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Review

# Bioactive Functional Foods for Cardiovascular Diseases

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**Abstract:** Cardiovascular Disease (CVD) is a chronic pathological disorder regarded as a serious health concern round the globe. It is a multifactorial disease, with a range of various causative agents, among that dietary factor is considered the most important and may to a large degree determine CVD risk. Unfortunately, it has been less widely investigated. This review outlines the general aspects of CVD, epidemiology, risk factors and emphasizes the use of functional foods for the prevention and treatment of cardiovascular diseases. It highlights the importance of various foods used in daily routine and their activity against CVDs particularly. Recent studies have investigated the consumption of various foods including soybeans, oats, psyllium, flaxseed, garlic, tea, fish, grapes, nuts, fruits, vegetables, chocolate and sterol ester enhanced margarine etc., on CVD patients and their role as a natural/socioeconomic cure over chemical based drugs. Adequate intake of these foods on a constant basis, help in decreasing the risk of cardiovascular disease by several potential mechanisms e.g., lowering blood lipid levels, improving arterial compliance, reducing low-density lipoprotein oxidation, decreasing plaque formation, scavenging free radicals and inhibiting platelet aggregation etc. This review not only emphasizes the dire need of exploring safe functional foods against alarming rise of CVD cases, but also provides future insight in the use of bioactive food components in CVD therapeutics, as they are cost effective and have fewer side effects.

**Keywords:** Functional Foods, Bioactive Compounds, Cardiovascular Disease

## Introduction

Cardiovascular diseases are one of vast group of diseases involving the heart and blood vessels. Cardiovascular diseases are still the leading cause of mortalities in the world (Sacco *et al*., 2016), in 1990 the mortality was 12.3 million (25.8%) and in 2016 it reached up to 17.6 million deaths (Lozano *et al*., 2012; Abubakar *et al*., 2015; Naghavi *et al*., 2017). The categories of CVD include coronary artery diseases (plaques build up inside the coronary arteries) and angina leading to heart attack (blockage of arteries). Other types involve the stroke, hypertensive heart diseases, heart failure, cardiomyopathy, heart arrhythmia, venous thrombosis, rheumatic heart disease, congenital heart diseases and valvular heart diseases. Coronary artery disease and stroke are responsible for 80% of CVD deaths in males and 75% in females (Berrington de Gonzalez *et al*., 2010). According to statistics by American Heart Association in 2016, one in every citizen in US was victims of CVD in 2013 (Mozaffarian *et al*., 2016). Initiation and progression of atherosclerosis (hardening of arteries) is the basis of many cardiovascular diseases, e.g., stroke, coronary artery disease and peripheral artery disease (Keenan *et al*., 2011; Herrera *et al*., 2020). The current theory of atherosclerosis formation postulates that endothelial injury by classical CVD risk factors (smoking, high blood pressure, elevated blood cholesterol) leads to trapping of LDL cholesterol within the arterial wall, which then oxidized and further activates the endothelium to secrete cytokines. This condition attracts circulating mononuclear cells expressing receptors for these cytokines and initiates a self-perpetuating inflammatory process. It causes the abnormalities in lipoprotein metabolism, chronic inflammation, oxidative stress and thrombosis (Singh *et al*., 2012).

**Table 1:** Risk factors of cardiovascular diseases (Berry *et al*., 2012; Basharat, 2020)

| Non-modifiable metabolic | | Life style | Novel |
|---|---|---|---|
| Advancing age | Obesity | Physical | Elevated homeostatic factors |
| Male gender | Metabolic syndrome | Activity | Elevated inflammatory marker |
| Family history | Diabetes | Smoking | Small dense LDL-C |
| | Hyperlipidemia | Diet | Elevated lipoprotein level |
| | - Hypertension | | Elevated homocysteine level |
| | | | Oxidative stress |
| | | | Endothelial dysfunction |

Currently, the conventional cardiovascular risk factors (Table 1) have been broadly investigated, among them the dietary factors are considered very important and it may lead to determine high CVD risk factors such as blood pressure and dyslipidemia (Meier *et al*., 2019). As it is reported in 2011, High blood pressure resulted in 13% of CVD deaths, of which tobacco contributed 9%, diabetes 6%, lack of exercise 6% and obesity 5% of global deaths (Emerging Risk Factors Collaboration, 2011; Danaei *et al*., 2011).

Extensive epidemiologic studies suggest that diet habits and healthy life style could have a preventive effect on chronic illnesses like cardiovascular disease and on the other hand, poor habits exacerbate them. According to the report by World Health Organization (WHO), those populations consuming a large amount of fruits; vegetables as well as sea foods, were less prone to CVD cases (Meier *et al*., 2019). This finding brought a revolution in people's diet, they became more concerned about their daily diet intake that not only fulfill their nutritional demand but also down regulate the level of cholesterol, thus ultimately reducing the risk of cardiovascular diseases. As the name indicates, the term *Functional food* encompasses the food which is not only nutritionally important for our body but it is also involved in resolving diseased state of the body. It has various mechanism of actions, such as lowering elevated blood Total Cholesterol (TC) and Low-Density Lipoprotein (LDL) cholesterol, beyond the supply of basic nutrition (Boussageon *et al*., 2011). Thus, this review highlights the remarkable role of functional food, the active food components and their mechanism of action against CVD. The use of phytomedicine, plant and microbe-based food can play a feasible and socioeconomically beneficial role against chronic illnesses including CVD, compared to conventional therapy accompanied by poor health benefits. Thus, this review emphasizes the dire need for clinical trials investing in tremendous range of mentioned functional foods/nutraceuticals and directs researchers to explore more functional foods or bioactive food components against CVD and other chronic disorders as well.

