

Nutraceuticals: Potential therapeutic agents for the treatment and prevention of cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are presently considered a leading cause of death worldwide, ranked first, both in the developing as well as in the developed nations. An estimated number of deaths due to CVDs are found to be more than 17.5 million that accounts for nearly one-third of all deaths annually. The current medications used for the treatment and prevention of CVDs comprise of statins, aspirin, beta-blockers, and angiotensin I-converting enzyme inhibitors. However, some of these conventional medications have serious side effects, and few instances even suggest the discontinuance of such medications. In this context, we have focused on nutraceuticals which have potential preventive and therapeutic values that are now considered as powerful alternatives against CVDs and in the maintenance of good health. Nutraceuticals have ushered in a new era of health and medicine since they comprise of natural dietary products with no or fewer side effects. Nutraceuticals are widely available in various forms including capsules, tablets, and powders and have shown the potential to work as a better and safer alternative against the conventional medical regimen for CVDs. In spite of such progress, each of these nutraceuticals has their own limitations that demand more research in the near future. This review highlights the Indian scenario in the occurrence of CVDs and focuses on a number of nutraceuticals with the potential to prevent and treat CVDs.

KEY WORDS: Nutraceuticals, Cardiovascular Diseases, Anti-oxidants

INTRODUCTION

According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are the disorders of the heart and blood vessels which include atherosclerosis, coronary heart diseases (CHD), acute myocardial infarction, angina pectoris, aneurysms, arrhythmia, hypertension, congestive heart failure (CHF), rheumatic heart diseases, and cerebrovascular diseases that account for 17.5 million deaths, i.e., an estimated one-third of all deaths worldwide.^[1] An estimation in 2014 by the WHO came to a conclusion that CVDs are the most leading cause of death, and one in two deaths in western societies is due to CVDs. The usual common risk factors are high blood pressure (BP), diabetes, increased tobacco intake, smoking, hyperlipidemia, high level of low-density lipoprotein (LDL), obesity, insulin resistance, high triglyceride level, declined levels of high-density lipoprotein

(HDL), hypertension tolerance, obesity, and physical inactivity.^[2] Unhealthy lifestyles with poor dietary choices would lead to CVDs even in individuals with low risk of CVD. Nutritional imbalances in the diet are causing a number of physiological dysfunctions which lead to the adoption of diet-based therapies.

Nutraceuticals are referred to any product derived from natural food sources having extra health benefits in addition to the basic nutritional value found in foods. Dietary supplements (proteins, vitamins, minerals, and healthy fats), specific diets, herbal products, or processed foods (such as cereals, soups, and beverages) usually comprise the broad umbrella of nutraceuticals. Nutraceuticals have become an integral component of our diet due to its preventive and therapeutic potential with no or minimal side-effects against various physiological disorders (i.e., CVD, hypercholesterolemia, osteoarthritis, periodontal disease, cognitive dysfunction, neurodegenerative diseases, hyperglycemia, and cancer). In this review, the focus is to highlight the Indian scenario in the occurrence of CVDs and depict the importance of a

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number of nutraceuticals with the potential to prevent and treat CVDs.

CVD IN INDIA

In India, CVD is one of the prime killers that can affect people of all ages. Although the risk of CVDs increases with aging, due to rapid changes in lifestyles, more and more young people are being affected in India; usually, obese youth in the age group of 5–17 years are more likely to have risks for CVD because of high cholesterol intake or high BP. Over the past two decades, India has seen a rapid transition in the burden of heart diseases. Today, there are around 30 million heart patients in India and cardiac hospitals perform over 2, 00,000 open heart surgeries per year, which seems to be one of the highest worldwide.^[3] The prevalence of CVD has doubled in Indian rural and urban poor population due to lack of awareness and economic weakness. To counter this higher occurrence of CVDs in India, the Government of India has taken initiatives to combat CVDs by passing stricter laws/acts to curb the usage of cigarettes and other tobacco products.

SYMPTOMS, DIAGNOSIS, AND TREATMENT

Usually, one might not be diagnosed with CVDs unless and until the concerned individual has a heart attack, angina, stroke, or heart failure, and it is more important to watch carefully for the symptoms and discuss concerns with doctor. Sometimes, CVDs can be detected early with regular examinations. Each type of heart diseases have wide symptoms including shortness of breath, chest pain (angina), chest discomfort, numbness, weakness or coldness in arms or legs or feet swelling, sweating, dizziness, fluttering in chest, pain in the neck/jaw/throat, irregular heartbeats, fatigue, extreme weakness, and anxiety.^[4]

