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NUTRACEUTICALS: EMERGING CONCEPTS AND PROSPECTS IN CARDIOVASCULAR DISEASE PREVENTION.

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ABSTRACT

Consumers are deeply concerned about how their healthcare is managed, administered and priced. They are frustrated with the expensive, high-tech disease treatment approach predominantly in modern medicine. Positioned at the interface between food and drugs, a growing body of products is assuming importance i.e nutraceuticals. Nutraceuticals are food or part of food that provides medical or health benefits including the prevention and/or treatment of a disease. Nutraceuticals have an advantage over the medicine because they have fewer side effects and are a dietary supplement, etc. Nutraceutical products represent a value-added growth opportunity in both domestically and internationally. Global nutraceutical market is estimated as USD 117 billion. FDA regulated dietary supplements as foods to ensure that they are safe. Herbal nutraceutical is used as a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity and quality of life. This article briefly discusses the basic information of nutraceuticals and its importance in cardiovascular health prevention.

KEYWORDS: Nutraceuticals, Functional Foods, Dietary Supplement, Green tea, Marketed Nutraceuticals.

INTRODUCTION

Approximately 2500 years ago, Hippocrates (father of modern medicines) correctly articulates "**Let food be your medicine and medicine be your food".** Nutraceuticals are termed as a substance that belongs to a plant (herb) food or an important component of food providing definitive medicinal usefulness and health promotion, physiological benefits and

ultimately reduces the possible risk of the prevailing chronic diseases significantly. Nutraceutical is a food (or food part) which provides us medical-health benefit, including the prevention as well as treatment of disease. Stephen DeFelice (MD) the founder chairman of the Non-Profit Foundation for Innovation in Medicine Cranford NJ (USA) who first and foremost carried the term nutraceuticals in 1989. Researchers have identified many compounds with their functional quality and are making compounds which surround the complexes of photochemical in food. Scientific research illustrates many potential health advantages from food components. These advantages could expand up the health claims which are given to identify by Food and Drug Administration. Nutraceutical is divided into two words Nutrition and Pharmaceutical. It ranges from some specific dietary supplements, natural and herbal product, nutrient, processed food as it also includes beta-carotene, tea, fish oil, green tea, olive oil and various herbs, oat bran, which are sometimes said to be as functional food. Currently, around 470 nutraceuticals and functional food are providing health benefits with are documented.[1]

In the past couple of decades, nutraceuticals have gained sufficient ground in terms of their:
Wide acceptance.
Overall confidence.
Due recognition.
Amongst the mankind not only as a mere health-promoting factor but also as a superb nutritional contributing factor. Now, with the advent of an ever-expanding in-depth knowledge with regard to the so-called natural bliss of nutritional values of the host of food product their respective chemical entities *vis-a-vis* the critical inherent biological valves has succeeded largely in combating human ailments to a significant extent.

In rather broader perspective it may be duly considered that the nutraceutical does exert their action more\less synergistically so as to check and control such critical significantly as:
Deteriorating health condition.
Protect cells.
Ward off human diseases.

In the sense, the nutraceutical has enormously captured the noticeable professional interest and curiosity of an array of such interesting allied discipline as:
Health care products.
Professional scientists.

Processed food manufacturers.

Pharmaceutical industries.

Diet control conglomerates.

Nutraceuticals as pharmaceutical aids for major human diseases:

Nutraceuticals are associated largely with the following cardinal aspects:

Prevention, Relief, Treatment of certain specific and common major human diseases such as: Arthritis, Cancer, Coronary Diseases, Diabetes, Hypertension, Nervous Debility, Neural Tube Problem, Osteoporosis, Impaired Digestive Problems.[2]

Advantages

Fewer side effects.

Useful for treating nutritional deficiencies.

Expand health benefits.

Usually, does not require prescriptions.

Effortlessly available and cheap.

It provides food for a population with special needs.[3]

Disadvantages

Often nutraceutical lacks clinical trials and evidence for their effectiveness.

Elimination of nutraceuticals from the body does not provide any medical benefits and have poor bioavailability.

The International market of nutraceutical asserts to use an organic product, but due to depletion in regulation may concede in safety\effectiveness of product.

Proper advice about the product is not providing to the consumers with its detailed information.

Concept of Nutraceuticals

In the process of development of pharmaceutical, for the verification of effects clinical trials and animal testing is required. In case of nutraceutical no testing or validation method for food in preventing diseases in the past. Currently, food composition has proved scientifically the cause of lifestyle-related diseases which have become social issues.[4] The concept of Nutraceutical was rising to acknowledge as a means of preventing such diseases. (Figure 1).

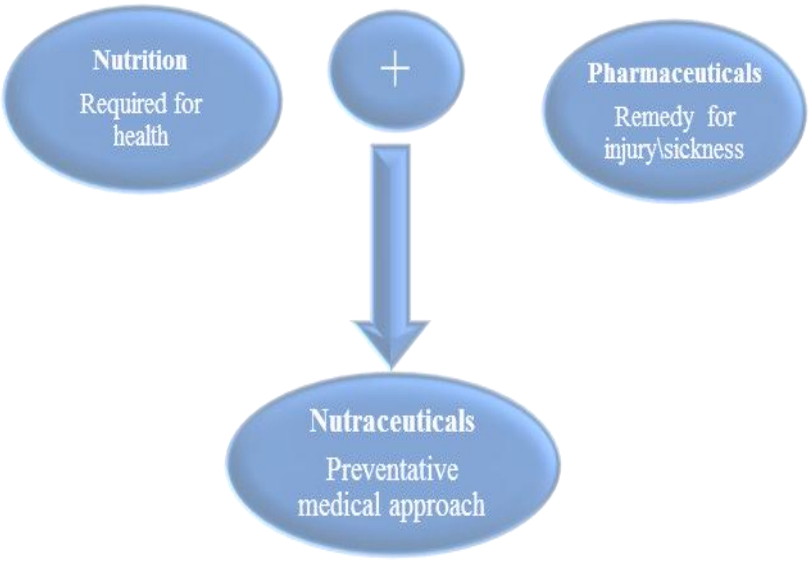

Figure 1. The concept of Nutraceuticals (Nutr+aceuticals) Coined by Stephan DeFelice in 1989.

CLASSIFICATION

It is explained in form of flow chart in (Figure 2).

