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A COMPREHENSIVE REVIEW: ROLE OF NEUTRACEUTICALS IN MANAGEMENT OF CARDIOVASCULAR DISEASES

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ABSTRACT
Nutraceuticals have received considerable interest due to their presumed safety and potential nutritional and therapeutic effects". The concept of nutraceuticals was gazed from the overview in U.K., Germany and France which reasoned that diet is appraised more profoundly by buyers than practice or genetic elements for accomplishing great wellbeing. In recent years there is a growing interest in nutraceuticals which provide health benefits and are alternative to modern medicine. By utilizing nutraceuticals, it may be possible to reduce or eliminate the need for conventional medications, reducing the chances of any adverse effect. Nutraceuticals frequently have one of a kind substance activities that are inaccessible in drugs. The current article focuses on the need for consuming appropriate diets, health issues surrounding failure to adhere to the known healthy eating models, development of new nutraceuticals/food supplements with novel health benefits, elucidation mechanisms of action of these products, to define and understand the analytical, formulation and regulatory aspects of nutraceutical. This article might go about as an apparatus to side by side with the recent improvements in nutraceutical research.

KEYWORDS: Neutraceuticals, Cardiovascular diseases, Cardiovascular risk factor, Hypertension.

INTRODUCTION

The word neutraceutical was coined in 1989 by Stephen L. Defelice, founder and chairman of the Foundation of Innovation Medicine. Nutraceuticals are products derived from food sources that are purported to provide extra health benefits, in addition to the basic nutritional value found in foods.[1] Depending on the jurisdiction, products may claim to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, or support the structure or function of the body.[2]

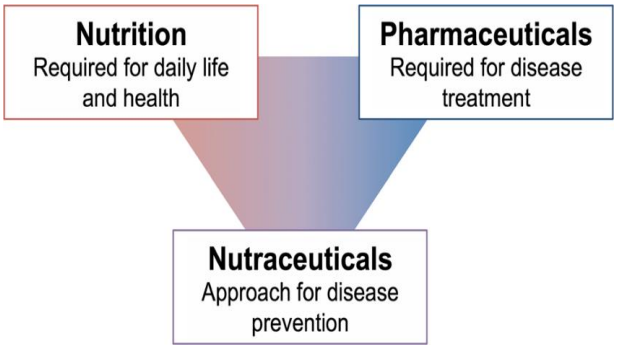

Fig 1: Nutrition, Nutraceuticals and Pharmaceutical.

The cardiovascular disease (CVD) is common, morbid and responsible for about 17.3 million deaths annually worldwide.[3] The modifiable risk factors for CVD include obesity, hypertension, hyperlipidaemia, T2DM, and lifestyle risk factors such as smoking, physical inactivity and dietary factors.[4] The nutritional factors have an important bearing on the cardiovascular 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, and these simple lifestyle interventions open practical, potentially easy and affordable possibilities for population-based strategies for CVD risk reduction.[5]

Several compounds from everyday foods and certain dietary supplements, when judiciously taken, have been documented to protect against the development and progression of CVD.[6] 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.[7]

There are certain dietary patterns and nutritional factors that have the potential to reduce arterial stiffness and improve endothelial function.[8] Whereas general and functional foods, and nutraceuticals play important role in ensuring and preserving CV health, the pharmaceuticals have significant role in CV therapeutics. 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.[9]

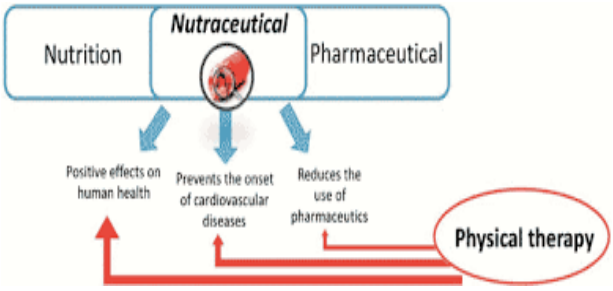

Fig 2: Role of nutraceuticals.

The reasons behind shift towards nutraceuticals are[10,11]

- Health care provider recognize the fact that our heavily processed food supply, coming from crops grown with chemical fertilizers, pesticides, herbicides, and often genetically modified seeds, lacks sufficient nutrients necessary for optimum Health.
- Economically challenged patients.
- Increasing numbers of consumers, concerned about healthcare costs.
- Dissatisfied with pharmaceutical agents in promoting health, are turning to nutraceuticals to improve their health and prevent chronic disease.
- People believing more in prevention than a cure.
- People who have chronic diseases and have found no solution in allopathic medicines.

With few exceptions, the U. S. Food and Drug Administration (FDA) has not approved nutraceuticals for health benefits or disease prevention; nonetheless, the manufacturers of nutraceuticals have been touting them as health-promoting agents.

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'. 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 3).