CVDs can be diagnosed by electrocardiogram that detects and records the heart's electrical activity, whereas echocardiogram provides information about size and shape and also shows poor blood flow to the heart. Chest X-ray, blood tests, coronary angiography, cardiac magnetic resonance imaging, and cardiac catheterization are used to determine the state of the coronary arteries; however, early signs of CVDs cannot be found out until a heart attack or angina occurs. Each type of heart problem requires different treatment but shares similar warning signs. Treatments for CVDs include cardiopulmonary resuscitation, usage of stents, angioplasty,^[5] heart bypass surgery, valve disease treatment,^[6] and cardioversion. Conventional medications that are used by cardiologist are statins which slow down the cholesterol production by the

liver and speed up the removal of LDL-cholesterol (LDL-C) from the bloodstream; bile acid sequestrants remove bile acids because body produces these acids from LDL-C, more LDL-C will be broken down to replace them; alpha-beta blockers, angiotensin I-converting enzyme (ACE) inhibitors, calcium channel blockers, aspirin therapy, antiarrhythmic, and digoxin are some of the well-known medications for CVDs.^[7,8]

LIMITATIONS

The preferred treatments for CVDs are though accepted worldwide as the primary treatment; some have their own limitations which lead to several side effects and health problems including hypertension, atrial fibrillation, multidrug resistance, edema, and nausea [Table 1]. Considering that these methods are expensive and time-consuming, a new era of phytopharmaceuticals has begun, wherein minimal or no side effects are observed with cheaper cost and safer recovery.

DIETARY CHOICE AND LIFESTYLE

The growth of CVDs is dependent on a number of interlinked factors mainly aging, bad food habits, an unhealthy and sedentary lifestyle, and high career stress. The diet in today's life has been shifted from traditional high fiber and carbohydrate diet to processed and packaged total fat diet. Due to lack of physical activities and change in lifestyle, there is an increased risk of developing CVD. To maintain healthy heart, one must be aware of foods which have to be added in the diet and the ones which are to be avoided. Below mentioned are few suggestions in this connection –
 Trans-fat: Processed and packaged food products should be avoided as the content of trans-fat is usually more in such types with less hydrogenated oils to longer shelf life.
 Red meat: Even though red meat contains zinc, iron, Vitamin B complex, and amino acids, it is suggested that limited intake of red meat is necessary. White meat (fish and chicken) can be a good replacement for red meat.

Egg yolk: Limited consumption of egg yolk is preferred as it consists of high cholesterol and saturated fats.

Salt and sugar: Limited intake of both sugar and salt is preferred as both increase BP and diabetes which are the root cause for the risk of CVD.

In continuance to the above discussion, oats (rich in fibers), nuts (unsaturated fats), berries (rich in antioxidants and lowers BP), legumes (rich in antioxidants, proteins, and fibers), and salmon (cold water fish rich in ω -3 fatty acids) must be added in the

Table 1: Limitations of conventional medications/therapeutics and treatments for CVDs

Category of drugs/therapeutics	Common drugs	Side effects
Anti-platelet	Plavix (clopidogrel bisulfate), ticlid (ticlopidine), effient (prasugrel), reopro (abciximab), integrilin (eptifibatide), and aspirin	Diarrhea, rash, or itching, abdominal pain, headache, chest pain, muscle aches, and dizziness
Anti-coagulant Vasodilators	Coumadin (warfarin) and heparin Nitrosat and Nitropress (nitroglycerin), Ismo (isosorbide mononitrate), and Isordil (isosorbide dinitrate) Procardia (nifedipine)	Bleeding and necrosis (gangrene) of the skin Lightheadedness or dizziness, increased or irregular heart rate, or headache
Calcium channel blockers Anti-arrhythmics	Cordarone (amiodarone), Tambocor (flecainide acetate), and Rythmol (propafenone hydrochloride)	Constipation, nausea, headache, rash, edema, low BP, drowsiness, and dizziness Dizziness, blurred vision, anorexia, unusual taste, fatigue, nausea and vomiting. Can affect kidney function
Catecholamines Anti-anginals	Dopamine and dobutamine Ranexa (ranolazine)	Headache and cold extremities Indigestion, nausea, loss of appetite, taste changes, and constipation or diarrhea
ACE inhibitors	Zestril (lisinopril)	Cough, elevated blood potassium levels (hyperkalemia), low BP, dizziness, headache, drowsiness, weakness, abnormal taste, and rash
Statins	Atorvastatin (lipitor), fluvastatin (lescol), lovastatin (altoprev), pitavastatin (livalo), pravastatin (pravachol), rosuvastatin (crestor), and simvastatin (zocor)	Muscle pain, digestive problems and mental fuzziness in some people and may rarely cause liver damage
Stem cell therapy	Induces acute coronary syndromes, formation of occlusive human plaque leads to atherosclerosis, increased rate of in-stent restenosis, cases of sudden death have been reported	

ACE: Angiotensin I-converting enzyme, CVDs: Cardiovascular diseases

diet to prevent chronic diseases like CVDs as natural-based dietary choices are the best solution to combat such diseases.

