Review paper

The Nutraceuticals: A Voluminous Torrent in Pharmaceuticals- Coupling Health & Drugs

ABSTRACT

The present review is focused on the nutraceuticals which are present in our surroundings having an excellent impact over the health of humans but are not known for their pharmaceutical use. .Nutraceuticals include vitamins, minerals and other dietary supplements, which may be herbs, enzymes, animal extracts etc. Various researchers have proved that nutraceuticals are having an important role in reducing the risk of various diseases such as diabetes, cardiovascular diseases, Parkinson's disease etc. with very few or negligible side effects.

Keywords: Nutrients, Drugs, Dietary supplements, Functional foods.

1. INTRODUCTION

"Let food be your medicine and medicine be your food" the great line said by great scientist Hippocrates is all related with the chemicals having nutritious and therapeutic value i.e. Nutraceuticals. Which states the value of nutraceuticals in therapeutics. [1]

Nutraceuticals are a multifarious product category which has a number of synonyms that are used internationally. The term "Nutraceutical" was given by Stephen De Felice who was the founder and chairman of the Foundation for Innovation in Medicine. This term has been a part of the industry lexicon for almost a decade. [2] The term "Nutraceutical" is derived from the combination of two words, "nutrient" which means a nourishing food or food component and second "pharmaceutical" which means a medical drug. Nutraceuticals may contain substances that are "natural" intended to treat or prevent number of diseases but may not be generally recognized as safe. Hence these are the food products intended for health and medical benefit. [3, 4] It have been proved by research that nutraceuticals are useful in providing protection from a number of diseases like diabetes, cancer, cardiac disease, hypertension etc e.g. carotenoids and anti-oxidants found in carrots help in avoiding chronic diseases, by preventing free radical damage. [5] In the present scenario Nutraceuticals have become more popular in modern society because of negligible chances of adverse effects of pharmaceuticals, ease of self-medication and aging in population.

2. TYPES OF NUTRACEUTICALS

2.1 Dietary Supplements

Dietary supplements (ds) have basic objective to provide nutrition which are otherwise not consumed in sufficient quantities like herbs, minerals, vitamins, or products obtained from plant sources, animal sources such as yeasts, fungus, algae, seafood and many more e.g. Enzymes, energy bars, amino acids, and liquid food supplements. U.S. authorities say that dietary supplements may be regarded as foods, while elsewhere they may be classified as drugs or other products. [6, 7]

2.2 Functional Foods

Japan introduced the concept of functional food in 1980s, to promote health or reduce the risk of diseases. The functional food include those food items which are advised to be consumed as part of the normal diet containing biologically active constituents offering the potential to enhance health or reduce

risk of various diseases. Various examples are food that comprises fatty acids, vitamins, specific minerals or dietary fibers, food with added biologically active substances such as phyto-chemicals or other antioxidants and probiotics that have live beneficial cultures. [8] Some examples of functional food products are; milk, cheese and eggs (enriched with omega-3 fatty acids); probiotics (yogurt enhanced with live active cultures); fruit juices and drinks (having antioxidant); cereals and grains such as wheat, oat, barley (having enriched amounts of dietary fibre); modified fatty acid vegetable oils; and soy, canola and hemp (vegetable proteins) , legumes and fruit products.[9, 10].

As per established requirement of functional food in Japan: food should be consumed-

- in its natural form, rather than a prepared dosage form like capsule, tablet, or powder;
- daily , in sufficient quantity ; and
- in a way which should be regulating a biological process to prevent or cure disease.[11]

2.3 Drugs, Dietary supplements and food additives

A drug is a substance used in diagnosis, cure, mitigation, treatment, or prevention of diseases, while dietary suppliments are any substances that are either deliberately added to food to enhance its shelf-life, nutrition, texture, or other aspect of quality or which unintentionally contaminates food (indirect additive) are known as food additives. (Figure 1) [12]