## Functional Food as Prevention and Treatment

In 2014, American Dietetic Association emphasizes that functional food must have a beneficial effect, even when consumed as a part of a diet at regular basis. It must be included as a whole, fortified, enriched or enhanced food forms (Lackland *et al*., 2014). Oxidative stress is one of the major causes of physiological disorders, such as cancer, diabetes and CVDs. Free radicals are continuously being produced during normal cellular metabolism as a consequence of leakage of electrons from electron transport chain to outside, that happens in different circumstances, such as part of cell signaling, homeostasis and cellular defense against invading pathogens (Kamiloglu *et al*., 2014; Dibanda *et al*., 2020). The antioxidant combat can be achieved either endogenously or exogenously by food. Thus, functional foods show significant benefits by releasing the Phytochemical, vitamins and minerals that is thought to be able of scavenging the free radicals produced during oxidative stress (Granato *et al*., 2020). Thus, they reduce the risk of CVD as well as it is beneficial for preventing and treating the CVD (Liu *et al*., 2012) and other disorders. This review summarizes, with an emphasis on clinical findings, recent literature supporting the efficacy for various functional foods in CVD risk reduction and treatment: Soybeans, oats, psyllium, flaxseed, garlic, ginger, tea, dark chocolate, fish, grapes, nuts, fruits, vegetables and stanol and sterol ester-enhanced margarine etc.

### *Soy Proteins*

The obesity and CVD are the common physiological disorders in the world (Basharat, 2020). Food and Drug Administration (FDA) approved the soy protein as a functional food to reduce the risk of cardiovascular diseases a long ago. A meta-analysis based on 46 studies by FDA proved that soy protein confers heart protective role by decreasing significantly total cholesterol and LDL in the blood of adult population (Blanco Mejia *et al*., 2019). It was observed that the vegetarian Chinese and Japanese population consuming soy-protein in their diet, have a low cholesterol, LDL-C, low ischemic and cerebrovascular events (Food and Drug Administration, 1999). Soy-protein contains plant substances like isoflavones similar to estradiol, is responsible for lowering of cholesterol. In addition to isoflavones, soy-proteins contain saponins, phytic acids, trypsin inhibitors, fibers and globulins. These chemicals make the soy protein a beneficial functional food as it lower the blood lipids, improved arterial compliances, lipid metabolism and reduce the LDL-oxidation (Gil-Izquierdo *et al*., 2012).

These findings direct the addition of soy-protein in daily diet, as it reduces the risk of the onset of diseases as well as it has a therapeutic potential. FDA set the daily dose of soy-protein as 25 g/day. Some data also suggest that even less than 25 g may effectively lower the blood lipids. 51 premenopausal women consumed the 20 g soy protein per day in 5 weeks resulted in 7% reduction in LDL and 6% in total cholesterol (Hodis *et al*., 2011). In another study it is revealed that the significant level of isoflavones is involved in down regulation of cholesterol. 13 cardiac patients who consumed three different levels of isoflavones (10, 64.7 and 128.7 mg), only the highest intake of isoflavones significantly lowered LDL cholesterol by 7.6 to 10% ($P<0.05$) (Wofford *et al*., 2012).

Food enriched in soybean has been reported conferring lipid lowering effect and thus reducing CVDs and obesity as well. Soya bean and soy based products have bioactive components such as, globulin proteins including glycinin and beta-conglycinin, oligosaccharides, phytosterols (campesterol, sitostanol and sitosterol) and anti-oxidant compounds. They have been reported to confer health promoting beneficial effects on both human and animal health. A supplemented product of soybean protein, glycine max has been found effective against CVDs by improving triglycerides and lipids profile and obesity (Basharat, 2020).

## *Oat Soluble Fiber*

Oat soluble fiber is also known as viscous soluble fibers, contains β-glucan (Joyce *et al*., 2019). It reduces the LDL in the blood and confers protection against CVDs. It also contains phenolic compounds, xyloglucan, arabinoxylan, insoluble fiber, lipids, protein, vitamins and minerals. It reduces the blood lipid either by reducing the absorption of cholesterol and bile acids or by delaying the lipid digestion. Another mode of decreasing cholesterol in blood was found rise in thickness of gut contents (Wolever *et al*., 2010), which increases the excretion of cholesterol and bile salts from the gut. Now a day, large amount of research has indicated that not only the viscous properties of β-glucan confer cholesterol lowering impact but also there is a role of gut microbiota in maintaining the cholesterol homeostasis in the gut (Jonsson and Bäckhed, 2017; Joyce *et al*., 2019). The Oat meal or Oat β-glucan regulates the gut microbiota as well. The gut microbes metabolizes the bile acids (precursor of which is cholesterol) and hence increases the excretion of cholesterol from the body along with the faces, thus reducing the serum cholesterol level in experimental animals, humans and in-vitro fermentation systems (Wolever *et al*., 2010). A microbe centered review suggested that signaling of bile acids via farnesoid X receptors also influence the transport of cholesterol from gut into the blood, it increased the *de novo* synthesis of bile acids and increased the Trans intestinal cholesterol excretion (Joyce *et al*., 2019). Moreover the microbes in the gut also produce short chain fatty acids that also interfere with the metabolism of cholesterol (Ryan *et al*., 2015) via production of short chain fatty acids, degradation of cholesterol or microbial exopolysaccharides (Joyce *et al*., 2019). Overall these mechanisms altogether regulate the cholesterol homeostasis in the host and confer protection against heart diseases. Some studies on pigs fed with β-glucan also suggested that changes in cholesterol metabolism (lowering of serum cholesterol) were in agreement with the changes in gut microbiota (Begley *et al*., 2006). Fibers also have a function in preventing the constriction of arteries by reducing the LDL oxidation, thus work as a preventive and treatment agent for CVD disease (Othman *et al*., 2011).

