

**NUTRACEUTICALS-AN EMERGING ERA IN THE TREATMENT AND PREVENTION OF DISEASES**

AMIT SINGH\*, RACHİYATA DUBEY, R T PALIWAL, GAURAV K SARAOGI, A K SINGHAI

Lakshmi Narain College of Pharmacy, Bhopal, India. Email:gauravsaraogi13@gmail.com, amitsingh\_pharmacist@yahoo.com

Received: 12 May 2012, Revised and Accepted: 19 Jun 2012

**ABSTRACT**

In the past few decades, the world has witnessed the explosive growth of a multi billion dollar industry known as nutraceuticals. The word 'nutraceutical' was coined to represent substances found in food and herbs that are not technically considered nutrients such as vitamins or minerals, but which may have a profoundly beneficial impact on the health of the body. Nutraceuticals appear to be of benefit in both the treatment and prevention of disease. 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. An attempt is made in this article to re-define nutraceuticals and functional foods as well as to summarize the application of nutraceuticals.

**INTRODUCTION**

Today the exploration and exploitation of the disease fighting properties of a multitude of phytochemicals 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"<sup>1</sup>, 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<sup>2</sup>.

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 along side the expansion and exploration of modern technologies<sup>3,4</sup>.

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 nutraceuticals 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 nutraceuticals are efficacious to treat and prevent various disease conditions<sup>5</sup>. This review article summarizes the various diseases which may treated by use of nutraceuticals.

**CLASSIFICATION OF NUTRACEUTICALS**

The food products used as nutraceutical contain the following except probiotics; all the components are fruits, vegetables and different type of herbal foods. They are classified on the basis of their potential activities as Antioxidants, Prebiotics, Probiotics, Omega-3 fatty acids and Dietary fibers etc<sup>6</sup>.

**Antioxidants**

Antioxidants are substances, which retard or prevent deterioration, damage or destruction caused by oxidation. During the last few years researches has confirmed that many have the common disease (CVS, diabetes, cataracts, high blood pressure, infertility, respiratory infection and rheumatoid arthritis) are associated with tissue deficiency and/or low dietary levels of compounds called

antioxidants which make them an essential part of the nutraceutical market. During oxidation free radicals are generated, these free radicals at a molecular level burn everything they touch<sup>7</sup>. Antioxidants are quite large in number and diverse in nature which opposes the process of oxidation largely by neutralizing free radicals at relatively small concentrations and have the potential to inhibit the oxidants chain reactions and ultimately reconstitute the damaged membranes<sup>8</sup>. Dietary antioxidants and some accessory molecules, such as zinc and certain vitamins are important in maintaining free radical scavenging systems, biosynthetic capacity, membranes, enzymes and DNA<sup>9</sup>. Antioxidants are found in the vegetable oils e.g., Soybean oil, canola oil, corn oil, oat oil, wheat germ oil, palm oil, evening prime rose oil<sup>10</sup>.

**Probiotics**

Probiotics are live microbial food ingredients, which are beneficial to health. The prerequisite for probiotic action include survival in and adhesion to specific areas of the gastrointestinal tract and competitive exclusion of pathogens or harmful antigens. Probiotics are situated as health or functional foods whereby they are ingested for their purported positive advantages in the digested tract and/or systemic area like the liver, brain, vagina or blood stream<sup>11</sup>.

**Probiotic bacterial species**

The various types of bacteria that are having the probiotics characteristics are:-Lactobacilli, Lactobacillus rhamnosus, Lactobacillus reuteri, Lactobacillus case, Bifidobacterium, Bifidobacterium lactis, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Streptococcus, Lactococcus, Lactococcus platinum, Lactococcus reuteri, Lactococcus agilis, Enterococcus, Saccharomyces, Bacillus, Pedicoccus.

**Characteristics of probiotic bacteria**<sup>12</sup>

Probiotic bacteria should have the following features:

1. GRAS (generally recognized as safe).
2. In vitro resistance to hydrochloric acid and pancreatic juice.
3. Produce antimicrobial substances.
4. Compete with bad bacteria to adhere on the gut wall.
5. Compete for the nutrients and stimulate immunity.
6. Alter the intestinal micro flora balance, inhibit growth of harmful bacteria, promote good digestion, boost immune function and increase resistance to infection.