NUTRACEUTICALS IN CVD

The cardioprotective effects of selected nutraceuticals in CVD (Table 2) are reviewed and discussed as follows:

CARDAMOM

The essential oil of cardamom has been reported to contain certain bioactive components that exhibit hypocholesterolemic, hypoglycemic, hyperlipidemic, oxidative stress, anti-inflammatory, and antimutagenic activities. It possesses oxidative stress by activating antioxidant enzymes that reduce unfavorable oxidation of LDL-C. Cardamom oil treatment has increased HDL ratio, while triglyceride, total cholesterol, phospholipid, LDL, and very LDL (VLDL) in the serum were significantly lowered.^[9] Cardamom extract has anti-atherosclerotic potential as it causes and decreases in total cholesterol triglyceride and phospholipid insides of aortic tissues. It has defensive effect over severe and acute anxiety persuaded myocardial indemnities.^[10] Consistent intake of large amounts of cardamom is valuable in treatment for patients with ischemic heart diseases.

CINNAMON

Cinnamon is a delicious spice with impressive effects on health and has proved beneficial in CVDs. 2-methoxycinnamaldehyde, an active component of *Cinnamomum cassia* is known to decrease the expression of vascular cell adhesion molecule-1 in TNF α -activated endothelial cells, hence proving beneficial in ischemia/reperfusion injury due to induction of hemeoxygenase-1.^[11] Cinnamophilin, one of the important lignans isolated from *C. philippinensis* mainly inhibits thromboxane receptor-mediated vascular smooth muscle cell proliferation and possesses the potential to be used in the prevention of vascular diseases and atherosclerosis.^[12] Several studies have reported the protective effects of compounds such as cinnamaldehyde and cinnamic acid isolated from *C. cassia* on the cardiovascular system, especially against myocardial ischemia.^[13] Cinnamaldehyde has shown to expand rat vascular smooth muscle in an endothelium-independent manner and the ability of cinnamaldehyde in vasodilatory function is attributed to the impediton of both Ca²⁺ influx and Ca²⁺ release.^[14]

TURMERIC

Active component in turmeric is curcuminoids (curcumin). Researchers have reported that hypocholesterolemic potential of curcuminoids lowers