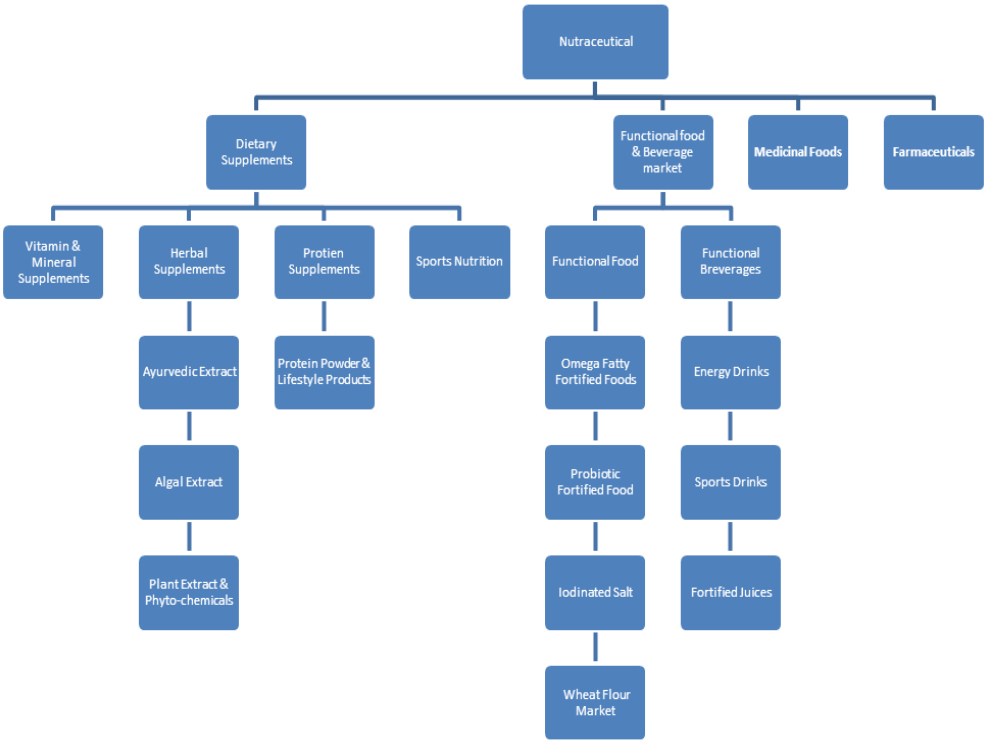

Figure 2. Classification in form of flow chart.

Nutraceuticals are classified into categories of a wide variety of products and on basis of chemical nature and source (Figure 3).

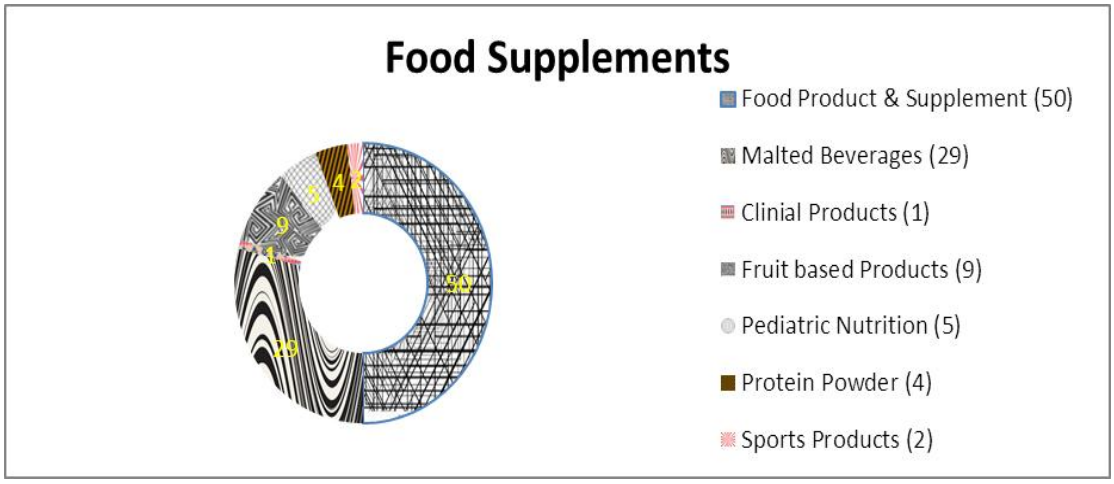

Figure 3. Categories of Food Supplements.[5]

Dietary supplement

Food product which is concentrated in capsules and\or liquids which contain nutrients which are a product of dietary supplement. It is defined as Dietary Supplement Health and Education Act 1994 (DSHEA). Dietary Supplement is helpful to treat a variety of diseases.[6] Ketogenic diets consist of foods increases in fat and decreases in protein and carbohydrate, which have been reported to improve seizure control. However, these diets are broadly acknowledged to be unpalatable, difficulty in making sustained compliance with dietary restrictions. Food products like nite-bite and bar (uncooked cornstarch food products) contain protein, sucrose in form of bars and uncooked starch to provide continuous glucose release in a diabetic patient during the night. Health promoting the example of nutraceutical is milk, identification of various casein and whey protein derived angiotensin-converting enzyme inhibitory peptides\hydrolysates. Classification of these peptides\hydrolysates as nutraceuticals which provide the ability for health benefits. It includes dietary ingredient as vitamins, minerals, herbs, amino acids, coenzymes Q and botanical products and so on.[7]

Functional Food

It is different from other nutraceuticals products, using the scientific intelligence when food is been prepared without knowing how\why it is to be used and provide categorically medical advantages and good health including prevention, treatment of specific diseases called functional food. It also provides vitamins, fat, proteins, to the body which helps in healthy survival. It is said to be nutraceutical when it is aids for treatment and prevention of disorder apart from anemia.[7] **Examples:** a host of fortified dairy product for instance: Milk powder, Malled milk food, Baby food also called functional food.

Medicinal Foods

Medical food regulated by Food And Drug Administration (1988) which is formulated to intake by the consumers under the prescription of medical supervision\physician, which is intended for specific diseases conditions for which scientific principle on distinctive nutritional requirement are established for medical evaluation. Category of a medical food is distinct from dietary food, traditional food that bring health claim.[8]

Medical food considers

Food ingested through mouth\tube feeding.

Labelled for a medical disorder, specific diseases condition, for which distinctive nutritional is required.[9]

Classification of medical food

Nutritionally complete (eg: ready to use (liquid form) Carbohydrates, Fat, Minerals, Proteins)\incomplete formulas (eg: Single sourced by particular nutrient; Carbohydrates, Fat, Minerals, Proteins).

Metabolic disorder formulas (eg: Phenylketonuria (PKU), Maple Syrup).

Oral rehydration products (eg: Sodium Chloride, Sodium Citrate).

Farmaceuticals

Term farmaceutical is recently combined into the agriculture circle, with medical benefits and genetically contrive crops\animals. It (Farmaceuticals) is a melding of words farm and pharmaceuticals. Farmaceuticals is termed as medically valuable compounds produced from modified agriculture crop\animals (usually through biotechnology).[10] Proponent accepts that use of animals and crop as pharmaceutical industries\ factories are cost effective than conventional method with providing agriculture producers with higher earnings.[6] The global market of nutraceuticals is shown in (Figure 4).

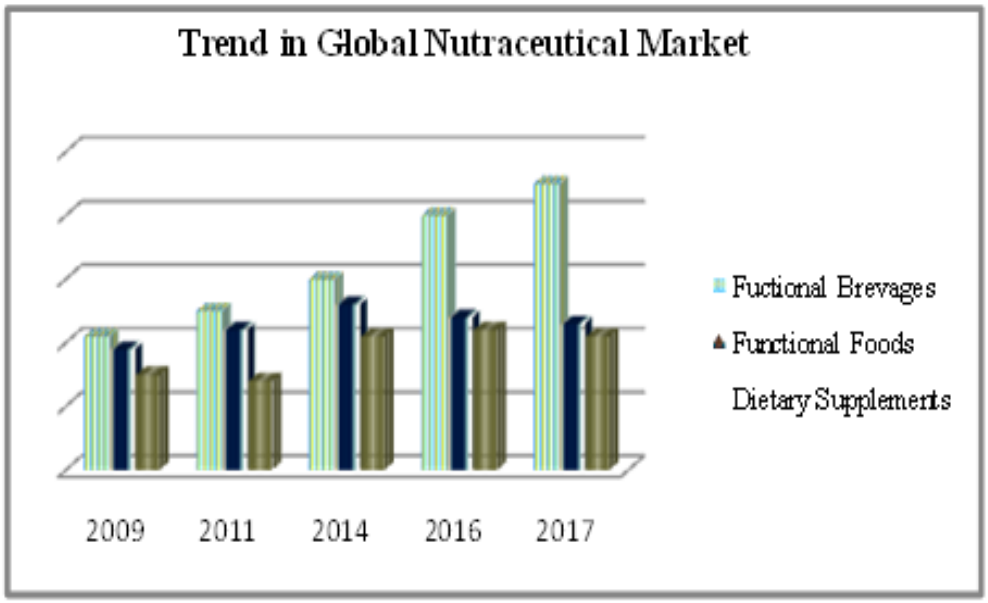

Figure 4. Nutraceuticals Market.

