



ISSN (E): 2277- 7695

ISSN (P): 2349-8242

NAAS Rating: 5.03

TPI 2021; 10(2): 419-427

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[www.thepharmajournal.com](http://www.thepharmajournal.com)

Received: 22-12-2020

Accepted: 24-01-2020

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## Herbal nutraceuticals

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### Abstract

Nutraceutical refers to a non-toxic food extract supplement or any natural functional/medical foods or bioactive phytochemicals that have scientifically proven health-promoting, disease preventing, therapeutic and medicinal properties. These nutraceuticals contains vitamins, lipids, proteins, carbohydrates, minerals and other necessary nutrients and are used in nutritional therapy based upon their chemical structures and biological functions. In these days, nutraceuticals considered as one of the most efficacious substance as it have potential nutritional, safety and therapeutic effects. Recent records reveal that the Indian nutraceutical market has reached the value of around US \$2 billion which retains 1.5 per cent of global nutraceutical industry. In the present review, emphasis has been made to present new concepts about nutraceuticals based on their health promoting as well as diseases curing potential along with their present and future market demands. In present work, more attention has been devoted to herbal nutraceuticals due to their ability to maintaining health and to act against acute and chronic diseases induced oxidative stress, thereby promoting optimal health, longevity and quality of life.

**Keywords:** nutraceutical, phytochemicals, herbal nutraceuticals, oxidative stress, market demands

### Introduction

The term nutraceutical was coined from “nutrition” and “pharmaceutical” by Stephen Defelice in 1989. According to him “nutracetuicals are food or part of a food that provides medical or health benefits including the prevention and treatment of diseases.” Greek physician Hippocrates said “let food be your medicine” the philosophy behind is “focus on prevention”<sup>[1]</sup>. A nutraceutical may be a naturally nutrient rich food such as spirulina, garlic, soy or a specific component of a food. France, Germany and United Kingdam were considered that diet is more important factor than exercise or hereditary factors for achieving a good health. Canada defined them as ‘a product produced from foods but sold in pills, powders and other medicinal forms not generally associated with food. The nutraceuticals may range from isolated nutrients, herbal products, dietary supplements to genetically engineered “designer” foods and processed products such as cereals, beverages and soups. Majority of food stuffs such as whole grains, beans, fruits, vegetables and herbs contain phytochemicals. Amongst these, fruits and vegetables contribute to the significant sources of phytochemicals. These phytochemicals, either alone or in combination have tremendous therapeutic potential in curing various chronic degenerative disorders, such as cancer, cardiovascular and neurodegenerative diseases. Epidemiological and animal studies suggested that the regular consumption of fruits, vegetables and whole grains, reduces the risk of chronic diseases associated with oxidative damage. Among the phytonutrients mentioned as potentially providing the fortification are polyphenols, flavonoids, isoflavonoids, anthocyanidins, terpenoids etc<sup>[2]</sup>.

Herbal medicine is the oldest form of healthcare known to mankind. It is a major component in all traditional medicine and a common element in Ayurveda, homeopathy, naturopathy etc. The World Health Organization (WHO) estimates that 4 billion people, 80 per cent of the world population, presently use herbal medicine. Much of the medicinal use of plants seems to have been developed through observations of wild animals and by trial and error. The collected information on herbs developed well-defined herbal pharmacopoeias. About 25 per cent of the prescription drugs dispensed in the United States contain at least one active ingredient derived from plant origin. Some are made from plant extracts and others are synthesized to mimic a natural plant compound. WHO estimate that of 119 plant-derived pharmaceutical medicines, about 74 per cent are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines<sup>[3]</sup>.

Plant biotechnologists have put lots of effort to engineer plants and crops in order to improve their nutritional value to maintain a healthy human and animal body. It has been proved that excess intake of any nutrient may not benefit or even can be harmful to health [4].

Pre-partum nutritional management and energy status of a dairy cow determines the post-partum productivity, health status and birth weight of new-borns. The nutritional avoidance during dry period adversely affect milk production, reproduction in ensuing lactation and renders animals susceptible to disease and disorders around calving and after calving. During this transition phase pregnant animal undergo an endocrine, metabolic and other physiological adjustment that leads to increased energy requirements and may cause reduction in body weight of animals. Hormones and other additives have been used to augment milk production but their use is limited due to residual effects in body and milk<sup>5</sup>. A 'big bang' is currently impacting the food, health food and pharmaceutical industries. This big bang derives from an explosion in research and publications providing scientific evidence to support hypotheses that phytochemicals in foods and isolated form provide health benefits to the consumers. Animals have evolved to utilize these components for hormonal and growth regulatory functions and as it is now being understood the presence of these molecules in animal tissues also provides a measure of protection from certain diseases especially those related to chronic damage and growth deregulation [6]. Today most studies have focused on consumer awareness and acceptance of functional foods and nutraceuticals. Nutraceuticals are found in a mosaic of products emerging from the food industry, the herbal, dietary supplement market and pharmaceutical industry [7].