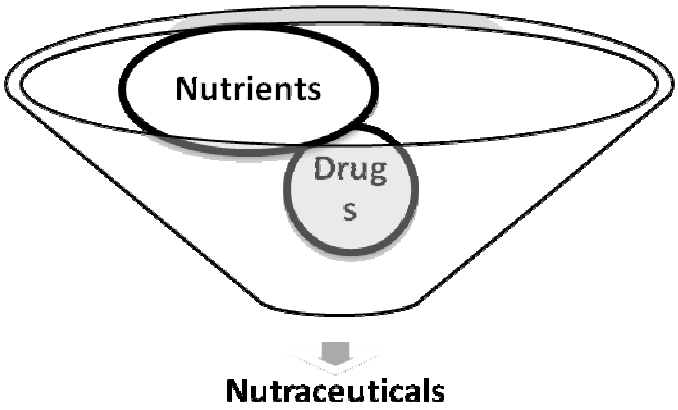

Figure 1: Diagrammatic Representation of Nutraceuticals Nutrients

Nutrients are the nutritive constituents present in food that a person consumes for his/her survival and growth. Macronutrients provide the bulk energy required for functioning of metabolic system, whereas micronutrients are helpful in providing the necessary cofactors for metabolism. Plenty of these nutrients are available in the environment. These nutrients are helpful in building and repairing of tissues, to regulate body processes. [13] Inorganic chemical compounds like water, minerals, and oxygen should also be considered as nutrients**.** [14]

2.4 Herbals

In ancient time; a large number of herbs were used to prevent and treat a number of diseases. A plant containing a number of non-nutritive phyto-chemicals provides health benefits if included in diet . [15, 16, 17] Nutraceuticals as herbals are big boon to human being in aspect of improving their health and to prevent them from chronic diseases e.g. willow bark (Salix nigra), helps as anti-inflammatory, analgesic, anti-arthritic, astringent as well as antipyretic. [18]

2.5 Phyto-chemicals

Phyto-chemicals are the plant components having bio-activities which are used to get health benefits. But their use always requires to be defended with some scientific rational in food, as potential nutraceutical. Phyto-chemicals are having following health benefits:

(1) These are used as substrates for biochemical reactions.

(2) These are used as cofactors of enzymatic reactions.

(3) ~~These work as inhibitors of enzymatic reactions.~~

(4)~~These are used as absorbents/sequestrate which bind to unwanted constituents present in intestine and eliminate them.~~

(5) These act as ligands which agonize or antagonize cell surface or intracellular receptors.

(6) These are used as scavengers of various reactive or toxic chemicals.

(7) These are used as compounds to increase the absorption and or improve stability of many essential nutrients.

(8) These work as selective growth factors for gut friendly bacteria.

(9) Fermented phyto-chemicals are beneficial for non-pathogenic bacteria found in GI tract.

(10) These are selective inhibitors of deleterious intestinal bacteria. Phyto-chemicals which consists terpenoids, phenolics, alkaloids and fiber, are extensively examined and used for their ability to get health advantage. [19]

2.6 Probiotic/ Prebiotics

Probiotic bacteria are “living microbes taken in tolerable quantity for health advantage by recipient”. These may interact with commensal bacteria to have a direct impact on the host. [20] Metchinkoff was the first person who successfully revamped the toxic flora of the large intestine into a host-sympathatic colony of Bacillus bulgaricus, found by Hord**.** [21, 22] Hence probiotics are gut friendly bacteria which aids in digestion and absorption of some nutrients. They act by eliminating the disease causing pathogens, like yeasts, other bacteria and viruses which mutually develop advantageous symbiosis within gastrointestinal tract. (Table 1) [23] The Japanese were the first to recognize the value of non-digestible oligosaccharides, and added these in feed of piglets to relieve and prevent from the diarrhoea. It was observed that fructo-oligosaccharides and galacto-oligosaccharides cause an increase in intestinal bifido-bacteria which stimulated their growth in the human gut. Hence a prebiotic is “a selectively fermented ingredient that causes changes in the activity of the gastrointestinal microbiota that are beneficial for human health”. [24] A number of marketed nutraceuticals are available in market as mentioned in Table 2.