Clinical study reveal that 3 g of β-glucan is required to reduce the 5% serum cholesterol which is approximately equals to 60 g of oat meal and 40 g of oat bran. FDA approved the use of 60 g oat meal per day either in one serving (60 g oat meal = 3 g β-glucan) or in different servings (20 g oat meal = 1 g β-glucan). It will reduce the total cholesterol and LDL by 2% and act as a treatment of CVD (Matthews *et al*., 2011).

## *Psyllium Seed Husk*

Another viscous soluble fiber that has been shown to be very effective in lowering blood lipids is derived from the husk of the blonde psyllium seed, defined as the dried seed coat (epidermis) of the seed of *Plantago ovata*. Like soy-proteins, it also reduces the LDL cholesterol by lowering the oxidation (Ahmadi *et al*., 2012a). The FDA determined that the effective daily intake of soluble fiber from psyllium associated with a significant reduction in serum lipids was 7 g/day (equivalent to 10.2 g of husk) and would be expected to reduce total cholesterol 4 to 6% and LDL cholesterol, 4 to 8% (Smith and Tucker, 2011). The efficacy of psyllium in the treatment of hypercholesterolemia, even in the treatment of individuals with mild-to-moderate hypercholesterolemia who have type 2 diabetes, appears clear. In another study, 163 subjects treated with psyllium results in reduction of LDL cholesterol by 5-7% (Ahmadi *et al*., 2012b). Thus, it is the functional food that fills the gap between the diet and drug therapy.

## *Flaxseed*

Flaxseed is a unique plant contains two significant components: (1) α-linolenic acid, mega-3 fatty acid; and (2) the lignans, a primary class of phytoestrogens. The α-linolenic acid content of flaxseed is the highest of any seed oil (57%) and the lignan content of flaxseed is 800 times higher than in 66 other plant foods, gives it a unique property. It shows a potential benefit for cardiovascular diseases, hypertensive, cancer and hormone replacement therapy (Khalesi *et al*., 2015). The antiesterogenic activity gives it a therapeutic effect used by the cancer patients as well as an alternative to hormone replacement therapy in women of Australia, United Kingdom and New Zealand (Rodriguez-Leyva *et al*., 2013). The research was conducted on 29 hyperlipidemic subjects (22 men and 7 postmenopausal women), consumed 20 g of fiber per day in 3 weeks, results into 4.6% TC and 7.6% LDL reduction with highly significant P value = 0.001 (Caligiuri *et al*., 2014). Thus, it is also being used as a treatment of cardiovascular diseases as it reduces the blood pressure, LDL cholesterol and total cholesterol.

## *Mushrooms*

Mushrooms are considered as an excellent source of antioxidants, extremely valuable for health promotion and disease prevention including heart diseases protection. Thus, many mushrooms species are available in market as functional food as well as nutraceuticals for medical health benefits (Reis *et al*., 2017). It has a large number of antioxidant compounds e.g., phenolic compounds, Vitamin E and vitamin C and carotenoids (Ferreira *et al*., 2009). Besides, mushrooms have unsaturated fatty acids, proteins and amino acids like leucine, valine and lectins, carbohydrates, mainly polysaccharides e.g., lentinan (Giavasis, 2014). Many studies reported direct association between mushroom extract and its bioactive compounds mainly phenolic compounds, thus such studies suggested the use of mushrooms in the form of various formulations as functional foods or its extract as a natural source of antioxidants in human food (Kimatu *et al*., 2017). Most of the studies on mushrooms are based on in-vitro assays, however some in vivo studies also reported the anti-oxidant potential of mushrooms, such as a study based on the ethanol extract of a mushroom (*Agaricus bisporus*), rich in gallic acid, catechin, ferulic acid, protocatechuic acid, caffeic acid and myricetin, involved feeding this extract to mice for 30 days on a daily basis (Liu *et al*., 2013). They found increase activity of antioxidant enzymes in the serum, liver and heart of mice. Similar findings were reported about *Pleurotus* species of mushrooms on the rats fed with the extract (200 mg/kg of body weight) for 4 days (Liu *et al*., 2013). Some of these studies recognized these anti-oxidant properties to were due to lectins, rutin, chrysin, β-carotene as well as α-tocopherol, total phenolic compounds and ascorbic acid. In rats induced with oxidative stress by $CCl_4$ treatment, mushrooms (specifically *Pleurotus ostreatus*) have been found to improve the activity of anti-oxidant enzymes and decreased MDA in blood serum and in vital organ (Jayakumar *et al*., 2008). It was found that insoluble/non-starch polysaccharides from these mushrooms played important anti-oxidant role. Apart from most studied anti-oxidant, immune-modulatory and anti-tumor properties, mushrooms also confer anti-inflammatory, anti-diabetic and hypocholesterolemic effects which ultimately confer cardio-protective role (Valverde *et al*., 2015). All of these studies spotted light on the importance of mushrooms to use as functional foods and nutraceuticals. On the basis of these bioactive compounds, mushrooms have a great potential in food market, but there are some problems and concerns regarding their safety, standardization, efficacy and regulation and mode of action (Jayakumar *et al*., 2008; Wasser, 2014).

## *Garlic*

Garlic (*Allium sativum*) is ranked as the top herbal product used by all over the world. Its beneficial or health promoting effects are vital to treat atherosclerosis and heart diseases. This is the best functional food as far as known yet. The intact garlic bulb contains odorless amino acid known as alliin, when the garlic is crushed the enzymes allinase releases and convert the alliin into allicin. Allicin is the compound which gives a characteristic odor to the garlic, then spontaneously, the allicin decomposes into many sulphur containing compounds (Beato *et al*., 2011). These compounds give it a medicinal property by lowering the cholesterol level and blood pressure in cardiovascular patients (Omar and Al-Wabel, 2010). The garlic has excellent ability to lower the cholesterol level in blood, maintaining lipid profile, reduce LDL oxidation, increase the fibrinolysis and decrease fibrinogen level in the blood (Sobenin *et al*., 2019).