Global marketing of nutraceuticals was USD 128.4 billion in 2008. Japan holds the largest figures of 70 per cent of marketing share in Asia. Current global markets with a value of nutraceuticals in market share worldwide. The Indian nutraceutical market segment has undergone annual growth at 20 per cent rate for past 3 years which contributes to 2 per cent of global market. Currently India is in the category of showing promising drift toward nutraceuticals also known as Fast Moving Health Care Goods. The Indian nutraceutical market has reached the value of around US \$2 billion which retains 1.5 per cent of global nutraceutical industry. Indian nutraceutical market was found to be the US \$2731 million in 2016 [8].

The use of herbal medicine as a treatment modality has significantly increased over the last decade. This is due to several factors and principal of which is that herbal medicine is a cheaper alternative with fewer undesired side effects. However the increased desire to use herbal treatment is not a reflection of the economic status of an individual from a certain region or a country. Approx 70 per cent of the population in developed countries have resorted to Complementary and Alternative Medicine (CAM) for treatment purposes. Indeed, plants and herbs have actually provided a starting point for synthesis of over 50 per cent of currently used pharmaceutical drugs [9].

### Classification of herbal nutraceuticals

Herbs have been used as food and as medicine for centuries. Since the beginning of human civilization herbs have been an integral part of the society. Based on their use and toxicity, herbs can broadly be categorized into three categories.

1) **Food herbs:** These are gentle in action with very low

toxicity and are unlikely to cause an adverse response when consumed. It can be utilized in substantial quantities over long periods of time without any acute or chronic toxicity.

- 2) **Medicinal herbs:** These are strong acting and need to be used as drug for specific medical conditions and usually for a limited period of time as prescribed by a medical practitioner. These herbs may often cause adverse reactions and in some cases may interact with drugs.
- 3) **Poisonous herbs:** These have strong potential for both acute or chronic toxicity and need to be utilized strictly under the supervision of trained clinicians.

The superior drugs are non-toxic and are tonic remedies. The middle class drugs may have some mild toxicity and they support the superior medicines. The last category is the lower class remedies that are toxicant used only for specific diseases for limited periods of time [10].

### Nutraceuticals as therapeutic agents

#### Bael (*Aegle marmelos*)

- **Antibacterial activity:** Leaf extract of bael show antibacterial activity against Gram positive and Gram negative bacteria.
- **Anti-inflammatory activity:** Leaf extract of bael cause significant inhibition of Carrageenan induced paw oedma and cotton-pellet granuloma in rats.
- **Analgesic activity:** By reducing the early and late phases of paw licking in mice.
- **Hepatoprotective activity:** Administration of 30 per cent ethyl alcohol for a period of 40 days and fine crude plant leaves powder fed to animal for next 21 days and result compared with standard herbal drug Silymarin [11].

#### Brahmi (*Centella asiatica*)

- **Wound healing activity:** The aqueous extract of this plant apply to an open wounds in rats (3 times daily for 24 days) resulted in increased cellular proliferation and collagen synthesis at the wound site and increase in collagen content and tensile strength.
- **Gastric ulcer:** A laboratory study was reported in which aqueous extract of *Centella asiatica* was found to be effective in inhibiting gastric lesions induced by ethanol administration. The authors concluded that the *Centella asiatica* extract presumably strengthened the gastric mucosal barrier and reduced the damaging effects of free radicals.
- **Radioprotection:** 100 mg/kg dose increased the survival time of the mice significantly. Body weight loss of the animals in the drug treated group was significantly less in comparison with the animals that were given radiation only [12].

#### Garlic (*Allium sativum*)

- **Rumen modifier:** Garlic, its oil, extracts in different organic and aqueous solvents and individual components of essential oils have been examined as a feed additive to manipulate rumen function for controlling enteric methane emission and improving feed conversion efficiency. The results reported so far indicate that garlic and its essential oils inhibit methanogenesis significantly accompanied with lower acetate to propionate ratio indicating a diversion of fermentation in a favourable direction.