NUTRACEUTICAL USE IN DISEASES TREATMENT

In the current scenario, a nutraceutical is bringing up acceptance as a beneficial role in the diseases like Alzheimer, Cardiovascular, Parkinson, Constipation, Osteoarthritis, Coronary Heart diseases, Obesity, Diabetes, Antioxidant, Cancer, Anti-inflammatory, Vision improving, Hypertension, Hyperlipidemia and so on. Mechanistic action of natural compounds involves a large array of biological process, which included activation of antioxidant defenses, signal transduction pathways, cell survival-associated gene expression and cell proliferation. It seems that these properties play an essential role towards protection against the pathologies of many age-related and\or choric diseases. Nutrition found in food products i.e. fruits, vegetables which are essential and plays a crucial role in health benefits and is documented.[11]

Different nutraceuticals are used to provide health benefits in various diseases as follows:

Cardiovascular diseases

Antioxidants, dietary fibers, n-3 and n-6 essential fatty acids, flax lignans, coenzyme Q10, lycopene, flavonoids, polyphenols, black and green tea, grapes seed, carnitine and 25 g of soy foods are used in the prevention of cardiovascular diseases.

Cancer

Phytoestrogens is recommended to prevent prostate/breast cancer, tea, flaxseed, lycopene concentrates in the skin, testes, adrenal and prostate protects against cancer, melatonin, polyunsaturated fatty acid, saponins contains antitumor and antimutagenic activities.

Anti-inflammatory activities

The nutraceutical use is Cucurmin which is a polyphenol of turmeric which has anticarcinogenic\antioxidative\anti-inflammatory properties.

Eye health (Vision)

Zeaxanthin and Lutein (found in tomatoes, carrots, and leafy vegetables) is used for the treatment of visual disorders.

Osteoarthritis (Joint Health)

Glucosamine (GLN) and chondroitin sulfate (CS), methylsulfonylmethane, fish oil, acetylated fatty acid is used for the treatment of osteoarthritis.

Mental Health

Acetyl-L-carnitine, soy isoflavones, phosphatidylserine are used in the treatment of mental health.

Diabetes

Lipoic acid, an antioxidant is used for the treatment of diabetic neuropathy; dietary fibers from psyllium have been used for glucose control in diabetic patients.

Obesity

Herbal stimulants, caffeine ephedrine, and green tea help for a reduction in body weight, a mixture of glucomannan, chitosan, fenugreek and vitamin C in dietary supplement significantly reduced body weight.

Animal Health

Use of nutraceutical in diseases related to animals is a Cardiovascular Disorder, Joint Diseases, Periodontal Diseases, Cognitive Dysfunction and Cancer.[3]

CARDIOVASCULAR DISEASES

Cardiovascular a class of diseases involves heart and blood vessels diseases. It includes diseases like coronary artery diseases i.e. angina and myocardial infarction (heart failure\attack). CVDs also includes diseases like stroke hypertensive heart, rheumatic heart, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis. Millions of death per year are caused by cardiovascular diseases which affect circulatory system and chronic disorders (heart failure\attack).[12] The result shows the increase from 12.3 million deaths (25.8%) in 1990 to 17.9 million deaths (32.1%) in 2015. CVDs in 1999 contributes third in global death and in the year 2010 a death cause leading in developing countries.

CVDs is increasingly given information related to their dietary habits, related with fats and cholesterol intake which increase the risk of CHD (chronic heart diseases); it is not increasing only by poor dietary habits but also by lifestyle habits such as smoking and alcohol intake.[13] Nutraceutical are essential in prevention\symptom reduction of CHD (chronic heart diseases) which includes black and green tea with their flavonoids, soy protein and isoflavones, essential fatty acids, flax lignans, coenzyme Q10, lycopene, policosanol and pycnogenol, melatonin, resveratrol, grape seed proanthocyanidin extract (GSPE), lutein, carnitine and dehydroepiandrosterone (DHEA).[14]

The risk factor of CVD according to National Health Services (NHS) the UK.

Hypertension: (high blood pressure) its damages the artery wall and increases the risk of developing the blood clot.

Smoking: Blood vessels get narrowed, especially coronary arteries.

Hyperlipidemia: (high blood cholesterol) it increases the narrowing of blood vessels and blood clots.

Unhealthy eating: Lack in the proper amount of vegetables, fruits, fibers, whole grain, important nutrients and proper diet each day is not good for CV health.

Different Nutraceuticals used in Cardiovascular System

Green and Black Tea

Tea is probably the most popular drink in the world. Worldwide per capita consumption of tea has been estimated at 40 L/year. Catechin derivatives during the production of green tea are produced, depending on the raw material and treatment conditions. Black tea (fermentation processing) used in the production of complex polymeric components. Amino acid theanine is a component of tea which reduces blood pressure in hypertensive rats.[15] MOA is shown in (Figure 5).

Mechanism of Action

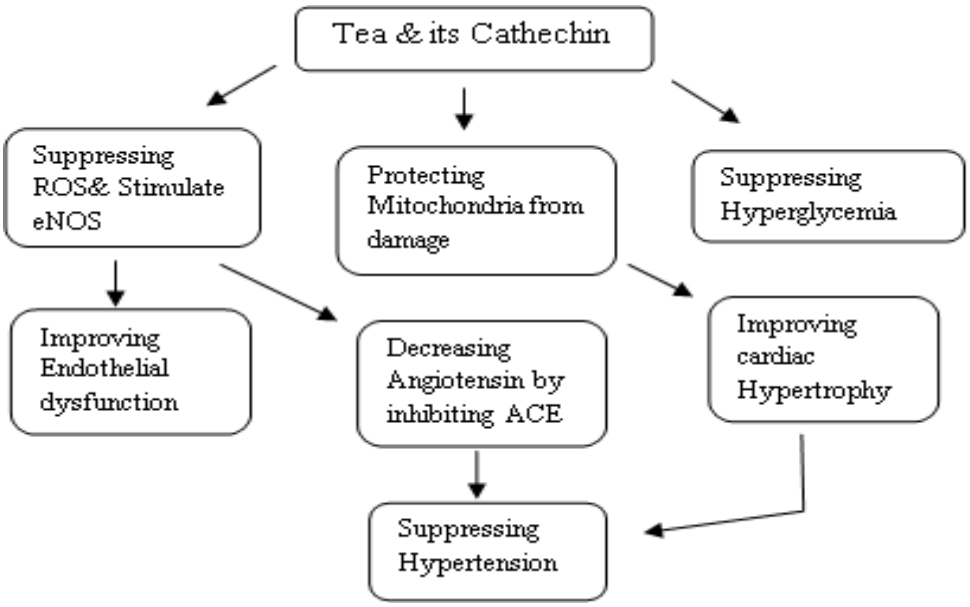

Figure 5. ROS: Reactive Oxygen Species; eNOS: Nitric Oxide Synthase; ACE: Angiotensin Converting Enzyme.