A study conducted in 60 cardiac rehabilitation patients who received either two garlic capsules daily (each capsule contained ethyl acetate extract from 1 g peeled and crushed raw garlic) or placebo for 3 months showed a significant reduction in serum TC and triglycerides as well as an increase in HDL-cholesterol and fibrinolytic activity. FDA sets two capsules of garlic as a daily dose to reduce the risk as well as for treatment of the CVD (Ried *et al*., 2013). The lipid lowering effect of garlic has been most studied, the garlic oil, of which the bioactive component Diallyl disulfide, has been found to have effect as statins (Badr and Arafa, 2020). It was reported to inhibit the 3 Hydroxy 3 Methylglutaryl CoA (HMG CoA) reductase enzyme. It keeps the inactivated state of this enzyme by forming internal protein disulfide bridges that become unavailable for reductase (dithiothreitol) enzyme (Badr and Arafa, 2020). The aged garlic extract contained another active agent with antioxidant as well as hypolipidemic properties, S-allyl cysteine that reduced the blood cholesterol level, significantly reduced the level of triglycerides, ALT, AST and glutathione activity in the rats (Tran *et al*., 2018; Badr and Arafa, 2020). These effects were reported to be higher for the garlic extract rather than S-allyl cysteine alone, thus there must be some more bioactive ingredients with lipid lowering and antioxidant/anti-inflammatory properties in the garlic extract (Badr and Arafa, 2020; Raji *et al*., 2019).

Another study reported the effect of garlic oil and onion oil on blood lipid profile of hyperlipidemic rats (Yang *et al*., 2018). In this study, rats received volatile oil extract of garlic and onion for 60 days, they reduced the body weight, fats, total fats, total cholesterol and LDL-C and improved HDL-C, thus both of mentioned oils improved blood lipid profile and decreased body weight of rats effectively (Yang *et al*., 2018).

Apart from hypolipidemic effects, garlic also confers anti-hypertensive effects by inhibiting enzyme that converts angiotensin, reduces prostanoids that causes vasoconstriction (Asdaq and Inamdar, 2010).

The evidences suggest the use of garlic as a therapy against atherosclerosis and prevention (Sobenin *et al.*, 2019).

## *Ginger*

Ginger (*Zingiber officinale* Roscoe) has been cultivated for medicinal and cooking purposes for at least two millennia. It contains several hundred valuable compounds. It is demonstrated that ginger has a potential to reduce the heart related issues (Shoaib *et al*., 2016). It inhibits the production of NO, inflammatory cytokines, Cyclo-Oxygenases (COX) and Lipoxygenases (LOX) which oxidizes the arachidonic acid and causes the arterial inflammation (Mojani *et al*., 2014). Ginger has great antioxidant ability, scavenges the free radicals and protects the cell membrane lipids from oxidation (Bak *et al*., 2012). A study evaluated the effect of garlic and ginger oil alone and along with exercise on post-menopausal women (Basharat *et al*., 2019). It demonstrated a reduction in body weight, % of body fat, body mass index, the cholesterol level, LDL and triglyceride significantly as a result of combination therapy of exercise and garlic as compared to either treatment alone. Moreover, the garlic demonstrated superior effects as compared to ginger alone. Several studies reported lipid lowering effect of ginger (Shoaib *et al*., 2016); a meta-analysis based study reported the favorable effect of ginger on Triglycerol level and LDL-C, while having no effect on TC and HDL-C. Moreover, the low dose of ginger was found to have greater lowering influence on total cholesterol and Triglycerols (Pourmasoumi *et al*., 2018).

The study demonstrated that 4g of ginger given daily for 4 months to coronary artery disease patients reduces the serum total cholesterol, LDL, triglycerides and phospholipids, reduced atherosclerotic lesions and raised HDL as effectively as conventional hypolipidemic drugs. It acts on the liver, reduces the cholesterol biosynthesis and increases its excretion (Saptarini, 2013). Another study suggested that the minimum effective dose of ginger is 1 g, with a linear increase in efficacy with the increase of dose. In principle, ginger exhibits safer therapeutic effect than conventional cardiovascular drugs since its side effects to date are negligible.

## *Dark Chocolate*

Cocoa (*Theobroma cacao*) is enriched with flavonoid, responsible for preventing and treating the cardiovascular disease. Flavonoid improves the NO-dependent vasorelaxation, arteries dilation as well as reduces the blood pressure and LDL level (Ried *et al*., 2017). Furthermore it was found that it reduced the serum cholesterol level, meanwhile it raised the HDL-cholesterol by reducing the oxidation of LDL. Another study revealed that white chocolate doesn’t contain the flavonoid and thus show no response in CVD prevention and treatment (Katz *et al*., 2011).

A study on consumption of dark chocolate and serum level of liver enzymes and the risk of cardiovascular diseases, found that 81% of people consuming chocolate looked younger, physically more active and with fewer chronic illnesses. Chocolate consumption was found inversely associated with risk factors of cardio metabolic disorders, e.g., liver enzymes and insulin resistance (Alkerwi *et al*., 2016). Dark chocolate has low degree of absorption into intestine and hence low bioavailability, thus, lycosomal formulation of dark chocolate and Astaxanthin improved the signs of oxidative stress and hypoxia in aging population as indicated by blood markers (Petyaev *et al*., 2018). There are growing evidences reporting numerous health benefits of dark chocolate, it includes not only protection against CVDs but also maintain homeostasis, cognitive and brain development. Dark chocolate and raw cocoa powder has been reported to be most beneficial for the health as compared to milk added chocolates which reduces the bioavailability of flavanols. Many biological health benefits of cocoa derived products are mainly because of alkaloids and flavanols, which are enriched in dark chocolate and cocoa powder. Many in-vitro and in-vivo studies revealed the anti-oxidant potential of cocoa based products on signaling pathways, NO production and endothelial cells function. Dark chocolate currently is at center of scientific research because it has not only flavanols and alkaloids, but also fatty acids, polyphenols, amino acids and microelements as well.

