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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, parts of food providing medical or health benefits, including the prevention and treatment of disease. They include medicinal products 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 include flavonoids, phenolic acids, 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 in relation to the development and

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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.

Keywords: Cardiovascular health; Cardiovascular disease; Cardiovascular aging; Hypertension; Hyperlipidaemia, Nutraceuticals, Obesity; Resveratrol; Coenzyme Q10; Cardiovascular risk factors

Abbreviations: OxS: Oxidative Stress; CVD: Cardiovascular Disease; CHD: Coronary Heart Disease; α-TOH: α-tocopherol; ARE: Antioxidant Response Element; RES: Resveratrol; IR: Insulin Resistance

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: Epidemiological and clinical studies indicate that the risk of CVD is reduced by a diet rich in fruits, vegetables, unrefined grains, fish and low-fat dairy products, and foods low in saturated fats and sodium are helpful. Other foods such as mono- and polyunsaturated fats, brans, nuts, plant sterols, and soy proteins have all been shown to have a favourable effect on lipid profile and blood pressure, and the overall CV health. Foods and nutrients 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 (Fig 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 supplement the diet and also aid in the prevention and/or treatment of disease (Fig 2). Early research evaluated the benefits of plant-derived foods based on their vitamin C, vitamin E, and carotenoid content. More recent work pointed out correlation of benefits with individual compounds. However, the effects noted by testing them alone may be related to the synergistic action of the myriad of other bioactive components present in foods. In each family of bioactive compounds there are usually various members present.

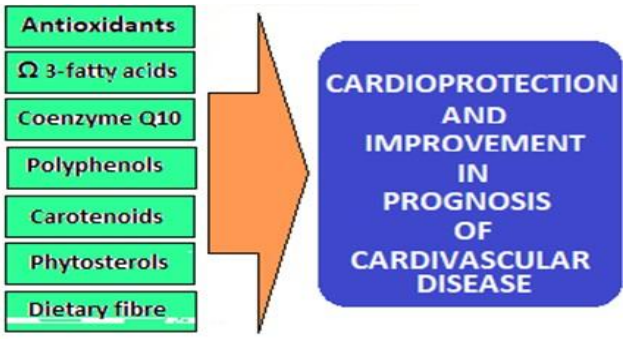

Figure 2: Nutraceuticals for Protection and Maintenance of CV health

Phytochemicals: Plant foods contain many bioactive compounds known as phytochemicals. The groups of phytochemicals having significant health potentials are carotenoids, phenolic compounds (flavonoids, phytoestrogens, phenolic acids), phytosterols and phytostanols, tocotrienols, organosulfur compounds and nondigestible carbohydrates (dietary fibre and prebiotics). Isoflavones are found in high concentration in soybean, soybean products (e.g., tofu) and red clover. Lignans are mainly found in flaxseed.

Phytosterols: Plant sterols/stanols are phytosterols, present in a range of plant products including various fruits and vegetables, cereals, seeds and nuts [9]. Plant sterols or phytosterols are structurally similar and functionally analogous to cholesterol. Stanols or phytostanols are saturated forms of phytosterols. Dietary sources include vegetable oils, nuts, seed and grains, but the amounts are often not large enough to have significant cholesterol-lowering effects. Phytosterols and phytostanols inhibit intestinal absorption of cholesterol, do not affect HDL and/or VLDL. Yet, their effects on LDLs have been found to be 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: Plant-derived flavonoids are contained in vegetables and fruits as well as in beverages such as cocoa, tea, and wine. Some isoflavones like lignans are phytoestrogens, a group of nonsteroidal plant constituents that elicit estrogen-like biological response. They are associated as minor components with dietary fibre in dietary items like oilseeds, cereal grains, vegetables, fruits, and legumes. Like other phenolic compounds, phytoestrogens have antioxidant activity, and like estrogens, they can influence lipoprotein metabolism and enhance vascular reactivity. Intake of flavonoids has been associated with decreased CV mortality and general mortality among elderly Dutch individuals [19]. Several prospective studies have reported inverse associations between flavonoid intake and CVD incidence or mortality. For the CV protective mechanisms of flavonoids, mechanisms include antioxidant activity and properties as metal chelators, for transitional elements such as copper and iron that catalyse lipid oxidation; inhibits of platelet aggregation; modulates of the activity of eicosanoid generating enzymes in inflammatory cells enhancers of nitric oxide synthesis; lowering of superoxide production; beneficial effects on lipid profile and modulation of proinflammatory gene expression. A systematic review of the effectiveness of different flavonoid subclasses and flavonoid-rich foods on CVD concluded that some flavonoid-rich foods, including chocolate or cocoa, red wine or grape, and green or black tea may have some measurable effects on CVD risk factors, including a reduction in blood pressure and a favourable influence on endothelial function. In fact, the flavonoid-rich foods and extracts contain many 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]. Soy products are rich in