Table 1: Different species of microbes used as Probiotic

Genus	Species
Lactobacillus	acidophilus
	delbrueckiia
	brevis

	fermentum
	gasseri
	johnsonii
	paracasei
	plantarum
	reuteri
	rhamnosus
	salivarius
Bifidobacterium	adolescentis
	animalisb
	breve
	bifidum
	infantis
	longum
Streptococcus	thermophilus
	salivarius
Saccharomyces	cerevisiae
Escherichia	coli
Enterococcus	faecium
Bacillus	coagulansc
	clausii

PRODUCTS	CATEGORY	CONTENTS	MANUFACTURER
Coral calcium	Calcium supplement	Calcium and trace minerals	Nature's answer, Hauppauge,NY, USA
Weight smart™	Nutritional supplement	Vitamins and trace elements	Bayer corporation, Morristown, NL, USA
Omega woman	Immune supplement	Antioxidants, vitamins and. phytochemicals (*eg.* Lycopene, and resveratrol)	Wassen, Surrey, U.K
Appetite Intercept™	Appetite suppressant	Caffeine, tyrosine and Phenylalanine	Natrol, Chatsworth, CA, USA
Chaser™	Hangover supplement	Activated calcium carbonate, and vegetable carbon	Living essentials, Walled lake MI,USA
Rox® Glucon-D Glucose-D	Energy drink	Taurine, caffeine and glucuronolactone Glucose	Rox America, Spartanburg, SA, USA Dabur
Mushroom optimizer™	Immune supplement	Mushrooms polysaccharides and Folic acid	Jarrow formulas, Los Angeles,CA, USA
Biovinca™	Neurotonic	Vinpocetine	Cyvex nutrition, Irvine, USA
Proplus®	Nutritional supplement	Soy proteins	Campbell soup company, Camden, NJ, USA
Snapple-aday™	Meal replacement beverage	Vitamins and minerals	Snapple beverage group, White Plains, NY, USA
WelLife®	Amino acid supplement	Granulated-L-glutamine	Daesang America Inc., Hackensach, NJ, USA
PNer plus™	Neuropathic pain supplement	Vitamin and other natural supplement	NeuroHelp, San Antonio, Texas, USA
Olivenol™	Dietary supplement	Natural antioxidant, Hydroxytyrosol	Cre Agri, Hayward, CA, USA
Threptin®	Diskettes Protein supplements	Proteins and vitamin B	Raptakos, Brett & Co. Ltd., Mumbai, India
GRD®	Nutritional supplement	Proteins, vitamins, minerals and carbohydrates	Zydus Cadila Ltd. Ahmedabad, India
Proteinex®	Protein supplement	Predigested proteins, vitamins, minerals and carbohydrates	Pfizer Ltd., Mumbai, India
Calcirol D-3®	Calcium supplement	Calcium and vitamins	Cadilla healthcare limited, Ahmadabad, India
Appetite Intercept	Appetite suppressant	Caffeine, tyrosine and phenylalanine	Natrol, chatsworth, CA, USA
Betafactor™	Immune supplement	Beta glycan	Ameridan Inernational Inc. USA
Brainspeed Memory®	Brain Health supplement	vitamin and minerals	Natrol, Chatsworth, CA, USA
Red bull®	Energy drink	Taurine, Caffeine, Glucuronolactone, b-group vitamins	Austrian red bull GmbH
5 hour energy®	Energy drink	Vitamins, tyrosin, Taurine, malicacid, caffeine, Glucuronolactone	Living essential, USA
Revital®	Daily health suppliment	Ginseng, vitamin and minerals	Ranbaxy, India
Becadexamine®	Nutritional supplement	Multivitamins	GSK, India
Glowelle®	Beuty drink	Antioxidants, vitamins and fruit extracts	Nestle, India
Threptin® Diskettes	Protein supplement	Protein and vitamin B	Raptakos Brett & co. ltd, India
HiOwna	Nutriional supplement	Protein, multivitamins, minerals and antioxidant	Himalaya herbal hdi
PediSure®	Nutritional supplement	Protein, multivitamins, minerals and antioxidant	Abbott India ltd, India
Orgazyme®	Sex stimulating	L-arginine & l-ornithine	
R-Gene® 10	Growth stimulant	L- arginine HCl	Pfizer Inc, NY
Alamin SE®	Protein supplement	L-arginine & other Protein	Albert David Ltd., India
Albumen Care	Protein supplement	L-arginine & other Protein with multivitamins and minerals	B.V. Bio-Corp Pvt. Ltd., India
Argipreg	Protein Supplement	L-argnine, proanthocyanidis	Manikind Pharma Pvt. Ltd, India