## *Tea Flavonoid*

Tea is the second most widely used beverage after water. Tea production is in million tones, with black tea

(76%), green tea (22%) and oolong tea (2%) in total (Cao *et al*., 2019). Green tea is derived from fresh dry leaves by steaming and drying at high temperature in a process that avoids oxidation of the polyphenolic compound (Bogdanski *et al*., 2012). These compounds comprise up to 30% of the total dry weight of fresh tea leaves and include flavandiols, flavonoids, phenolic acids and flavonols (commonly known as catechins). The four major green tea catechins are Epigallocatechin-3-Gallate (EGCG), Epigallocatechin (EGC), Epicatechin-3-Gallate (ECG) and Catechin (EC) (Cao *et al*., 2019). During the manufacture of black tea, fully dried tea leaves are subjected to a full fermentation process, during which the polyphenolic compounds are extensively oxidized. Thus, catechins are reduced to only 3 to 10% of the remaining solids while bisflavanols, the aflavins, other oligomers and the arubigins are formed, the latter accounting for more than 20% of the remaining solids. Oolong tea is a partially fermented tea product (van der Hooft *et al*., 2012).

The emerging evidences explain its efficacy against cancer and the heart diseases as well (Yuan, 2013). Study found that consumption of 1 cup of tea per day or more reduced the risk of MI by 44% in 340 cases compared with age, sex and community-matched non–tea-drinking controls. Moreover, tea consumption also reduces the aortic atherosclerosis. The reported odds ratio for developing severe aortic atherosclerosis decreased from 0.54 to 0.31, with the daily consumption of 1 to 2 cups of tea to the consumption of 4 or more cups per day, respectively (Hartley *et al*., 2013).

Some epidemiological studies revealed the protective effect of tea bioactive compounds in reducing CVD risk. A study demonstrated that flavonoids from tea showed strong anti-oxidant effect in reducing risk of CVD in dose dependent fashion, with 100 mg/day intake of tea flavonoids decreased the mortality rate due to CVD by 4% (Grosso *et al*., 2017). Moreover, It has been found that intake of tea flavanoids was inversely associated with CVD mortality the data from Department of Agriculture, United states demonstrated 0.34 HRs (Ivey *et al*., 2015). Apart from it, Polish community was found with high intake rate of polyphenols mainly derived from tea and coffee (Grosso *et al*., 2014). Further studies exhibited high tea intake and reduced CVD cases among same polish community. A cohort study on 700 Dutch men with the age of 65 to 84 years, intake of epicatechin among CVD patients was associated with reduced death rate due to heart diseases (Dower *et al*., 2016). Similarly a case control study conducted on Japanese men of middle age indicated that high blood serum level of EGCG was associated with decrease stroke rate among non-smoking individuals, with the OR of 0.53 at CI of 95% (Ikeda *et al*., 2018).

Oxidative stress has been found directly associated with the chronic ailments, including CVDs. Green tea is rich in polyphenols, glutamine, theanine and caffeine which were found to reduce the post stroke depression among mice and reduced oxidative stress and effectively modulated the defense (Di Lorenzo *et al*., 2016). Moreover EGCG were found to reduce oxidative stress in mice via MAPK and ERK pathway (Yang *et al*., 2015). Furthermore EGCG was found to reduce oxidative stress in myocardial muscles and free fatty acids in blood thus stopped the heart failure rate in mice induced with heart failure (Oyama *et al*., 2017). Theanine was also proved to protect H9c2 cells from oxidative damage by increasing the antioxidant capacity such as increasing SOD and glutathione peroxidase, decrease in ROS level and NO level (Li *et al*., 2018).

All kinds of tea, like black tea, green tea and white tea along with their bioactive components as catechins, theanine, EGCG possess outstanding protective effects against CVD cases. The mechanism of actions involve decrease in blood lipid level, improvement of ischemia/reperfusion injury and endothelial cell's functions, decreasing oxidative damage and associated inflammation, as well as the safety of cardiomyocytes.

### *Nuts*

Different types of nuts are studied as a functional food such as walnut, almonds, hazelnut, pecans and olive oil. Nuts are complex foods containing cholesterol lowering mono and polyunsaturated fatty acids, arginine (a precursor to the vasodilator nitric oxide), soluble fiber and several antioxidant polyphenols. The first study that involved mixed nuts (almonds, hazelnuts, or pecans) involved 12 hyperlipidemic women in a crossover design that lasted for two 4 week periods. Two tablespoons of almonds, hazelnuts, or pecans per day was consumed by the subjects, thus 13% total cholesterol, 16% LDL reduction was observed. Only walnut diet lowered the triglycerides by 8% and very low-density lipoprotein by 12% (Orem *et al*., 2013). A clinical trial was done for 3 months on 772 participants, diet enriched with virgin olive oil, walnuts and almonds were given to them. These nuts differ in fatty acid and micronutrient composition. Walnuts have a high content in Polyunsaturated Fatty Acids (PUFAs), particularly linoleic acid and α-linolenic acid, n-3 fatty acid, while almonds are rich in MUFA. Whereas both nut types contain sizable amounts of phenolic compounds, walnuts are particularly rich in γ-tocopherol, while almonds contain abundant α-tocopherol and are richer in phytosterols (Choudhury *et al*., 2014). The results of this experiments is clearly explained in the Fig. 1.