polyunsaturated fatty acids, fibre, vitamins and minerals, and have low saturated fat content. They contain many isoflavonoids (genistein, daidzein, glycitin) that are natural phytoestrogens able to inhibit LDL oxidation, thus decreasing 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 endorsed the relationship between diet and CVD, and various dietary factors are important in the pathogenesis of CVD. Further, rather than the individual components of the diet, a combination of nutrients and even dietary habits appear to be responsible for 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, the US Institute of Medicine's Food and Nutrition Board has defined *functional food* as 'any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains'. Functional foods are those that are thought to have physiological benefits and/or 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 into the cardio-protective potential of food and dietary components supports the role of functional foods and nutraceuticals (Figure 3).

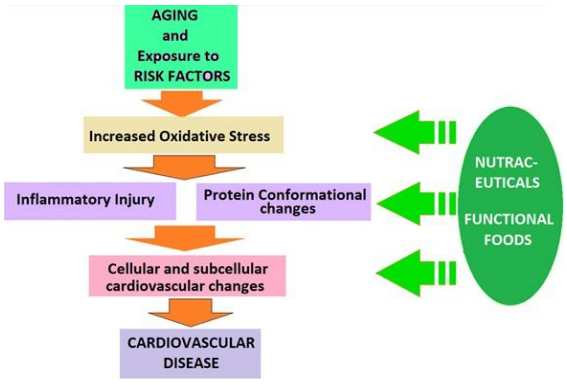

Figure 3: Nutraceuticals and Functional foods and their impact on CV Health.

Coenzyme Q10 (CoQ10): # 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 coenzyme Q10 (CoQ10H2) 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 coQ10 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 Q10 was more effective in inhibiting atherosclerosis than supplementation with either α-TOH or coenzyme Q10 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 CoQ10 significantly decreases the expression of integrins, another mechanism for the inhibition of atherosclerosis by coQ10 [26]. In view of the detrimental role of free radicals and reactive oxygen species (ROS) in pathophysiology of atherosclerosis, supplementation with antioxidants (vitamins A, C, and E, folic acid, β-carotene, selenium, and zinc) may expected to be protective. But, though some supplements (e.g., marine n-3 FAs and niacin) are effective in improving CVD risk factors, others (like B-vitamins: folate, vitamin B12, vitamin B6, antioxidants; vitamin E and selenium) have little effect on CVD. But, 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]. CoQ10 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 as a by-product of ATP production. If not neutralized by antioxidants, ROS may damage mitochondria over time leading to the functional loss.

The myocardial CoQ10 content tends to decline with age and myocardial dysfunction. The CoQ10 functions in the

mitochondrial inner membrane to transfer electrons from complexes I and II to complex III. By virtue of its redox activity, also acts as a membrane antioxidant. Various studies have documented that supplemental CoQ10 is associated with improvements in functional parameters such as ejection fraction, stroke volume and cardiac output, and the long-term therapy with CoQ10 reduces major adverse cardiovascular events (MACE), improves HF symptoms and is safe and well tolerated (Table 1).

CoQ10: Therapeutic Benefits
Improves NO availability
Improves Endothelial function
Improves LV Function
Decreases ROS & Inflammation
May Reduce Atherosclerosis
PreventsLVHypertrop
DecreasesLVFibrosis
ImproveOverallFunctionalStatus
ImprovesCVSrelatedQOL
ReduceHospitalizationandMortality

Table 1: Physiological and clinical benefits of CoQ10

 # Ischemia-reperfusion injury: The heart muscle may become oxygen-deprived (ischemic) as the result of myocardial infarction. Increased generation of ROS when the heart muscle's oxygen supply is restored (reperfusion) can be a contributor to myocardial damage during ischemia-reperfusion. Pre- treatment with coenzyme Q10 has been found to preserve myocardial function following ischemia- reperfusion injury by increasing ATP concentration, enhancing antioxidant capacity and limiting oxidative damage and reducing cardiomyocyte apoptosis [33]. Another potential source of ischemia-reperfusion injury is aortic clamping during some types of cardiac surgery, such as coronary artery bypass graft (CABG) surgery. The CoQ10 pre-treatment (60-300 mg/day for 7-14 days prior to surgery) appears to provide benefit in outcome measures after CABG surgery [34].

