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Review Article

Nutraceuticals for Improving Cardiovascular Health and Prognosis in Cardiovascular Disease

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Abstract

Nutrition and cardiovascular health: CVD is common, morbid and responsible for about 17.3 million deaths annually worldwide. The modifiable risk factors include obesity, hypertension, hyperlipidaemia, T2DM, MetS and lifestyle risk factors such as smoking, physical inactivity and dietary factors. Foods and nutrients play a vital role in functioning of various body organs and are helpful in maintaining health and in reducing the risk of various diseases. Several compounds from everyday foods and certain dietary supplements, when judiciously taken, have been documented to protect against the development of cardiovascular disease (CVD).

Potential nutritional factors for CV health: The nutraceuticals are foods or parts of food which provide health benefits, including the prevention and treatment of disorders and diseases. They also include medicinal compounds made from natural ingredients. The phytosterols, sterols and stanols are present in a range of plant products including various fruits and vegetables, cereals, seeds and nuts. Polyphenols are phytochemicals in fruits, vegetables, cereal and legumes, and also found in beverages produced from plant products such as tea, coffee, wine and cocoa. These compounds include flavonoids and phenolic acids, as well as stilbenes and lignans. The phenolic compounds are found in grapes and these include anthocyanins, flavanols, flavonols, phenolic acids and stilbenes including resveratrol (3,5,4'-trihydroxy-trans-stilbene). Resveratrol is present in smaller quantity in cranberries, blueberries and peanuts. Spirulina (*Cyanobacterium*) is a rich source of carotenoids and phycocyanins, and its supplementation has been associated with beneficial alterations in TC and LDL-C concentrations.

Modifying CVD and retarding CV aging: The nutraceuticals with the potential to modify the plasma lipid profile, retard and potentially reverse atherosclerosis process and reduce the CVD risk. The sterols/stanols reduce LDL-C through reduction in intestinal absorption of cholesterol, upregulation of hepatic LDL receptors and reduced production of endogenous cholesterol. The sterol/stanol consumption is inversely related to circulating LDL-C concentrations. Polyphenols, too, influence plasma lipid concentrations favourably. The flavanols in cocoa products are associated with improvement of lipid profile. Consumption of grapes and grape juice, containing resveratrol, has been linked with improvement in HDL-C levels. Coenzyme Q10 use appears to improve myocardial function and improve endothelial function. Hypertension is another modifiable risk factor for CVD and lowering blood pressure reduces CV risk. Polyphenols consumption of flavonoid-rich fruits and vegetables may lower blood pressure.

Nutraceuticals and functional foods: The nutrients in diet are important as concerns the development and progression of CVD. The functional foods incorporated into diet to provide CV benefits and lower CV risk. The functional foods, containing physiologically active components either from plant or animal sources, exert their cardioprotective effects by lipid lowering effect, decreasing homocysteine levels and their antioxidant activity.

Conclusion - Nutrition modification benefits: The dietary interventions open novel, potentially easy and affordable possibilities for population-based strategies for CVD risk reduction, and opportunity to utilize the nutraceuticals to positively influence CV risk factors should be recognized as an enormous opportunity.

Keywords: *Cardiovascular Health; Cardiovascular Disease; Cardiovascular Aging; Hypertension; Hyperlipidaemia; Nutraceuticals; Obesity; Resveratrol; Coenzyme Q10; Cardiovascular Risk Factors*

Introduction

Nutrition and CV health

The cardiovascular disease (CVD) is common, morbid and responsible for about 17.3 million deaths annually worldwide [1]. The modifiable risk factors for CVD include obesity, hypertension, hyperlipidaemia, T2DM, MetS and lifestyle risk factors such as smoking, physical inactivity and dietary factors [2]. The nutritional factors have an important bearing on the cardiovascular (CV) health, either directly, or through their effects on various CV risk factors including hypertension, dyslipidemia and diabetes mellitus. The protective effects against CVD have been demonstrated for various nutraceuticals and dietary supplements [3] and these simple lifestyle interventions open practical, potentially easy and affordable possibilities for population-based strategies for CVD risk reduction.

Epidemiological and clinical data

Various epidemiological and clinical studies have documented that the risk of CVD is reduced by the diet rich in fruits, vegetables, unrefined grains, fish and low-fat dairy products, and foods like brans, nuts, which are low in saturated fats and sodium are helpful. In addition, other foods containing mono- and polyunsaturated fats, plant sterols and soy proteins have all been documented to have a favourable effect on lipid profile and the overall CV health. Foods and nutrients, thus, play a vital role in functioning of various body organs and are helpful in maintaining health and reducing the risk of various diseases.

The concept of bioactive nutrients

Several compounds from everyday foods and certain dietary supplements, when judiciously taken, have been documented to protect against the development and progression of CVD [4]. Nutraceuticals are medicinal components of foods that play a role in maintaining well-being, enhancing health, modulating immunity and thereby preventing as well as treating specific diseases [5].

