Bioactive Food Components in the Prevention of Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVDs) remain one of the leading causes of death globally. The risk factors such as lipids, lipoproteins, and inflammation play a critical role in CVD. Lifestyle factors directly influence the risk of CVD. Understanding of the risk factors and the disease-causing mechanisms will lead to novel therapeutic treatments. Emerging data have explored the utility of natural food-based strategies in the management of diseases. Increasing interest has been grown up in recent years on the health-related products of food industry and to understand how foods products can help and maintain the individual cardiovascular health. Plant extracts rich in bioactive components could be used as the

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functional ingredients for providing many health benefits. The recent advances in health benefits of bioactive components provide novel therapeutic approaches, which have played an important role in the reductions of CVD worldwide. This chapter presents a critical review of the potential benefits of bioactive foods consumed through diet to reduce the incidence of cardiovascular disease.

Keywords
Cardiovascular disease · Coronary heart disease · Atherogenesis · Dyslipidemia · Inflammation · Active ingredients · Bioactive components of foods

1 Introduction

Cardiovascular diseases (CVDs) cover a wide group of disorders that involve the cardiac muscles and the vascular system. CVDs are regarded as the most common human health problem throughout the world. The mortality rates differ considerably from country to country with Japan and other Mediterranean countries having the lowest rates [1]. CVD is the major cause of the death increasing day by day in developed and developing countries [2, 3]. Heart failure is more common in countries with lower socioeconomic status and with those who tend to adopt unhealthier lifestyle, such as smoking and careless dietary habits [4–6]. CVD alone is responsible for taking 17.7 million lives every year, and atherosclerosis has been recognized as the prominent symptomatic anomaly responsible for CVD-related deaths [7]. The most important CVDs includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, heart failure, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism. Heart attacks and strokes that usually caused by a blockage of blood flow to the heart or brain are the most important acute manifestations of CVD in human. The causes of this global epidemic have been largely explained to originate from lifestyle factors which directly impact the novel pathways of CVD risk [8]. The increased lipids in the blood and build-up of fatty deposits on the inner walls have been strongly correlated with the increased incidence of CVD. Usually, combinations of risk factors are involved in causing the heart attacks and strokes. The most important factors associated with the incidence of CVD are lack of physical activity, drinking alcohol, use of tobacco, unhealthy diet, obesity, hypertension and hyperlipidemia. Diabetes mellitus is regarded as another epidemiological factor associated with an increasing prevalence of CVD [9, 10].

Atherosclerosis, mainly located in the intima of middle sized and large arteries, is the major cause of myocardial infarction, heart failure, and stroke. Dyslipidemias in vascular endothelium [11] and cholesterol deposition are the major contributors of atherosclerosis. Low-density lipoprotein (LDL) cholesterol when oxidized is pro-inflammatory and immunogenic and acts as an independent risk factor for CVD. The increase in oxidized LDL cholesterol results in endothelial dysfunction and directly influences the development of atherosclerosis. The decline in high-density lipoprotein (HDL) cholesterol increases the susceptibility to atherosclerosis substantially while the increase in the HDL cholesterol may reduce the incidence of coronary

heart disease (CHD) [12] and reduces the risk of CVD [13]. Appropriate levels of HDL cholesterol may also be responsible for clearing oxidized LDL cholesterol from the tissue by obstructing the monocytes attachment to the endothelium layer of blood vessels. Maintaining the HDL cholesterol level may also initiate the nitric oxide release that stops vascular bed atherogenesis [14]. Since the built up of atherosclerosis lesions require a long period of time, therefore, initiation of early lipid management may help prevention of atherosclerotic vascular diseases [15]. To manage the lipid level in patients with dyslipidemia, alternatives therapies have been designed in recent years [16]. Lifestyle modifications have been suggested as the primary prevention strategy in managing cardiovascular risk whereas food supplements were prescribed to patients to reduce the risk factors and symptomatic relief from CVD. The natural foods obtained from medicinal plants have been tried that might confer some benefit on some patient. However, more research is required that may include clinical trials with long follow-up outcomes to conclude their effectiveness against CVD illnesses.

The past few years have witnessed the extensive expansion of research on the association between dietary food and CVD. Certain foods have been recognized showing the effectiveness in reducing the risk of chronic diseases. These specific foods and food components appear as therapeutic strategies in the reduction and prevention of the risk of CVD. In recent years, a considerable importance has been given to functional foods. Apart from their basic nutritional effects, the functional foods exhibit an important role in disease prevention, or slowing the progression of many chronic illnesses. These functional foods work on two basic principles either possess a component with positive health benefits or remove a component with negative effects on the body functions. The relationship between the nutritional value of food components and the prevention of several chronic diseases led to increase in their demand in the market. However, to sustain in the market these foods must be safe, healthy, and delicious. They may be composed of a single compound that physiologically active or may include the addition of other food components to make them functional including omega fatty acids, prebiotics, phytochemicals, and bioactive peptides.