 # Angina pectoris: The patients with angina pectoris often experience symptoms when the demand for oxygen exceeds the capacity of the coronary circulation to deliver it. In several studies, CoQ10 supplementation improved exercise tolerance and reduced or delayed electrocardiographic changes associated with myocardial ischemia compared to placebo. Presently, there is some evidence that CoQ10 may be a useful adjunct to conventional angina therapy. # Endothelial dysfunction: The normal functioning vascular endothelium promotes blood vessel relaxation (vasodilation) when needed (for example, during exercise) and inhibits clotting. Atherosclerosis is associated with impairment of vascular endothelial function, thereby compromising vasodilation and normal blood flow. Similarly, endothelium-dependent vasodilation is impaired in individuals with elevated serum cholesterol concentrations, as well as in patients with coronary heart disease or diabetes mellitus. A 2012 metanalysis examining the results of five small randomized controlled trials in 194 subjects in total found that supplemental coenzyme.

Q10 (150-300 mg/day for 4 to 12 weeks) resulted in a clinically significant, 1.7% increase in flow- dependent endothelial-mediated dilation [35]. In several small randomized controlled trials in CAD patients the supplemental CoQ10 reduces inflammatory markers, such as CRP, interleukin-6 and tumor necrosis factor-α. The recommended dosage for CoQ10 is between 100-300 milligrams per day.

 # Congestive heart failure: Impairment of the heart's ability to pump enough blood for the body's needs is known as congestive heart failure. In coronary heart disease (CHD), accumulation of atherosclerotic plaque in the coronary arteries may prevent parts of the cardiac muscle from getting adequate blood supply, ultimately resulting in heart damage and impaired pumping ability. Heart failure can also be caused by myocardial infarction, hypertension, diseases of the heart valves, cardiomyopathy, and congenital heart diseases. The supplemental CoQ10 appears to improve symptoms and prognosis in heart failure [36].

α-Tocopherol: α-Tocopherol (vitamin E) and CoQ10 are the main fat soluble antioxidants. When α-tocopherol (α-TOH) neutralizes a ROS, such as a lipid peroxyl radical (LOO·), it becomes oxidized itself, forming α-TO·, which can in turn promote the oxidation of lipoproteins. However, when the reduced form of coenzyme Q10 (CoQ10H2) reacts with α-TO·, α-TOH is regenerated and the semiquinone radical (CoQ10H·) is formed. It is possible for CoQ10H· to react with oxygen (O2) to produce superoxide anion radical (O2··), which is a less reactive pro-oxidant than LOO·. However, CoQ10H· can also reduce α-TO· back to α-TOH, resulting in the formation of fully oxidized coenzyme Q10 (CoQ10), which does not react with O2 to form O2·

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 24 h 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 [38].

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 [39]. 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 [40]. 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 [41]. 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 an effect on serum lipid profile, but it appears to act on various factors involved in the atherosclerotic process [42]. The antihypertensive action of RES, as evaluated by the increase in acetylcholine-evoked vasorelaxation, was more pronounced if RES was administered to hypertensive and dyslipidaemic subjects. 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 [43]. RES also activates SIRT-1 (a class III histone deacetylase), eNOS, Nrf2 and antioxidant response element (ARE), and decreases TNFα production. It, thus, decreases of endothelial apoptosis, endothelial activation and vascular inflammation, and improves the endothelial function [44].

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 [45]. 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 [46]. Several well-designed human studies have documented curcumin's ability to combat chronic inflammation [47]. 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 [48]. Another study has highlighted that curcumin supplementation has a lipid modifying effect [49]. 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 appears to improve HDL-C [50].

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 [51] and appears to improve endothelial function [52] and retards development of diabetic microangiopathy and cardiomyopathy [53,54].

