Journal of Medicinal Plants and By-Products (2024) Special: 726– 740
https://doi.org/10.22034/jmpb.2024.366010.1703

Review Article

The Role of Natural Antioxidants on Heart Diseases: A Review Article

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Article History

Received: 05 June 2024
Accepted: 12 August 2024

Keywords
Antioxidants
Oxidation
Free radicals
Heart diseases

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ABSTRACT

Reactive oxygen species and oxidants cause cell damage. Antioxidants are compounds that neutralize reactive oxygen species and protect body structures against these factors. Some enzyme antioxidants such as superoxide dismutase and catalase are naturally present in the body and some are derived from people's habits and diet. Research shows that the main cause of cardiovascular diseases in a pro-inflammatory state is excessive production of reactive oxygen species and irregular levels of plasma lipids. Antioxidants are among the most important molecules in preventing cardiovascular diseases, and inhibiting the oxidation of other molecules is one of the important capabilities of antioxidants. In this study, oxidative stress and the state of antioxidant defense are addressed as the most important mechanisms involved in preventing heart diseases. Related articles published in this research between 1987 and 2024 were used from Google Scholar, PubMed, Web of Science and Scopus scientific databases using the terms antioxidant, oxidative stress, free radicals, and heart diseases. The effects of tocopherol, flavonoids, phenols, carotenoids, lycopene, and vitamin C antioxidants in heart diseases have been investigated. The present research states that reactive oxygen species or oxidants react in free form or in combination with the vital components of the cell and cause serious oxidative damage. These damages become a prelude to many heart diseases. Therefore, antioxidants are useful compounds that neutralize reactive oxygen species but care must be taken in how they are used.

INTRODUCTION

Patients with chronic heart disease (CHD), intima-media thickness of common carotid arteries (IMT-CC) is a reliable, validated, and non-invasive marker of the progression of patients [1]. Cardiovascular diseases (CVD) are the main cause of death in Iran and about 300 people die every day in this country due to heart diseases. Cardiovascular diseases include coronary artery disease (CAD), high blood pressure, congenital heart disease, and stroke [2]. Cardiovascular diseases (CVD) are complex conditions with difficult pathophysiological pathways. Oxidative stress is one of the ways to influence this disease and the cause of death of many diseases, and there must be a balance between oxidative stress and antioxidants [3]. Cardiovascular diseases are the leading cause of death in the world and 17.3 million people die from this disease every year [4]. The greatest burden of cardiovascular disease is related to the risk factor of hypertension [5]. According to the estimate of the World Health Organization, deaths from cardiovascular diseases will reach more than 23.3 million people per year by 2030 [6] and according to the report of the World Health Organization, about 41.3% of all deaths in Iran in 2005 were caused by cardiovascular diseases, and this amount is expected to reach 44.8% by 2030 [7]. In recent years, a 25% reduction in premature deaths from non-communicable diseases in the age group of 30 to 70 years in 2025 compared to healthy people, which is known as the 25/25 target. Achieving this goal requires identifying modifiable risk factors of cardiovascular diseases and estimating the effect of reducing risk factors on the burden of cardiovascular diseases [8-10].

Several different reactive oxygen species (ROS) are generated in vivo. They have roles in the development of certain human diseases whilst also performing physiological functions. ROS are counterbalanced by an antioxidant defence network,

which functions to modulate ROS levels to allow their physiological roles whilst minimizing the oxidative damage they cause [11]. Oxidative stress (OS) is characterized by an inconsistency between the generation of reactive species (RS) and antioxidant (AO) defenses [12, 13].

Numerous natural antioxidants, commonly found in our daily diet and medicinal plants, have demonstrated significant benefits for human health and various diseases by counteracting the impact of reactive oxygen and nitrogen species [14-17]. Their chemical properties enable a range of biological actions, including antihypertensive, anti-ischemia, antimicrobial, anti-inflammatory, anti-fibrotic, and anticancer effects [18].

Antioxidants are compounds that, in addition to preventing damage to body cells, delay the oxidation of foods that can be oxidized by autoxidation. Antioxidants as hydrogen donors or free radical acceptors cause autoxidation by increasing the induction period. Antioxidants can be divided into artificial and natural antioxidants based on their function [19]. Important synthetic antioxidants that have been approved in most countries, include butylated hydroxyanisole (BHA), butylated hydroxytoluene (TBHQ), propyl, dodecyl gallates, and scurvy palmitate. The use of these antioxidants is usually determined by regulations. For example, in some countries, the allowed amount of each of these antioxidants alone is 0.01% and the allowed amount of a combination of antioxidants is 0.02%. These regulations are different from country to country [20].

In recent years, a lot of research has been done in the field of extracting natural antioxidants from plant sources. Other sources of natural antioxidants include carotenoids, flavonoids, amino acids and proteins, the products of protein hydrolysis of phospholipids and sterols. Several of these are naturally derived from phenolic antioxidants found in plant sources and plant extracts [21, 22].