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.[12]

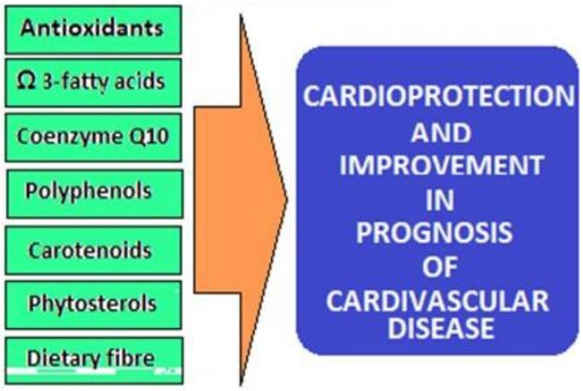

Fig 3: Nutraceuticals for Protection and Maintenance of CV health.

Polyphenols: Polyphenols include flavonoids, phenolic acids, stilbenes and lignans. They are found in fruits, vegetables, cereal and legumes, and in beverages produced from plant products such as tea, coffee, wine and cocoa.[13] The phenolic compounds found in grapes, include anthocyanins, flavanols, flavonols, phenolic acids and stilbenes including resveratrol (3,5,4'-trihydroxy-transstilbene). Resveratrol is also present in small quantity in cranberries, blueberries and peanuts. Polyphenols also influence plasma lipid concentrations and consumption of grapes and grape juice has been associated with improvement in HDL-C levels.[14] 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.[15]

Phytosterols: Plant sterols/stanols are phytosterols, present in a range of plant products including various fruits and vegetables, cereals, seeds and nuts. 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.[16]

Spirulina and Soy Nutrients: Spirulina (Cyanobacterium) is a rich source of protein, vitamins, minerals, carotenoids and phycocyanins. 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. 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.[17]

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. 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 cheaters, 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.[18]

Omega 3-fatty acids (Ω3Fas): Ω3FAs are among the most commonly prescribed supplements with a worldwide market. 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 signalling favourably. Further, the integration of Ω3FAs into cell membrane in animal studies has been related to changes in H-Ras signalling protein and suppressed protein kinase C-theta signalling.[19] Ω3FAs also exert anti-inflammatory properties through different proposed mechanisms. They suppress the production of interleukin-2 and inhibit lipopolysaccharide-induced inflammation.[20] 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, and 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 lymphocyte.[21]

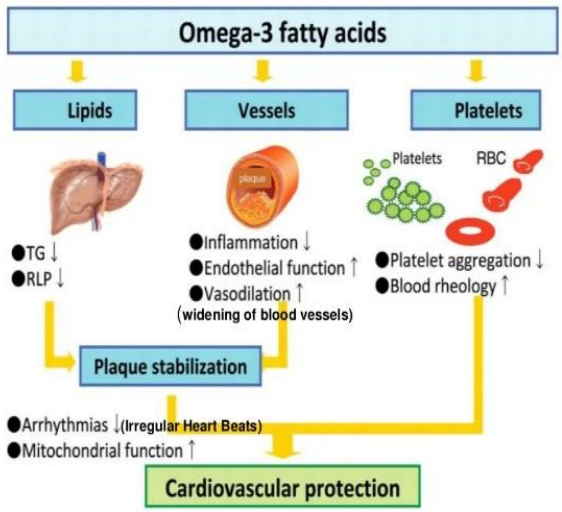

Fig.4: Mechanism of Omega-3 fatty acids.

Ω3FAs may also lead to improved endothelial function by promoting the release of nitric oxide from endothelial cells.[22] 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.[23] 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.[24] 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. 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 accelerating triglyceride clearance from the plasma.[25] But with regard to their effects on lipoproteins, randomized controlled trials have yielded mixed results. Some studies have shown the effect of omega-3 fatty acid supplements on improving flow-mediated arterial dilation and improvement of the mechanical function of the heart.[26] 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.[27] 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.[28]

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. 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. Several well-designed human studies have documented curcumin's ability to combat chronic inflammation. 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. Another study has highlighted that curcumin supplementation has a lipid modifying effect. 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. 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 and appears to improve endothelial function and retards development of diabetic microangiopathy and cardiomyopathy.[29,30]

Fig.5: Role of Curcumin in CVS Disease.