- **Antimicrobial activity:** Anti-microbial activity of phenolic extracts of garlic against bacteria (*Staphylococcus aureus*, *Salmonella enteritidis*) and fungi (*Aspergillus niger*, *Penicillium cyclopium* and *Fusarium oxysporum*) was demonstrated to be more potent than onion.
- **Prebiotic:** Garlic acts as a prebiotic, a nutrient which is not digested in the gut but acts as a stimulator for the beneficial gut microbes leading to improved microbial eco-system.
- **Anti-methanogenic:** Patra [13] evaluated ethanol, methanol and water extracts of garlic bulb in, *in-vitro* gas production test using rumen liquor of buffalo as inoculum and reported 55 per cent inhibition in methane emission with the methanol extract. Feeding of garlic bulb at the rate of 1 per cent of dry matter intake resulted in 11 per cent inhibition in methane emission in sheep estimated in an open circuit respiration chamber along with an increase in nutrient digestibility [14].

### Onion (*Allium cepa*)

- **Wound Healing and Anti-scar:** Onion is widely used in preparation of Ayurvedic formulations for wound healing. It also shows biological efficacy for prevention of median sternotomy wound in pediatric patients. Its extract shows the therapeutic effect on human skin fibroblast cell line and is used for the treatment of keloids. Onion peel extract shows biological efficacy for prevention of hypertrophic scar and keloid. Onion extract gel also shows pre-sternal hypertrophic scar protection.
- **Anti-parasitic:** Administration of onion oils was found effective against experimental infection of mice with *Cryptosporidium parvum* and *Schistosoma mansoni*. Onion oil is proved highly beneficial in worm infection. The onion is found effective against eelworm (*Ditylenchus dipsaci*) a tiny parasitic soil living nematode.
- **Anti-hyperlipidemic:** Onion derived sulfur-compounds including S-methyl cysteine sulfoxide and allylpropyl disulfide, showed hypolipidemic effects. These are established in rats and rabbits and lower down effects of diet-induced atherosclerosis, maintain hypolipidemic action and inhibitory effects on platelet formation. Raw onion contains these compounds in optimum amount and antithrombotic effects.
- **Anti-allergic:** Onion showed anti-allergic and antihistaminic effects *in-vitro* and in animal models. Anti-allergic profile of ALC-02 shows potential antioxidant, anti-inflammatory and antihistaminic activities in onion and garlic exposure patients synthesize sulfur compounds specific immunoglobulin-E antibodies that indicate sensitization and allergenic potential of these food materials.
- **Immunomodulatory:** Red onion scale extract shows immunomodulatory effect on experimentally induced atypical prostatic hyperplasia in Wistar rats. Flavonols present in processed onion showed hyaluronidase inhibiting activity and radical scavenging potential. A similar protective effect was seen in rutin against acute gastric mucosal lesions induced by ischemia-reperfusion extract of onion in mice.
- **Cardioprotective:** Onions contain flavonoids which are used for prevention and treatment of cardiovascular diseases and prevent from heartburn.

- **Hepatoprotective:** Onion and garlic extracts showed hepatoprotective potential on cadmium-induced oxidative damage in rats. Onion and garlic extracts significantly attenuated these adverse effects of cadmium. Onion extract proffered a dose dependent hepatoprotection, prevent and protect cadmium induced hepatotoxicity. Aqueous extract of onion bulb has significant hepatoprotective activity against ethanol-induced hepatotoxicity [15].

### *Aloe vera* (*Aloe barbadensis*)

- **Anti-inflammatory action:** A novel anti-inflammatory compound, C-glucosyl chromone was isolated from gel extracts of *Aloe vera*. *Aloe vera* inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Fresh *Aloe vera* gel significantly reduced acute inflammation in rats (carrageenin-induced paw oedema) but not in chronic inflammation. *Aloe vera* gel sterols were able to reduce inflammation by up to 37 per cent.
  - **Wound healing:** The wound healing property of *Aloe vera* gel has been attributed to Mannose-6-phosphate used for first to second degree burns. Glucomannan and plant growth hormone gibberellin interacts with growth factor receptors of fibroblast and stimulate its activity and proliferation for increased collagen synthesis in topical and oral administration of *Aloe vera*. The Aloe gel has been used for the treatment of radiation burns and radiation ulcers. Aloe gel treated lesions healed faster (11.8 days) compared to burns treated with petroleum jelly gauze (18.2 days).
  - **Immunomodulatory:** In a study on mice that had previously been implanted with murine sarcoma cells, acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumour necrosis factor from macrophages in mice, which in turn initiated an immune attack that resulted in necrosis and regression of the cancerous cells. Alprogen inhibit calcium influx into mast cells, thereby inhibiting the antigen-antibody-mediated release of histamine and leukotriene from mast cells.
  - **Laxative effects:** Anthraquinones present in latex are a potent laxative it stimulating mucus secretion, increase intestinal water content and intestinal peristalsis. The Aloe effects are primarily due to the 1, 8-dihydroxyanthracene glycosides, Aloin A and B. Aloe latex is known for its laxative properties.
  - **Antiviral activity:** Electron micrograph examination of anthro-quinone treated herpes simplex virus demonstrated that the envelopes were partially disrupted. Such results indicate that anthraquinones extract from variety of plants are directly virucidal to enveloped viruses.
  - **Antifungal activity:** *Aloe vera* reduced the rate of colony formation of *Fusarium Oxysporum*, *Rhizoctonia solani*. Aloe gel inhibited the growth of *Trichophyton mentagrophytes* while the leaf possesses inhibitory effects on both *Pseudomonas aeruginosa* and *Candida albicans* [16].
- ### Curcumin (*Curcuma longa*)
- **Anti-inflammatory:** Several animal studies have investigated the anti-inflammatory effects of curcumin. Anti-inflammatory action of curcumin demonstrated in a