There are certain dietary patterns and nutritional factors that have the potential to reduce arterial stiffness and improve endothelial function [6]. Whereas general and functional foods, and nutraceuticals play important role in ensuring and preserving CV health, the pharmaceuticals have significant role in CV therapeutics (Figure 1). Further, the ability of nutraceuticals to influence CV health and positively modify the CV risk factors should be recognized as a potential opportunity for active dietary interventions and nutraceuticals therapy [7].

Figure 1: *Nutrition, nutraceuticals and pharmaceuticals.*

Potential nutritional factors for cardiovascular health

Potential Nutraceuticals

The nutraceutical is defined as 'a food component that provide potential medical or health benefits, including the prevention and treatment of disease' [8]. The definition includes medicinal products made from natural ingredients. The nutraceuticals supplementing diet, play a significant role in the prevention and treatment of disease (Figure 2).

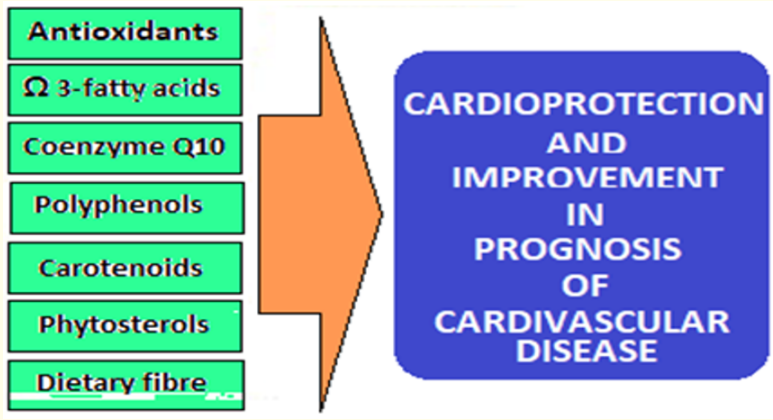

Figure 2: *Nutraceuticals for protection and maintenance of CV health.*

Early research in this context, was preoccupied with benefits of plant-derived foods containing vitamin C, vitamin E, and carotenoids, whereas the recent works have correlated the individual benefits with specific compounds. However, the effects noted by testing them alone may be different, though correlated to the synergistic action of various other bioactive components present in particular foods. Additionally, in each family of bioactive compounds there are usually various members present in variable proportions.

Phytochemicals

Phytochemicals are the bioactive compounds present in plant foods. The phytochemicals having significant health potentials are carotenoids, phenolic compounds - flavonoids, phytoestrogens, phenolic acids, phytosterols and phytostanols, tocotrienols, organosulfur compounds, nondigestible carbohydrates and dietary fibres, and prebiotics. Additionally, isoflavones are present in high concentration in soybean and red clover. Flaxseeds contain lignans.

Phytosterols

Plant sterols/stanols are phytosterols, present in a range of plant products including various fruits and vegetables, cereals, seeds and nuts [9]. The phytosterols bear a structural similarity to cholesterol. Whereas, stanols or phytostanols are the saturated forms of phytosterols. Dietary sources include dried fruits, nuts and seeds, but often the amounts are not large enough to have a cholesterol-lowering effect. The phytosterols and phytostanols are known to inhibit intestinal absorption of cholesterol, do not affect HDL and/or VLDL levels and effects on LDLs is additive to diets and cholesterol-lowering drugs. The sterols and stanols compete with cholesterol to form micelle with bile salts, thus improve serum lipid profile, lower LDL-C levels, and thus, decrease the risk of CVDs.

Polyphenols

Polyphenols include flavonoids, phenolic acids, stilbenes and lignans [10]. They are found in fruits, vegetables, cereal and legumes, and in beverages produced from plant products such as tea, coffee, wine and cocoa. The phenolic compounds found in grapes, include anthocyanins, flavanols, flavonols, phenolic acids and stilbenes including resveratrol (3,5,4'-trihydroxy-trans-stilbene). Resveratrol is also present in small quantity in cranberries, blueberries and peanuts [11]. Polyphenols also influence plasma lipid concentrations and consumption of grapes and grape juice has been associated with improvement in HDL-C levels [12-15]. Polyphenols have been shown to exert anti-atherosclerotic effects in the early stages of atherosclerosis development (decrease LDL oxidation); improve endothelial function and increase nitric oxide release (potent vasodilator); modulate inflammation and improve antioxidant status; protect against atherothrombotic episodes including myocardial ischemia and platelet aggregation [16-18].