Omega 3-fatty acids (Ω3Fas): Ω3FAs are among the most commonly prescribed supplements with a worldwide market [55]. They appear to decrease TG, inflammation and platelet aggregation, cause vasodilatation, and improve blood rheology, endothelial and myocardial function. While Ω3FAs have been tried in various medical conditions including gastrointestinal, rheumatic, metabolic, renal, dermatologic, pulmonary and even psychiatric disorders, most commonly they have been used for primary and secondary prevention of CVD. There have been documented several molecular and cellular effects of Ω3Fas. Animal studies have shown that adding Ω3FAs to cell membrane improves cellular function by interaction and modulation of membrane channels and altering the physiochemical properties of cell membrane. The membrane- incorporated Ω3FAs might be able to alter membrane protein signaling favourably. Further, the integration of Ω3FAs into cell membrane in animal studies has been related to changes in H-Ras signaling protein and suppressed protein kinase C-theta signaling [56].

Ω3FAs also exert anti-inflammatory properties through different proposed mechanisms. They suppress the production of interleukin-2 and inhibit lipopolysaccharide-induced inflammation [57]. They also bind to specific nuclear receptors and transcription factors such as PPAR-α, HNF-4α and SREBP-1c regulating gene expression. Furthermore, they also suppress the acute phase reactants and modify the production of eicosanoids, such as thromboxane A2, leukotriene B4, leading to reduced inflammation. It has been hypothesized these anti-inflammatory properties may reduce vascular atherosclerosis. Some studies, however, have questioned the effect of Ω3FAs on inflammation. 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 [58].

Ω3FAs may also lead to improved endothelial function by promoting the release of nitric oxide from endothelial cells [59]. Ω3FAs also decrease resting systolic and diastolic blood pressure by incorporation of EPA and DHA into membrane phospholipids and therefore increasing systemic arterial compliance. They have been also considered anti-thrombotic at very high doses, potentially increasing the bleeding time [60]. This might be explained by the ability of omega-3 fatty acids to inhibit platelets. EPA and DHA can lower tissue levels of arachidonic acid and replace it in cell membrane. EPA-derived eicosanoids are less vasoconstrictive and lead to less platelet aggregating effects than those derived from arachidonic acid [61]. In contrast to arachidonic acid that is metabolized to thromboxane A2, Ω3FAs are metabolized to thromboxane A3, which is not as potent as thromboxane A2 in activating platelets and triggering vasoconstriction. However, human trials are not suggestive of a consistent effect on coagulation factors and platelet aggregation, at least for commonly prescribed doses of Ω3FAs. Ω3FAs might directly influence heart rate because they can inhibit myocyte voltage-gated sodium channels and prolong the relative refractory period. Accelerating triglyceride clearance from the plasma [62]. But with regard to their effects on lipoproteins, randomized controlled trials have yielded mixed results. Some studies have shown the effect of omega-3. As far as the CVD risk factors concerned, Ω3FAs decrease serum levels of triglycerides, through reduced hepatic synthesis of very low-density lipoprotein and by boosting the degradation of fatty acids and fatty acid supplements on improving flow-mediated arterial dilation and improvement of the mechanical function of the heart [63]. Despite the abundance of studies concerning omega-3 supplements, evidence is not clear about the benefits of these supplements, with both positive and negative trials. One potential challenge over the past several years has been the reporting of positive pieces of evidence by both industry and pro-omega-3 nutritionists/academics while undervaluing the equally robust, if not more robust, negative studies. Also, these products might not be free from risk and the particular risks for bleeding and haemorrhagic stroke deserve further attention. [64]. In summary and in light of the current best evidence, we can conclude that omega-3 supplements might possibly confer cardiovascular benefits but their benefits will be minimal, if any [65].

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 [66]. 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 [67]. 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.

Figure 4: The Antioxidant Defence System: Exogenous Nonenzymatic Nutrients and Endogenous Enzymatic Antioxidants.

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). Several dietary nutrients, both water soluble and lipid soluble, comprise an important aspect 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. The OxS can be defined as a disturbance in the pro-oxidant/antioxidant balance, in simple terms. The free radicals and Ros are generated as part of metabolic processes. On the other hand, beyond their normal occurrence in cells and tissues of living organisms, free radicals and ROS are also produced as part of the food consumption and assimilation. Their regular production poses challenge to metabolic homeostasis and undesirable metabolic reactions like oxidation of lipids, proteins and nucleic acids, and carbohydrates.