mouse and rat by model of carrageenan induced paw edema. In mice curcumin inhibited edema at doses between 50-200 mg/kg. A 50 per cent reduction in edema was achieved with a dose of 48 mg/kg body weight, with curcumin nearly as effective as cortisone and phenylbutazone at similar doses. In rats, a lower dose of 20-80 mg/kg decreased paw edema and inflammation. Curcumin also inhibited formaldehyde induced arthritis in rats at a dose of 40 mg/kg [17].

- **Pancreatitis treatment:** In two rat models of experimentally-induced pancreatitis, curcumin decreased inflammation by markedly decreasing activation of NF-KB and AP-1 as well as inhibiting mRNA induction of IL-6, TNF- $\alpha$  and iNOS in the pancreas. Treatment effect on pain patterns as well as erythrocyte malonyl-aldehyde an indicator of lipid peroxidation and glutathione (GSH) were assessed at baseline and after six weeks [17].
- **Anti-protozoal activity:** The first work to relate the activity of curcumin and some semi-synthetic derivatives in the literature against tripanosomatids was studied in promastigotes (extracellular) and amastigotes (intracellular) forms of *Leishmania amazonensis*. Curcumin derivative was tested *in-vivo* in mice and showed a good activity with 65.5 per cent of inhibition of protozoa [18].
- **Anti-nematodal activity:** Curcuma oil was studied on *Paramecium caudatum* in different concentrations, varying from 1 in 2,000 to 1 in 5,000. The ciliates became sluggish and ultimately died. In this work they isolated a new curcuminoid and cyclocurcumin. All the substances did not show activity when applied independently, but the activity was observed when they were mixed, suggesting a synergistic action between them [18].
- **Antivenom activity:** The Ar-turmerone fraction is isolated from Curcumin neutralized both the hemorrhagic activity and lethal effect of venom in mice. In this study ar-turmerone was capable of abolishing the hemorrhagic activity of Bothrops venom and about 70 per cent of the lethal effect of Crotalus venom. Ar-turmerone can act as an enzymatic inhibitor in the case of venom enzymes, with proteolytic and hemorrhagic activities [18].

#### Flaxseed (*Linum usitatissimum*)

- **Cardioprotective:** Flax seed or oil contains alpha- linoleic acid. The consumption of flaxseed lowers the blood pressure [19].

#### Milk thistle (*Silybum marianum*)

- **Hepatoprotective:** The consumption of fruits of milk thistle prevents the liver cirrhosis [19].

#### Ginger (*Zingiber officinale*)

- **Effect on production and economic efficiency of milk and physiology of blood:** Three non-pregnant local Friesian dairy cows were at same live weights, fourth production season and during first month of calving they were divided into three treatments. 2nd and 3rd treatments were reared on standard ration supplemented with 75g and 150g of ginger roots powder per cow per day respectively while the 1st treatment reared on standard ration only. Cows were fed individually on standard ration during three periods (28 days per period). The results indicated that feed intake, milk yield, fat,

protein and milk lactose per cent, red and white blood cell counts, haemoglobin concentration, packed cell volume, lymphocyte per cent, total protein and globulin were increased significantly [20].

- **Effects on the gastrointestinal tract:** The active components of ginger are reported to stimulate digestion, absorption, relieve constipation and flatulence by increasing muscular activity in the digestive tract. The effectiveness of ginger (940 mg) in motion sickness was compared to that of dimenhydrinate (100 mg) in 18 male and 18 female college students who were self-rated as having extreme or very high susceptibility to motion sickness. The study concluded that ginger was superior to dimenhydrinate in preventing motion sickness. The effect of ginger was similar to that observed with 100 mg metoclopramide. In addition a double blind study in 27 pregnant women suffering from motion sickness demonstrated that oral administration of 250 mg of powdered ginger 4 times daily over 4 days significantly reduced symptoms of nausea and vomiting [21].
- **Antimicrobial effects:** Ginger has strong antibacterial and to some extent antifungal properties. *In-vitro* studies have shown that active constituents of ginger inhibit multiplication of colon bacteria. These bacteria ferment undigested carbohydrates causing flatulence. This can be counteracted with ginger. It inhibits the growth of *Escherichia coli*, Proteus species, Staphylococci, Streptococci and Salmonella. Ginger inhibits aspergillus a fungus known for production of aflatoxin a carcinogen. Fresh ginger juice showed inhibitory action against *Aspergillus niger* and *Mycoderma* species [21].