Tea has an effect on different diseases which are related to CVD i.e. Myocardial Infarction, Hypertension, Atherogenesis and so on.

Myocardial Infarction

Polyphenols of tea have antiplatelet, antithrombotic, anti-inflammatory properties and study on animals concluded that it improves vascular function. This implies that consumption of tea decreases the risk of cardiovascular diseases and cause myocardial infarction. Many epidemiology studies in different countries stated that consumption of tea decreases the risk of MI in CVDs. The Boston Area Health Study stated ingestion of at least a cup of tea each day decreases the risk of MI almost half as related to non-tea-drinkers. Study on Dutch

populations stated that tea drinkers consuming 375 ml/day had a lower relative risk of MI related to non-tea-drinkers.[16]

Hypertension

It is one of the most common forms of CVD which affect around 20% of adult population of countries; it is also an important risk factor for cardiovascular mortality with cause around 20-50% death. Epidemiology study in Norway experienced the decrease in systolic BP (Blood Pressure) with an increase in consumption of black tea. A study in Japan conducted no relation between an intake of green tea and BP, but clinical trials in Australia and England showed a correlation between green and black tea decreases BP. A long-term effect of tea drinking shows the risk of developing hypertension. Consumption of 120 mL of tea per day for one year has a 46% lower risk of hypertension than non-tea drinkers. Consumption of 600ml or more decreases risk of hypertension by 65%.[17]

Atherogenesis

Death over 6.5 million people worldwide each year is due to CHD, most of the incidence caused due to atherosclerosis of the coronary arteries, the epidemiological study stated that consumption of two cups of black tea each day decrease risk of CHD (Chronic Heart Diseases).[18] Related to lipid level negative correlation is shown in Norway in black tea drinkers and no correlation in green tea drinkers in Japan. Atherosclerosis decrease by 26-46% in the low dose of tea about 0.0625%, with a decrease in about 48-3% in a high dose about 1.25%.[15] Consumption of both black and green tea in human trial show the increase in plasma antioxidant capacity after 1hrs of consumption of tea 1-6 cups each day, this can protect cells\tissue cause damage by scavenging oxygen-free radicals, after being absorbed from the gut after ingestion.[19]

Soy

Food and Drug Administration (FDA) US in 1999, approved to manufacture soy food in the state, as consumption of soy 25g each day benefits and decreases the risk of CHD. Analysis to result depending on cholesterol level showed that consumption of soy food rather than animal proteins reduces LDL-C by 7-24%. Soy decreases the micellar absorption of lipids by fiber, isoflavones, and phytoestrogens and (low-density lipoproteins-cholesterol) soy proteins increase LDL (low-density lipoproteins) receptor expression in human beings. It was not reported clearly that the benefits were due to soy protein or isoflavones constituents.[20] Animals and clinical evidence with relation to soy and soy protein consumption has been

disclosed in many areas of cardiac health. There are many mechanisms, Alfredo Galvez in 2007 found that bioactive soy peptide lunasin is responsible for much of soy's cholesterol-lowering effects, whereas, in cell culture HepG2 liver cells, Lunasin significantly reduced HMG-CoA reductase (enzyme responsible for cholesterol biosynthesis) expression by 50% through histone H3 acetylation. Dr. Galvez said that effect of Lunasin on histone H3 acetylation provides a plausible and testable mechanism of action to explain the LDL-C and total cholesterol-lowering effect attributed to soy proteins.[21]

Effect of soy has shown the different effect on diseases of CVDs i.e. Blood pressure, Atherogenesis.

Blood pressure (BP)

Hypertension is the common form of CVD, it is subjected after comparing several trials of cardioprotective effects after intake of soy protein, and effect of soy on blood pressure during hypertension is a concern in some data which are reviewed recently. The trial of soy protein supplementation on normotension men and women results that 40gm of protein and 118mg isoflavonoids per day for 3 months significantly show a decrease in systolic, diastolic and mean BP. Again a trial was carried on men and women shows mild to moderate hypertension in which person intake 500mL of soy milk twice each day for 3 months, at the end of trial soy milk consumers was seems to have lower systolic, diastolic and mean BP.[22] Another clinical trial data on patients with essential hypertension intake 55mg of isoflavonoids from red clover each day for 8 weeks has shown no hypotensive effect, recently 22 random trails of soy protein and isoflavones resulted that soy products are beneficial to cardiovascular health as it contains polyunsaturated fatty acids, vitamins, minerals, fat, as effect of isoflavones study have negligible effect.[23]

Atherogenesis

One of the major factors in CHD is atherogenesis of coronary arteries; studies showed that soy protein has an important effect on prevention and development of atherogenesis. Many *in-vitro* studies carried out on human trials to identify mechanism involved in the activity of isoflavones in atherogenesis, these experiments show causes of both genistein and daidzein in inhibition of LDL oxidation in vascular subendothelium. Due to antioxidant activity soy isoflavones shows an antiatherogenic effect in humans through inhibition of LDL oxidation. The activity of mechanism shows binding to estrogen receptors, reduction in hyperlipidemia,

and inhibition of the migration and proliferation of smooth muscle cells by genistein, and inhibition of tyrosine kinase by genistein.[24]

Essential fatty acids

Bioactive components in oily fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (22:6) with Long-chain -3 PUFAs, eicosanoid biosynthesis alter by Omega-3 PUFAs which affects signalling and alter membrane fluidity, influences enzymatic reactions and receptor binding which is directly activate transcription factors and regulate genes affecting hyperlipidemia and inflammation. Membrane fluidity influenced by cellular membranes of Omega-3 PUFAs is essential for cognitive development.[25] Use of Omega-3 fatty acids is increasing for CVDs because it reduces platelet aggregation, blood viscosity, plasma levels of fibrinogen, PF4 and thrombi globulin and also increases capillary flow. Researchers like, found that fish oil in clinically used doses (typically 4gm each day of eicosapentaenoic acid and docosahexaenoic acid) decreases high triglycerides[26] also found that intake of 223mg EPA plus 149mg DHA or 1.9gm ALA exerted a protective effect against ventricular arrhythmia-related events in post-myocardial infarction patients with diabetes.[27]

Cardioprotective Effect

Experimental data of evidence recommended that long chain n-3 polyunsaturated fatty acids found in fish have antiarrhythmic properties, a random trial of n-3 fatty acids (dietary supplements) decreases the risk of sudden death among survivors of myocardial infarction. Recent data gives a confirmation that n-3 PUFA is bioactive compounds decreases the risk of cardiac death.