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. 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 cardio toxicity in animal studies. Further, animal studies have shown that RES improves cardiac function and survival when co-administered with the treatment for established HF.[31] 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 remodelling, endothelial, diastolic and systolic functions, and myocardial energy metabolism.[32]

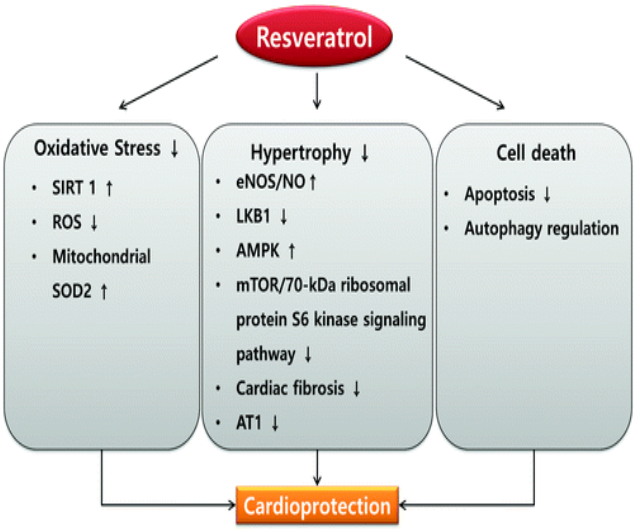

Fig.6: Mechanism of Resveratrol.

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. 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, and an improvement of calcium cycling and an inhibition of hypertrophic gene expression. 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.[33]

Coenzyme Q10 (CoQ10)

- **Dyslipidemia and Atherosclerosis:** The nutraceuticals with the potential to modify the plasma lipid profile favourably can reduce the CVD risk. The mechanism by which sterols/stanols reduce LDLC is associated with a reduction in intestinal absorption of cholesterol, upregulation of hepatic LDL receptors and reduced production of endogenous cholesterol. 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 Edeficient 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 by monocytes. The supplementation of CoQ10 significantly decreases the expression of integrin, another mechanism for the inhibition of atherosclerosis by coQ10. In view of the detrimental role of free radicals and reactive oxygen species 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.
- **Hypertension:** Hypertension is an important modifiable risk factor for CVD and lowering blood pressure reduces CV risk. Polyphenols consumption of flavonoid-rich fruits and vegetables may lower blood pressure. CoQ10 also has BP lowering effect.
- **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.
- **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. Pretreatment 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. 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.

- **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. 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, and diseases of the heart valves, cardiomyopathy, and congenital heart diseases. The supplemental CoQ10 appears to improve symptoms and prognosis in heart failure.[34]

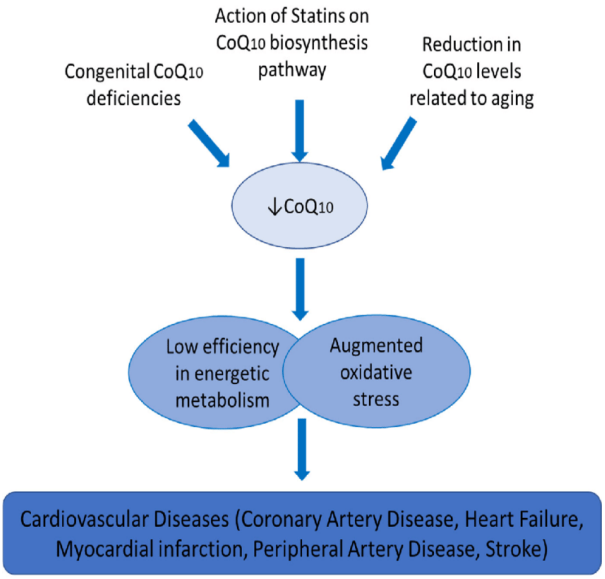

Fig 7: Mechanism of Coenzyme Q10 (CoQ10).

MODIFYING CVD AND RETARDING CV AGING

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 (Fig. 8).

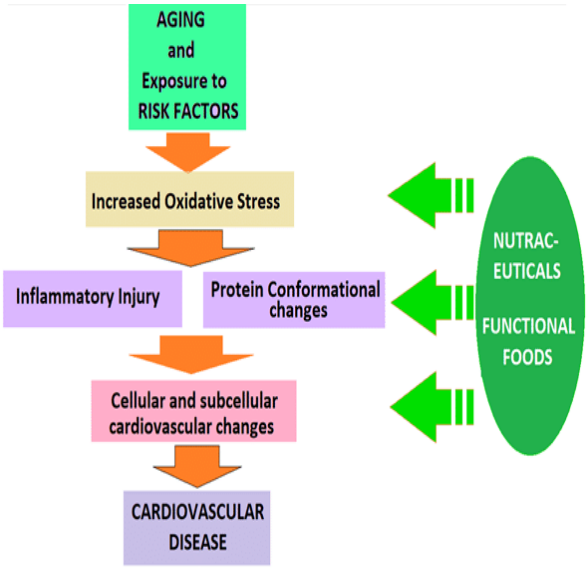

Fig 8: Nutraceuticals and Functional foods and their impact on CV Health.

CONCLUSION

Nutraceuticals provide all the essential substances that should be present in a healthy diet for the human. From the above study it can be concluded that various chemical constituents from natural sources can be obtained and prepared into various optimized, safe, stable formulations for the treatment and diagnosis of cardiovascular diseases. 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. 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 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. Results of study indicate that demand and consumption of nutraceuticals are now going on increasing due to safety, therapeutic efficacy, and stability of formulations.

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