Bioactive food components are physiologically active constituents that are present in minute quantities in plant products and lipid-rich foods [17]. They are being extensively studied to evaluate their beneficial effects on health. These compounds vary widely in chemical structure and function and are grouped accordingly. Scientific evidence indicates that those certain bioactive food components participate in the prevention of CVD [17, 18]. Oral supplements of bioactive food components when taken along with the routine diet may increase the absorption of nutrients that will have clinical benefit in some diseases. Usually, bioactive components of foods are taken in addition to a healthy diet but they do not serve as the substitution to conventional food [19]. Their consumption as part of basic nutrition exerts useful physiologic effects in reducing the risk of diseases [20]. They may act at the different metabolic pathways that control various metabolism including lipid disorders in humans. By virtue of their targeted actions on various metabolic pathways, they are believed to have the therapeutic advantages for reducing the risk of CVD by combating the inflammation and dyslipidemias [21]. They have well-illustrative

beneficial biological effects such as antilipidemic, antihypertensive, antiglycemic, antithrombotic, and antiatherogenic. With the perceptible health benefits of bioactive components against various diseases, a wide array of the metabolomics and physiological relevance of these compounds were established [22]. A recent study in the United States, adults showed the associations of suboptimal intakes of dietary factors with mortality due to CVDs [4]. These functional foods, apart from providing basic nutritions, provide therapeutic benefits in the management of chronic diseases [23]. In this chapter, we thoroughly examined the beneficial effects of bioactive food components in reducing the risk factors of CVD including hypertension, dyslipidemias, oxidative stress, and inflammation.

2 Risk Factors of Cardiovascular Disease

A number of risk factors such as changes in lifestyle, age, physical inactivity, blood pressure, smoking, alcohol, obesity, hyperlipidemia, and diabetes have been listed for the pathogenesis of CVD [24–26]. Inflammation has been regarded as the principal molecular mechanisms responsible for atherogenesis [27–29]. During inflammation nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a family of transcription factors that regulate varied processes in immune cells, initiates encoding of a number of genes responsible for cytokines and chemokines production [30]. The NF-κB signaling and cytokine secretion are found increased in atherosclerosis [31]. The IkappaB kinase/NF-kappaB (IKK/NF-κB) signaling pathway plays an important role in inflammation. In addition, this signaling pathway also regulates many other biological functions, including growth and survival of cells. These authors further elaborated that the activation of IKK/NF-κB pathway, which is an important regulator of inflammation, in cardiovascular tissues produce an excessive inflammatory response that causes cardiomyopathy leading to heart failure. Oxidative stress is another risk factor affecting the cardiovascular tissue in many ways. Oxidative stress can influence the functioning of endothelial layer of blood vessels, thereby leading to cardiovascular disease [32]. Reactive oxygen species (ROS) can have a direct effect on cardiac cells by oxidizing cellular constituents and disrupting the functions of proteins and enzymes [33]. The increase in ROS during the myocardial ischemia, hypoxia, and reoxygenation is the principal causes of reperfusion injury in cardiac tissues. During reoxygenation, increase in ROS cause direct oxidative damage to cellular components [34]. The obesity has been extensively correlated with the incidence of CVD, particularly among women [35]. Studies have shown an important connection between the obesity and dyslipidemia and the metabolic syndrome [36]. Dyslipidemia is mainly characterized by elevated levels of LDL-cholesterol and decline in HDL-cholesterol [37]. Hypercholesterolemia with total cholesterol level above 190 mg/L is the major form of dislipidemia and considered as one of the major risk factors for the CVD.