Flax lignans

The quantity of fixed oil in flaxseed is about 35-45%, with 50% ALA (α-linolenic acid) accounting, defatted flaxseed and fiber contain a level of about 10-30mg\gm lignin secoisolariciresinoldiglucoside (SDG). Canadian researchers found that hypercholesterolemic atherosclerosis reduced by 46% in rabbits fed 7.5 gm/kg whole flaxseed, afterwards it was shown that 69% reduction in atherosclerosis has seen after given flaxseed oil containing only 3% ALA (to check whether the effects caused by the lignans\ALA) and then used SDG supplementation 15mg\kg found 73% reduction in development of hypercholesterolemic atherosclerosis, involvement of the lignan SDG was clearly shown in the resulting outcome.[28]

Use of flaxseed and\or flaxseed oil range of subjects was compared in recent outcomes clinical trials, five trials out of six used of flaxseed (38–50 gm each day) and showed a significant decrease in total cholesterol and LDL-C and three trials out of four using flaxseed oil showed no decrease in cholesterol parameters. Whereas the use of one trial with high-dose of 60 gm each day of flaxseed oil for two weeks showed a reduction in triglyceride levels, and there were reductions in total cholesterol and LDL-C levels in specific patient groups. Coating of flaxseed contains viscous soluble and insoluble fiber which is thought to be involved in cardiac protection; in the meta-analysis, it has shown that 2–10 gm each day approximately 26-130gm of flaxseed, of viscous soluble fiber produces a small and significant reduction in total cholesterol and LDL-C.[29]

Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 (CoQ10) is powerful protein-lipid phase antioxidant and free radical scavenger, manufactured and used as a medicine in Japan. Occurs naturally in body part located in mitochondria of myocardium, liver and kidney cells which have membrane stabilizing effects. In CVDs it is used in the treatment of including heart failure, hypertension, angina and arrhythmias.[25] Clinically CoQ10 is used for a treatment of hypertension, as it causes a reduction in total peripheral resistance. CoQ10 serum level decreases with age and are lower in patients with diseases which are characterized by oxidative stress i.e. hypertension, CHD, hyperlipidemia, atherosclerosis and also which are involved in aerobic training, patients on total parenteral nutrition (TPN), those with hyperthyroidism and patients who take statin drugs (reductase inhibitors), hydroxymethyl glutaryl statins is a first line agent reduces level of cholesterol which prevents from CVDs, risk of myopathy carried through statins therapy which can range from muscle aches to rhabdomyolysis, statins by reducing the production of mevalonate also inhibits the synthesis of cholesterol.

Intake of CoQ10 was found to improve heart failure in patients, in further studies intake of 120 mg each day does not affect the for 28 days was resulted to reduce angina, improve ventricular function and reduce total arrhythmias. A trial of using CoQ10 200 mg each day with the supplement of hypertrophic cardiomyopathy resulted in symptomatic relief of fatigue\dyspnoea and improvements in measurements of left ventricular thickness and diastolic function. CoQ10 improves the efficiency of mitochondrial energy production, hence greater energy is available for contractile function, it benefits in many CVDs it is

supplementation should be sufficient to raise serum blood levels to at least 2.5 gm/ml. CoQ10 is used for cardiac surgery to increase cardiac recovery, decrease myocardial damage, prevent arrhythmias, decrease angina, lower blood pressure and overall improve the clinical outlook for the patient.[30-31]

Lycopene

Lycopene is present in tomato juice, sauce, concentrated extracts and are also present in fruits and vegetables for example watermelons, pink grapefruit and pink guava, Lycopene is are found in beta-carotene which reduces the risks of coronary heart disease.[32] Study on is beta-carotene showed intake in high level of beta-carotene from normal diet, based on adipose tissue concentrations reduced risk of MI, particularly in smokers, whereas further study was failed to show a decrease in cardiovascular symptoms in smokers receiving beta-carotene supplements and suggested that beta-carotene may be harmful in smokers which cause heart diseases and lung cancer.[33] Studies were carried in ten different countries on the men population on age about 54 years from coronary care units, which had undergone a first acute MI to see effects of alpha-carotene, beta-carotene and lycopene. Mechanisms of action including modulation of intracellular gap junction communication, hormonal, immune system in which metabolic pathways can also be involved, cause of ROS and the oxidative damage can be been connected with the pathogenesis of atherogenesis and carcinogenesis, mechanism also includes inhibition of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase and also inhibition of cholesterol synthesis, many more types of research are determined for the extract mechanisms of action of lycopene, another study at lycopene and MI risk resulted that low levels of adipose tissue lycopene are associated with an increased risk of heart attacks.[34] The current study on the effect of supplement with 250 mg per day of tomato extract which contains 15mg of lycopene shown the decrease in blood pressure in a patient with type 1 hypertension with around treatment period of 8 weeks. Researchers concluded that lycopene is not responsible for cardioprotective effects whereas tomato juice is, lycopene is helpful for prevention of CHD as it has antioxidant property, some more evidence is necessary before lycopene is made use clinically for CHD prevention.[35]

Melatonin

Melatonin overcomes cardiac injury is shown in *in-vivo* research on animals, it is tested that melatonin is best and powerful than any other antioxidant, in terms of ameliorating hypoxia and reoxygenation damage, 150gm\kg of intraperitoneal dose was found effective, 3mg of

oral melatonin in human dose showed an increase in plasma melatonin concentrations 1830-848 pg/ml before ingestion which was compared to be 14-11 pg/ml, with maximal level at 75 minutes after ingestion. In the human, it was shown that melatonin attenuates the reflex sympathetic increases which occur in response to orthostatic stress.[36-37]

Carnitine

Carnitine has an important function with its prevention of lactic acid formation which is damaging to the myocardium, it is found in heart muscles in high concentration, it is seen that heart failure is reduced up to 50% of both free and total carnitine.[38] Whereas in myocardial ischemia, blood flow to the heart is reduced and 40% decrease of carnitine in myocardial muscle. Carnitine supplements are used patients with ischaemic heart disease. Patient use medication includes nitro-compounds, calcium channel blockers, beta-blockers, antihypertensives, diuretics, cardiac glycosides, antiarrhythmics, anticoagulants and hypolipidaemic, which show progressive improvements in cardiac function\quality of life. Addition to standard cardio-active medication, a patient with recent acute MI intake 2gm of carnitine twice a day for one year, positive results were seen with significant differences all parameters studied in cardiac events and life expectancy.[39] Studies with, patients of suspected acute MI were supplemented with 2 gm of carnitine in 3 divided doses each day, after treatment of 28 days the mean infarct size was decreased in the carnitine group, as were cardiac events, including angina pectoris, left ventricular failure and arrhythmias with no adverse effect seen and use of other heart medication was reduced. Use of 50 mg/kg carnitine per day for 15 days in children will decrease the recovery time of heart failure. Carnitine supplementation shows improvement into cardiac parameters which show decreases in mortality in post-MI patients, the role of carnitine in heart disease seems promising in conclusion. Deficiency of carnitine (acquired and can result in failing myocardium) is genetically predisposed in some peoples which are associated with cardiomyopathy and skeletal muscle dysfunction and can be treated with carnitine supplementation.[40] Administration of carnitine supplements for a shorter period of time in a patient with CHD do not increase cardiac ejection fraction, but increases skeletal muscle phosphocreatine and led to improvements in muscle strength, endurance and metabolism.[38]