Active oxygen species or oxidants that are free or combined with vital components such as cell membrane structure, lipids, and proteins, can react with cellular DNA and cause serious oxidative damage. These injuries are a precursor to many chronic and non-chronic diseases [23]. Some antioxidants such as superoxide dismutase and catalase are naturally present in the body. Many communities around the world use natural antioxidants to treat various disorders and improve general health, which is derived from people's habits and diet [24]. On the other hand, unhealthy diet is considered the main cause of many pathological diseases, including cardiovascular diseases [25]. Research shows that the main cause of cardiovascular diseases in a pro-inflammatory state is excessive production of reactive oxygen species and irregular levels of plasma lipids. The important thing is that there are natural molecules that protect the heart and blood vessels and prevent the risk of diseases. Antioxidants are among the most important molecules in the prevention of cardiovascular diseases. Inhibiting the oxidation of other molecules is one of the important capabilities of antioxidants [24].

Despite the availability of successful treatment strategies for dyslipidemia and hypertension, the prevalence of cardiovascular disease is high and increasing [26]. Therefore, prevention and avoidance of risk factors such as smoking, oxidative stress, inflammation, and obesity lifestyle, such as unhealthy diet, inactivity, high blood pressure, diabetes, and dyslipidemia should be prioritized to prevent diseases. Nevertheless, in addition to lifestyle, genetic, epigenetic, and environmental factors may fundamentally influence CVD risk [27]. The mentioned conditions are due to the continuous production of high levels of ROS, which reduces endogenous antioxidant capacities. These patients often show low levels of antioxidants in their blood and increased oxidative stress. This is usually due to increased demand in situations of massive ROS production by activated immune effector cells such as macrophages. Adsorption of exogenous antioxidants is suggested to interact beneficially with oxidative stress associated with diseases, however, the interaction of endogenous and exogenous antioxidants should take place [28].

Vulnerable stressors activate multiple mechanisms, such as immune responses, that are effective in the initiation of many disease complications, in such a way that it is useful for oxidants [29]. On the other hand, the living system is equipped with enzymatic and non-organizational defense systems to counter and balance these conditions. Enzymatic defense of antioxidants including superoxide dismutase SOD, glutathione peroxidase GPx and catalase CAT and non-enzymatic antioxidants include ascorbic acid or vitamin C, vitamin E, glutathione GSH, carotenoids,

flavonoids, and other antioxidants [30]. Antioxidant enzymes are highly regulated at the level of gene expression. Oxygen free radicals or reactive oxygen species, like reactive nitrogen species, are products of natural cell metabolism and have beneficial and harmful effects on biological systems. Free radicals play a role in cardiovascular diseases. Excessive production of free radicals' damages biomolecules such as lipids, proteins and nucleic acids [31, 32]. This action causes the creation of oxidants such as OH, H2O2, O2-. This issue also happens during myocardial infarction, surgery, transplant stroke, arterial occlusion under pathological conditions, etc. During ischemia in the heart, the conversion of ATP to adenosine causes the production of O2- [33, 34]. Most of these damages are related to the excessive production of free radicals during this condition. The basal level of free radicals is kept at a non-toxic level by a variety of defensive antioxidants and repair enzymes, but this capacity balance can be lost by antioxidant deficiency or excessive production of ROS. Many studies point to an increase in ROS production and a decrease in antioxidant capacity in heart patients [33].

Heart disease is a growing epidemic worldwide. For example, atherosclerosis is the main mechanism of cardiovascular diseases, including heart attacks and peripheral artery diseases and causes many diseases and deaths around the world, and is related to inflammation and oxidative stress. Therefore, the need for strong natural antioxidants with greater effectiveness is a serious necessity, which are able to prevent or delay the oxidation of oxidizable cellular substances and block the harmful effects of free radicals. In some sources, their effectiveness has been discussed and in other sources, their reverse effects have been discussed, we found it necessary to examine the expression of this issue [35, 36]. The pro-oxidant system results in an excessive increase in oxidative stress that, in turn, results in the manifestation of a dysfunctional endothelium [37, 38].

The purpose of this research is to present the status of antioxidant defense as one of the most important mechanisms involved in the prevention of heart diseases.

METHOD

Related articles published in this research between 1987 and 2024 were used from Google Scholar, PubMed, Web of Science and Scopus scientific databases using the terms antioxidant, oxidative stress, free radicals and heart diseases.

Antioxidants and their Mechanism of Action

Free radicals and other ROS, either from the natural metabolic processes that are essential to the human body or from external sources. They result from exposure to X-rays, ozone, smoking, air pollutants, and industrial chemicals [39]. Free radical formation occurs continuously in cells due to enzymatic and non-enzymatic reactions. Enzymatic reactions that are sources of free radicals include those involved in the respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P-450 system Free radicals can also be formed in non-enzymatic reactions of oxygen with organic compounds, as well as in responses that are initiated by ionizing reactions [40]. An antioxidant is a molecule stable enough to donate an electron to neutralize a free radical, thus reducing its ability to cause harm. These antioxidants delay cell damage primarily through their ability to inhibit free radicals [41]. These low-molecular-weight antioxidants can safely interact with free radicals and stop the chain reaction before any damage is done to vital molecules. Some antioxidants, including glutathione, ubiquinol, and uric acid, are produced during normal metabolism [42]. Other, lighter antioxidants are found in food. Although several enzyme systems in the body destroy free radicals, The most important micronutrient antioxidants (vitamins) are vitamin α-tocopherol or vitamin E, vitamin C (ascorbic acid) and B-carotene, phenols, flavonoids and carotenes and...[43]. Two main mechanisms of antioxidant action have been proposed [44]. The first mechanism is chain breaking, where the primary antioxidant donates an electron to the free radical in the system and they break the chain. The second mechanism involves the elimination of ROS/active nitrogen species initiators (secondary antioxidants) by switching off the chain initiation catalyst. Antioxidants can exert their effects on biological systems through various mechanisms, including electron donation, metal ion chelation, or regulation of gene expression [45].