Flavonoids

The flavonoids are present in vegetables and fruits. They are also present in beverages such as cocoa, tea, and wine. Some isoflavones such as lignans are phytoestrogens with nonsteroidal plant constituents, having estrogen-like biological response. They are also associated with dietary fibre in dietary items like oilseeds, cereal grains, vegetables, fruits, and legumes. The phytoestrogens have antioxidant activity and by virtue of estrogen-like response, influence lipoprotein metabolism and enhance vascular reactivity.

The intake of flavonoids has been linked with decreased CV and general mortality among elderly Dutch individuals [19]. Several prospective studies have also reported inverse correlation between flavonoid intake and CVD incidence or mortality. The CV protective mechanisms of flavonoids include antioxidant activity as well as metal ion chelating properties for transitional elements such as copper and iron that catalyse lipid oxidation. In addition, flavonoids inhibit of platelet aggregation; modulate of the activity of eicosanoid generating enzymes in inflammatory cells, enhance nitric oxide synthesis, lower superoxide production and have beneficial effects on lipid profile.

Further, a systematic review relating to different flavonoid subclasses and the effect of flavonoid-rich foods on CVD concluded that flavonoid-rich foods like chocolate or cocoa, red wine or grape, and green or black tea may have a measurable effect on CVD risk, including reduction in blood pressure and a favourable influence on endothelial function. In fact, the flavonoid-rich foods and extracts contain several potentially bioactive compounds, therefore the observed effects on vascular function may be related to compounds other than flavonoids contained in the food source.

Spirulina and soy nutrients

Spirulina (*Cyanobacterium*) is a rich source of protein, vitamins, minerals, carotenoids and phycocyanins [20]. Spirulina supplementation has been associated with beneficial alterations to blood lipid profiles. Spirulina maxima, taken orally is associated with significant changes in TC and LDL-C concentrations [21,22].

The soy products are rich in polyunsaturated fatty acids and have low saturated fat content. They contain fibre, vitamins and minerals, and several isoflavonoids (genistein, daidzein, glycitin) that are natural phytoestrogens, which are able to inhibit LDL oxidation and thus decrease the risk of atherosclerosis [23].

Modifying CVD and retarding CV aging: The role and benefits of nutraceuticals

Nutraceuticals and functional foods

The nutrition is a complex process and serves to provide through food intake not only basic nutrition and calories (fuel) for physiological functioning but also ensure healthy living, prevent diseases and assure longevity. The epidemiological studies have documented the relationship between diet and CVD and identified various dietary factors which are important in the pathogenesis of CVD. On the other hand, rather than the individual components of the diet, a combination of nutrients and to some extent, dietary habits appear to be important for the cardioprotective effects.

The term Nutraceuticals as defined by the US Foundation for Innovation in Medicine is 'any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease'. Whereas, functional food has been defined by the US Institute of Medicine's Food and Nutrition Board as 'any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains'. Further, the functional foods have physiological benefits and reduce the risk of chronic disease beyond their basic nutritional functions. The importance of nutraceuticals for CV health and CVD prevention is highlighted from observations that consumption of the particular dietary factors is associated with a reduced CV event rate. The research relating to the cardio-protective potential of food and dietary components supports the role of functional foods and nutraceuticals (Figure 3).

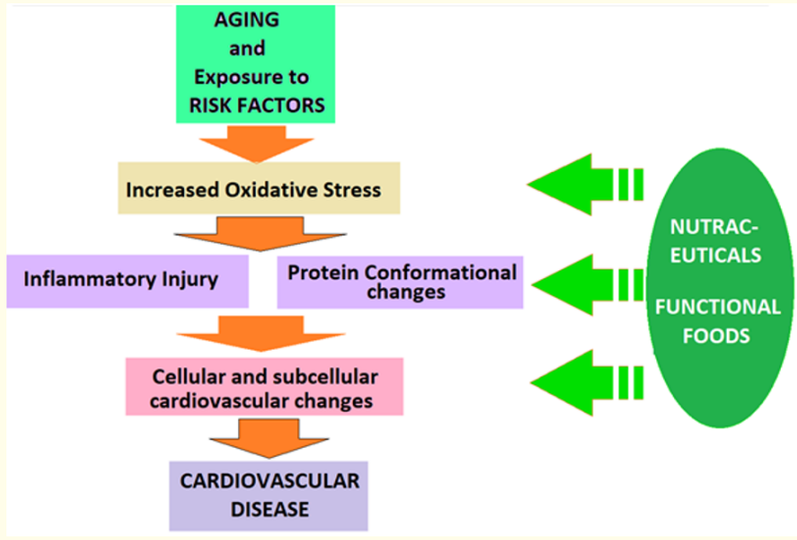

Figure 3: *Nutraceuticals and functional foods and their impact on CV Health.*

Coenzyme Q_{10} (CoQ_{10})

Dyslipidemia and Atherosclerosis

The nutraceuticals with the potential to modify the plasma lipid profile favourably can reduce the CVD risk [24]. The mechanism by which sterols/stanols reduce LDL-C is associated with a reduction in intestinal absorption of cholesterol, upregulation of hepatic LDL receptors and reduced production of endogenous cholesterol [25].