Table 2: List of marketed nutraceuticals

3. PHARMACOLOGICAL USE OF NUTRACEUTICALS

Better life quality is achieved with food items filled with nutrient values and remarkably potent in preventing diseases which may be cancer, diabetes, heart diseases, hypertension etc as . (Table 3 & Figure 2) Such products may be dietary supplements, food additives, phyto-chemicals, prebiotics, probiotics, genetically modified food, processed food and plant products.

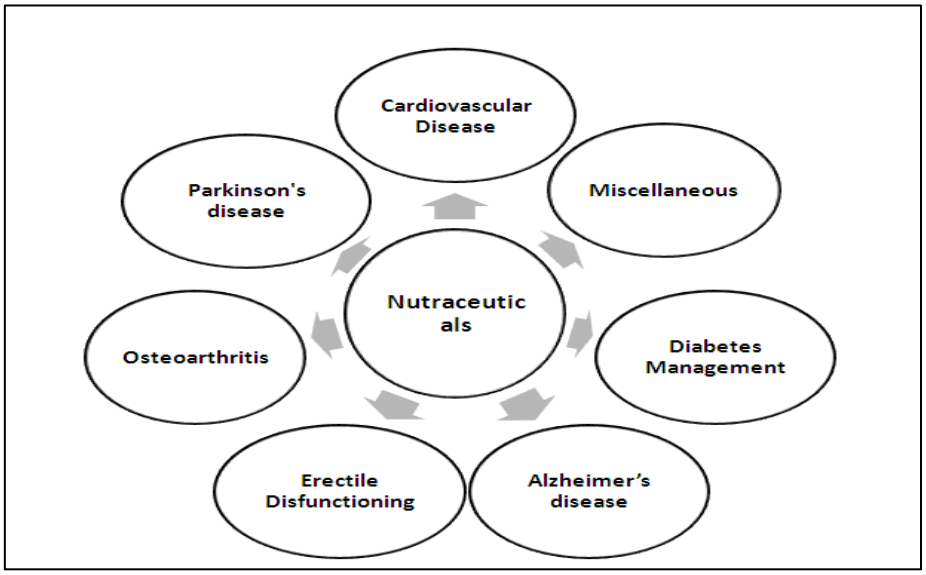

Figure 2: Pharmacological Uses of Nutraceuticals

Table 3: Detailed Review on Various Nutraceuticals

Types of Nutraceuticals	Sources	Active Constituents	Applications
Dietary Fibre	Whole grain foods wheat and corn bran, nuts	Insoluble Fibre	Reduce chances of colon or breast cancer (anticancer) [74, 75], maintain health of digestive tract[76]
	Oats, barley	Beta-Glucan	Reduce risk of cardiovascular disease, lower down Low Density Lipids and total cholesterol[77,78]]
	Beans e.g. Legumes, oats, barley and some fibrous fruits	Soluble Fibre	Anticancer (Colon Cancer), Digestive [79.80]
Fatty Acids	Salmon and other fish oils	Long chain omega-3 Fatty Acids-DHA/EPA	Reduce risk of CVD Improve mental, visual functions[81-83]
	Cheese, meat products	Conjugated Linoleic Acid (CLA)	Improving of body composition Decreases chances of certain cancers[84-8 6]
Phenolics	Fruits	Anthocyanidins	Antioxidant ; reduce risk of cancer[87-89]
	Green Tea	Catechins	Antitumor[90]
	Citrus	Flavonoids	Antioxidative activity, Prevention of coronary heart disease, hepato-protective, Effective in inflammation and cancer.[91]
	Cocoa, Chocolate, Cranberries & cranberry products	Tannins	Anti-microbial, Reduce risk of cardiovascular disease [92]
	Corn, soy, wheat, wood oils	Plant Sterols, Stanol ester	Lower blood cholesterol levels by inhibiting cholesterol absorption[93]
Carotenoids	Tomatoes	Lycopene	Antioxidant, protect against prostate cancer[94]
	Corn, various fruits, egg yolk, spinach	Lutin	Antioxidant, Muscle regeneration, anti cancer activity, protect eyes against age related muscular degenerations, cataract[95,96]

	Carrots, various fruits (Guava, papaya, Water melon etc) and vegetables (tomatoes etc)	Beta carotene	Antioxidant, protection of cornea against UV light.
	Soya beans	Saponins	Effective against colon cancer, reduces cholesterol level[97]
