancer cells and malignant lymphoblast cells by DNA fragmentation, poly ADP-ribose polymerase (PARP) cleavage, and caspase-3 activation.
2	Stilbenes	Obtain from grapes, peanuts, and pines Resveratrol (3,5,4-trihydroxy-trans-stilbene)	Induces apoptosis and inhibits the growth of various human tumour cells, including oral squamous carcinoma, promyelocytic leukaemia, human breast cancer cells, and prostate cancer cells, oesophageal carcinoma cells by induction of p53 at the mRNA and protein levels.

6) Nutraceuticals in Stem Cell Therapy³⁶⁻³⁹

Recently the application of stem cell research is found to be significant in curing various diseases. Some researchers also have investigated the effects of certain nutraceuticals on stem cell growth and proliferation which could stimulate endogenous stem cells to reach healing and regenerating goals, as an alternative to stem cell transplantation.³⁶ Bickford et al reported a dose-related effect of blueberry, green tea, catechin, carnosine, and vitamin D3 on proliferation with human bone marrow as compared with human granulocyte macrophage colony-stimulating factor, and combinations of nutrients can synergistically promote proliferation of human hematopoietic progenitors, suggesting another potential role or mechanism by which nutraceuticals promote health and healing capability of human body³⁷. Although any medication including herbs during pregnancy needs to be carefully checked^[38] the effects of nutraceuticals on pregnant women, development and differentiation of the infants and young children are essential for health of new generations. It is believed that nutritional factors during early development not only have short-term effects on growth, body composition and body functions but also exert long-term effects on health, disease and mortality risks in adulthood. There are indications for some beneficial effects of nutraceuticals such as antioxidant vitamins, essential amino acids, and polyunsaturated fatty acids in infant foods on the developing immune response. Actually,

mineral intakes such as Ca, P, Mg, Fe, Zn, I, F, and B, as well as vitamins D and K are important for the growth and development of bone and human nervous system.³⁹

7) Diabetes⁴⁰⁻⁴⁵

Diabetes mellitus is characterized by abnormally high levels of blood glucose, either due to insufficient insulin production, or due to its ineffectiveness. The most common forms of diabetes are type 1 diabetes (5%), an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes occurs in pregnancy.^[40] Globally the total number of people with diabetes is projected to raise from 171 million in 2000 to 366 million in 2003.⁴¹

Docosahexaenoic acid modulates insulin resistance and is also vital for neurovisual development. This is especially important in women with gestational diabetes mellitus which foster the recommendation for essential fatty acids during pregnancy.⁴²

Lipoic acid is a universal antioxidant, now used in Germany for the treatment of diabetic neuropathy. It is possible that lipoic acid may be more effective as a long-term dietary supplement aimed at the prophylactic protection of diabetics from complications.⁴³

Dietary fibers from psyllium have been used extensively both as pharmacological supplements, food ingredients, in processed food to aid weight reduction, for glucose control in diabetic patients and to reduce lipid levels in hyperlipidemia.⁴⁴

Good magnesium status reduces diabetes risk and improves insulin sensitivity; chromium

picolinate, calcium and vitamin D appear to promote insulin sensitivity and improve glycemic control in some diabetics; extracts of bitter melon and of cinnamon have the potential to treat and possibly prevent diabetes. However it has been suggested that Nutraceuticals with meaningful doses of combinations may substantially prevent and presumably could be marketed legally⁴⁵.

8) Osteoarthritis^{46,47}

Osteoarthritis (OA), a debilitating joint disorder, is the most common form of arthritis in the United States, where it affects an estimated 21 million people. In 2004, the direct and indirect health care costs associated with all forms of arthritis were approximately 86 billion dollars. Joint discomfort from OA and other joint disorders may reduce physical activity in individuals experiencing this condition, resulting in energy imbalance and weight gain. Increased weight can exacerbate existing problems, through additional stress on joints⁴⁶. Glucosamine (GLN) and chondroitin sulfate (CS) are widely used to alleviate symptoms of OA. These nutraceuticals have both nutrient and pharmaceutical properties and seem to regulate gene expression and synthesis of NO and PGE2, providing a plausible explanation for their anti-inflammatory activities⁴⁷.

9) Nutraceutical Management of Adrenal Dysfunction⁴⁸⁻⁶⁰

Adaptogens

Adaptogens are natural herbs that have non-specific, normalizing effects on physiology; they influence normal body functions only enough to encourage non-specific resistance to stressors.⁴⁸ Adaptogens include herbs—*Eleutherococcus senticosus*, *Ginkgo biloba*, *Ocimum sanctum*, *Panax ginseng*, and *Withania somnifera*—and the mushroom *Cordyceps sinensis*. Following is a short description of each.

Eleutherococcus senticosus (Siberian ginseng) has been long used in Chinese herbal medicine to enhance general health, longevity, appetite, and memory. While only distantly related to *Panax ginseng* it was popularized in Russia in the 1950s due to the relative scarcity and cost of panax^{49,50}. The active portions of *Eleutherococcus* are the glycosides eleutherosides A through M.⁵¹ *Eleutherococcus* is known to have antistress⁵¹ and antifatigue⁵¹ effects as well as immunomodulatory properties.⁵¹ A study examining the effects of *eleutherococcus* on steroidal hormone indices of stress showed an increase in cortisol production in endurance

athletes. The authors suggest a threshold may exist below which *eleutherococcus* increases and above which it decreases the stress response.⁵² Another study showed an improvement in quality of life for elderly patients given *eleutherococcus* but only during the first 4 weeks of treatment. By the end of 8 weeks, the treatment group had returned to baseline scores.⁵³ This suggests that a pulsed dose may be more effective than continued use.

Ginkgo biloba has been used for several thousand years by the Chinese for various maladies, including vertigo, short-term memory loss, and lack of attention or vigilance.^[54]

Standardized extracts of ginkgo have been shown to possess antioxidant⁵⁵ and neuroprotective properties, including slowing the progression of dementia.⁵⁶ Recent studies have shown ginkgo to possess antistress properties as well.⁵⁷ When subjects were given a single dose of ginkgo extract and then exposed to a memory and handgrip test, their levels of post-test salivary cortisol were significantly lower than those who were treated with placebo, yet there was no change in resting salivary cortisol compared to placebo.⁵⁷

Another study comparing acute and chronic stressors in rats treated with ginkgo, panax, or placebo showed that ginkgo was effective in reducing corticosterone levels in rats subjected to acute stress, although it had little or no effect when rats were exposed to chronic stress.⁵⁴

Ocimum sanctum (Holy basil or tulsi) is used in Ayurvedic medicine and has been shown to have antistressor effects.^[58] Sembulingham, et al, subjected rats to acute or chronic noise stress, with and without *Ocimum* administration. Those rats that had been pre-treated with *Ocimum*, whether exposed to acute or chronic noise, had significantly reduced levels of corticosterone.⁵⁸

Withania somnifera (ashwagandha, Indian ginseng, winter cherry) has been used in Ayurvedic medicine for thousands of years as an aphrodisiac, liver tonic, anti-inflammatory agent, and astringent.^[51] The active constituents are withanolides, the most active of which are withaferin A and withanolide D.⁵⁹ In a study comparing *withania* and *panax*, both chronic and acute stress effects were reduced by both herbs almost equally.⁶⁰

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