Table 2: Common nutraceuticals for the treatment of CVDs

Nutraceuticals	Compound	Health benefits	Evidence on potential cardiovascular effects
Cardamom (<i>Amomum subulatum</i> and <i>Elettaria subulatum</i>)	Essential oil contains α -terpineol, myrcene, limonene, menthone, β -phellandrene, 1,8 cineol, sabinene, heptane. Seeds of Round cardamom (<i>A. kepulaga</i>) contains - 1, 8 cineol, plus β -pinene, α -pinene, humulene	Control of cholesterol; anti-depressant, antimicrobial dental diseases, antiseptic, antispasmodic, carminative, cephalic, digestive, diuretic, expectorant, stimulant, stomachic and tonic; anti-carcinogenic, anti-inflammatory properties, detoxification. Improves blood circulation; relieves hiccups High antioxidant properties providing protection from oxidative stress caused due to free radicals; anti-inflammatory, anti-microbial, anti-cancerous, anti-thrombotic, antiplatelet, anti-sclerotic properties; blood- sugar lowering effects observed.	More in-depth research required focussing on each of the properties that may prove beneficial for CVDs.
Cinnamon	Cinnamaldehyde, alpha-capaene, alpha-murolene, para-methoxycinnamaldehyde delta-cadinen	Antioxidant, scavenges reactive oxygen species; anti-inflammatory, anti-atherosclerotic, anti-cancerous, effective against arthritis, anti-ageing properties having beneficial effects in depression Lowers total & LDL-C, reduces hypertension, rich in antioxidants that protects against oxidative damage, helps in detoxification of heavy metals, improves bone health, combat sickness (Common cold). Powerful antioxidant, anti-inflammatory; help in osteoarthritis, highly effective against nausea, reduce muscle pain, helps in treating chronic indigestion, drastically lowers blood sugars, 6-gingerol are known to prevent cancer.	Cinnamons are under preliminary research for their potential in treating CVDs.
Turmeric (<i>Curcuma longa</i>)	Active polyphenolic flavonoid constituting approximately 3% of turmeric. Curcumin is an active compound	Prevents the generation of free radicals, myocardial protection action, antiaging, LDL oxidation suppression.	Administration of 10 mg of curcumin per day for 30 days to human subjects increased HDL cholesterol and decreased LDL cholesterol ^[19]
Garlic <i>Allium sativum</i>	Contains high concentration of sulfur compounds than any other <i>Allium</i> spp. Includes, allin, allicin, ajoene, allylpropl, diallyl, disulfide, sallylcysteine, vinylidithines and others	Combats sickness	In a meta-analysis on garlic, by Reinhart KM <i>et al.</i> ^[132] was found to reduce total cholesterol but it was found that there was no significant effect on LDL or HDL cholesterol.
Ginger	Zingerone, shogaols, and gingerols with [6]-gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone) consists of more than 50 antioxidants isolated from rhizomes of ginger, rich in polyphenols, Vitamin C, β carotene, flavonoids, and tannins	Prevents the generation of free radicals, myocardial protection action, antiaging, LDL oxidation suppression.	Limited research on the impact of ginger on CVDs; more research required.
Co-enzyme Q ₁₀	Powerful endogenous antioxidant, fat-soluble, and vitamin-like quinone	Prevents the generation of free radicals, myocardial protection action, antiaging, LDL oxidation suppression.	Conflicting results observed in clinical trials for CVDs.
PUFA, ALA	Flaxseed, canola, olive oil, walnuts and other tree nuts contains ALA, fish oils are rich in omega-3 PUFAs	Anti-atherosclerotic, antiaging, and cardioprotective in nature	Burr <i>et al.</i> , ^[133,134] in 2 large randomized controlled trials (RCTs) demonstrated that EPA + DHA supplements significantly reduced fatal cardiac events Absolute no effect on clinical endpoints on CVD or mortality has been demonstrated
Plant sterols/ stanols	β - sitosterol, campesterol, stigma sterol, ergosterol, cycloartenol, lupeol	Esterified plant stanols are proved to reduce cholesterol in a number of randomized, placebo-controlled, double-blind clinical trials. Plant sterols lowers the LDL-C, β -sitosterol boosts immunity also has antioxidant properties	

(Contd)...

Table 2: (Continued)

Nutraceuticals	Compound	Health benefits	Evidence on potential cardiovascular effects
Proteins and peptides	Milk protein (caseins and whey), meat protein, soy protein	Proteins from different sources have antithrombotic, hypocholesterolemic, hypertensive actions also antioxidant and antimicrobial activities	Zhang <i>et al.</i> ^[64] showed that CCH has potential preventive effect on atherosclerosis
Beverages	Wine, beer, coffee, tea (green and lack) rich in resveratrol, cinnamates and gallic acid	Rich in flavonoids and non-flavonoids, polyphenols, Resveratrol which is cardioprotective in nature also inhibits LDL-C oxidation. Coffee and tea are rich in high antioxidant properties, has high content of melanoidins, chlorogenic acid, flavonoids, lipid-soluble compounds furans, anmaltol, pyrroles, etc. Catechins, the major polyphenolic compounds in tea exert vascular protective effects through multiple mechanisms	De Koning <i>et al.</i> ^[105] gave a conclusion that moderate coffee drinking has positive effects on CVD. More research would be welcome. Epidemiological, clinical and experimental studies have established a positive correlation between tea (green and black) consumption and cardiovascular health ^[79,80,98]
Polyphenols	Quercetin, catechins, lignans, flavonoids, stilbene	Phytochemicals that are present in roots and leaf extracts of <i>Digitalis purpurea</i> , <i>Rauvolfia serpentine</i> , <i>Crataegus</i> , and <i>Ginkgo bilob</i> are known to lower serum cholesterol level, decrease the ischemia, and possess antioxidative, cardioprotective, antilipemic, antihypertensive, and hypoglycemic properties. Polyphenols that are present in fruits and its seeds are proved to be cardioprotective which lowers LDL-C, enhances HDL-C and inhibits oxidative stress.	In a meta-analysis study by Serban <i>et al.</i> , ^[135] it was proved that, there was a significant reduction in both systolic BP and diastolic BP following supplementation with quercetin
Vitamins	Vitamin A, B-complex, C, D, E, K	Oxidizes LDL-C, regulate arterial calcification, regulate BP and arterial hypertension	In a study of 3488 people by Ginde <i>et al.</i> , ^[118] it was found out that the risk of CVD triples with the deficiency of Vitamin D.
Minerals	Magnesium, potassium, zinc, calcium, chromium, selenium, silicon, manganese, cadmium, lead, and copper	Antioxidative in nature lowers serum lipids, have protective role against hypoxic damage of the heart, and reduces BP	No sufficient trials were demonstrated to draw conclusion