Hypertension is one of the major risk factors for cardiovascular-related illness. It is believed that hypertension is the single greatest contributor to cardiovascular disease [38]. With aging population throughout the world, the prevalence of

hypertension has a steep increase [39]. In addition to its detrimental effects on cardiovascular tissues, the hypertension is also associated with other cardiovascular risk factors, such as metabolic syndrome [40] and renal disease [41]. Changes in lifestyle, lowering sodium intake, reducing alcohol consumption, and weight reduction or physical exercise may lower blood pressure and thus reduce CVD [42]. Cigarette smoking is another important risk factor for CVD. An estimated 34.7% of all deaths resulting from cigarette smoking is related to CVD. Tobacco use cause impairment in endothelium-dependent vasodilation in the coronary microcirculation. The vasodilation response which was partly initiated by the release of nitric oxide (NO) was reduced in individuals who smoked [43]. Sera from smokers contain a reduced expression of endothelial nitric oxide synthase (eNOS) [44], whereas a brief exposure to tobacco smoke has caused the production of peroxynitrite ($ONOO^-$) [45]. Consumption of tobacco has been linked with the increase in the oxidation of LDL cholesterol, platelet aggregation, and impairment of endothelial layer [46]. Smoking for long-term increases the prevalence of hypertension, stroke, and atherosclerosis. Alcohol consumption is also associated with CVD. Although moderate consumption of alcohol cause lower risk of coronary heart disease, excess consumption of alcohol is detrimental to cardiovascular tissue [47]. These studies suggest that lifestyle changes such as physical inactivity, tobacco smoking, and heavy alcohol consumption are the risk factors contribute to CVD. The oxidizing chemicals, nicotine, carbon monooxide, and other particulate matters are believed to be accountable for cardiovascular disease.

3 Diet and Cardiovascular Disease

The life style and dietary patterns are often directly related with the development of hypertension, diabetes, and CVD. The nutritional diets may have a direct impact on the functioning of circulatory system physiology, thus affecting the occurrences of these diseases [48]. The metabolic abnormalities and the risk factors for CVD including dyslipidemia, central obesity, and hypertension are mostly depend upon the intake of an excess of total energy such as consuming high calorie or fatty meal [49, 50]. Individuals with dyslipidemia and high cholesterol levels were advised to take a diet rich in bioactive substances, fiber, and antioxidants and minimize the consumption of saturated and *trans* fatty acids. The dietary interventions that interfere with the reduction of plasma cholesterol and triglyceride levels may be effective in the prevention and management of CVD [51]. The diet consisting of nutritionally poor foods with high calorie and highly processed with deficiency of functional foods has been found to enhance systemic inflammation [52]. Food rich in fruits and vegetables along with moderate amounts poultry, fish, and meat has been associated with the reduction of inflammation thus prevent the occurrence of CVD. The direct correlation between serum total cholesterol and the heart attack and stroke was known since long time. Similarly, the importance of the Mediterranean diet in reducing the risk of coronary heart disease (CHD) [53–58] was also known since many years ago. Several studies were conducted describing the lifestyle and diets of

a population in the Mediterranean region and their relation to the rates of heart diseases [59, 60]. The traditional Mediterranean diet consisting of cereals, olive oil, fish, legumes, fruits, vegetables, dairy and meat products and moderate quantity of wine is quite beneficial for the heart. Consuming such diet provides a low risk of CHD and prevents the heart disease. Studies in individuals who opted for Mediterranean food [61] have shown a reduction in the incidence of CHD. Similarly, the choice of the Mediterranean diet with extra-virgin olive oil or nuts among individuals who are at high cardiovascular risk showed a reduction in CVD [62]. The studies performed on the composition of diet that should be useful for the prevention of CVD is limited. Thus, there is an urgent need to undertake such meticulously designed studies on the dietary food components that may be useful in reducing the lifestyle generated cardiovascular risk.

4 Types of Food Components Used for Prevention of Cardiovascular Disease

A critical role of lifestyle and diet in the prevention and treatment of CVD has become widely accepted. Besides classical food components, i.e., carbohydrates, proteins, fats, vitamins, and minerals, the diet prescribed to promote health and prevent diseases also includes the foods derived from medicinal plants known by various terms such as medicinal foods, bioactive foods, functional foods, or therapeutic foods [63], the consumption of which is believed to reduce the risk of many diseases including CVD [64]. The functional food refers to products with certain health benefit and reduced the risk of diseases. Foods such as fruits vegetables, cereals, fish, and red wine can be considered as functional foods that can prevent or cure several diseases. Medicinal food refers food product that can be considered to have therapeutic value in treating or preventing certain diseases and plays beneficial effects on physiological functions of a specific tissue. Medicinal foods are considered important in reducing the risk of certain diseases. Bioactive food components refer to constituents in foods supply with the basic human nutritional needs and taken with diet or as supplements. These food components exhibit the power to regulate one or more processes of metabolism that exerts the health benefits in reducing the risk of chronic human diseases [65]. These food components taken in appropriate quantities must be a part of the standard diet and consumed on a regular basis in order to beneficially affecting at various metabolic targets.