**Prebiotics**

Prebiotics are the substances, which reach to colon in intact form i.e., without getting depleted by the gastric pH and digestive acids. These prebiotics also selectively promote the growth of colonial probiotic bacteria; hence they act as fertilizers for these bacteria<sup>6</sup>. These are collectively term for non-digestive but a fermentable dietary carbohydrate that may selectively stimulates growth of certain bacterial groups resident in the colon, such as *Bifidobacteria*,

*Lactobacilli* considered to be beneficial for the human host e.g., - inulin, which is soluble dietary fibers and resistant to digestive enzyme and thus reaches to large intestine or colon intact, where it is fermented by resistant bacteria, *Lactobacilli*<sup>13</sup>.

#### Criteria for food components or ingredients as prebiotics<sup>11</sup>

A prebiotic nature has been attributed to many foods and their components those fulfill the following properties-

1. Resists host digestion, absorption and absorption processes.
2. Fermented by the micro flora colonizing the gastrointestinal system.
3. Selectively stimulates the growth and/or the activity of one or a limited number of bacteria with the gastrointestinal system.

#### Polyunsaturated fatty acids<sup>14, 15</sup>

Essential fatty acids are needed for normal growth and development but cannot be synthesized by our body. Omega-3 fatty acids belong with this class. Long chain omega-3 fatty acids such as eicosapentaenoic acid and docosahexaenoic acids are built up in algae and plankton and the fish living on them. The natural vegetable oils and marine animal oils containing polyunsaturated fatty acid belong with linoleic group (omega 6-type and omega 3-fatty acid) help to reduce cholesterol formation/deposition and prevent thromboxane formation e.g., safflower oil, corn oil, soybean oil, mustard oil, evening primrose oil, flax oil, hemp seed, borage seed. The followings are diseases for which polyunsaturated fatty acids are preferred:-

- Heart disease and stroke
- Rheumatoid arthritis
- Inflammatory arthritis
- Inflammatory bowel disease
- Asthma
- Cancer
- Chronic lung failure

- Kidney transplant

#### Dietary Fibers<sup>16</sup>

Dietary fibers are used in health food products for normalization of intestinal transit time. They have dual effect on intestinal transit. First effect is on the bulk faeces, which are often increased, in significant proportion (127% after ingestion of 20 g of wheat bran), this action is concerned with insoluble fibers. The other effect of dietary fibers is on the duration of transit, which gets normalized around in 48 hrs. Long transit time gets shortened and short transit gets longer. Dietary fibers are categorized into two groups.

##### 1. Water soluble fibers

Soluble fibers dissolve in water and form a gel that binds the stool and inhibit the non-propulsive colon contractions, helps in bulking of stool and their quick passage through digestive tract e.g., Oats, dried beans, legumes and chicory.

##### 2. Water insoluble fibers

Insoluble fibers are present in brown rice, banana, vegetables and whole grains.

#### ROLE OF NUTRACEUTICAL IN TREATING VARIOUS DISEASE CONDITIONS

##### In Apoptosis and Disease Prevention<sup>17</sup>

It has been suggested by various epidemiological and animal model studies that nutraceuticals, mostly phytochemicals 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 are 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 phytochemicals that belong with the following structural classes: carotenoids, flavonoids, stilbenes, or other sulfur-containing compounds which are listed in Table 1.