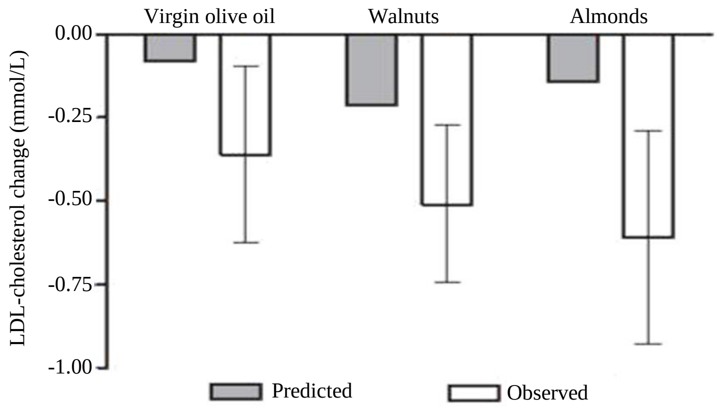


**Fig. 1:** Comparison of LDL cholesterol reduction by olive oil, almond and walnut (Damasceno *et al*., 2011)

A review based on interventional and observational studies from past 25 years indicated that nut intake conferred protection against CVDs, fatal as well as non-fatal heart diseases, sudden death because of heart attacks (Bitok and Sabaté, 2018). While a relatively weak protective effect was found against strokes. The nuts intake conferred protection against CVD basically by improving lipid profile as well as apolipoprotein profile in the blood. Further evidences reported other mechanisms of protection, such as decreasing inflammation and oxidative stress and refining the function of endothelial cells. Various bioactive compounds found in nuts impart crucial CVD protective role which are phytosterols, unsaturated fatty acids, phenolic compounds and L-arginine. Another cohort study conducted in Spain, on 7447 individuals with high CVD risk, were fed with olive oil supplemented Mediterranean diet, nuts supplemented Mediterranean diet and control group fed with reduced fat intake (Estruch *et al*., 2018). After 4.8 years of study, it was observed that Mediterranean diet supplemented with either nuts or extra virgin olive oil, confers maximum protection against major cardiovascular (stroke, myocardial infarction, or death from cardiovascular causes) events (Estruch *et al*., 2018).

A larger than predicted hypocholesterolemic effect of nut-enriched diets indicated that the constituents responsible for this must be other than fatty acids, such as fiber, plant protein, tocopherols, phytosterols and possibly other bioactive components. Almond rich diet reduces the LDL cholesterol more than other two nuts. This diet is recommended as a treatment for the CVD patients (Berryman *et al*., 2011).

## *Grapes, Grape Juice and Red Wine*

The grape juice in raw form may confer a lot of healthy effects, including the cardio-protective effect and curing CVDs. The bioactive compounds in grape juice influence on blood pressure, oxidative stress and inflammation, formation of fatty streaks, endothelial functioning and blood glucose level. Studies exhibited the effect of bioactive compounds in grape juice on LDL cholesterol, atherosclerosis and blood lipid profile as well (Ahmadi *et al*., 2019).

Over the last 20 years, numerous studies have been launched in an effort to explain the observation that the French population has a lower incidence of CVD than other Western populations despite the fact that they consume more fat (Ahmadi *et al*., 2019). In 1979 it was known as French paradox, the link between the wine intake and cardiovascular diseases is opposite. The mechanism behind the preventive effect of more grapes against the CVD is associated with its phenolic antioxidants (Li and Förstermann, 2012). Grapes contain a variety of antioxidants, including catechin, epicatechin, resveratrol and proanthocyanidins. Proanthocyanidins are present primarily in the seeds, whereas resveratrol (3, 4', 5 trihydroxystilbene), a naturally occurring phytoalexin, is present mainly in grape skin at concentrations ranging from 50 to 100 mg/g (Hügel *et al*., 2016). Resveratrol may contribute to the heart health, other beneficial effects of grapes include, inhibition of lipid peroxidation, free radical scavenging activity, inhibition of platelet aggregation and vasorelaxation (Xia *et al*., 2010; Manna and Maiti, 2016) in humans.

In one study of 15 adults with angiography documented CVD, participants ingested 7.7 mL/kg/d of purple grape juice for 14 days. Short-term ingestion of purple grape juice reduced LDL oxidation and improved flow mediated vasodilation, which increased from 2.2 to 6.4% ($P = 0.003$). The flavonoids in grapes are involved in reduction of platelet aggregation. In a randomized crossover study design, each of 10 healthy human subjects drank 5 to 7.5 mL/kg/d of purple grape juice, orange juice, or grape fruit juice, for 7 to 10 days. Drinking purple grape juice for 1 week reduced the whole blood platelet aggregation response to 1 mg/L of collagen by 77%. Consuming red, purple and black grapes and grape juice on a constant basis may prove to be a practical recommendation as an adjunct therapy for preventing and managing heart diseases (Chamorro *et al*., 2012).

**Table 2:** Comparison of phenolic compounds between grape juice and red wine (Barbalho *et al*., 2020)

| Red wine | | Grape juice | |
|---|---|---|---|
| Flavanoids | Non-flavanoids | Flavanoids | Non-flavanoids |
| Quercetin | Resveratrol | Flavanols | Phenolic acids |
| Catechin | Benzoic acid | Flavonols | Resveratrol |
| Epicatechin | Cinnamic acid | Anthocyanins | |
| Anthocyanidin | Tannins | | |
| Procyanidins | | | |

The grapes species used for wine/juice production are, American variety (Vitis labrusca) and European variety (Vitis vinifera). The polyphenols found in red wine are gallic acid, caffeic acid, stilbenes also called trans-resveratrol, p-coumaric acid and many flavonoids e.g., quercetin, myricetin, rutin, epicatechin and catechin (Ditano-Vázquez *et al*., 2019). Another study compared the grape juice and red wine in terms of health promoting benefits (Barbalho *et al*., 2020). They found that many antioxidant compounds can be lost during the processing of raw grapes to make wine or grapes juice. They found both the grape juice and red wine reduced the body mass index, peroxidation of serum lipids, glucose level, waist line, blood pressure, TC, LDL-C etc. (Barbalho *et al*., 2020). Both grape juice and red wine have many bioactive compounds conferring numerous health benefits for humans. Table 2 depicts the qualitative difference in phenolic compounds among red wine and grape juice.