5 Bioactive Food Components in the Prevention of Cardiovascular Disease

One of the most favorite topics in the modern world is how to keep healthy and reduce the diseases caused by aging or changes in lifestyle. The most efficient ways to decrease the risk of common diseases, including CVD and cancer, are by limiting intake of carbohydrate/fat enriched food, limiting consumption of alcohol, limiting

salt intake, and adding the plant-derived food items, including vegetables, fruits, whole grains, legumes, nuts, and oils in the routine diet. Generally, bioactive foods are referred to those compounds that have potent antioxidative, anti-inflammatory, antithrombotic and immunomodulatory properties. These compounds possess the property to protect the body against the inflammation, cholesterol accumulation in the cardiovascular tissues, and protect against the oxidative stress, thus prevent the development of cardiovascular diseases and cancer as well as other pathological conditions such as neurodegenerative diseases [18]. Some of the most important bioactive components found in fruits and vegetables that possess the potential for promoting a healthy metabolism and in the prevention of diseases are flavonoids, carotenoids, organosulfur compounds, phytoestrogens, tocopherols, and L-ascorbic acid (Table 1). Figure 1 shows the schematic presentation of source and effects of some of the important bioactive compounds. The detailed account of occurrences and biological effects of these bioactive compounds and their role in the prevention of CVD are described individually in the following sections.

5.1 Carotenoids (Lycopene)

Carotenoids belong to a class of natural fat-soluble pigments found mainly in plants. The dietary carotenoids including lycopene, beta-carotene, lutein, beta-cryptoxanthin, zeaxanthin, and astaxanthin provide health benefits in decreasing the risk of many chronic diseases. Lycopene, the major carotenoid obtained from plants such as tomatoes, watermelon, and pink or red grapefruit, is very important in attenuating the risk of CVD. Lycopene extracted from plant sources predominantly exists in an all-*trans* isomer; however, *cis*-lycopene is the more bioavailable form [66]. The isomerization of *trans-cis* isoforms occurs with exposure to light of heat or in the gastric cavity under acid conditions [67]. Heat generated during cooking and processing converts some of the *trans*-lycopene to *cis*-lycopene increasing its bioavailability in the tissue [68, 69]. Thus the bioavailability of lycopene is greater in tomato paste and tomato puree than from fresh tomatoes [70, 71]. Thus the bioavailability of dietary lycopene is greater after cooking or when consumed with oil and other dietary fats [72, 73]. In addition, other nutrition present in tomatoes such as carotenes and lutein would also be absorbed by cells. Thus consuming whole processed tomato products will have more advantages than consuming lycopene alone. Although some studies concluded that consumption of a carotenoid-rich diet have no positive effect on plasma antioxidant status or markers of oxidative stress [74], but the majority of epidemiological and clinical studies have shown beneficial effects of lycopene or tomato-based food preparation in cardiovascular health. Lycopene supplementation has been shown to improve biomarkers associated with CVD. Studies involving a large group of people reported the association of higher intake of tomato with a reduced risk of CVD and myocardial infarction [75]. Lycopene level in the blood serum also improved the common carotid artery intima-media thickness which is an indicator of early atherosclerosis [76]. The intake of lycopene caused the reduction in cholesterol synthesis and enhanced the

Table 1 List of important bioactive food components that may influence cardiovascular diseases

Category	Bioactive components	Source	Cardiovascular effects	References
Carotenoids	Lycopene (carotenoid)	Tomatoes, watermelon, and pink or red grapefruit	Hypolipemic, inhibitor of proinflammatory and prothrombotic factors	[77–80]
Flavonoids	Genistein (Isoflavone)	Soybean, soy products	Antiatherosclerotic by inhibiting the expression of ICAM-1 and VCAM-1 and NFk-B on human endothelial cells	[105]
	Sulforaphane (isothiocyanate)	Cruciferae Family	Anti-inflammatory and antioxidant by stimulating Nrf2	[119]
	Apigenin (flavone)	Celery, parsley, and chamomile	Myocardial ischemia/ reperfusion injury reduction, inhibition of lymphocyte proliferation, and proinflammatory cytokine expression	[110, 112, 113]
	Quercetin (Flavanols)	Onions and shallots	Antiplatelet aggregation activity, reduction of mycocardial infarction	[121, 122]
	Resveratrol (polyphenolic compound)	Grapes, red wine	Reduction in LDL oxidation, vasorelaxation, reduction of platelet aggregation, antiatherosclerotic,	106–109
	Anthocyanins (glycosides of anthocyanidins)	Fruits and vegetables	Antiatherosclerotic, reduction in CVD mortality, protect DNA damage	[131–141]
	Hesperetin (flavanone)	Citrus plants	Block oxidized LDL-induced endothelial apoptosis	[94]
	Catechins (Flavanol)	Green tea	Reduction in blood cholesterol; antihypertensive; triglyceride, total cholesterol and low-density lipoprotein cholesterol	[91, 93]
Vitamins	Ascorbic acid	Fruits and vegetables	Prevent HDL from lipid oxidation	[144]
	Alpha-tocopherol	Oils, nuts, and leafy green vegetables	Prevent HDL from lipid oxidation	[147–150]