CVDs: Cardiovascular diseases, ALA: Alpha-linolenic acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, LDL-C: Low-density lipoprotein-cholesterol, HDL: High-density lipoprotein, PUFAs: Polyunsaturated fatty acids, BP: Blood pressure, CCH: Chicken collagen hydrolysate

serum cholesterol and triglyceride levels through fecal excretion.^[15] Long-term ingestion of curcumin subsequently modifies genetic expression which is involved in cholesterol homeostasis.^[16] Curcumin possesses an effect in the prevention of cardiac hypertrophy and heart failure.^[17,18] Curcuminoids have a role in membrane-stabilizing effects in myocardial infarctions, cardiac hypertrophy, also have antiproliferative effects, and maintains calcium homeostasis.^[19] They are known to decrease serum lipid peroxides, total serum cholesterol, and also

lowers LDL levels and cause increase in serum HDL levels in patients with atherosclerosis. The effect of curcumin in lowering the serum cholesterol level protects against the pathological changes seen in atherosclerosis.^[20,21]

GARLIC

Epidemiologic studies have indicated the inverse correlation between garlic consumption and progression of CVD.^[22] Multiple factors are known to induce CVDs

that include raised serum total cholesterol, raised LDL and an increase in LDL oxidation, increased platelet aggregation, hypertension, and smoking.^[23] Garlic has proved beneficial in treating CVDs by inhibiting enzymes involved in lipid synthesis, decreasing platelet aggregation, preventing lipid peroxidation of oxidized erythrocytes and LDL, increasing antioxidant status, and inhibiting ACE.^[24] The formation of fatty streaks in the aortic sinus has been lowered significantly by allicin, an active compound of garlic.^[25] An organosulfur compound S-allyl cysteine present in aged garlic extract has shown potential to inhibit cholesterol synthesis.^[26,27] These findings have also been evidenced in clinical trials too. Garlic also reduced nitric oxide-dependent relaxation in pulmonary arteries.^[28,29] Interestingly, Subhendhu *et al.*^[30] have observed that freshly crushed garlic exerts superior cardioprotective activity than processed garlic. Thus, garlic has multiple properties in the prevention of CVDs and can act as a suitable dietary supplement for prevention of CVD.

GINGER

Ginger is a medicinal plant that has been used for a wide range of unrelated ailments because of its various medicinal properties. The most active ingredient in ginger is gingerol, a compound that causes relaxation of blood vessels and stimulation of blood flow. In a placebo-controlled clinical trial, a significant reduction in platelet aggregation was observed in coronary artery disease patients when administered with 10g of powdered ginger without affecting the blood sugar and lipid profile.^[31] However, no significant impact of fresh or cooked ginger (doses up to 15 g of fresh ginger or 40 grams of cooked ginger) was observed on thrombotic activity or platelet thromboxane production involving human volunteers.^[32] In a separate study involving hyperlipidemic rabbits, a 50% ethanolic extract of ginger showed a reduction in total cholesterol and serum LDL-C. Similar alterations were also observed in the tissue lipid profiles of liver, heart, and aorta highlighting the beneficial impact of ginger.^[33] Consumption of ginger extract inhibited the progression of aortic atherosclerosis in atherosclerotic, apolipoprotein-E deficient mice, and this beneficial impact may be attributed to its direct antioxidative effects on macrophages as well as on plasma LDL.^[34] Importantly, gingerol isolated from *Zingiber* inhibited platelet function by inhibiting thromboxane formation as evidenced by Guh *et al.*^[35] Besides, a pure constituent from ginger [E-8 beta, 17 epoxyabd-12-ene-15, 16-dial (ZT)] has proved beneficial in inhibiting cholesterol biosynthesis in homogenated rat liver.^[36] Thus, enough evidence exist that highlights the cardioprotective potential of ginger, and thus, ginger should be included in our day-to-day dietary intake.