The oxidation of LDL-C in arterial walls is an early event for development of atherosclerosis. The reduced form of coenzyme Q_{10} inhibits the oxidation of LDL *in vitro* and together with α-tocopherol (α-TOH) inhibits LDL oxidation by regenerating α-TO· back to α-TOH. Studies in apolipoprotein E-deficient mice, an animal model of atherosclerosis, have documented that high dose coQ_{10} supplementation inhibited lipoprotein oxidation in the vessel wall and formation of atherosclerotic lesions. Further, the co-supplementation of these mice with α-TOH and coenzyme Q_{10} was more effective in inhibiting atherosclerosis than supplementation with either α-TOH or coenzyme Q_{10} alone. Another step in the development of atherosclerosis involves recruitment of monocytes which is dependent in part on expression of cell adhesion molecules (integrins) by monocytes. The supplementation of CoQ_{10} decreases the expression of integrins, which is another mechanism for the inhibition of atherosclerosis by coQ_{10} [26].

In light of the role of free radicals and reactive oxygen species (ROS) in pathophysiology of atherosclerosis, supplementation with antioxidants like vitamins A, C, E, folic acid and β-carotene, and selenium and zinc may be considered to be protective. But, apart from some supplements like marine n-3 FAs and niacin which are effective in improving CVD risk factors, others like B-vitamins: folate, vitamin B12, vitamin B6, antioxidants; vitamin E and selenium have negligible effect on CVD progression. But, in some studies a high dietary intake of foods rich in vitamin E, vitamin C, and β-carotene appears to be inversely associated with the incidence of CAD. Further, the cocoa flavanols are associated with a significant lowering CV risk through their favourable effect on lipid profile [27-29].

Hypertension

Hypertension is an important modifiable risk factor for CVD and lowering blood pressure reduces CV risk [30]. Polyphenols consumption of flavonoid-rich fruits and vegetables may lower blood pressure [31]. CoQ_{10} also has BP lowering effect [32].

Cardiovascular aging

The oxidative damage to cellular structures by ROS plays an important role in the functional decline with aging. ROS are generated by mitochondria during the of ATP production process and carry a risk of damaging mitochondria, if not neutralized by antioxidants. The damage due to ROS over time leads to the myocardial functional loss.

The myocardial CoQ_{10} content tends to decline with age and myocardial dysfunction. The CoQ_{10} functions at the level of mitochondrial inner membrane to transfer electrons from complexes I and II to complex III, and by virtue of its redox activity, also acts as a membrane antioxidant. Various studies have documented that supplemental CoQ_{10} is associated with improvements in functional parameters such as ejection fraction, stroke volume and cardiac output, and the long-term therapy with CoQ_{10} reduces major adverse cardiovascular events (MACE), improves HF symptoms and is safe and well tolerated (Table 1).

CoQ_{10}: Therapeutic Benefits
• Improves NO availability • Improves Endothelial function • Improves LV Function
• Decreases ROS and Inflammation • May Reduce Atherosclerosis • Prevents LV Hypertrophy • Decreases LV Fibrosis
• Improve Overall Functional Status • Improves CVS related QOL • Reduce Hospitalization and Mortality

Table 1: *Physiological and clinical benefits of CoQ_{10}*

Ischemia-reperfusion injury

The ischemic heart muscle becomes oxygen-deprived as the result of myocardial infarction. This is followed by increased generation of ROS when the heart muscle's oxygen supply is restored, which can be a contributor to myocardial damage during ischemia-reperfusion. Pre-treatment with coenzyme Q_{10} has been documented to preserve myocardial function following ischemia-reperfusion injury by increasing ATP concentration and enhancing the antioxidant capacity, and thus limiting myocardial damage and reducing cardiomyocyte apoptosis [33]. Another potential source of ischemia-reperfusion injury is aortic clamping during cardiac surgery, such as coronary artery bypass graft (CABG) surgery. Here also, the CoQ_{10} pre-treatment (60 - 300 mg/day for 7-14 days prior to surgery) is helpful in improving the outcome following CABG surgery [34].

Angina pectoris

The CVD patients with angina pectoris experience symptoms when the demand for oxygen exceeds the capacity of the coronary circulation to deliver it. As documented in several studies, CoQ_{10} supplementation may improve exercise tolerance and reduce or delay electro-cardiographic changes associated with myocardial ischemia. Presently, there is some evidence that CoQ10 may be a useful adjunct to conventional angina therapy.