#### Ginseng (*Panax*)

**Immunity booster:** Ginseng has been well known as an immune modulator. Roots, stems, leaves and their extracts have been used for maintaining immune homeostasis and enhancing resistance to illness or microbial attacks through effects on immune system ginseng extract enhances NK cell functions. Oral administration of aqueous extract of panax shows immunomodulatory effects. Panax increased natural killing activity in mice and boost immunity [22].

- **Ginseng rescues neuronal cells either *in vivo* or *in vitro*:** Recently, it has been shown that ginseng or its components, ginsenosides, have a wide range of actions in the central nervous system. These effects include increased cell survival, extension of neurites growth and rescuing of neurons from death due to different insults either *in vivo* or *in vitro*. Ginsenosides Rb1 and Rg3 protected neurons from glutamate-induced neurotoxicity [23].
- **Cardioprotective:** Ginseng has been shown to produce a number of actions on the cardiovascular system. Intravenous administration of ginseng to anaesthetized dogs resulted in reduction followed by an increase in blood pressure and transient vasodilatation. In rats and rabbits found that extracts of panax notoginseng decreased systemic blood pressure and ginsenosides exerted relaxing effects in rings of rat and rabbit aorta respectively [23].

#### Senna (*Cassia angustifolia*)

- **Anthelmintic activity:** Crude ethanol extract from leaves were prepared in rotary evaporator and different concentrations (10, 20 and 40 mg/mL) of leaf extracts

were used for treatment on different representatives of helminthes extract show early paralysis in all worms treated followed by *Cassia angustifolia* in combination with *Cassia alata* [24].

- **Antidiabetic activity:** Hypoglycemic properties of ethanolic extract of *Cassia auriculata* leaves and flowers was reported in alloxan-induced diabetic rats at doses of 120 mg per kg of body weight for 15 days. The results of the experiment showed that both the extracts significantly reduced the blood glucose level may be attributed to stimulated insulin secretion from the  $\beta$ -cells or regenerate the  $\beta$ -cells.
- **Hepatoprotective activity:** Aqueous extract of *Cassia auriculata* leaves was evaluated for hepatoprotective activity against alcohol intoxication at doses of 250 and 500 mg per kg of body weight orally once daily for 30 days. They reported tissue lipid lowering effect comparable to control group with a reversal of steatosis in the liver and spongiosis in the brain.
- **Nephroprotective activity:** Nephroprotective activity of ethanolic extract of *Cassia auriculata* roots at doses of 300 and 600 mg kg<sup>-1</sup> body weight. In cisplatin and gentamicin induced renal injury in animals. Significant reduction in elevated blood urea, serum creatinine and normalization of histopathological changes in the curative regimen were observed.
- **Anthelmintic activity:** The anthelmintic activity of aqueous extract of *Cassia auriculata* leaves (Awali) against earthworms, tapeworms and roundworms at 10-50mg per ml dose of each plant extract. They concluded that plant extract exhibited significant anthelmintic activity at highest concentration of 50 mg per ml.
- **Immunomodulatory:** The immunomodulatory activity of methanolic extract in rats was evaluated by administered doses of 100 and 200mg per kg orally. The extract showed a significant stimulation of the cell mediated immunity in immune responses with the antigenic challenge by sheep RBCs a significant increase in neutrophil adhesion and delayed type hypersensitivity response and no effects on the humoral immunity. *Cassia auriculata* significantly potentiated the cellular immunity by facilitating the foot pad thickness responses to the sheep RBCs in sensitized rats with a dose of 50 and 100mg per kg body weight [25].

#### **Bhringraj (*Eclipta alba*)**

- **Anti-neoplastic activity:** This plant is abundant in zinc generally zinc could be efficacious in the prevention and treatment of several cancers as colon, pancreas, esophageal head and neck. Zinc is known to be an essential component of DNA-binding proteins as well as copper or zinc superoxide dismutase and several proteins involved in DNA repair. Zinc plays an important role in the functions of transcription factor, antioxidant defence system and DNA repair. Dietary deficiencies in the intake of zinc can contribute to single and double-strand DNA breaks and oxidative modifications to DNA that increase risk for cancer development. *Eclipta alba* is rich in manganese. Manganese deficiency is often observed in cancer patients. Mostly cancerous cells are very low in

manganese content. Potassium content in this plant is also high. Cancerous cells need a high amount of sodium and cannot function when there is no potassium. So it is recommended for cancer patients to have a diet that is low in sodium and high in potassium [26].