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. In fact, the functional foods have broad ranging physiologic effects *in vivo* that lessen inflammatory cascades 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 (with pectin), garlic and oily seeds (walnut, almonds, etc.), and fish oils have lipid-lowering effects in humans, through both inhibition of fat absorption and suppression of hepatic cholesterol synthesis. There is a substantial evidence about the beneficial effects of diets rich in vegetables and fruits on CVD risk. Conversely, inadequate consumption of fruit and vegetables has been linked with higher incidence of CVD. The benefits of fruit and vegetable intake appear to be dose and frequency-related [68].

The fruit and vegetables exert their protective effects through their several bioactive components such as carotenoids, vitamin C, fibre, magnesium and potassium act synergistically or antagonistically to promote a holistic beneficial effect. Soluble fibres including pectins from apples and citrus fruits, *β*- glucan from oats and barley, and fibres from flaxseed and psyllium are known to lower LDL-C. Homocysteine increases the risk of both cardiovascular and cerebrovascular disorders by enhancing arteriolar constriction and decreasing endothelial vasodilation. A suitable dietary intake of folate, antioxidant vitamins, whole grains and phytochemicals counteract the deleterious cardiovascular effects of elevated homocysteine levels.

Nuts are complex foods containing cholesterol lowering mono- and polyunsaturated fatty acids, arginine (a precursor to the vasodilator nitric oxide), soluble fibre, and several antioxidant polyphenols. The evidence supporting the cardioprotective effects of diets high in nuts is robust. Legumes are also complex foods rich in soluble fibers and polyphenols, as well as folic acid. The cholesterol-lowering effect of legumes is probably due to the combined effects of several bioactive components, such as protein, soluble and insoluble fibres, and phytosterols.

Cocoa is a flavonoid-rich food that has possible role in the prevention of CVD. In healthy adults, drinking flavonoid-rich cocoa may improve NO-dependent vasorelaxation and flow-mediated dilation in the brachial arteries. Administration of dark chocolate in essential hypertensives reduced ambulatory blood pressure and serum LDL-C levels as well as led to a significant rise in HDL cholesterol in addition to a marked reduction of circulating oxidized LDL. Similarly, the coffee is apparently responsible for cardioprotective effect through diterpenes, such as kahweol and cafestol. Coffee consumption may possibly reduce the risk of coronary arterial disease, but data are as yet inconclusive. Green tea consumption appears to protect from CVD, but results are again 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, more antioxidant nutrients are present in the germ of whole grains. 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 contain high levels of fruits, vegetables, cereals, beans, nuts and seeds, and olive oil, and are low in red meat and dairy products. Fish and poultry are consumed 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 [69,70].

The traditional Okinawa diet is low in calories yet nutritionally dense, especially with regard to phytonutrients in the form of antioxidants and flavonoids [71]. 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. Features such as the low levels of saturated fat, high antioxidant intake, and low glycemic load in these diets seem to contribute to a reduced CVD risk.

The Healthy Dietary Pattern: A diet high in fruits, vegetables and nuts is rich source of the antioxidant nutrients and polyphenols, and has anti-inflammatory potential. The low-energy, nutrient- dense diets with high-quality carbohydrates with low glycemic load may be beneficial for reducing the risk of CVD. The low consumption of saturated fat along with the high contents of phytochemicals and antioxidant intake is likely to contribute to cardioprotective effects [72].

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 is too 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.

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.

Footnotes

References

1. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, et al. (2015) Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation 132(17): 1667-78.

2. O'Keeffe C, Kabir Z, O'Flaherty M, Janette Walton, Simon Capewell, et al. (2013) Modelling the impact of specific food policy options on coronary heart disease and stroke deaths in Ireland. BMJ Open.

3. Alissa EM, Ferns GA (2012) Functional foods and nutraceuticals in the primary prevention of cardiovascular diseases. J Nutr Metab.

4. Sosnowska B, Penson P, Banach M (2017) The role of nutraceuticals in the prevention of cardiovascular disease. Cardiovasc Diagn Ther 7(Sup 1): S21–S31.