Abbreviations: *ICAM-1* Intercellular adhesion molecules-1, *VCAM-1* Vascular cell adhesion molecule-1, *Nrf2* nuclear factor-erythroid 2, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *CVD* Cardiovascular disease, *DNA* deoxyribonucleic acid

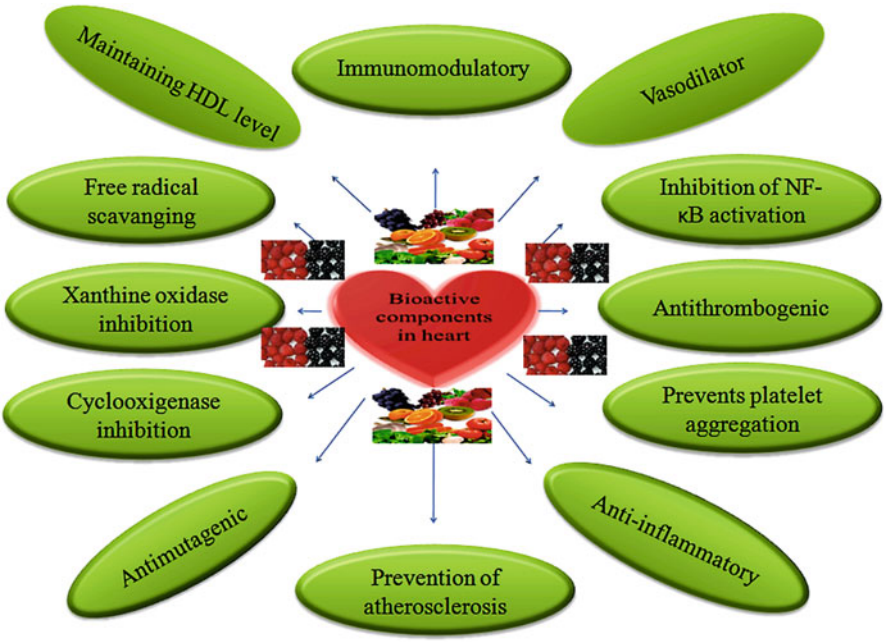

Fig. 1 Schematic diagram illustrating the role of bioactive components of food in the prevention of cardiovascular diseases (CVDs). As shown, bioactive components act on cells or tissue by targeting many physiological and metabolic processes. Together regulating multiple processes, these components of food prevent or cure cardiovascular diseases

degradation of LDL [77]. Oxidative damage related parameter such as lipid peroxidation and LDL oxidation were significantly declined in the subjects who were prescribed lycopene supplementation [78]. Similarly, individuals who were treated with lycopene (40 mg/day) for 6 weeks showed decline in triglyceride levels and LDL cholesterol levels whereas the HDL cholesterol was significantly increased [79]. The increase in HDL cholesterol and decline in total cholesterol/HDL cholesterol ratio was also reported in a study comprised of healthy men and women consuming the soy-tomato beverage that contain 21 mg lycopene/day on an average daily [80]. These studies suggest that lycopene or tomato-based products with a significant amount of lycopene improves the cardiovascular health by reducing the triglycerides, scavenging LDL, and maintaining HDL level thus reducing the risk of CVD.

5.2 Phenolic Acids and Flavonoids

Flavonoids are a group of polyphenolic compounds found in significant amount in many fruits, vegetables, grains, and beverages. They are classified as flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, and isoflavones. The flavonols

include compounds namely isorhamnetin, kaempferol, myricetin, and quercetin. Apigenin and luteolin compounds are grouped under flavones. Flavanones include compounds eriocitrin, hesperetin, and naringenin whereas flavan-3-ols include compounds such as catechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, and gallocatechin. Anthocyanidins include compounds such as cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin, whereas compounds daidzein and genistein are grouped under isoflavones. These compounds have varied chemical structure and biological functions and are grouped accordingly. The isoflavones genistein, daidzein, and glycitein occur predominantly in legumes. Genistein and daidzein found in soy, and resveratrol occurs in grape skin and red wine, are nonsteroidal polyphenolic compounds and considered as a phytoestrogen. The flavonoids contain sulfur are grouped under organosulfur compounds, prominent among are sulforaphane found in crucifer plants and γ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxides found in garlic (Allium sativum L., family Liliaceae). Anthocyanins are a group of most studied flavonoid occurs in a wide variety of plant kingdom. Anthocyanins are providing the bright red-orange to blue-violet colors in many fruits and vegetables. Their consumption has been estimated to be up to ninefold higher than that of other dietary flavonoids [81].