COENZYME Q₁₀

Supplements are used in the treatment of various cardiovascular conditions, including heart failure, cardiomyopathy, and hypertension. Evidence suggest that naturally occurring substance coenzyme Q₁₀ has properties with the potential to prevent CVDs that include cellular damage during myocardial ischemia and reperfusion, angina pectoris, hypertension, arrhythmia, and CHF. Coenzyme Q₁₀ has the capability to maintain the integrity of myocardial calcium ion channels, especially during ischemic insults.^[37] It has been reported that patients with low levels of endogenous coenzyme Q₁₀ are at higher risk of heart failure than in normal. The rationale for using coenzyme Q₁₀ in the treatment of coronary heart failure is to its deficiency in myocardium. A study revealed that myocardial deficiencies of coenzyme Q₁₀ were seen in the majority of patients with aortic and mitral valve disease, congenital valvular defects, and diabetic cardiomyopathy.^[38]

POLYUNSATURATED FATTY ACID (PUFA)

Alpha-linolenic acid (ALA) is found in flaxseed, canola, olive oil, walnuts, and other tree nuts and in trace amounts in green leafy vegetables. Humans typically convert ALA to long chain n-3 PUFA eicosapentaenoic acid and docosahexaenoic acid (DHA) that reduces all-cause mortality, cardiac sudden death, and stroke. Omega-6 and -3 PUFAs are known to play important roles in heart and brain functions and normal growth and development. Earlier reports suggest that increased intake of ALA is associated with reduced risk for non-fatal myocardial infarction.^[39]

PLANT STEROLS/ PHYTOSTEROLS

Phytosterols are plant-based ingredients that are classified as naturally occurring, known to lower LDL-C levels, therefore decreasing the risk of CVDs.^[40] Phytosterols are cholesterol homologs, mainly found in nuts, fruits, and seeds are present in the diet in quantities similar to cholesterol (200–400 mg/day).^[41-43] When natural plant sterols were omitted from the diet, there occur increased concentration of serum LDL-C.^[44]

Garlic (*Allium sativum*) supplements are known to treat conditions such as hyperlipidemia, hypertension, and type 2 diabetes mellitus, thus reducing the risk of CVD. A number of studies have demonstrated the multiple beneficial cardiovascular effects that include lowering of blood pressure BP, LDL-C levels, serum cholesterol, and triglyceride levels.^[45] Organosulfur

compounds that are present in garlic and onions, isothiocyanates in cruciferous vegetables, and monoterpenes in citrus fruits, cherries, and herbs have cardioprotective effects as evidenced in experimental models. Hydroxytyrosol, one of many phenolics in olives and olive oil, is a potent antioxidant that reduces the risk of CVD.^[46] Flavonoids are polyphenolic compounds which are found in numerous plant foods that include fruits and vegetables, herbs and spices, nuts and seeds, wine, and tea in small quantities,^[47,48] that act as antioxidants, and thus reduce the oxidation of LDL-C involved in the development of atherosclerotic diseases.^[49-51]

PROTEINS AND PEPTIDES

Dietary proteins and peptides are known to possess multiple bioactive properties, and their consumption plays a significant role in promoting cardiovascular health.^[52] Reduced BP and LDL-C,^[53,54] lowered HDL-C levels, and raised fasting triglycerides^[55,56] are associated with high-carbohydrate, low-protein diets. Recent evidence demonstrated that increased intakes of protein, particularly plant proteins, further lower the risk of hypertension and cardiovascular-related diseases.^[57,58] Partial substitution of carbohydrates with protein sources, low in saturated fat, can improve lipid levels, facilitate weight loss, lower BP, and reduce the risk of CVD.^[59]

Milk Proteins

Caseins (80%) and whey (20%) are the two major classes of protein that is largely found in bovine milk. Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) are the lactotripeptides derived from milk casein, which have been shown to potently reduce BP, one of the major risk factors for CVD by inhibiting the ACE as observed in clinical trials.^[60-62]

Meat Proteins

They are derived from the skeletal muscle tissue of red meat, fish, and poultry.^[63] Chicken collagen hydrolysate was found to have potential preventive effect on atherosclerosis which was recently investigated by Zhang *et al.*^[64]

Soya Proteins

Soyabean (*Glycine max*) proteins have gained prominence among all legumes because of high protein and no cholesterol/low-saturated fat content with high content of fiber, iron, calcium, and zinc and Vitamin B.^[65] Soybean protein is the only vegetable food that contains all the eight essential amino acids. In addition, a statistical reduction in serum LDL-C:HDL-C ratio and apolipoprotein B:apolipoprotein A-I has been observed the following consumption of soya proteins.^[66]

BEVERAGES

Intake of alcoholic beverages brings about positive effects on its lipid profile, antioxidant capacity, and the coagulation system^[67] that reduces the risk of CVD^[68,69] and overall mortality.^[70] Current evidence suggests that moderate drinking of beverages has protective effects on cardiovascular events that include ischemic stroke,^[71] CHF,^[72] CHD,^[73] and peripheral arteriopathy.