#### **Shatavari (*Asparagus racemosus*)**

Shatavari has galactagogue and mammogenic function through enhancing blood prolactin and cellular division in mammary gland to augment lactation. Shatavari use during pregnancy improves indigestion, acidity disorders, quality of milk and immunity of both mother and foetus. Traditionally, Shatavari root powder is used for the treatment of productive, reproductive and udder disorders of livestock in several parts of India<sup>4</sup>.

#### **Mechanism of action of nutraceuticals**

Evidences indicate that the mechanistic actions of natural compounds involve a wide array of biological processes including activation of antioxidant defences, signal transduction pathways, cell survival-associated gene expression, cell proliferation and differentiation and preservation of mitochondrial integrity. It appears that these properties play a crucial role in the protection against the pathologies of numerous age-related or chronic diseases. It is very imperative that the nutrients found in many foods, fruits and vegetables are responsible for the well documented health benefits [27]. The mechanism through which nutraceuticals prevent chronic diseases has not been fully elucidated. Many of these phytochemicals have been found to alter antioxidant defence of cells through the induction of DNA repair processes or enzymic antioxidant defence at the gene level. It has been suggested that they may also affect cell cycle progression, cell communication, hormone and growth factor signalling and apoptosis. Lycopene is a potent hypocholesteremic agent found in tomato has been shown to prevent atherosclerosis by inhibiting LDL-C oxidation. Also indole-3-carbinol the most vital and important indole present in broccoli has been found to inhibit the Human Papilloma Virus (HPV) that may cause uterine cancer. This phytochemical acts by blocking the estrogen receptors specifically present in the breast cancer cells as well as down regulating CDK6 and up regulating p21 and p27 in prostate cancer cells. It brings about G1 cell-cycle arrest and apoptosis of breast and prostate cancer cells significantly and enhances the p53 expression in cells treated with benzopyrene [28].

#### **Antioxidants mechanism in heart diseases**

Macrophage cell surface receptors such as oxidized cholesterol scavenger receptors and lectin like receptors recognizes oxidized LDL promptly phagocytosing it and transforming phagocytes in 'foam-like' cells present in earlier atherosclerotic plaques and later atherosclerotic thrombus. Many vitamins can inhibit LDL oxidation and protecting against heart diseases. Pre-incubation with ascorbic acid, erythorbic acid and dehydroascorbic acid abrogated macrophage recognition of oxidized mouse erythrocytes effects better performed by catechins. This could be explained by higher nut content of tocopherols, omega-3 fatty acids and selenium. Vitamin C is a promising anti-hypertensive once its plasmatic levels were inversely associated with arterial blood pressure [29].

### **Anti-hypertensive and other cardio-protective mechanisms**

Functional foods can promote relevant vasodilatory effects by stimulation of nitric oxide (EDRF) production. Beyond inducible effects of ginseng on SOD-1, ginsenosides trigger vascular relaxation by nitric oxide releasing and stimulation of calcium-potassium channels and subsequent cascade events of guanylate-cyclase or GMP system actions that make ginseng a promise to control hypertension. Black tea intake also improved circulation by potent endothelial dependent dilation of brachial artery in coronary artery disease patients. Guava leaves could control hypertension, decreasing myocardial force and inducing atrial relaxation by inhibition of cell inward calcium current. Quercetin administration, an onion and garlic to spontaneously hypertensive rats increased antioxidant status and decreased arterial blood pressure and heart rate without vasodilatory effects. Garlic inhibits macrophage nitric oxide synthase activity resulting in lesser atherosclerotic effects [29].

### **Neuroprotective antioxidant mechanism**

Higher intake of vegetables and fruits rich in vitamin C and carotenoids was positively associated with better cognitive function in the body. Besides contradictory results of epidemiological studies regarding aging-related dementia and intake of antioxidants has been postulated that a rich consumption of fruits and vegetables. Plenty of antioxidants can enhance cognition in the elderly. In these manner phenolic antioxidants such as tocopherols, green tea, polyphenols and phytoestrogens decrease oxidative cell injuries and inflammatory reactions improving brain's health [29].