**Table 1: Table shows the various phytochemicals used in disease prevention by their apoptotic action**

S.No	Phyto chemicals	Source and Content	Action
1	Flavonoids	Obtain from black tea <ul style="list-style-type: none"> <li>• Theaflavin (TF-1)</li> <li>• Theaflavin-3-gallate and theaflavin-3'-gallate (TF-2)</li> <li>• Theaflavin-3 3'-digallate (TF-3)</li> </ul> Obtain from green tea Epigallocatechin gallate (EGCG) also known as epigallocatechin 3-gallate.	Induce apoptosis in human stomach cancer cells, virally transformed human fibroblasts, and hepatoma cells.  Apoptotic in human lymphoid leukemic cells, human carcinoma cells, lung tumor cell lines, colon cancer cells, breast cancer cells, virally transformed human fibroblasts, prostate cancer cells, stomach cancer cells, brain tumor cells, head and neck squamous carcinoma, and cervical cancer cells.
2	Carotenoids	Genistein, quercetin, rutin. Obtain from tomato Lycopene and $\beta$ -carotene.	Inhibit carcinogenesis in tumor cells. Induce apoptosis in prostate cancer cells and malignant lymphoblast cells by DNA fragmentation, poly ADP-ribose polymerase (PARP) cleavage, and caspase-3 activation.
3	Stilbenes	Obtain from grapes, peanuts, and pines Resveratrol (3,5,4-trihydroxy- <i>trans</i> -stilbene)	Induces apoptosis and inhibits the growth of various human tumor cells, including oral squamous carcinoma, promyelocytic leukemia, human breast cancer cells, prostate cancer cells, esophageal carcinoma cells by induction of p53 at the mRNA and protein levels.
4	Sulphur containing compounds	Obtain from garlic. Diallyl-sulfide and diallyl-disulfide  Obtain from Brassica plants (e.g., broccoli and cauliflower) Isothiocyanates such as sulforaphane	Induce apoptosis in lung cancer cells, prostate cancer, breast cancer cells by changing Bax to Bcl-2 ratio in cells.  Induces apoptosis in colon cancer cells, prostate cancer cells, and leukemia cells by increasing of Bax in the treated cells.

#### Nutraceuticals in Stem Cell Therapy

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<sup>18</sup>. 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 granulocytemacrophage 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 body<sup>19</sup>.

Although any medication including herbs during pregnancy needs to be carefully checked<sup>20</sup>, 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<sup>21</sup>.

#### Nutraceuticals against Alzheimer's Disease (AD)

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<sup>22</sup>

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.

##### Ginkgo biloba<sup>23</sup>

Ginkgo biloba is perhaps the most studied herb with reference to memory, cognition, overall brain performance, and certainly AD. Wettstein compared the efficacy of four cholinesterase inhibitors (tacrine, donepezil, ravastigmine, metrifonate) to Ginkgo (EGB 761) in AD patients. The differences in the effects of the active substances and placebo were calculated using ADAS (Alzheimer's Disease Assessment Scale) cognition scale, taking into account the different degrees of dementia and the dropout rate due to adverse drug reaction. The efficacy was expressed as a delay in symptom series or the difference in response rates between placebo and active substrate. Results showed that there was no difference between the four drugs and the Ginkgo extract. This means that they all work equivalently. Having an over the counter dietary supplement work as effectively as a drug is fine. It doesn't even have to work better than the drug; it can work equally to the drug. And in this particular study, the Ginkgo biloba extract was equal in efficacy to those four cholinesterase inhibitors. Wettstein concluded that new prescription medications should be critically reviewed, and that these drugs and Ginkgo should be considered equally effective in treating mild to moderate Alzheimer's dementia.

##### Huperzine alpha<sup>24</sup>

Huperzine alpha or huperzine A is a very appealing plant compound that is extracted from club moss, or *Huperzia serrata*. It is a sesquiterpene alkaloid, which is a potent and reversible inhibitor of acetylcholinesterase. Therefore it works very much similar to the cholinesterase inhibitor drugs. Human and animal safety data authenticate that it is safe and nontoxic. There is fast penetration and absorption into the brain, very much like with Ginkgo biloba. Compared to tacrine and donepezil, huperzine A has a longer duration of action and elevated therapeutic index. The cholinergic side effects are negligible and are not noteworthy when compared to other drugs. Zhang *et al* conducted a study of 202 AD patients from 15 centers. Participants received either 400 micrograms of huperzine A each day or a placebo for 12 weeks. Results showed amazing enhancements on several scales, including the ADAS cognitive scale, the CIBIC-Plus (Clinician Interview Based Impression of Change-Plus) scale, and the activities of daily living (ADL) scale. Huperzine A was found to improve appreciably cognition, behavior, activity of daily life and mood in AD patients. Moreover it is a safe and effective treatment.