Flavonoids

Flavonoids (phenolic compounds) increased owing to their antioxidant capacity and possible beneficial implications on human health, which include treatment\prevention of cancer,

cardiovascular disease and other pathological disorders.[41] Blockage in angiotensin-converting enzyme (ACE) is done through Flavonoids which raises blood pressure; by blocking the "suicide" enzyme cyclooxygenase which breaks down prostaglandins, they prevent platelet stickiness and hence platelet aggregation, it also protects vascular system and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells. Flavonoids are found in onion, endives, cruciferous vegetables, black grapes, red wine, grapefruits, apples, cherries, and berries.[42] Flavonoids in plants available as flavones, flavanones play important role in curing the cardiovascular diseases. One study of reported that black tea which contains increases doses of flavonoids but very similar to caffeine, ingestion dose-dependently improved endothelial function. Biological activities of flavonoids are aspects of their antioxidant properties and free radical scavenging capabilities. Recent trials show that inhibition of breast cancer cell proliferation and tumor growth by polyphenolic catechins, the risk of estrogen-induced cancers is reduced by flavonoids which block the enzymes that produce estrogen. Researchers also revealed that intake of flavonols and flavones have chemopreventive effects of flavonoids on carcinogenesis, but not on any other flavonoid subclasses\total flavonoids were included in reducing the risk of breast cancer, particularly among postmenopausal women.[43-44]

Resveratrol

Resveratrol acts as an antioxidant and with chelating and free radical scavenging mechanisms inhibits LDL oxidative susceptibility *in-vivo*, platelet aggregation is inhibited through the ability of cardioprotection, platelet aggregation is reduced by ~41% in healthy subjects at a physiological concentration of 1.2 gm/L of resveratrol with the increasing the dose by 78.5%.[45] Effect of cardioprotective on resveratrol also contributed in inhibition of endogenous cholesterol biosynthesis, by inhibition of squalene monooxygenase (rate-limiting enzyme in cholesterol biosynthesis) which gives the proper information about the protective effects on CVD.[46]

CURRENT STATUS

Production of nutraceutical have moved towards the preventive health care seen in pharmaceutical industries like Novartis, GlaxoSmithKline, Cadila healthcare and so on, some fast-moving industry like Cadbury and Dabur have market with slew of supplements and additives, whereas industries of ayurvedic\ herbal product i.e. Himalayas, Patanjali (fastest growing FMCG company), Amway are specialized companies in market scenario, market is

controlled by FMCG (Fast-Moving Consumer Goods) and pharmaceutical monster. Nutraceutical products also help in treatment\prevention of diseases are done with herbal and botanical raw materials. This is a rapid growth on the industrial scale about 7-12% per year where millions of people are using the natural product in the world. Nutraceutical market has reached $450 billion by 2015. In a current analysis from Euro monitor international global scale of health and wellness products has reached about $1 trillion by 2017.[47] Marketing of nutraceuticals in the USA and other countries of the world is very highly popular among the consumers. Other countries like Japan, England, and other countries have already become the dietary landscape of nutraceuticals. Nutraceutical market in India is growing very fast on the infant stage. Increase in demand of nutraceuticals has increased the physical acceptance in medical benefits of the nutritional product. The demand for nutraceutical product in future is based on consumer's perception with relation to diet\disease.[10] Graph of nutraceutical market is shown in (Figure 6).

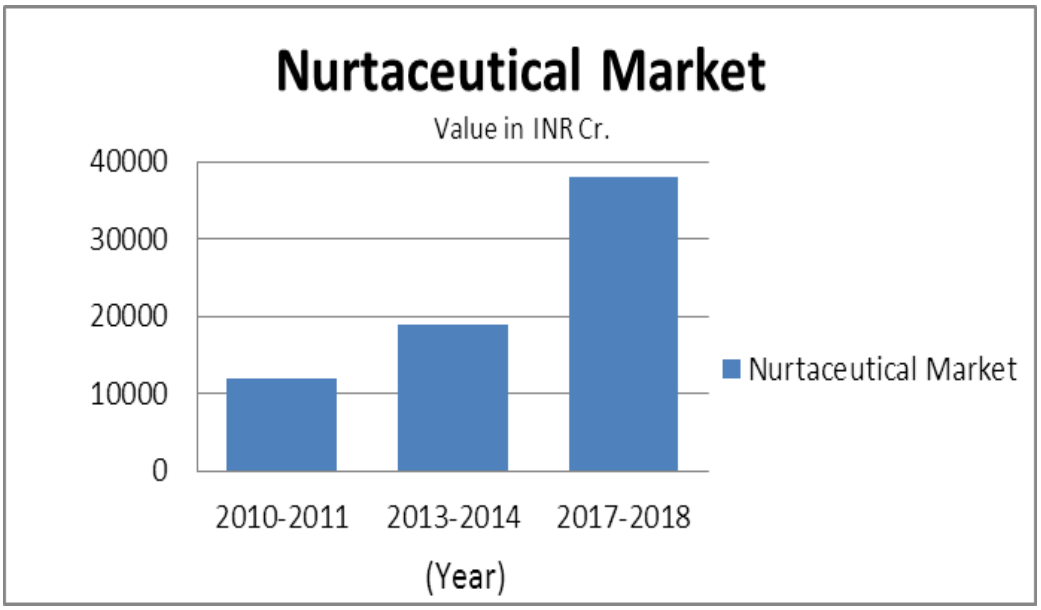

Figure 6. Nutraceutical Market Yearly.

Current Status in India

Nutraceutical market in India is one to the fastest-growing market in Asia-Pacific Region, it is due to the awareness being created\rising about the fitness and health and aging population\changing lifestyle is increasing the market growth. In the present scenario, Indian health care market has arisen as a profitable growth avenue for existing players and upcoming entrants. Cygnus (northern constellation lying on the plane of the Milky Way, deriving its name from the Latinized Greek word for swan) estimates the nutraceutical market of India in

2007 was approx. INR 18.75 billion. In 2009 total marketing in India was approx INR 44 bn, it reached around INR 95 bn in 2013. It is expected to reach $8.5 billion by 2022 from $2.8 billion in 2015. In 2015 India accounted a share of 2% of global market, by 2022 it anticipated to reach 3% owing to country largest population base in urban belt awareness.[10] Due to its huge population, India has become the center of attraction for everyone. Increase in population of the middle class has been doubled today. Since the year of independence to now, the remarkable educational goals have met India and now moved apart from basic food security issues. In the category of FMCG the mainstream market India includes products like cosmetics, care products, toiletries. Consumers of this class are absolutely the main target for many companies. India has not yet exploited market of Ayurveda and other medicinal\botanical plants; this is the reasons of each one for moving towards India.[5] Graph of Nutraceutical market in India per year is shown in (Figure 7).