Probiotics/ Prebiotics	Curd	Lactobacillus	Antibacterial, acute diarrhea[98]
	Whole grains, onions, combination of Pro & Prebiotics	Fructo–oligosaccharides	Improve GI health, restore gut flora[99]
Phytochemical	Grains	Tocotrienols and tocopherols	The growth of diverse tumors cell lines was suppressed via initiation of apoptosis and concomitant arrest of cells in the G1 phase of the cell cycle[100]
	Cereal grain, dairy & egg products and plants oil	Phytosterols	Exhibitantioxidant, anti-inflammatory, anti-neoplastic, anti-pyretic & immune- modulating activity, decrease cholesterol[101-103]
	Various plants, wholegrain	Phenolic constituents	Antioxidants, Anti-hyperglycemic, and anti hypertensive[104]
	Grapes, berries, cocoa, green tea, acacia spp.	Catechin & gallic acids	Antioxidants, Antiradical property, cyto-protective.[105,106]
	Soybeans	Isoflavonoids	Treating cancers & attenuates bone loss[107, 108]

3.1 In cardiovascular disease

It is not easy to set up a clear impact of nutrition/physical exercise on major cardio vascular diseases because history of cardiovascular diseases is too long. [25] The effect of calcium over hypertension and pre-eclampsia (a condition in pregnancy characterized by high blood pressure, sometimes with fluid retention and proteinuria) is unpredictable as well as ambiguous. [26] Treatment with vitamin C and selenium need further study to observe its effect on mortality. [27] It has been observed that some

nutraceuticals may be useful to forbid and superintend the risk of thrombosis in women with thrombophilic gene mutations. [28]

Vitamins, minerals, omega-3 poly-unsaturated fatty acids (n-3 PUFAs), dietary fibers and antioxidants, as nutraceuticals and physical exercise are advised to prevent and treat cardio vascular diseases. Researchers have proved that polyphenols found in grapes and in wine are helpful in reducing arterial disease by altering cellular metabolism and signaling. [29]

Onion, black grapes, cherries, cruciferous vegetables, grapefruits, red wine, apples and berries are good sources of flavonoids [30] and also available as flavones and flavonols which are beneficial for the treatment of cardiovascular diseases.[31, 32, 33] Antioxidant activity of ascorbic acid, alpha-tocopherol, and beta-carotene as have been studied and reviewed.[34]