## *Fish Oil*

The inverse relationship between fish consumption and CVD was first brought to light nearly 30 years ago when it was reported that Greenland Eskimos had low rates of this disease despite consuming a diet containing approximately 7 g/day of omega-3 (n-3) fatty acids from marine fish (Saravanan *et al*., 2010). Fatty fish (salmon, tuna, mackerel, sardines and herring) and its oils are the predominant sources of the n-3 fatty acids Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) (Behera, 2019). Supplements of EPA and DHA (1 g/d) are known to reduce the blood lipid (Peter *et al*., 2013). Potential mechanisms for the cardiovascular protective effects of n-3 fatty acids are suggested to be; anti-inflammatory, antithrombotic (reduced platelet aggregability) and antiarrhythmic (reducing the risk of potentially fatal cardiac arrhythmias), lowering of heart rate and blood pressure, hypotriglyceridemic and improved endothelial function (De Caterina, 2011). Fish oil increased platelet survival ($P<0.05$) and lowered malondialdehyde formation. Platelet activation changes were related with significant reductions in total cholesterol (2.9%), LDL cholesterol (3.5%) and triglycerides (12.4%). So, consumption of moderate amounts of fish (one to two servings per week) has been associated with reduced CVD related deaths, thus it acts as a therapy (Einvik *et al*., 2010).

A follow up study examined the diabetic patients of 18 years or high for cardiovascular disease associated mortalities and examined that the individuals consuming higher amount of fish were at low risk mortalities due to CVDs, especially strokes among diabetic patients (Deng *et al*., 2018). Another study suggested that consumption of mono-unsaturated fatty acids and medium chain triglycerides along with background diet can improve the effect of fish oil on CVD patients (Kondreddy *et al*., 2016); however it needs to be consulted prior to intake with the medical supervisor while taking heart disease therapy.

Another study in Egypt was conducted by using a mathematical model to find an association between fish consumption and mortalities due to chronic heart diseases. It was reported that when the consumption of fish from the total harvested fish increased with the avoidance of the behavioral and metabolic risk factors for coronary heart diseases, the associated mortalities decreased significantly in a specific duration of time (Ameen *et al*., 2020).

## *Plant Sterol and Stanol Esters*

The cholesterol-lowering effect of plant sterols was first identified in the 1950 s. Early research investigated the efficacy of large amounts of plant sterols (such as β-sitosterol, campesterol and stigmasterol), which are natural components of vegetable fats/oils and pine trees. Studies have found that plant stanols, the saturated derivatives of sterols (i.e., sitostanol), result in greater cholesterol-lowering than plant sterols because of their enhanced ability to reduce intestinal cholesterol absorption while remaining almost unabsorbed (Mensink *et al*., 2010). Structurally, plant sterols and stanols resemble cholesterol, which allows them to compete with cholesterol during its absorption in the digestive tract. Many researches have been conducted to find the mechanism of action of plant sterols (Scolaro *et al*., 2020), thus it was found that difference in hydrophobicity of plant sterols prevent the cholesterol from entering into the micelles and it precipitate along with cholesterol in the intestinal lumen, hence reduces the absorption of cholesterol into the blood stream. Moreover, it also interferes with the cholesterol transport in the blood along with affecting the metabolism of cholesterol (Bai, 2019). As such no significant side effects, including gastrointestinal effects, have been observed with the consumption of plant stanol or sterol esters, only conferred a minor effect on decreasing the serum carotenoid concentration (Smet *et al*., 2012). A clinical trial based study demonstrated that a plant stanol ester-containing margarine could significantly reduce both total and LDL cholesterol by 10 and 14%, respectively, in mildly hypercholesterolemic patients. The consumption of foods containing at least 0.65 grams per serving of plant sterols, eaten twice a day with meals for a daily total intake of at least 1.3 grams, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart diseases (Ras *et al*., 2014).

### *Fruit and Vegetables*

There is a large amount of literature that reported 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 (Key, 2011; Miller *et al*., 2019). The mechanisms by which fruit and vegetables exert their protective effects depend upon its constituents. Several bioactive components are carotenoids, vitamin C, fiber, magnesium and potassium these compounds give antioxidant property and ultimately reduce the LDL cholesterol (Zhang *et al*., 2011). Plant foods also contain bioactive compounds known as “phytochemicals.” Some groups of phytochemicals which have or appear to have significant health potentials are carotenoids, phenolic compounds (flavonoids, phytoestrogens, phenolic acids), phytosterols and phytostanols, tocotrienols, organosulfur compounds and non-digestible carbohydrates (dietary fiber and prebiotics). The powerful antioxidant functions of vitamin C serve to reduce tissue reactive oxygen species concentrations, which in the atherosclerotic condition help prevent endothelial dysfunction, inhibit vascular smooth muscle proliferation and reduce oxidized LDL cholesterol (Song *et al*., 2010). In addition to its role as a free radical scavenger, vitamin E is also a potent anti-inflammatory agent, at high doses. Mounting evidence supports the strong inverse association between plasma vitamin E and CVD as well as that between vitamin E intake and risk of CVD. Fruits and vegetables must be consumed more in order to reduce the CVD as well as during the treatment of CVD (Boffetta *et al*., 2010).