Phenolic acid and flavonoids have three most important health benefit effects on the prevention of cardiovascular tissue. The most important effect is attributed to their antioxidant activity [82]. Secondly they have prominent effects on the prevention of atherosclerosis [83], and lastly, they have a significant effect on the platelet aggregation [84]. In vitro studies indicate that flavonoids inhibit the oxidation of LDL and decrease the thrombotic tendencies [85]. They delay the development of atherosclerotic plaque and prevent the development of atherosclerosis by reducing the endothelial dysfunction. Another mechanism by which flavonoids help prevent CVD is through their effect on platelet aggregation. Flavonoids interact with membrane lipids and modifying the membrane fluidity [86], which is partly responsible for the antiaggregatory and disaggregatory effects on human platelets.

Catechins are polyphenolic compounds found in food and in all kinds of tea with cardioprotective properties [87]. Catechins have an important role in the prevention of cardiovascular disease [88, 89]. Catechins have been shown to reduce the accumulation of cholesterol and its oxidation products in the walls of arteries, thus help in smooth blood circulation [90]. Supplementation of catechins may reduce the serum triglyceride, total cholesterol, and low-density lipoprotein cholesterol, thus preventing atherosclerosis [91]. Catechins may improve the vascular endothelial environment by eliminating ROS [92]. In addition, catechins exhibit very strong antihypertensive activity [93]. Both (−)epigallocatechin gallate and hesperetin flavonoids block oxidized LDL-induced endothelial apoptosis thus may function as antiatherogenic agents [94]. However, there is no clear evidence to suggest a beneficial effect of tea catechins on the prevention of CVD.

Phytoestrogens are polyphenolic compounds occur in many legumes, beans, nuts, soybeans, seeds of sesame and so on, and mimic the properties of estrogens. These compounds include certain isoflavonoids, flavonoids, stilbenes, and lignans [95]. The best-studied dietary phytoestrogens are the soy isoflavones and the flaxseed

lignans. Isoflavones, such as genistein and daidzein, occur in soybeans, legumes, lentils, and chickpeas. Lignans are the most abundant nonflavonoids occur in most cereals, linseed, fruits, and vegetables. The phytoestrogens are the most intensively studied bioactive components of food with regard to their health benefits. Isoflavone content of foods such as soybeans is sold as nutritional supplements. Good scientific evidence supports the observation that phytoestrogens may play a beneficial role in reducing the risk of cardiovascular disease [18]. Diet is the chief source of phytoestrogens in human. The bioavailability of phytoestrogens in body organs may be dependent on the metabolism of intestinal bacteria. After ingestion in their *beta*-glycosidic forms, most of these phytoestrogens are hydrolyzed in the intestine to their aglycones. Then in the intestinal wall and liver aglycones are absorbed and glucuronidated [96, 97].

Isoflavones have beneficial biological effects in the cardiovascular system. They exert antiestrogenic effects by competitive inhibition at the estrogen receptor and help maintain cellular proliferation, vascular reactivity, lipid profiles, and thrombosis [98]. Epidemiologic studies reported that consumption of dietary isoflavones from soy products protects women not only from cardiovascular disease but also from breast and uterine cancer [99–102]. The lipid-lowering functions of isoflavones will have profound effects on cardiovascular protection. Although very little evidence presented to show the protective roles of phytoestrogens for cardiovascular disease, clinical studies involving Japanese women concluded that intake of high isoflavone was correlated with the reduced risk of cerebral and myocardial infarctions [103]. Phytoestrogens intake could delay the progression of atherosclerosis in vascular tissue by their pathophysiologic effects on lipid profile, reactive oxygen species production, inflammation, and tissue damage [104]. Atherosclerosis is initiated when monocytes bind to the endothelium layer of blood vessel, migrate into the tunica intima, and later develop into the foam cells. Lipid-induced and oxidant-sensitive transcription of adhesion molecules and chemokines promote the monocyte binding to endothelium. Genistein has been reported to be capable of inhibiting the expression of intercellular adhesion molecules-1 and vascular cell adhesion molecule-1 (ICAM-1 and VCAM-1) on human endothelial cells cocultured with monocytes [105], thus protecting against atherosclerosis. Resveratrol, a phytoestrogen found in high concentration in red wine, has been proposed to be the agent responsible for cardiovascular protection [106]. Its protective role in the cardiovascular system occurs by mechanisms of stimulation of reduction of low-density lipoprotein oxidation, vasorelaxation, suppression of platelet aggregation, anti-atherosclerotic properties, and also providing defense against ischemic-reperfusion injury [107]. This compound has the ability to stimulate Ca^{++}-activated K^{+} channels so as to increase endothelium nitric oxide signaling, thus exerting vasorelaxant activity [108, 109].