##### Phosphatidylserine<sup>25</sup>

Phosphatidylserine is a very interesting complex. Phosphatidylserine is the key phospholipid 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, norepinephrine, 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. The FDA has agreed health claims for phosphatidylserine for reducing dementia and age-related memory decline. Several studies demonstrate that phosphatidylserine improves memory, brain wave activity, and brain metabolism in the early stages of AD. Engel *et al* conducted a double-blind placebo-controlled crossover study of 33 patients with AD. Participants were given 300 milligrams of phosphatidylserine each day or a placebo for eight weeks. Results showed that the Clinical Global Improvement score significantly improved with phosphatidylserine, but not with placebo.

##### Alpha-lipoic acid<sup>26</sup>

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 acetylcholinesterase 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.

##### Nutraceuticals and Natural Supplements for Treating Type 2 Diabetes<sup>27</sup>

“Using natural dietary supplements to support healthy blood sugar levels and minimize the impact of glycation is a rational continuation of this green philosophy,” says Steven Joyal, MD, vice president of Scientific Affairs and Medical Development for the Life Extension Foundation in Ft. Lauderdale, Florida. “Optimal diabetes management is a partnership between patient and physician,” Dr. Joyal notes. “Proactive, involved patients do best with diabetes management. Patients interested in natural diabetes solutions should read and digest as much information as possible on available natural options for diabetes. Further, partnerships with a physician knowledgeable in natural diabetes treatment options are important”. Some are interested in treating themselves naturally.

The various nutraceuticals used to treat diabetes are listed in Table 2:

Table 2: Table shows the nutraceuticals used in diabetes treatment

S. No	Nutraceuticals	Active constituents	Mode of action
1.	Coffee berry	Antioxidants and other phytonutrients known as poly phenols i.e., chlorogenic acid and caffeic acid	Reduces the gene expression of key enzymes involved in glucose production from glycogen stored in the liver, chlorogenic acid decreases the intestinal absorption rate of glucose.
2.	Cinnamon	Water soluble poly phenol called MHCP (methylhydroxy chalcone polymer)	Up regulated the expression of genes involved in activating the cell membrane's insulin receptors, thus increasing glucose uptake and lowering blood glucose levels
3.	Aloe vera	Water-soluble polysaccharide Glucomannan	By insulin sensitizing glucose-lowering activities.
4.	Coccinia indica		A component of the plant possesses insulin-mimetic activity.
5.	Opuntia (Nopal)	Very high soluble fibers and pectin	Recover glycemic control and improved insulin sensitivity
6.	Gymnema sylvestre (Gurmar)	Glycosides, a peptide gurmarin several amino acid derivatives and water-soluble acidic division called GS4	Increased glucose uptake and utilization, increased insulin secretion, and increased $\beta$ -cell number

### Nutraceutical burst through in lyme disease<sup>28</sup>

Lyme disease was first reported in the United States in the town of Old Lyme. Lyme disease is caused by bacteria called *Borrelia burgdorferi* (*B. burgdorferi*). Black legged ticks carry these bacteria.

### Pentacyclic Alkaloid Chemotype *Uncaria tomentosa*

Also known as TOA-Free Cat's Claw is a rare chemotype of a medicinal plant generally known as Cat's Claw, botanical name *Uncaria tomentosa*. Unlike traditional Cat's Claw products, this chemotype does not hold a group of chemical antagonists called tetracyclic oxindole alkaloids (TOAs) that proceed on the central nervous system and can greatly reduce the positive effect of the pentacyclic oxindole alkaloids (POAs).

The pentacyclic oxindole alkaloids (POAs) contained in this chemotype are generally accepted as the prime immunomodulating and immunostimulating agents. POAs are actively involved in the repair of many elements and purposeful mechanisms of both the innate and acquired immunity damaged by *Bb* and other co infections, assisting in restoration of structural and functional integrity of the immune system, enhancing its ability to get rid of the pathogens in a natural way. In addition, this chemotype contains quinovic acid glycosides having natural antibiotic properties.