3.2 In management of diabetes

Various *in-vitro* and *in-vivo* studies (animal) have proved that plant polyphenols including phenolic acids, stilbenes, lignans and flavonoids are effective nutraceuticals in diabetes and its prevention. Although human clinical trials are required to check the efficacy of poly-phenol compounds in treatment of diabetes. [35]

Vitamin C (ascorbic acid) is a chain-breaking antioxidant which avoids the propagation of chain reactions that may lead to a reduction in protein glycation. It has been reported that ascorbic acid helps in reducing diabetes-induced sorbitol in animals. [15]. Ascorbic acid (800 mg/day) partially replenishes ascorbic acid levels in patients with type 2 diabetes but endothelial dysfunction or insulin resistance is not effected at all. [16].

N. Bunyapraphatsara *et al* observed a combined effect of Aloevera juice with glibenclamide in diabetic patients and concluded that glibenclamide alone did not show any effect while Aloevera juice showed significant reduction in fasting blood glucose level and triglycerides within two weeks and four weeks respectively. Although it did not show any effect on level of cholesterol but the effectiveness of Aloe vera was found in the treatment of diabetes. [36] Acacia is a non-starch polysaccharide which is not digested in the intestine, but generate short chain fatty acids in large bowel; hence, it produces extensive biological effects. Philips AO *et al* conducted study over the extract of Acacia Arabica and confirmed the anti-diabetic effect of acacia resulted by increasing the insulin release. [37] Hou *et al* demonstrated significant hypoglycemic effects of Acacia Arabica powder in healthy rabbits, whereas no significant decrease in blood sugar was observed in the alloxan-induced diabetic rabbits was observed. [38] Wadood *et al* concluded that Acacia arabica initiates the release of insulin from pancreatic beta cells of normal rabbits. [39] Antidiabetic activity of glycerrhiza in non insulin dependent diabetic model was observed by Takii. [40]

High intake of isoflavone (20–100 mg/day) is helpful in lowering of rate of mortality in diabetes of type 2, osteoporosis, cardiac disease and certain cancers.[41] Docosahexaenoic acid is vital for neurovisual development which helps in modulating insulin resistance and nurture the advocacy for essential fatty acids in pregnancy in women with gestational diabetes mellitus. [42]

Omega-3 fatty acids helps in reducing blood glucose tolerance in patients predisposed to diabetes. Insulin is needed to synthesize long chain n-3 fatty acids; thus heart may be victim to their depletion in case of diabetes. Hence it is concluded that ethyl esters of n-3 fatty acids may be advantageous in diabetic patients. [43] Lipoic acid is a well known antioxidant, ~~and in Germany being used~~ to cure diabetic neuropathy. Lipoic acid; as a long-term dietary supplement is aimed at the prophylactic protection of diabetics from complications**.** [44] α-Lipoic acid enhances insulin sensitivity by approximately 18–20% in patients suffering from type 2 diabetes. [45] Clinical trial studies on α-lipoic acid reported advantageous in the treatment of diabetic neuropathy.[46]

Dietary fibers obtained from psyllium have been used to reduce weight and lipid levels in hyperlipidemia as dietary supplement. [47] Intake of Chromium supplements may be helpful to enhance sensitivity to insulin and boost glucose tolerance in type II diabetic patient. [48] Magnesium-rich diet intake may reduce risk of diabetes by improving in insulin sensitivity.[49] Diabetes management is supported by one of the nutraceuticals Biotin which increase insulin production and stimulates liver glucokinase activity, thus improves the uptake of glucose in muscle cells. [50, 51, 52] Pharmacological effect of epinephrine can be inhibited by Azadirachta Indica which results in enhanced utilization of peripheral glucose [53, 54] and reduce hypo-glycaemic activity without change in the serum cortisol level. [55, 56]