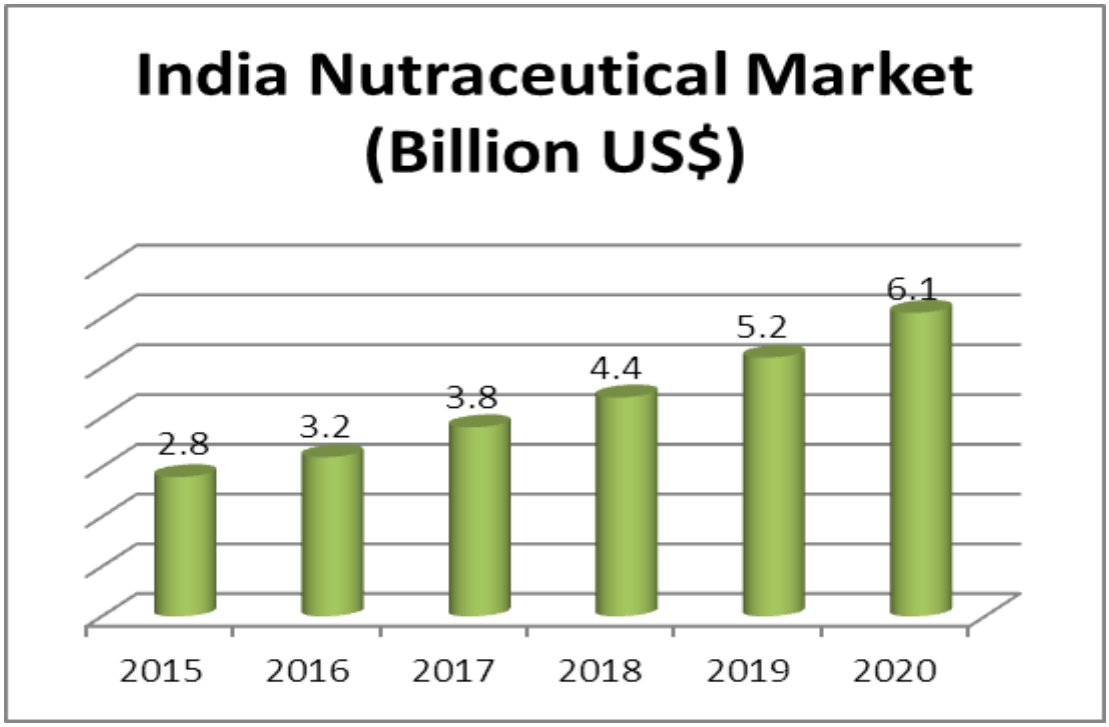

Figure 7. Growing Market of Nutraceuticals in India every Year.

Table 1. List of marketed Nutraceutical Products.[1][8]

Marketed Nutraceutical	Categories	Ingredients	Formulation Available	Manufacturer
Omega Woman	Immune Supplement	Antioxidants, Vitamins	Soft gel Capsules	Wassen, Surrey
Coral calcium	Calcium Supplements	Calcium, Trace Minerals	Capsules	Kenilworth, NS, USA
ROX®	Energy drink	Taurine, Caffeine	Drink	ROX America, SA
Proteinex®	Protein Supplement	Predigested proteins, Vitamins, Minerals, Carbohydrates	Powder	Pfizer Limited
Calcitriol D-3®	Calcium Supplement	Calcium, Minerals	Inject solution, Soft gel Capsules	Cadilla Healthcare Ltd
Betafactor® Capsules	Immune supplement	Beta-glucan	Capsules	Ameriden® International INC
Red Bull®	Energy Drink	Taurine, Caffeine	Drink	Austrian Red Bull Gmbh
Pediasure®	Nutritional Supplement	Protein, Vitamins	Powder	Abbott Nutrition
Revital®	Daily health supplement	Vitamins, Minerals	Capsules, Tablets	Ranbaxy Lab Ltd
Proplus	Nutritional Supplements	Soy Proteins	Capsules	Qurax pharma, Sadashiv peth, India
Appetite Intercept	Appetite suppressant	Caffeine, Tyrosine, Phenylalanine	Capsules, Patches	Natrol, Chatsworth, CA, USA
PNer plus	Neuropathic pain Supplements	Vitamins	Powder	Neuro Help, San Antonio, Texas, USA
Mushroom Optimizer	Immune Supplement	Mushroom, Polysaccharides, Folic acid	Capsules	Jarrow Formulas, Los Angeles, CA, USA
Weight smart™	Nutritional Supplement	Vitamins, Trace elements	Capsules	Bayer corporation, Morristown, NL, USA
Chaser™	Hangover supplement	Activated Calcium Carbonate, Vegitable Carbon	Capsules, Cream	Living essentials, Walled Lake, MI, USA
Snapple-a-day™	Meal Replacement Beverages	Vitamins, Minerals	Syrup, Powder	Snapple beverages group, USA
5-Hour energy®	Energy Drink	Vitamins, Tyrosine, Taurine, Malic acid, Caffeine, Glucurono-lactone	Drink	Living essentials, USA
WelLife®	Amino acid Supplement	Granulated-L-glutamine	Capsules	Daesang America Inc., Hackensach, NJ, USA
Olivenol™	Dietary Supplement	Natural antioxidant, Hydroxytyrosol	Capsules, Powder, Cream	Cre Agri, Hayward, CA,

				USA
Ferradol Food® Powder	Nutrition Supplement	Carbohydrates, Proteins, Niacinamide, Calcium, Iron, Zinc, Vitamins	Syrup	Pfizer Limited, India
Muscle Optimeal®	Meal Replacement Drink Mix	Protein, Vitamines, Dietary fibres, Xylitol, Trace Elements	Powder	Jarrow formulas, USA
Biovinca™	Health Supplement	Neuotonic, Plant Fibres, Fruits	Capsules	Cyvex, nutrition Irvine, CA, USA
Threptin ® Diskettes	Protein Supplement	Fortified B-Vitamins	Powder	Raptokos, brett & Co. Ltd, India
Becadexamine®	Nutritional Supplement	Mutivitamins	Capsules, Powder	Glaxosmith kiln
Glowelle®	Beauty Drink	Antioxidants, Vitamins, Botanical, Fruit Extracts	Syrup, Powder	Nestle

CONCLUSION

Growing interest of nutraceuticals in current scenario provides health advantages and is a substitute to modern medicines. Interest towards the relationship between diet and health in consumers increased the demand for information on nutraceutical. It is also a fastest growing segment of the food industry. In a human organization, nutraceuticals are important as it provides the essential nutrients which should be present in our daily healthy diet. In the day-to-day life of self-medication, nutraceutical play an important role in therapeutic development, the correct way of administration of nutritive products provide as good health and better quality of life, confidence, conscious mind, self-confidence, working capabilities, and healthy environment. Nutraceuticals also have a significant way in promotion to human health and\or diseases prevention, long duration of clinical studies are demanded to scientifically validate nutraceuticals in other medical conditions. These all success depends on the quality, safety, efficacy, and purity of product. Nutraceuticals are used as in an attempt to bring about desirable beneficial outcomes with lesser side effects, as for considering with other beneficial agents which have met with greater commercial success.