Currently, World Health Organization (2003) recommends a minimum intake of fruits along with vegetables to at least 400 g/day. Recently a meta-analysis based study reported that a fruit intake of 800 g/day was associated with 27% reduction in the risk for CVDs (Aune *et al*., 2017). Some epidemiological studies on postmenopausal women found an inverse relationship between grapefruit and strawberries intake and coronary heart diseases (Mink *et al*., 2007). Consumption of berries rich in anthocyanin and procyanidins was found to reduce the CVD risk factors including endothelial dysfunction, aggregation of platelets and atherosclerosis (Basu *et al*., 2010). Citrus fruits were found to improve the blood lipid profile by decreasing high cholesterol level. Similarly, fruit juices and fruit powder are effective way to deliver antioxidants rich compounds with less fibers. Fruit juice contains vitamins, polyphenols and minerals (Kamiloglu *et al*., 2014). Some other research based studies suggested that processing of fruits can increase the carotenoids especially lycopene content in the fruit juices (Kamiloglu *et al*., 2014). A review suggested that intake of fruit/vegetable juices confers similar benefits as do the whole fruit or vegetable (Kamiloglu *et al*., 2014).

Another systemic review explained the effect of consuming cherries, citrus fruit and berries on CVD risk factors, reported that cranberry or cherry juice can significantly decrease the blood pressure (Wang *et al*., 2020).

Apples are the most economical fruit crops with top nutrients and largely consumed in the world (Wang *et al*., 2018). Beneficial properties of apples are due to high content of total phenolic compounds and richness of fibers. Although environmental conditions, growing and storage conditions influence the diversity of apples, still the phenolic compounds found in apples mainly in their red peel are 4.6-25.48 g/kg flavanols, 0.05-3 g/kg of hydroxycinnamic acids, anthocyanins and 0.049-0.434 g/kg of dihydrochalcones. Moreover, the apples are also rich source of vitamins (B1, B2, A, C, K) and other essential minerals (Iron, potassium, phosphorus and sugars) (Stirpe *et al*., 2017). A review based on eight observational studies and eight randomized trials, concluded that daily consumption of 100 to 150 g of whole apples is associated with reduction of blood pressure, pulse rate, inflammation, total cholesterol and LDL-C and increased HDL-C and improved the functions of endothelial cells. Thus, daily intake of apples helps in protecting against CVDs (Sandoval-Ramírez *et al*., 2020).

The mechanisms of functional foods used to prevent and treat the cardiovascular diseases along with their compounds are briefly explained in the Table 3.

**Table 3:** Functional food and their mechanism

| Potential mechanism | Bioactive compounds | Functional foods |
|---|---|---|
| Lowering blood cholesterol | Tocopherol, omega-3 fatty acid | Nuts |
| | Fibers, polyphenols | Legumes |
| | Fiber | Fruits and vegetables |
| | Phytosterols | Margarine |
| | Omega-3 fatty acids | Fish oil |
| | Fiber, Phytochemicals | Whole grains |
| | Flavonoid | Dark chocolate |
| | Omega-3 fatty acids | Fish |
| | Carotenoids | Green leafy vegetables |
| Inhibition of LDL-C oxidation | Vitamin C Polyphenolic, oleic acid | Citrus fruits vegetables Extra virgin olive oil |
| | Tea polyphenolics | Green tea |
| | Flavonoids | Dark chocolate |
| | Polyphenol | Fruits, Pomegranate |
| Lowering blood triglycerols | Omega-3 fatty acids | Fish |
| Decreasing blood pressure | Omega-3 fatty acids | Fish |
| | Fiber, Phytochemicals | Whole grains |
| | Ascorbic acid | Citrus fruits |
| | Tea polyphenolics | Green and black tea |
| | Grapes Polyphenol | Grapes and red wine |
| Lowering blood homocysteine | Folates | Fruits and vegetables |
| | Fiber, Phytochemicals | Whole grains |
| | Vitamin C | Citrus fruits vegetables |
| | Vitamin E | Nuts, seeds, oil |
| Antioxidant action | Lycopene | Tomatoes |
| | Carotenoids | Green leafy vegetables |
| | Vitamin C | Citrus fruits vegetables |
| | Tea polyphenolics | Green and black tea |
| | Anthocyanins, catechins, flavonols | Grapes and red wine |
| Anti-inflammatory action | Vitamin E | Nuts, seeds, oil |
| | Omega-3 fatty acids | Fish |
| | Anthocyanins, catechins, flavonols | Grapes and red wine |
| Endothelial function | Omega-3 fatty acids | Fish |
| | Polyphenols | Nuts |
| | Vitamin C | Citrus fruits vegetables |
| | Anthocyanins, catechins, flavonols | Grapes and red wine |
| | Flavonoid | Dark chocolate |
| Platelets aggregation | Anthocyanins, catechins, flavonols | Grapes and red wine |

## Conclusion

As CVD continues to be the leading cause of mortality all over the world, the alternatives and additional therapies are needed for prevention and treatment. Researchers found that the consistent consumption of some foods reduces the risk of CVDs. These foods such as psyllium seed husk, nuts, whole grain, tea, dark chocolate, garlic, ginger, grapes, wine, Oat fibers, fruits and vegetables provides beneficial effects to prevent and treat the cardiovascular diseases and thus known as functional foods. These are the best, cheap and less dangerous way of reducing the risk of CVDs. This food may potentially provide benefit alone, in combination and in addition to cholesterol lowering medications and with other therapies. Functional food is not only used to reduce the risk and for treatment of cardiovascular diseases but also used for many other diseases like cancer, blood pressure, asthma, hepatitis and other chronic diseases. The advances in the knowledge of both the disease and healthy dietary components have provided a new avenue to develop dietary strategies to prevent and to treat CVD. Although many of these functional foods have been found to have high therapeutic potential, future studies should include well-designed clinical trials assessing different combinations of these nutrients to realize possible additive and synergistic effects on health outcomes.

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## Author’s Contributions

**Kiren Mustafa:** Proof reading, modification and review.

**Iqra Ajmal:** Initial draft writing.
**Tahira Naz:** Table designing and critical analysis.
**Abu Bakr Ahmad Fazili:** Figure and interpretation.
**Xueyuan Bai:** Review and editing.
**Yuanda Song:** Conception and review.

## Competing Interests

The authors announce that they have no competing interests.

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