Endothelial dysfunction

The normal functioning vascular endothelium promotes vasodilation as during physical activity. It also inhibits clotting. The atherosclerosis is associated with impairment of normal vascular endothelial function, it compromises vasodilation and adequate blood flow. The endothelium-dependent vasodilation is also impaired in those with hypercholesterolemia, CVD and diabetes mellitus. A 2012 metanalysis examining the results of five small randomized controlled trials in 194 subjects documented that supplementing coenzyme Q_{10} in a dose of 150 - 300 mg/day for 4 to 12 weeks, resulted in an improved and clinically significant endothelium-mediated dilation [35]. In several small randomized controlled trials in CAD patients the supplemental CoQ_{10} reduces inflammatory markers, such as CRP, interleukin-6 and tumor necrosis factor-α. The recommended dosage for CoQ_{10} is between 100 - 300 milligrams per day.

Congestive heart failure

The impaired ability of heart to pump adequate blood for the physiological need leads to congestive heart failure. The atherosclerotic plaques in the coronary arteries prevent parts of the myocardium from getting sufficient blood supply, resulting in myocardial damage

and impaired ejection fraction. In addition, heart failure may also be caused by myocardial infarction, hypertension, diseased heart valves, cardiomyopathy and congenital heart diseases. The supplemental CoQ_{10} has been shown to improve symptoms and prognosis in heart failure [36].

α-Tocopherol

Apart from CoQ_{10}, Vitamin E or α-Tocopherol (α-TOH) is one of the main fat soluble antioxidants. When α-TOH neutralizes a ROS, such as a lipid peroxyl radical (LOO·), it becomes oxidized itself, forming α-TO·, which in turn can promote the oxidation of lipoproteins. But, the reduced form of coenzyme Q_{10} ($CoQ_{10}H_2$) reacts with α-TO·, leading to regeneration of α-TOH and formation of semiquinone radical ($CoQ_{10}H$·). This radical, $CoQ_{10}H$· either reacts with oxygen (O_2) to produce superoxide anion radical (O_2·-), which is a less reactive pro-oxidant than LOO·, or can also reduce α-TO· back to α-TOH, leading to formation of fully oxidized coenzyme Q_{10}(CoQ_{10}), which does not react with O_2 to form O_2·

Carnitine and L-carnitine

In animal studies, administration of carnitine increases glucose oxidation in the isolated perfused rat heart by increasing the acetyl-carnitine concentration and decreasing the acetyl-CoA concentration, and thus relieving acetyl-CoA inhibition on PDH. In a randomized double-blind trial in myocardial infarction patients, oral carnitine therapy (6 g/day) initiated within 24h after onset of chest pain for over one year, failed to affect clinical outcome or LV ejection fraction; however, it significantly reduced the LV end-diastolic volume. There is some evidence that starting L-carnitine supplementation soon after myocardial infarction avoids another episode, death due to CVD or progression of heart failure [37].

l-Carnitine facilitates transport of long-chain fatty acids into the mitochondrial matrix, triggering cardioprotective effects through reduced oxidative stress, inflammation and necrosis of cardiac myocytes. Additionally, l-carnitine regulates calcium influx, endothelial integrity, intracellular enzyme release and membrane phospholipid content for sustained cellular homeostasis. The carnitine administration appears to be protective against ventricular dysfunction, ischemia-reperfusion injury, cardiac arrhythmia and myocardial cell loss that occurs in CVD. In addition, carnitine also improves hypertension, hyperlipidaemia, hyperglycemia, insulin resistance, metabolic syndrome and obesity. The favourable effect of l-carnitine is evident in young, adult and aged patients of sudden and chronic heart failure as well [4].

Resveratrol (RES)

RES (3,5,4 tri-hydroxy-stilbene), a polyphenol, is found predominantly in grapes and berries and a major component of red wine. It has multiple beneficial CV effects and its use as a nutraceutical for CVD and HF has been documented. There are indications that it prevents and retards the development of HF and it has efficacy of in humans with CVD and HF [38]. The administration of RES has been shown to improve outcomes of in animal models of HF induced by myocardial infarction, pressure overload, myocarditis, and chemotherapy-induced cardiotoxicity in animal studies. Further, animal studies have shown that RES improves cardiac function and survival when co-administered with the treatment for established HF [39].

Various studies have established the potential of RES in preventing or regressing defects in cardiac structure and function in experimental models of heart disease. With RES treatment, there is retardation of cardiac fibrosis and improvement in cardiac remodeling, endothelial, diastolic and systolic functions, and myocardial energy metabolism [40]. Resveratrol acts on the peripheral tissues to improve skeletal muscle and vascular function, and retards atherosclerosis by inhibiting LDL-C oxidation. Further, the anti-atherosclerotic effect of RES is not be limited to its effect on serum lipid profile alone, rather it appears to act on multiple factors linked with the atherosclerotic process [41]. The antihypertensive effect of RES is pronounced in hypertensive and dyslipidaemic subjects and operates through acetylcholine-mediated vasorelaxation.