Wine and Beer

Red wine is rich in polyphenols when compared to white wine (around 10-fold). Polyphenols that are present in red wine are a complex mixture of flavonoids (anthocyanin and flavan-3-ols) and non-flavonoids (resveratrol, cinnamates, and gallic acid). Resveratrol exhibited cardioprotective effects, inhibition of LDL oxidation, and platelet aggregation in animal studies.^[74,75] Moderate drinkers of alcohol have a lower risk of CHD compared with non-drinkers that have been proved in several case-control studies.^[76] The antioxidant effects of a polyphenol-rich alcoholic beverage (red wine) and polyphenol-free alcoholic beverage (gin) were compared in a recent study, it was found that red wine reduced plasma superoxide dismutase activity and malondialdehyde levels, and also there was an increased lag phase time of LDL oxidation analysis. This suggests that red wine has greater antioxidant effects, probably due to its high polyphenolic content.^[77] Beer, an alcoholic beverage, in moderate amounts can be good for heart and blood vessels mainly because of the alcohol in it. There is strong scientific evidence that consumption of 15–30 g of alcohol per day is associated with a 25% lower relative risk of CVD mortality compared to abstainers.

Tea

A work by Sasazuki *et al.*^[78] gave an evidence that there is 50% of reduction in the risk of heart attack with the consumption of a cup of black tea per day. Active compounds in green tea are found to be polyphenols like, epicatechin, epicatechin-gallate, amino acids, Vitamins C and B and alkaloids (such as theobromine). Caffeine containing pectins, quercetin, rutin, etc. has highest antioxidative properties which scavenges free radicals and thus has proved to be a good cardio-protective agent reducing LDL-C level in the serum.

Epidemiological, clinical, and experimental studies have established a positive correlation between green tea consumption and cardiovascular health. Catechins, the major polyphenolic compounds in green tea, exert vascular protective effects through multiple mechanisms, including antioxidative,^[79-83] antihypertensive,^[84-86] anti-inflammatory,^[87,88] antiproliferative,^[89-91] antithrombotic,^[92,93] and lipid-lowering effects.^[94-97]

Like in case of green tea, epidemiological data support a link between black tea consumption and a reduced risk of CVD.^[98] Lowering of BP leads to reduced risk of CVD associated with regular tea consumption,^[99] <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0103247> - pone.0103247-Stensvold1; however, reports of inconsistent results have been reported from intervention studies examining effects of tea on BP are inconsistent.^[100-104] There have been some meta-analyses that found no significant effect of black tea consumption on BP^[103] though several high quality, randomized, controlled trials have proved otherwise.^[103,104]

Coffee

Coffee is one of the most common and widely used beverages in the World and is important because of its high antioxidant properties and rich content of melanoidins, chlorogenic acid, flavonoids, lipid-soluble compounds furans, anmaltol, pyrroles, etc. It is important to note that heavy drinking of coffee leads to bone weakness and neurodegenerative diseases. There is a protective association between moderate coffee drinking and CHD morbidity and CVD mortality as evidenced from existing literature.^[105,106]

POLYPHENOLS

Polyphenols are a unique class of phytochemicals that have gained prominence in the treatment of CVDs because of multifactorial properties. For many decades, digitoxin, the drug derived from *Digitalis purpurea* (foxglove) or *Digitalis lanata*, has been used in the treatment of CHF.^[46] Drug obtained from *Rauwolfia serpentina* roots (natural source of the alkaloid reserpine) was one of the first drugs used on a large scale for the treatment of systemic hypertension. *Crataegus oxyacantha* and *Crataegus monogyna* extract antagonizes the increase in cholesterol, triglyceride, and phospholipid levels in LDL and VLDL in hyperlipidemic diet, thereby inhibiting the progression of atherosclerosis and angina pectoris.^[107] *Ginkgo biloba* leaf extract with respect to its flavonoid glycoside and terpene lactone content has shown to decrease the ischemia significantly. For the treatment of peripheral vascular disease including diabetic retinopathy, *Ginkgo biloba* extract have been proved beneficial.^[108,109] Polyphenols in pomegranate have been known to reduce LDL levels,^[110] whereas apple polyphenols have been shown to reduce LDL-c oxidation.^[111] Coconut oil contains good saturated fat, which increases HDL and reduces LDL: HDL ratio,^[112] in addition, coconut oil also reduces artery plaque and lipoprotein-A.^[113] The seeds of Cucurbitaceae are edible which holds the highest food value, seed flesh is nutty and is rich in proteins, unsaturated fatty acids, phenolic acids, minerals, carotenoids, tocopherol, phytosterol, squalene, etc.^[114]

Extract of Cucurbitaceae seeds exhibit antioxidative, cardioprotective, antilipemic, antihypertensive, hypoglycemic, and anticancer properties. Watermelon seeds contain high protein content, and based on its nutritional benefits, several food products have been formulated as ready-to-eat cereals, snack food, infant food, and bakery products etc.^[115] Seeds that are discarded as the by-products of food processing can be used for seed-based food formulations with high nutritive value. More research is essential to explore other Cucurbitaceae seeds in future.