### **Anticancer mechanism**

Functional food biomolecules can exert anti-carcinogenic effects through diverse pathways. Modulation of cytochrome P450 enzymes, antioxidant protection of DNA and induction of apoptosis of cancerous cells constitute the most important anticancer mechanisms of functional foods. Increasing DNA repair changing immunological response, inhibition of cyclooxygenase, restriction of caloric intake and absorption, decreasing time for transit of intestinal bulk, avoiding carcinogen formation and absorption, inhibition of angiogenesis and abrogation of tumour cells proliferation also constitute important anticancer properties of functional foods. Many compounds from functional foods could suppress DNA oxidation. Apoptosis a genetic cell death program is important to kill undesirable cells, avoiding inflammatory reactions [29].

### **Nutraceuticals in research and development**

The greatest scientific need in nutraceuticals pertains to standardization of compounds and products to carefully develop and execute clinical studies or trials to provide the basis for health claims for nutraceuticals that impact consumers as well as companies making strategic investments. Powerful market forces are fuelling the interest in nutraceuticals. Research on nutraceuticals should be addressed [30]:

- To test safety, purity and potency of products.
- To develop more effective and efficient means of producing ingredients for use in products.
- To develop testing methods for ensuring and verifying the consistency of the dosage of ingredients included in the company's products.
- To develop the new products either by combining

existing ingredients used in nutritional supplements or identifying new ingredients that can be used in nutritional supplements.

The development of nutraceutical requires a multidimensional approach [32]. Nutraceuticals are developed by incorporating either the whole food which contains the desired property into the product during processing. They can be mixed either in the form of powder or juice extract or by active component separation that involves isolation or purification of the active compound from food and it is incorporated in other food to have physiological benefit or to provide protection against diseases.

In recent years however as food composition has been scientifically proven to cause life-style related diseases and has become social issue. The concept of nutraceutical with new function to prevent diseases was started by the combination of genome science and technology which has been accomplishing remarkable development for the verification. Thus the genome technique called Nutrigenomics was created. Nutrigenomics is a newly developed methodology combined with multiple genomic techniques and molecular biology technologies. It has been then used as a basic technology that became a driving force for the creation of nutraceuticals.

For nutraceuticals there are three key issue of the technology

- Establishment of scientific assessment standard for prevention of disease
- Establishment of assessment system for disease by human trials
- Establishment of seamless system to transfer stage from basic research to industrialization

### **Market trends**

Nutraceutical is a new buzzword in Indian healthcare market. This promising term reflects lucrative market opportunities for domestic as well as international pharmaceutical and nutraceutical companies. Nutraceuticals has a spectacular annual growth rate of 25 per cent in Indian healthcare market. It is estimated that end of 2007 global nutraceutical market may cross USD 80 bn. The Indian nutraceutical market valued at \$ 1,480 million in 2011 could grow to \$ 2,731 million in 2016, a report said today. According to the report by business research and consulting firm Frost and Sullivan functional foods will be the quickest growing category followed by dietary supplements until 2015. At present the dietary supplements are the largest category accounting for 64 per cent of the nutraceuticals market. This market is driven primarily by the pharmaceutical sector in the form of vitamin and mineral supplements. Europe, Japan and US are being the largest regional markets accounting for nearly 93 per cent of the global nutraceutical demand [27].

This market is almost saturated with exceedingly high per capita spends on nutraceutical products hence compelling manufacturers to look at developing countries such as India and China which have considerably lower per capita spend on nutraceutical products. The market size is forecast to grow to \$210 billion in 2016 at 7 per cent compound annual growth rate. This current global growth is a motivation for improved processing and characterization procedures available in tablets, capsules, tinctures, beverages etc. Development of nutraceutical in tablet form was given a particular attention. Various processing techniques that are available for development of nutraceutical products were presented [32].



### The future of nutraceuticals

Due to increasing awareness levels about fitness and health encouraged by media coverage are prompting the majority of people to lead healthier lifestyles, more exercise and eat healthy. The expanding nutraceutical market indicates that users are seeking minimally processed food with extra nutritional benefits and organoleptic value. This development is propelling expansion in the nutraceutical markets globally. The emerging nutraceuticals industry seems destined to occupy the landscape in the new millennium. Its tremendous growth has implications for the food, pharmaceutical, healthcare and agricultural industries. Many scientists believe that enzymes represent another exciting frontier in nutraceuticals. "Enzymes have been underemployed they are going to be a hot area in the future". Fermentation technology using microbes to create new food products also represents potential [33].

Current trends in nutrition are a welcome change indeed compared to the negative, simplistic and biased approach of most nutrition research last century the fact that food marketers now see functional foods as a way of marketing junk foods is a worrying trend which raises huge doubts about

how much has really been learned about nutrition over the past few decades. The challenge here is for public health authorities to demonstrate quite clearly that their allegiance is to public health and not the profits of huge food, chemical and pharmaceutical companies. According to Lawrence In the current global economic environment and given the push by multinational companies to add dietary supplements to foods so they can make specific health claims to promote marketing of their foods the current global campaign to restrict the retail availability of dietary supplements in health food stores is hardly surprising. Now that the disease preventing potential of nutrients has been discovered by scientists and multinational food and drug companies the ability of consumers to "medicate" themselves must be prevented and therefore control of dietary supplements must be transferred to doctors, pharmaceutical companies and food manufacturers. All medicine has now finally realized that the dietary supplements freely consumed by nutritionally aware people for decades possess far more potential to prevent or perhaps even cure chronic diseases than all the vast array of prescription drugs they have at their disposal [34].