RES also interferes with several mechanisms implicated in the pathogenesis of cardiac hypertrophy and heart failure including oxidative stress, activation of eNOS, an inhibition of protein synthesis, an improvement of calcium cycling and an inhibition of hypertrophic gene expression [42]. RES also activates SIRT-1, eNOS, Nrf2 and antioxidant response element (ARE), and decreases TNFα production, thus, decreasing endothelial apoptosis, endothelial and vascular inflammation, and improves the endothelial function [43].

Curcumin

Curcumin have an effect in prevention of cardiac hypertrophy and heart failure. Its long-term ingestion appears to modify genetic expression involved in cholesterol homeostasis. It decreases serum lipid peroxides and total serum cholesterol. Further, the curcuminoids have a membrane-stabilizing effect in myocardial ischemia, cardiac hypertrophy and heart failure [44]. It may be effective in CVD, stroke and heart failure by improving the declining function of the heart and vasculature. The studies show that curcumin can reduce chronic inflammation induced by obesity and metabolic syndrome, mitigate the impact of insulin resistance (IR) and improve their vascular function. The IR, metabolic syndrome and adiposity contribute to chronic inflammation, which exposes tissues to continuous, low-grade oxidative stress, threatens the integrity of cellular DNA, proteins, and other fundamental structural and functional molecules essential for homeostasis [45].

Several well-designed human studies have documented curcumin's ability to combat chronic inflammation [46]. Three recent studies confirmed that taking curcumin enhanced with bioperine for improved bioavailability led to significant reductions in levels of numerous inflammatory cytokines that mediate the effects of chronic inflammation [47]. Another study has highlighted that curcumin supplementation has a lipid modifying effect [48]. It influences almost all of the pathways by which cholesterol reaches the bloodstream including absorption from diet, removal of cholesterol in the liver, transportation of cholesterol out of cells and removal of cholesterol from tissues throughout the body. In addition, it also improves HDL-C [49].

In addition, curcumin has ability to scavenge ROS, reducing the risk of oxidative injury and thereby inflammatory damage. Curcumin attenuates rapamycin-induced cell Injury of vascular endothelial cells in animal studies [50] and appears to improve endothelial function [51] and retards development of diabetic microangiopathy and cardiomyopathy [52,53].

Omega 3-fatty acids (Ω3Fas)

As on today, the Ω3FAs are among the most commonly prescribed supplements [54]. They appear to decrease TG, inflammation and platelet aggregation, cause vasodilatation, and improve blood rheology, endothelial and myocardial function. While most commonly used for primary and secondary prevention of CVD, they have been tried in various medical conditions including gastrointestinal, rheumatic, metabolic, renal, dermatologic, pulmonary and even psychiatric disorders.

There have been documented several molecular and cellular effects of Ω3Fas. The animal studies have documented that adding Ω3FAs to cell membrane improves cellular function by interaction and modulation of membrane channels and altering the physiochemical properties of cell membrane. It appears that membrane-incorporated Ω3FAs is able to alter membrane protein signaling favourably. Further, the integration of Ω3FAs into cell membrane has been related to changes in H-Ras signaling protein and suppressed protein kinase C-theta signaling [55].

The Ω3FAs also exert anti-inflammatory properties through various mechanisms. They suppress the production of interleukin-2, the acute phase reactants and modify the production of eicosanoids, such as thromboxane A_2, leukotriene B_4, leading to reduced inflammation. Further, they inhibit lipopolysaccharide-induced inflammation [56]. By binding to specific nuclear receptors and transcription factors such as PPAR-α, HNF-4α and SREBP-1c, they alter gene expression. These anti-inflammatory properties of Ω3FAs may reduce vascular atherosclerosis. Some studies, on the other hand, have raised doubts on these effects of Ω3FAs. In a trial of 20 healthy athletes, daily supplementation with 3.6 grams of Ω3FAs for 6 weeks did not alter cytokine response to strenuous exercise nor changed the blood concentrations of neutrophils and lymphocytes [57].

The Ω3FAs may improve endothelial function by promoting release of nitric oxide from endothelial cells [58] and decrease resting systolic and diastolic blood pressure by incorporating EPA and DHA into membrane phospholipids and altering favourably the arterial compliance. In high doses, Ω3FAs increase bleeding time and have anti-thrombotic effect [59], which may be explained by property of Ω3FAs to inhibit platelets. Further, EPA and DHA lower tissue levels of arachidonic acid and replace it in cell membrane with EPA-derived eicosanoids, which are less vasoconstrictive and have less platelet aggregating effects [60]. The Ω3FAs are metabolized to thromboxane A3, in contrast to arachidonic acid which is metabolized to thromboxane A_2. The thromboxane A_3 is not as potent as thromboxane A_2 in activating platelets and triggering vasoconstriction. However, human trials do not verify a consistent effect on coagulation factors and

platelet aggregation, at least in the commonly prescribed doses of Ω3FAs. Ω3FAs can inhibit myocyte voltage-gated sodium channels and prolong the relative refractory period, thus may influence heart rate.