Apigenin, a flavonoid found in many vegetables such as celery (Apium graveolens), parsley and chamomile have demonstrated to possess the cardio-protective effects. Apigenin ameliorates myocardial ischemia/reperfusion injury via the inactivation of p38 mitogen-activated protein kinase [110]. In a cardiac hypertrophy model, the supplementation of apigenin reduces hypertension,

cardiomyocyte cross-sectional area, and serum angiotensin II [111]. Similarly, in an autoimmune myocarditis mice model, dietary apigenin cause inhibition of lymphocyte proliferation thus mediating the protection of cardiac tissue [112]. Apigenin caused reduction of LPS-induced mortality in mice by inhibiting proinflammatory cytokine expression [113] and decrease heart injury by suppressing sphingosine kinase 1/sphingosine 1-phosphate signaling pathway [114]. In a recent study, Li et al. [115] demonstrated that apigenin protects cardiac tissue damage, cardiac injury, cardiomyocyte cell death, and cardiac dysfunction against LPS- induced toxicity by its anti-inflammatory and antioxidant effect.

Organosulfur compounds are chiefly found in cruciferous vegetables, as well as in garlic and onions. Vegetables belong to Cruciferae family such as cabbage, broccoli, and kale contain rich amount of sulfur-containing compounds known as glucosinolates. Isothiocyanates are biologically active breakdown products of glucosinolates. Different types of glucosinolates are found in different cruciferous vegetables, each of which upon hydrolysis forms a different isothiocyanate [116]. For example, glucosinolate glucoraphanin, most abundantly present in 3-day-old broccoli sprouts, is converted to the isothiocyanate sulforaphane by the endogenous enzyme, myrosinase. Sulforaphane protects the chronic diseases by upregulating the "phase 2 response" known as Kelch-like ECH-associated protein 1- nuclear factor erythroid 2 p45-related factor 2-antioxidant responsive element (Keap1-Nrf2-ARE) pathway. Sulforaphane has been regarded as one of the most potent known naturally occurring inducers of cytoprotective phase 2 enzymes [117]. Glucosinolates are rapidly hydrolyzed by myrosinase, generating metabolites when raw cruciferous vegetables are cut while processing the food. While cooked vegetables inactivate myrosinase, so as to prevent the glucosinolates breakdown. Light steam cooking for about 5 min will preserve some of the myrosinase and thus allow the conversion of isothiocyanate. Most of the absorption of glucosinolates occurs in the small intestine, however, a large proportion of it reaches the colon [118] where it generates a broad range of metabolites depending on the pH and the presence of cofactors. The sulforaphane has been shown to target pro-inflammatory pathways by stimulating Nrf2 induced antioxidant enzymes [119] and downregulating the expression of NF-κB target genes which code for proinflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1β), and IL-6 [119].

Allium vegetables are recognized to be a good source of organosulfur compounds [120] and its supplementation in human exhibits antiplatelet aggregation activity. Similarly, the quercetin, the main polyphenol found in onions and shallots, also inhibited platelet aggregation in vivo [121] and in vitro [122]. Higher intake of cruciferous and allium vegetables (per serving 75 g/d) were associated with lower risk of atherosclerotic vascular disease mortality [120]. This study was conducted in older Australian women with 15 years of follow-up and concluded that higher cruciferous and allium vegetables intakes render lower risk of atherosclerotic vascular disease (ASVD) mortality in old individuals and protect vascular health. Resveratrol has recently become a well-known potent antioxidant and is found in red grapes, blueberries, cranberries, and other types of Vaccinium berries [123].

It is also known for its antithrombotic, anti-inflammatory, anticarcinogenic, and lifespan elongation effects, as well as its positive role in protection against insulin resistance [18, 124–126].