VITAMINS

The most consistent findings in dietary research are that those who consume higher amounts of vitamins through consumption of fruits and vegetables have lower rates of heart disease and stroke, raising the possibility that vitamins are protective. Vitamin E oxidizes LDL-C that occurs at the initial stages of atherosclerosis and has proved to inhibit this oxidative reaction. Vitamin K₂ or menaquinone is known to regulate arterial calcification through the process of protein modulation. Insufficient Vitamin K₂ in the diet may also lead to atherosclerosis. In a meta-analyses study involving Vitamin D, it has been proved that Vitamin D deficiency is one of the risk factors for developing higher BP and arterial hypertension.^[116,117] In a separate study of 3488 people by Ginde,^[118] it was found out that the risk of CVD triples with the deficiency of vitamin D.

MINERALS

Mineral-based dietary supplements remain a well-established and consistent portion of the nutraceuticals market that has proved beneficial in the prevention and treatment of CVDs. In this particular category, minerals such as magnesium, potassium, zinc, calcium, chromium, selenium, silicon, manganese, cadmium, lead, and copper have gained prominence as evidenced from numerous scientific literature published in the last couple of decades. Below is a brief account of some of the important minerals that have proved beneficial in the prevention and treatment of CVDs.

Magnesium

The salts of magnesium have a protective role against hypoxic damage of the heart.^[119-121] Following sudden death from CVD, it was observed that there occurred diminished content of myocardial magnesium.^[122] It has been proved that magnesium acts as a defense against CVD which includes reduction of BP, cholesterol, and also risk of diabetes.^[123] With the loss of magnesium from the heart, cellular machinery gets compromised leading to an imbalance of cardiac potassium content in the heart.

Potassium

A number of epidemiological and clinical studies have demonstrated that increased intake of dietary potassium reduces the incidence of CVDs and also plays a role in the significant reduction of BP.^[123]

Zinc

From clinical trials, it has been proved that lowering of zinc level in blood serum acts as an important contributor for CVDs, especially death from myocardial infarction.^[124]

Calcium

High intake of dietary calcium results in lowering of serum lipids.^[125] However, high calcium build-up in arterial system possesses a great risk in the development of CVD by the formation of plaques on the walls of arteries leading to clot formation. Under such circumstances, high intake of calcium increases the occurrence of CVDs instead of decreasing CVDs.^[126]

Chromium

Lower or absence of aortic chromium induces atherosclerosis and also CHDs.^[127]

Selenium:

It has been proved in several animal studies that selenium is cardioprotective^[128,129] and death rates are lowered in areas with very high selenium content in soil compared to low selenium area.

Silicon

Clinical and epidemiological results of silicon on CVDs are contradictory. However, silicon seems to have a protective role on the elastic state of the artery walls and also in the maintenance of intimal impermeability to lipid infiltration.^[130]

Manganese:

Manganese has beneficial effect on lipid metabolism and helps in the prevention of atherosclerosis.^[131]

Cadmium, Lead, and Copper

Cadmium in high concentrations is known to develop hypertension, hypertrophy, and sclerosis of the arteries.^[131] On the other hand, increase in lead and copper content in serum has caused myocardial infarction.^[130]

Even though trace elements are required in very small amounts, imbalance in their availability poses serious effects on human health and increases risk of CVD. Limited evidence supports any benefit from vitamin and mineral supplementation for the prevention of CVD. Due to insufficient information to draw

conclusion therefore, more research work needs to be carried out in the near future.

CONCLUSION

The incidence of CVDs is increasing with time and with change in lifestyle. There is a need of creating awareness in society about CVDs as prevention is easier compared to treating it. Hence, following heart-healthy diets, performing physical activities, drinking sufficient water, and having adequate sleep would drastically reduce the risk of CVDs. Even though available treatments and medications are effective, they are not proved to improve the quality of life, also it is known to cause side-effects in one or the other form. Therefore, there is an urgent need for newer and safer therapeutic alternatives. To meet this demand, in recent years, therapeutic properties of naturally occurring phytochemicals in plants have been increasingly exploited in the prevention and treatment of human diseases including CVDs. The era of nutraceuticals has begun, and it is evident from the recent clinical trials that nutraceuticals are the most promising, considering their efficacy in treating chronic diseases like CVDs. Thus, in the long run, nutraceuticals may turn out to be the best alternative in the prevention and treatment of CVDs.

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