The Ω3FAs decrease serum levels of triglycerides by reducing hepatic synthesis of very low-density lipoprotein and accelerating degradation of fatty acids and triglyceride clearance from the plasma [61]. Some studies have documented that Ω3FAs improve flow-mediated arterial dilation and the mechanical function of the heart [62]. On the other hand, as regard to their effects on lipoproteins, randomized controlled trials have shown mixed results. Despite the abundance of studies concerning omega-3 supplements, both positive and negative trials, there is no clear evidence about their benefits. A potential challenge over several years, may have been, about reporting of positive findings by industry and pro-omega-3 nutritionists/academics while undervaluing the negative facts. Also, these products may not be free from side effects and risks. One particular risk for bleeding and haemorrhagic stroke deserve special attention [63]. In summary, based on the current evidence, it can be concluded that omega-3 supplements might possibly confer CV benefits but their benefits may be minimal, if any [64].

Nutraceuticals, functional foods and CVD prophylaxis

Bioactive nutrients and antioxidant defence system

Various plant products and extracts rich in bioactive components are useful as the functional ingredients for providing various health benefits including CVD prophylaxis [65]. Certain food components such as soluble fibre, sterols and stanols exert significant lipid-lowering activity, as well as improve endothelial dysfunction and arterial stiffness, by virtue of their anti-inflammatory and antioxidative properties [66]. Further, several epidemiological studies demonstrate a relationship between the intake of flavonoid-rich foods and the reduction of CV risk factors and morbidity. The flavonoids present in citrus fruits, such as oranges and lemons, and grapes have considerable nutraceutical value.

The somatic antioxidant defence system consists of endogenous enzymatic antioxidants, which are produced in cells and tissues of body organs and the exogenous nonenzymatic nutrients which are ingested and assimilated in form of diet as part of nutritional process (Figure 4). Various dietary nutrients, water soluble as well as lipid soluble, are important constituent of the antioxidant defence system. The oxidative stress (OxS) is an important etiological factor for various chronic diseases including CVD, stroke, IR, diabetes, neurodegenerative disorders and certain malignancies. In simple terms, the OxS can be defined as a mismatch in the pro-oxidant and antioxidant factors. The free radicals and Ros are generated as part of metabolic processes. But, beyond their normal occurrence in cells and tissues, free radicals and ROS are also produced in process of the food consumption and assimilation. Their regular production may disturb metabolic homeostasis and carries risk of undesirable metabolic reactions like oxidation of lipids, proteins and nucleic acids, and carbohydrates.

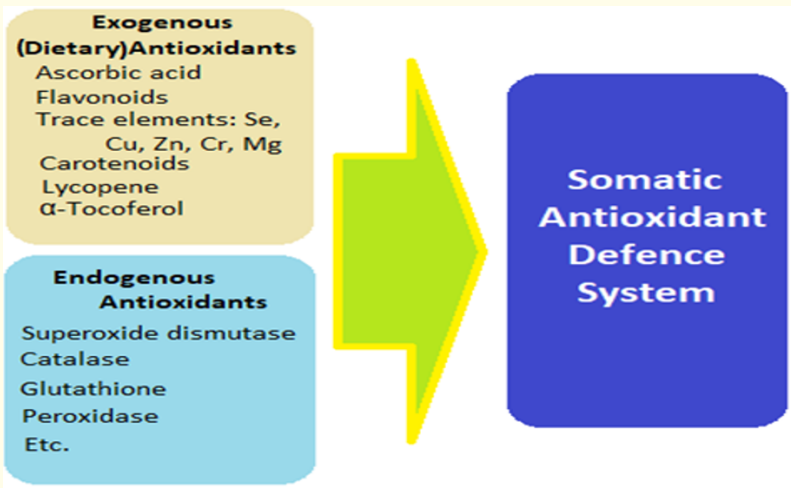

Figure 4: *The antioxidant defence system: exogenous nonenzymatic nutrients and endogenous enzymatic antioxidants.*

The impact of functional foods for CV health

The nutrients in diet are important in relation to the development and progression of CVD. The functional foods incorporated into diet to provide CV benefits and lower CV risk. The functional foods, containing physiologically active components either from plant or animal sources, exert their cardioprotective effects by lipid lowering effect, decreasing homocysteine levels and their antioxidant activity. The functional foods have broad ranging physiologic effects and reduce inflammatory process and vascular reactivity. Many functional foods have bioactive components having antioxidant and anti-inflammatory activities and have been found to have therapeutic potential (Table 2).