5. Ramaa CS, Shirode AR, Mundada AS, Kadam VJ (2006) Nutraceuticals--an emerging era in the treatment and prevention of cardiovascular diseases. Curr Pharm Biotechnol 7(1): 15-23.

6. LaRocca TJ, Martens CR, Seals DR (2017) Nutrition and other lifestyle influences on arterial aging. Ageing Res Rev 39: 106-19.

7. Garcia-Rios A, Delgado-Lista J, Alcala-Diaz JF, Lopez-Miranda J, Perez-Martinez P (2013) Nutraceuticals and coronary heart disease. Curr Opin Cardiol. 28(4): 475-82.

8. Zuchi C, Ambrosio G, Lüscher TF, Landmesser U (2010) Nutraceuticals in cardiovascular prevention: lessons from studies on endothelial function. Cardiovasc Ther 28(4): 187-201.

9. DeFelice SL (1995) The nutraceutical revolution: its impact on food industry R&D. Trends in Food Science and Technology 6(2): 59-61.

10. Moreau RA, Whitaker BD, Hicks KB (2002) Phytosterols, Phytostanols and Their Conjugates in Foods: Structural Diversity, Quantitative Analysis, and Health-Promoting Uses. Prog Lipid Res 41(6): 457-500.

11. Pandey KB, Rizvi SI (2009) Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev 2(5): 270-8.

12. Burns J, Yokota T, Ashihara H, Lean ME, Crozier A (2002) Plant foods and herbal sources of resveratrol. J Agric Food Chem 50(11): 3337-40.

13. Khadem-Ansari MH, Rasmi Y, Ramezani F (2010) Effects of red grape juice consumption on high density lipoprotein- cholesterol, apolipoprotein AI, apolipoprotein B and homocysteine in healthy human volunteers. Open Biochem J 4: 96- 99.

14. Yubero N, Sanz-Buenhombre M, Guadarrama A, Villanueva S, Carrión JM, et al. (2013) LDL cholesterol-lowering effects of grape extract used as a dietary supplement on healthy volunteers. Int J Food Sci Nutr 64(4): 400-6.

15. Feringa HH, Laskey DA, Dickson JE, Coleman CI (2011) The effect of grape seed extract on cardiovascular risk markers: a meta- analysis of randomized controlled trials. J Am Diet Assoc 111(8): 1173-81.

16. Zunino SJ, Peerson JM, Freytag TL, Breksa AP, Bonnel EL, et al (2014) Dietary grape powder increases IL-1β and IL-6 production by lipopolysaccharide-activated monocytes and reduces plasma concentrations of large LDL and large LDL-cholesterol particles in obese humans. Br J Nutr 112(3): 369-80.

17. Barona J1, Aristizabal JC, Blesso CN, Volek JS, Fernandez ML (2012) Grape polyphenols reduce blood pressure and increase flow-mediated vasodilation in men with metabolic syndrome. J Nutr 142(9): 1626-32.

18. Draijer R, De Graaf Y, Slettenaar M, De Groot E, Wright CI (2015) Consumption of a polyphenol-rich grape-wine extract lowers ambulatory blood pressure in mildly hypertensive subjects. Nutrients 7(5): 3138-53.

19. Vaisman N, Niv E (2015) Daily consumption of red grape cell powder in a dietary dose improves cardiovascular parameters: a double blind, placebo-controlled, randomized study. Int J Food Sci Nutr 66(3): 342-49.

20. Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC (2002) Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam study. Am J Clin Nutr 75(5): 880–6.

21. Khan Z, Bhadouria P, Bisen PS (2005) Nutritional and therapeutic potential of Spirulina. Curr Pharm Biotechnol 6(5): 373-79.

22. Serban MC, Sahebkar A, Dragan S, Stoichescu-Hogea G, Ursoniu S, et al. (2016) A systematic review and meta-analysis of the impact of Spirulina supplementation on plasma lipid concentrations. Clin Nutr 35(4): 842-51.

23. Miczke A, Szulińska M, Hansdorfer-Korzon R, Kręgielska-Narożna M, Suliburska J, et al. (2016) Effects of spirulina consumption on body weight, blood pressure, and endothelial function in overweight hypertensive Caucasians: a double-blind, placebo-controlled, randomized trial. Eur Rev Med Pharmacol Sci 20(1): 150-6.