### NUTRACEUTICAL MARKET

The preference for the discovery and production of nutraceuticals over pharmaceuticals are well seen in pharmaceutical and biotech companies. Some of the pharmaceutical and biotech companies, which commit major resources to the discovery of nutraceuticals include Monsanto, American Home Products, Dupont, BioCorrex, Abbott Laboratories, Warner-Lambert, Johnson & Johnson, Novartis, Metabolex, Scio-tech, Genzyme Transgenic, PPL Therapeutics, Unigen, and Interneuron<sup>29,30</sup>. The nutraceutical industry in the US is about \$86 billion. This figure is slightly higher in Europe and, in Japan, represents approximately a quarter of the \$6 billion total annual food sales. 47% of the Japanese population consumes nutraceuticals<sup>31</sup> even without specific financial figures, business reports continually suggest that the nutraceutical market is consistently growing. The approach to regulating and marketing nutraceuticals is notably heterogeneous on the global level. This is largely due to the challenges in classifying these products, absence of a suitable regulatory category for these hybrid products<sup>32</sup>.

GIA (Global Industry Analysts) announces the release of a comprehensive global report on Nutraceuticals market. The global nutraceuticals market is projected to exceed US\$243 billion by 2015, owing to consumer desire for leading a healthy life and increasing scientific evidence supporting health foods<sup>33</sup>.

### CONCLUSION

Nutraceuticals are intended to play a significant role in future therapeutic advancement but their victory will be governed by direction of purity, safety and efficacy without reducing innovation. Nutraceuticals will continue to plead because they are suitable for today's lifestyle. Some are also authentically

researched and offer novel ingredients that can bring about health profits faster than would normally be the case through eating conventionally healthy foods alone. Public health Authorities consider prevention and treatment with nutraceuticals- as a commanding gadget in maintaining health and to perform against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity and quality of life. A place for nutraceuticals in clinical practice is rising, but important pharmaceutical and clinical issues need to be addressed by further research.

### REFERENCES

- Ames BN, Mark KS, and Tory MH. Oxidants, Antioxidants and the Degenerative Disease of Aging. Proc. Natl. Acad. USA 1993; 90: 7915-7922.
- Biesalski HK. Nutraceuticals: the link between nutrition and medicine. In: Kramer K, Hoppe PP, Packer L, editors. Nutraceuticals in health and disease prevention. New York: Marcel Dekker Inc.; 2001: 1-26.
- Wildman REC. Nutraceuticals and Functional Foods. In: Wildman Handbook of Nutraceuticals and Functional Foods. 1<sup>st</sup>ed. New York: CRC Press 2007: 1-9.
- Shibamoto T, Kanazawa K, Shahidi F et al. Functional Food and Health: An overview. ACS Symposium series 2008; 993: 1-6.
- Rama CS, Shirode AR, Mundada AS, Kadam VJ. Nutraceuticals- an emerging era in the treatment and prevention of cardiovascular diseases. Curr Pharm Biotechnol 2006; 7 [1]: 15-23.
- Kalia AN. Textbook of Industrial Pharmacognocny. New Delhi: CBS publisher and distributor; 2005: 204-208.
- Sagar BPS, Zafar R, Tyagi K, Kumar V, Kumar S, Panwar R. Antioxidants. The Indian Pharmacist 2004: 29-35.
- Naik SR. Antioxidants and their role in biological functions: An overview. Indian Drugs 2003; 40 [9]: 501-512.
- Shahidi F. Antioxidants in food and food antioxidants. Nahrung 2000; 44:158-163.
- Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free Radicals and antioxidants in human health: current status and future prospectus. Journal of association of physicians of India 2004; 52:794-805.
- Gibson GR. Fibre and effects on probiotics (the prebiotic concept). Clinical Nutritional Supplements 2004; 1: 25-31.
- Patel CN, Shah N, Anand IS. Probiotic, Prebiotic and symbiotic. The Indian Pharmacist 2006: 20-24.
- Ghosh S, Playford RJ. Bioactive natural compounds for the treatment of gastrointestinal disorders. Clinical science 2003; 104: 547-556.
- Madgulkar A, Damle M. Omega-3 fatty acids. The Indian Pharmacist 2005: 20-26.
- Shah NC. Dietary supplements: Gaining medicinal recognition. Express Pharma Pulse 2004; 10 [27]: 24.
- Vasanti S. Nutraceuticals [Internet]. April 2008; c2012: [cited 2012 march 27]; 1-9. Available from <http://www.biologyonline.org/articles/nutraceuticals/classification.html>.