Anthocyanins are the polyphenolic compounds, possessing a characteristic C3–C6–C3 carbon structure and present in fruits, vegetables, berries, and red wine [127]. Anthocyanins are readily absorbed and metabolized in the tissue. These phenolic compounds found in the circulation and urine as intact, methylated, glucuronide derivatives, and/or sulfoconjugated forms [128–130]. Their anti-inflammatory and antioxidative properties show beneficial effects in the cardiovascular system. Compounds containing anthocyanin have been shown to reduce atherosclerosis in rodents [131]. Epidemiological studies have examined the relationship between total anthocyanin intake and risk of developing CVD. In a 16-year follow-up study period of consuming strawberry daily (intake of 0.2 mg/d of anthocyanins), the postmenopausal women participating in the Iowa Women's Health Study showed a significant reduction in CVD mortality [132]. Intake of blueberries also showed a significant decrease in coronary heart disease mortality. Moderate consumption of red wine will have a preventive effect in CVD-related mortality [133, 134]. The beneficial effects of anthocyanins in the prevention of CVD are strongly linked to the protection against reactive oxygen species-induced oxidative stress. Other mechanisms of anthocyanin beneficial role on cardiovascular tissues may be via providing protection from DNA damage, inhibiting enzyme, regulating immune responses through increased cytokine production, and exhibiting anti-inflammatory activity [135–139]. There is a significant reduction in ischemia in patients with vascular diseases who were consuming anthocyanin [140]. Inhibition of platelet activity and experimental coronary thrombosis in vivo was significantly achieved by commercial grape juice (10 mL/kg) [141]. These studies suggest that anthocyanins have a wide range of protective effects against CVD. However, epidemiological studies are insufficient to provide comprehensive information about their usefulness in CVD.

5.3 Vitamins

A substantial body of evidence has presented describing the possible role of several vitamins in the reduction of CVD risk. L-ascorbic acid or vitamin C found in a wide variety of fruits and vegetables has received a considerable attention in the past two decades as a powerful dietary antioxidant with a possible role in heart health. It is well known that HDL participates in the removal of cholesterol from sites of atherosclerotic lesion. In addition, the HDL also performs other functions that potentially have cardioprotective properties. Some of the beneficial functions of HDL include the inhibition of platelet activation, anticoagulant and profibrinolytic activities, preservation of vascular endothelial function, and protection of LDL from oxidation [142]. However, HDL is also vulnerable to lipid oxidation with ensuing loss of some cardioprotective properties [143]. Vitamin C has been shown to prevent the lipid oxidation in HDL and thus conserving the cardioprotective properties

of this lipoprotein [144]. Vitamin C also has been found to inhibit the oxidation of LDL-protein, thereby contributing to reduce atherosclerosis [145]. Although the cardiovascular other functions of vitamin C in cardiovascular diseases are not fully understood, it has been linked to improve the lipid profiles, protect arteries from arterial stiffness, and improve the endothelial function [145]. Vitamin E that includes tocopherols and tocotrienols was found in many types of oils, nuts, and leafy green vegetables and exhibit cardiovascular protective property [146]. Several studies have demonstrated the protective role of vitamin E in preventing HDL from lipid oxidation with subsequent cardioprotective benefits [147–150]. Initial studies found no correlation between serum or plasma vitamin E concentrations and death from cardiovascular diseases [151, 152]. Epidemiological studies in Finnish men found no association between serum vitamin E level and a coronary end point [153]. An extensive study on vitamin E supplementation was carried out in the USA involving 87,425 female nurses [154]. Their findings concluded that the benefit function of vitamin E supplementation was only apparent with the continued consumption for greater than 2 years. The benefit of vitamin E intake appeared to occur with both supplemental and dietary vitamin E. Overall studies suggest that there exists a relationship between consumption of vitamin E and the incidence of CVD [146].

6 Conclusion

Changes in lifestyle, dietary habits, and environmental and physiological factors directly influence the risk factors of CVD. The health benefits of fruits and vegetables are known since ancient times. However, investigations on their bioactive components and their physiological and metabolic targets attracted the significance of these compounds in preventing or treating certain chronic human diseases. Studies have shown that fruitful changes in lifestyle and regular consumption of recommended bioactive food components will help prevent chronic cardiovascular-related illness. Bioactive components of food are a challenging area in terms of its ability to regulate the metabolic process and control chronic diseases. Exact mechanism of their effects and appropriate doses on various signaling pathways needs to work out. The appropriate human dose and the risk of side effects of most of the bioactive food components are not known. Awareness among people and confidence among physicians on dietary recommendations to patients to prevent or to treat the disease are warranted. The key is to encourage people to make habit of consuming bioactive food components as part of their daily diet so as to prevent or eliminate lifestyle or age-related chronic diseases.

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