24. Wiseman H, O'Reilly JD, Adlercreutz H, Mallet AI, Bowey EA, et al. (2000) Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density

lipoprotein to oxidation in humans. Am J Clin Nutr 72(2): 395–400.

25. Andersson SW, Skinner J, Ellegard L, Welch AA, Bingham S, et al. (2004) Intake of dietary plant sterols is inversely related to serum cholesterol concentration in men and women in the EPIC Norfolk population: A cross-sectional study. Eur J Clin Nutr 58(10): 1378-85.

26. De Jong A, Plat J, Mensink RP (2003) Metabolic effects of plant sterols and stanols. J Nutr Biochem 14(7): 362-69.

27. Flammer AJ, Sudano I, Wolfrum M, Thomas R, Enseleit F, et al. (2012) Cardiovascular effects of flavanol-rich chocolate in patients with heart failure. Eur Heart J 33(17): 2172-80.

28. Lin X, Zhang I, Li A, Manson JE, Sesso HD, et al. (2016) Cocoa Flavanol Intake and Biomarkers for Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Nutr 146(11): 2325-2333.

29. Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP, et al. (2012) Effect of cocoa on blood pressure. Cochrane Database Syst Rev 15(8): CD008893.

30. Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, et al. (2012) Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: A systematic review and meta-analysis of randomized trials. Am J Clin Nutr 95(3): 740-51.

31. Antonakoudis G, Poulimenos L, Kifnidis K, Zouras C, Antonakoudis H, et al. (2007) Blood pressure control and cardiovascular risk reduction. Hippokratia, 11(3): 114-49.

32. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, et al. (2014) Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ 349: g4490.

33. Ho MJ, Li EC, Wright JM (2016) Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Cochrane Database Syst Rev 3: 3-CD007435.

34. Liang S, Ping Z, Ge J (2017) Coenzyme Q10 regulates antioxidative stress and autophagy in acute myocardial ischemia- reperfusion injury. Oxid Med Cell Longev 2017: 9863181.

35. Celik T, Iyisoy A (2009) Coenzyme Q10 and coronary artery bypass surgery: what we have learned from clinical trials. J Cardiothorac Vasc Anesth 23(6): 935-36.

36. Gao L, Mao Q, Cao J, Wang Y, Zhou X, et al. (2012) Effects of coenzyme Q10 on vascular endothelial function in humans: a meta-analysis of randomized controlled trials. Atherosclerosis 221(2): 311-6.

37. Tran MT, Mitchell TM, Kennedy DT, Giles JT (2001) Role of coenzyme Q10 in chronic heart failure, angina, and hypertension. Pharmacotherapy 21(7): 97-806.

38. Wang ZY, Liu YY, Liu GH, Lu HB, Mao CY (2018) l-Carnitine and heart disease. Life Sci 194: 88-97.

39. Sosnowska B, Penson P, Banach M (2017) The role of nutraceuticals in the prevention of cardiovascular disease. Cardiovasc Diagn Ther 7 (Sup1): S21–S31.

40. Zordoky BN, Robertson IM, Dyck JR (2015) Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular diseases. Biochim Biophys Acta 1852(6): 1155-77.

41. Dyck J, Schrauwen P (2015) Editorial - Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes. Biochim Biophys Acta 1852(6): 1069-70.

42. Bonnefont-Rousselot D (2016) Resveratrol and Cardiovascular Diseases. Nutrients 8(5): pii-E250.

43. Berrougui H, Grenier G, Loued S, Drouin G, Khalil A (2009) A new insight into resveratrol as an atheroprotective compound: Inhibition of lipid peroxidation and enhancement of cholesterol efflux. Atherosclerosis 207(2): 420–27.

44. Dolinsky VW, Soltys CL, Rogan KJ, Chan AY, Nagendran J, et al. (2015) Resveratrol prevents pathological but not physiological cardiac hypertrophy. J Mol Med (Berl) 93(4): 413–425.

45. Haskó G, Pacher P (2010) Endothelial Nrf2 activation: A new target for resveratrol? Am J Physiol Heart Circ Physiol 299(1): H10–H12.

46. Wongcharoen W, Phrommintikul A (2009) The protective role of curcumin in cardiovascular diseases. Int J Cardiol 133(2): 145-51.

47. Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A (2018) Curcumin as a potential candidate

for treating hyperlipidemia: A review of cellular and metabolic mechanisms. J Cell Physiol 233(1): 141-52.