17. Alexander G, Kuang YC. Nutraceuticals, Apoptosis, and Disease Prevention. *Nutrition* 2004; 20: 95-102.
18. Gennero L, Mortimer P, Sperber K, Carloni G, Ponzetto A. Stem cells: an alternative to organ transplantation in chronic, degenerative and infectious diseases. *New Microbiol* 2006; 29: 151-67.
19. Bickford PC, Tan J, Shytle RD, Sanberg CD, El-Badri N, Sanberg PR. Nutraceuticals synergistically promote proliferation of human stem cells. *Stem Cells Dev* 2006; 15:118-23.
20. Conover EA. Over-the-counter products: nonprescription medications, nutraceuticals and herbal agents. *Clin Obstet Gynecol* 2002; 45: 89-98.
21. Koletzko B, Aggett PJ, Bindels JG, *et al.* Growth, development and differentiation: a functional food science approach. *Br J Nutr* 1998; 80: 5-45.
22. Klatte ET, Scharre DW, Nagaraja HN, Davis RA, Beversdorf DQ. Combination therapy of donepezil and vitamin E in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2003; 17: 113-116.
23. Wettstein A. Cholinesterase inhibitors and Gingko extracts--are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration. *Phytomedicine* 2000; 6: 393-401.
24. Zhang Z, Wang X, Chen Q, Shu L, Wang J, Shan G. Clinical efficacy and safety of huperzine Alpha intreatment of mild to moderate Alzheimer disease, a placebo-controlled, double-blind, randomized trial. *Zhonghua Yi Xue Za Zhi* 2002; 82: 941-944.
25. Engel RR, Satzger W, Gunther W, Kathmann N, Bove D, Gerke S, Munch U, Hippus H. Double-blindcross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type. *Eur Neuropsychopharmacol* 1992; 2: 149-155.
26. Hager K, Marahrens A, Kenkies M, Riederer P, Munch G. Alpha-lipoic acid as a new treatment option for Alzheimer type dementia. *Arch Gerontol Geriatr* 2001; 32: 275-282.
27. Silberstein N. Nutraceuticals and natural supplements for treating type 2 diabetes: An overview [Internet]. July 2010; c2012: [Cited 2012 march 30]; <http://www.diabeteshealth.com/read/2010/07/20/6766/nutraceuticals-and-natural-supplements-for-treating-type-2-diabetes-an-overview/.html>.
28. The Nutrition Notebook [Internet]. Nutraceutical breakthroughs in lyme disease; c2012 [cited 2012 march 29]. Available from: [http://www.springboard4health.com/notebook/health\\_lyme\\_disease.html](http://www.springboard4health.com/notebook/health_lyme_disease.html).
29. Kalra EK. Nutraceutical-definition and introduction. *AAPS Pharm Sci* 2003; 5[3]: 27-28.
30. Palthur MP, Palthur SS, Chitta SK. Nutraceuticals: a conceptual definition. *Int J. pharmacy & Pharm. Sci* 2010; 2[3]: 19-27.
31. National Nutraceutical Center [Internet]. What are nutraceuticals. June 2005; c2012: [cited 2012 march 30]. Available from <http://www.answers.com/topic/nutraceutical>.
32. Palthur MP, Palthur SS, Chitta SK. Nutraceuticals: concept and regulatory scenario. *Int J. pharmacy & Pharm.Sci.* 2010; 2(2): 14-20.
33. Jose S. Nutraceuticals: A global strategic business report [Internet]. Sept 2010; c2012: [cited 2012 march 30]. Available from: [http://www.prweb.com/releases/nutraceuticals/dietary\\_supplements/prweb4563164.html](http://www.prweb.com/releases/nutraceuticals/dietary_supplements/prweb4563164.html).