Kernels of Eugenia jambolana are useful in diabetes management; their aqueous/alcoholic extract shows hypoglycemic effect. [57] Green Tulsi (Ocimum sanctum) leaves extract also reduces blood sugar significantly by cortisol inhibiting potency as proved in both normal and alloxan induced diabetic rats. [56, 58]

3.3 In Parkinson's disease

Latif S *et al* concluded that diet enriched with vitamin E may decreases the chances of Parkinson's disease [59] while Brower V reported that creatine is helpful in management of Parkinson's disease by decreasing the clinical symptoms. [60]

Antioxidant vitamin supplements such as tocopherol, ascorbic acid and beta-carotene are the abundantly occurring nutraceuticals. As per various earlier literature vitamin E supplements are becoming popular in treatment of Parkinson's disease, whereas epidemiological studies reported that vitamins C and E rich diets are associated with decreased risk of Parkinson's disease. [61, 62]

3.4 In Alzheimer's disease

Literatures have been reported that fulvic acid, an active principle of Shilajit is highly effective against brain disorders exclusively and in combination with vitamin B complex. [63]Treatment of patient suffering from Alzheimer's disease with donepezil and vitamin E found effective although future study was suggested to check and compare additive as well as indivisual effect. [64] Wettstein A. *et al* reported that mild to moderate Alzheimer's dementia could be treated with metrifonate, donepezil, rivastigmine which are second-generation cholinesterase inhibitors. [65]

Hager *et al* found stable cognitive function especially in those patients who were administered with 600 mg Alpha-lipoic acid along with acetyl-cholinesterase inhibitors, in comparison to the patient only on the therapy of standard acetyl-cholinesterase inhibitors since last 337 days. [66] Huperzine-alpha is a plant alkaloid derived from Club moss plant, Huperzine serrata, which is a member or the Lycopodium species. Huperzine-alpha is in phase III clinical trial in the USA and is available as a dietary supplement.[67] The meta-analysis of Huperzine A reported here highlights that this treatment has certain signific ant improvement for patients with Alzheimer's disease and Vascular Dementia, and longer durations may result in better efficacy for patients with Alzheimer's disease. [68]

Literature survey supports that Lipoic acid also helps to improves potential of mitochondrial membrane, memory loss due to ageing and brain ailments as well as in patient suffering from Parkinson´s and Alzheimer's disease. [69]

3.5 In Erectile Disfunctioning

L-arginine in combination with pycnogenol (a product obtained from the pine bark of Pinuspinaster) is found safe and effective in mild to moderate erectile dysfunction in Japanese patients. [70] When Patients suffering from moderate to severe ED and dyslipidemia were kept on Niacin rich diet, significant improvement was observed in patients. [71]

Kaempferia Parviflora Wall. Ex. Baker (KP), which is a Thai plant with name, Kra-Chai-Dum and rhizomes of which are used as a traditional medicine to alleviate male impotency, improve male libido, as energizer, control blood pressure and also reduce stomachache. Study reveals that KP is a potential nutraceutical compound effective in male erectile dysfunction caused due to ageing. [72]

3.6 Osteoarthritis

Chondroitin sulfate and Glucosamine both are commonly used to lighten the symptoms of osteoarthritis. Chondroitin sulfate and Glucosamine both act as nutraceuticals and possible mechanism of their anti- inflammatory activity may be due to synthesis of NO and PGE2.[73]

Conclusion

~~In the present scenario Nutraceuticals have become more popular in modern society and became important~~ due to increasing applications of Nutraceuticals which serves as a part of growing pharmaceutical industry. Modern society is now being aware about the food product that is beneficial for them in aspects of health and nutrition owing to very few or no side effects. Nutraceuticals are being used to treat fatal diseases like cancer, diabetes, cardiovascular diseases; as well as Parkinson's disease, osteoarthritis etc.

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