48. Ganjali S, Sahebkar A, Mahdipour E, amialahmadi K, Torabi S, et al. (2014) Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. Scientific World Journal 2014: 898361.

49. Panahi Y, Hosseini MS, Khalili N, Naimi E, Simental-Mendía LE, et al. (2016) Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomed Pharmacother 82: 578-82.

50. Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A (2014) Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. Complement Ther Med 22(5): 851-57.

51. Ganjali S, Blesso CN, Banach M, Pirro M, Majeed M, et al. (2017) Effects of curcumin on HDL functionality. Pharmacol Res. 119: 208-18.

52. Guo N, Chen F, Zhou J, Fang Y, Li H, et al. (2015) Curcumin Attenuates Rapamycin-induced Cell Injury of Vascular Endothelial Cells. J Cardiovasc Pharmacol 66(4): 338-46.

53. Karimian MS, Pirro M, Johnston TP, Majeed M, Sahebkar A (2017) Curcumin and Endothelial Function: Evidence and Mechanisms of Protective Effects. Curr Pharm Des 23(17): 2462-73.

54. Appendino G, Belcaro G, Cornelli U, Luzzi R, Togni S, et al. (2011) Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. Panminerva Med 53:(3 Suppl 1): 43-49.

55. Karuppagounder V, Arumugam S, Giridharan VV, Remya Sreedhar, Rajendran JC Bose, et al. (2017) Tiny molecule, big power: Multi-target approach for curcumin in diabetic cardiomyopathy. Nutrition 34: 47-54.

56. Schultz H (2012) Retail omega-3s sales to hit $34.7 billion in 2016, report predicts.

57. Mozaffarian D, Wu JH. 2011. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 58(20): 2047–67.

58. Adkins Y, Kelley DS (2010) Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. J Nutr Biochem. 21(9): 781–92.

59. Toft AD, Thorn M, Ostrowski K, Asp S, Moller K, et al. (2000) N-3 polyunsaturated fatty acids do not affect cytokine response to strenuous exercise. J Appl Physiol(1985) 89(6): 2401–16.

60. Massaro M, Scoditti E, Carluccio MA, De Caterina R (2008) Basic mechanisms behind the effects of n-3 fatty acids on cardiovascular disease. Prostaglandins Leukot Essent Fatty Acids 79(3-5):109–15.

61. Cohen MG, Rossi JS, Garbarino J, Bowling R, Motsinger-Reif AA, et al. (2011) Insights into the inhibition of platelet activation by omega-3 polyunsaturated fatty acids: beyond aspirin and clopidogrel. Thromb Res 128(4): 335–40.

62. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ, et al. (2008) Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. Atherosclerosis 197(1): 12–24.

63. Jacobson TA, Glickstein SB, Rowe JD, Soni PN (2012) Effects of eicosapentaenoic acid and docosahexaenoic acid on low- density lipoprotein cholesterol and other lipids: a review. J Clin Lipidol. 6(1): 5–18.

64. Kromhout D, Giltay EJ, Geleijnse JM (2010) Alpha Omega Trial Group n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 363(21): 2015–26.

65. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B (2012) Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 5(6): 808–18.

66. Martino A, Goanta E, Magnano R, et al. (2016) Diets and heart disease. Myths and reality. J Nutritional Health and Food Science 4(2): 1-10.

67. Parihar A, Parihar MS (2018) Bioactive food components in the Prevention of Cardiovascular Diseases. Bioactive Molecules in Food Reference Series in Phyto chemistry.

68. Pranaywal, Wal A, Nair VR, Nath B (2013) A review on nutraceuticals and diet in prevention of cardiovascular diseases. International Journal of Pharmaceutical and Chemical Sciences 2(3): 1273-81.

69. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ, et al. (2004) Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. Am J Epidemiol 160(12): 1223–33.

70. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, et al. (1999) Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 99(6): 779–85.

71. Esposito K, Ciotola M, Giugliano D (2006) Mediterranean diet, endothelial function and vascular inflammatory markers. Public Health Nutrition 9(8A): 1073–76.

72. Willcox DC, Willcox BJ, Todoriki H, Suzuki M (2009) The Okinawan diet: health implications of a low-calorie, nutrient- dense, antioxidant-rich dietary pattern low in glycemic load. J Am Coll Nutr Sup: 500S-516S.