Marketed nutraceutical products [31].

Component	Source	Health benefits
<b>Carotenoids</b>		
• Beta – carotene • Lycopene	Carrots and various fruits Tomatoes and processed tomato products	Neutralizes the free radicals and act as cellular antioxidant defences Maintain prostate health
<b>Dietary fiber</b>		
Insoluble fiber	Wheat bran	Maintain healthy digestive tract
<b>Fatty acids</b>		
Mono-saturated fatty acids	Tree nuts	Reduce risk of coronary heart disease
<b>Flavonoids</b>		
Flavonols	Onions, apples, tea and broccoli	Neutralize free radicals and prevent damage of cells
<b>Isothiocyanates</b>		
Sulforaphane	Cauliflower, broccoli and cabbage	Enhance detoxification of undesirable compounds
<b>Phenols-</b>		
Caffeic acid and Ferulic acid	Apple, pears, citrus fruits and some vegetables	Act as cellular antioxidants
<b>Prebiotics/probiotics-</b>		
Lactobacilli and Bifidobacteria	Yogurt and other dairy products	Enhance gastrointestinal health and systematic immunity
<b>Phytoestrogens</b>		
Isoflavones	Soybeans and soy-based foods	Improve health of bone, brain and immune functions
<b>Soy protein</b>		
	Soybeans and soy-based foods	reduce risk of coronary heart disease

### Regulatory aspects

For regulating the manufacturing and marketing of nutraceuticals Watershed legislation 1994 was passed in the USA. This law is known as the dietary supplement health and education Act. The FDA established good manufacturing practices for nutraceuticals as long as these regulations are molded after the less stringent regulations for foods as opposed to those for drugs. The law of the dietary supplement health and education Act developed in India to regulate manufacturing, importing and marketing of health foods or dietary supplements and other nutraceuticals. Also the central drug control department has put some structures in place for dietary supplements but it is taking a long time for states to co-operate and some states have rejected the structures when their own rules and regulations conflict. The new independent association has been formed in India to address some of these issues. The Indian health and dietary supplement association was created to represent pharmaceutical, nutraceutical, herbal, direct selling and other services. This association is planning a scientific conference to bring the industry and government

together to share information, experience and perspectives on the use and regulation of dietary supplements [35]. The regulatory framework of nutraceuticals in India needs attention from the relevant authorities. Globally the regulatory authorities are aware of changing needs of consumers and proactively protect consumers by amending existing laws to accommodate changes but in India old laws such as Prevention of Food adulteration Act, 1954 which regulates packaged foods still exist for manufacturers. In addition they need to abide by many other cumbersome laws [36] that are as follows:

- Standards of Weights and measures Act, 1976
- Packaged Commodities Rules, 1977
- Fruit Products Order 1955 (FPO)
- Meat product Order 1973
- Milk and Milk Products Order 1992
- Vegetable Oils Products Order 1998 (VOP)
- Consumer Protection Act 1986
- Environment Protection Act, 1986
- Agricultural Produce (Grading and Marking) Act, 1937

- General Grading and Marking Rules 1986

## Conclusion

The nutraceutical industry is growing at a rate far exceeding expansion in the food and pharmaceutical industries. In tomorrow's market the most successful nutraceutical players are likely to be those companies in which functional product are just a part of a broad line of goods satisfying both conventional and health value point. Future demand of nutraceutical depends on consumer perception of the relationship between diet and disease. The entire regulatory framework of dietary supplements in view of the role of nutraceuticals is deemed necessary to first give credit to their different purposes and definition and second to assess their specific role in the prevention and treatment of pathological conditions. The specificity of nutraceuticals would need a premarket approval system substantiated by scientific data showing their complete safety and efficacy profile. The regulatory approach could be based on the one adopted for drugs which is stricter and more complex. The likelihood of this occurring in the foreseeable future is unfortunately quite low. It may be reasonable for national competent authorities to ask manufacturers to provide data on the safety, efficacy and mechanism of action supporting any claims contained on the labels of their products especially when the term nutraceutical is used. Strict guidelines would be needed and shared at international level to ensure that proper information is used to substantiate any health claims on the product label and detailed in the safety guidelines which should be included in the packaged products.

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