Functional Foods	Bioactive Compounds
• Nuts	➢ Tocophenols, Ω-3-fatty acids
• Legumes	➢ Fibre and Polyphenols
• Fruits and vegetables	➢ Pectin (fibre), carotenoids
• Fish	➢ Omega-3-fatty acids
• Whole grain	➢ Fibre and Phytochemicals
• Soy protein	➢ Genistein and Daidzein
• Dark chocolate	➢ Flavonoids
• Tomato	➢ Lycopene
• Citrus fruits	➢ Vit C
• Turmeric	➢ Curcumin

Table 2: *The potential bioactive components of functional foods.*

Various functional foods

Vegetable and fruit fibers rich in pectin, walnut and almonds, and fish oils have lipid-lowering effects, through both inhibition of fat absorption and suppression of hepatic cholesterol synthesis. The diets rich in vegetables and fruits have a documented benefit on CVD risk. On the other hand, inadequate consumption of vegetables and fruits has been linked to higher CVD risk. What is more, the benefits of vegetable and fruit consumption are related to dose and frequency [67].

The bioactive components in fruits and vegetables such as carotenoids, vitamin C, fibre, magnesium and potassium exert their protective effects individually or synergistically to promote CV health and health in general. The soluble fibres like pectins in apples and citrus fruits, β-glucan in oats and barley, and other fibres in flaxseed and psyllium have LDL-C lowering effect. Homocysteine is known to increase both cardiovascular and cerebrovascular risks by enhancing arteriolar constriction and decreasing endothelial vasodilation. The dietary intake of folate, antioxidants and phytochemicals counteracts the damaging CV effects of elevated homocysteine levels.

The nuts contain various cholesterol lowering mono- and polyunsaturated fatty acids, soluble fibres, polyphenols and arginine, which is a precursor of NO. A diet with regular intake of nuts has cardioprotective effects. The legumes are rich in folic acid, soluble and insoluble fibers, polyphenols and phytosterols, and have a cholesterol-lowering effect due to the combined effects of these bioactive components as well as their high protein content.

Cocoa is a flavonoid-rich food that has possible role in the prevention of CVD. In healthy adults, drinking flavonoid-rich cocoa has been documented to improve NO-dependent vasorelaxation and flow-mediated dilation in the major arteries. The dark chocolate has been shown to reduce ambulatory blood pressure in hypertensives, and lower serum LDL-C and circulating oxidized LDL levels along with a significant rise in HDL cholesterol. Similarly, the coffee containing diterpenes, such as kahweol and cafestol, has cardioprotective effects. There are insufficient data to indicate that coffee consumption may possibly reduce the risk of CAD. Green tea consumption also appears to protect from CVD, but again the data are inconclusive and inconsistent.

Conclusion: Nutritional Factors, Dietary Patterns and CVD

Nutritional Factors and CV Health

There is a protective effect of whole grains on CV health mainly due to its effects on insulin sensitivity as the whole grain foods have a low glycemic index. Thus, the postprandial surge in blood glucose is lessened and is associated with reduced ROS generation after a meal

and reduced postprandial inflammation, blood pressure, lipids and reduced CVD risk. Additionally, the germ of whole grains contains a number of antioxidant nutrients.

Further, the effect of micronutrients is complex and not due to a single nutrient in isolation. Therefore, increasing consumption of vitamins-rich fruit and vegetables is recommended rather than use of vitamin supplements.

Dietary patterns and CV health

The Mediterranean diets, in general, are high in vegetables, fruits, cereals, beans, nuts and seeds, and olive oil content and low in dairy products and meat with fish and poultry in low-to-moderate amounts. There are numerous reports demonstrating better endothelial function and low rates of CVD associated among populations known to consume such diets [68,69].

The traditional Okinawa diet is low in calories yet nutritionally dense, especially with regard to phytonutrients in the form of antioxidants and flavonoids [70]. The traditional Okinawan diet is rich in vegetables and fruits. Many of the characteristics of the diet in Okinawa are shared with other healthy dietary patterns, such as the traditional Mediterranean diet or the modern DASH (Dietary Approaches to Stop Hypertension) diet. The Mediterranean diet characteristics such as low levels of saturated fat, high antioxidant intake and low glycemic foods contribute to the reduced CVD risk.

The healthy dietary pattern

A diet high in vegetables, fruits and nuts is rich in antioxidant nutrients and polyphenols. The low-energy, nutrient-dense diets with high-quality carbohydrates with low glycemic load have anti-inflammatory potential. They appear to be beneficial for reducing the CVD risk. The low consumption of saturated fat along with the high contents of phytochemicals and antioxidant intake is likely to contribute to cardioprotective effects.

The nutraceuticals and functional food recommendations

The process of nutrition and assimilation is a complex process. Similarly, the role of various nutrients with dietary intake, too, is surrounded by half-baked hypotheses, biased research studies and lack of long-term control studies. These factors ruin the scientific stance and pose hinderance to rational outlook. There are needed an unbiased position statement, rational directions for nutritional research and wholesome views about the results from the nutritional science-based research.

Disclosures

None.

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