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BIBLIOGRAPHY

1. Sarin R, Sharma M, Singh R & Kumar S. Nutraceuticals: A Review. Int Res J Pharm, 2012; 3(4): 95-99.

2. Kar A. Pharmaceutical Aids (eds.). Essentials of Pharmacognosy, Ahuja Publ H: 2013; pp. 302-303.
3. Srivastava S, Sharma PK & Guru SK. Nutraceutical: A Review. J Chronother & Drug Deliv, 2015; 6(1): 1-10.
4. Sumi Y. Research and Technology Trends of Nutraceuticals. Sci & Technol Trends, 2008; 28: 10-22.
5. Kulkarni S. A Brief Report on Nutraceutical Product in India. ASA & Assoc LLP, 2015; 2-7.
6. Parasuram RR, Rawat BS & Thangavel S. Nutraceuticals: An Area of Tremendous Scope. In J Res Ayurveda & Pharm, 2011; 2(2): 410-415.
7. Sapkele AP, Thorat MS, Vir PR & Singh MC. Nutraceutical- Global Status and Application: A Review. Int J Pharm & Chem Sci, 2012; 1(3): 1166-1181.
8. Hardy G. Nutraceuticals and functional foods: introduction and meaning. Nutr, 2000; 16: 7-8.
9. Keservani RK, Kesharwani RK, Vyas N, Jain S, Raghuvanshi R & Sharma AK. Nutraceutical and Functional Food as Future Food: A Review. Scholars Res Libr, 2010; 2(1): 106-116.
10. Kumari M, Jain S & Singh J. Nutraceutical- Medical of Future. J Glob Biosci, 2015; 4(7): 2790-2794.
11. Gupta SK, Yadav SK & Patil SMM. Nutraceutical- A Bright Scope and Opportunity of Indian Healthcare Market. Int J Res & Dev Pharm & Life Sci, 2013; 2(4): 478-481.
12. Cardiovascular Diseases. Wikipedia & Encyclopedia [no date]. [cited 2017 July 28]; Available from: https://en.wikipedia.org/wiki/cardiovascular_disease
13. Chintale AG, Kadam VS, Sakhare RS, Birajdar GO & Nalwad DN. Role of Nutraceuticals in Various Diseases: A Comprehensive Review. Int Res Pharm & Chem, 2013; 3(2): 290-299.
14. Lockwood B. Nutraceuticals- A Guide for Healthcare Professionals (eds.). Cardiovascular health, Pharm Press: 2007; 111-154.
15. Vinson JA & Teufel K. Green and black teas inhibit Atherosclerosis by lipid, antioxidant, and fibrinolytic mechanisms. J Agric Food Chem, 2004; 52: 3661-3665.
16. Geleijnse JM, Launer LJ & Van der Kuip DAM. Inverse of tea and flavonoid intakes with incident myocardial infarction: The Rotterdam study. Am J Clin Nutr, 2002; 75: 880-886.
17. Yang YC, Lu FH & Wu JS. The Protective Effect of Habitual Tea Consumption on Hypertension. Arch Intern Med, 2004; 164: 1534-1540.

18. Walker R & Edwards C. Churchill and Livingstone. Clinical Pharmacy & Therapeutics, J Pharm & Pharmcol: 2003.
19. Rietveld A, Wiseman S. Antioxidant effects of tea: evidence from human clinical trials. J Nutr, 2003; 133: 3285S-3292S.
20. Lichtenstein AH. Soy protein, isoflavones and cardiovascular disease risk. J Nutr, 1998; 128: 1589-1592.
21. Adams C. A New Era for Nutraceuticals in Cardiovascular Disease Prevention. Nutraceutical World: 2009.
22. Rivas M, Garay RP & Escanero JF. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. J Nutr, 2002; 132: 1900-1902.
23. Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P & Winston. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for Professionals from the Nutrition Committee Circ, 2006; 113: 1034-1044.
24. Anthony MS, Clarkson TB & Williams J K. Effects of soy isoflavones on atherosclerosis: Potential Mechanisms. Am J Clin Nutr, 1998; 68: 1390S-1393S.
25. Choudhary M & Tomer V. Cardioprotective Effect of Nutraceuticals- The Emerging Evidences. Proc Indian Natl Sci Acad, 2013; 79(4): 985-996.
26. Weitz D, Weintraub H, Fisher E & Schwartzbard. Fish oil for the treatment of cardiovascular disease. Cardiol Rev, 2010; 18: 258-263.
27. Kromhout D, Geleijnse JM, Goede J, Oude Griep LM, Mulder BJ, Boer MJ, Deckers JW, Boersma E, Zock PL & Giltay EJ. n-3 fatty acids, ventricular arrhythmia related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. Diab Care, 2011; 34: 2515-2520.
28. Westcott ND & Muir AD. Flax seed lignan in disease prevention and health promotion. Phytochem Rev, 2004; 2: 401-417.
29. Stavro PM, Marchie AL & Kendall CWC. Flaxseed, fiber, and coronary heart disease: clinical studies. Am Oil Chem Soc, 2003; 288-300.
30. Sewright KA, Clarkson PM &Thompson PD. Statin myopathy: incidence, risk factors, and pathophysiology. Curr Atheroscler Rep, 2007; 389-396.
31. Radcliffe KA & Campbell WW. Statin myopathy. Neurol Neurosci, 2008; 66-72.
32. Rao A & Agarwal S. Role of lycopene as antioxidant carotenoid in the prevention of chronic diseases: a review. Nutr Res, 1999; 19: 305-323.
33. Kohlmeier L, Kark JD & Gomez-Gracia E. Lycopene and myocardial infarction risk in the euramic Study. Am J Epidemiol, 1997; 146: 618-626.

34. Rao A. Lycopene, tomatoes and the prevention of coronary heart disease. Exp Biol & Med, 2002; 227: 908-913.
35. Engelhard YN, Gazer B & Paran E. Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double blind, placebo controlled pilot study. Am Heart J, 2006; 151: 100e1-100e6.
36. Chen Z, Chua CC & Gao J. Protective effect of melatonin on myocardial infarction. Am J Physiol, 2003; 284: H1618-H1624.
37. Ray CA. Melatonin attenuates the sympathetic nerve responses to orthostatic stress in humans. J Physiol, 2003; 551: 1043-1048.
38. Sole MJ & Jeejeebhoy KN. Conditioned nutritional requirements and the pathogenesis and treatment of myocardial failure. Curr Opin Clin Nutr & Metabolic Care, 2000; 3: 417-424.
39. Singh RB, Niaz MA & Agarwal P. A randomised, double-blind, placebo controlled trial of L-carnitine in suspected acute myocardial infarction. Postgrad Mel J, 1996; 72: 45-50.
40. Ergur AT, Tanzer F & Cetinkaya O. Serum-free carnitine levels in children with heart failure. J Tropical Pediatr, 1999; 45: 168-169.
41. Schroeter H, Boyd C, Spencer JPE, Williams RJ, Cadenas E & Rice-Evans C MAPK. Signaling in neurodegeneration: influences of flavonoids and of nitric oxide. Neurobiol Aging, 2002; 23: 861-880.
42. Hollman PCH, Hertog MGL & Katan MB. Analysis and health effects of flavonoids. Food Chem, 1996; 57: 43-46.
43. Cook NC & Samman S. Flavonoids - Chemistry, metabolism, cardioprotective effects, and dietary sources. J Nutr Biochem, 1996; 7: 66-76.
44. Hollman PCH, Feskens EJ & Katan MB. Tea flavonols in cardiovascular disease and cancer epidemiology. Proc Soc for Exp Biol & Med, 1999; 220: 198-202.
45. Bhat KPL, Kosmeder JWII & Pezzuto JM. Biological effects of resveratrol. Antioxid & Redox Signal, 2001; 3: 1041-1064.
46. Laden BP & Porter TD. Resveratrol inhibits human squalene monooxygenase. Nutr Res, 2001; 21: 747-753.
47. Shinde N, Bangar B, Deshmukh S & Kumbhar P. Nutraceuticals: A Review on current status. Res J Pharm & Technolo, 2014; 7(1): 110-113.