Pathogenesis

Oxidative stress caused by the increase of oxidants and the decrease of antioxidants play a role in the pathogenesis of many diseases, including diabetic nephropathy, vascular diseases, etc. Following oxidative stress, an adaptive cellular response occurs

that requires the production of antioxidants. As a result of oxidative stress, severe damage is done to DNA, protein and lipids. Various mechanisms are involved in the creation of oxidative stress in cardiac patients, which include increased production of reactive oxygen species (ROS) and decreased activity of protective mechanisms. Oxidative stress occurs when the production of reactive oxygen species exceeds the capacity of antioxidants [30].

There is a lot of evidence that the antioxidant defense is reduced in patients with the disease, which includes a decrease in plasma total antioxidants and or scavenger activities of free radicals by which superoxide dismutase, this enzyme is responsible for converting superoxide radicals into hydrogen and water [46].

Findings

In this research, the effects of tocopherol, flavonoids, phenols, carotenoids, lycopene and vitamin C antioxidants in heart diseases have been investigated.

Vitamin E

It is a fat-soluble vitamin with antioxidant capacity. Nuts, vegetable oils and seeds are among the best sources of alpha-tocopherol, as well as green leafy vegetables and fortified cereals also have a significant amount of vitamin E [47]. Many studies have shown that vitamin E can be useful in the prevention and treatment of diseases caused by free radicals. Increased consumption of antioxidants such as vitamin E and C has been reported to protect against cardiovascular disease among people. Vitamin E for people who have oxidative problems caused by free radicals should be prescribed at the right time and for a certain period of time [48]. Antioxidants should be used with caution, because excessive consumption can be toxic to the body. The mechanism of increased risk of vitamin E in high doses is unknown. This phenomenon may be due to the induction of cytochrome P450, which accelerates the metabolism of other drugs [49].

Basic research has provided valid mechanisms by which vitamin E may have benefits for the cardiovascular system (CV) ، It is associated with inhibition of oxidation of low-density lipoprotein (LDL) cholesterol in plasma. Vitamin E has also been shown to reduce CV disease through diet or supplementation [50, 51]. After oxidation, vitamin E can be recovered in its native, non-oxidized form by various soluble antioxidants such as vitamin C and ubiquinol. This process prevents the accumulation of vitamin E radicals and the subsequent peroxidation of lipids [52].

Inflammation is another area of interest in the research of vitamin E The anti-inflammatory effects of α-tocopherol mainly involve NFκB inhibition [53]. PGE2 acts as a pro-inflammatory mediator in cancer, arthritis, and cardiovascular disease [54]. The results obtained so far in in vitro and in vivo models suggest that vitamin E modulates the progression of cardiosclerosis. It plays an important role in cardiovascular disease, including ischemic heart disease and heart failure [55].

Flavonoids

The basic structure of flavonoids consists of three phenolic rings consisting of 15 carbon atoms. There are 20 polyphenolic compounds found in abundance in plants, vegetables and fruits. Their types include the family of flavonols, anthocyanins, isoflavones and oligomeric and polymeric forms [56, 57]. Flavonoids have antimicrobial, antiviral, anti-atherosclerosis, anti-cardiovascular, heart strengthening, anti-diabetic, anti-oxidant, and anti-inflammatory properties [58-60]. The positive effect of flavonoids is due to increasing the amount of intracellular vitamin C, preventing capillary penetration and rupture, and strengthening the body's defense system. Flavonoids can have a protective effect in cardiovascular diseases due to modulating the function of vascular endothelium, anti-oxidant, anti-inflammatory properties, induction of nitric oxide production, vasodilation, inhibition of platelet preactivation, inhibition of proliferation and angiogenesis [61-63].

Routine administration of flavonoids reduces heart contraction and blood vessel dilation Routine treatment also leads to a decrease in lipid peroxidation [64]. The levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6 were significantly decreased in the group treated with different flavonoids (hesperidin) Total antioxidant capacity was also increased. LDL cholesterol is also reduced and NO is increased [65, 66].

Phenols

Extensive studies have confirmed the positive effects of polyphenols on cardiovascular diseases. In terms of pharmacodynamics science, moderate consumption of polyphenol-rich chocolate can reduce insulin resistance, decreased systolic pressure,

blood diastole, dilation of blood vessels by improving the elasticity of arterial vessels, improving endothelial functions, increasing antioxidant function, reducing oxidative stress indicators, reducing LDL cholesterol, and increasing HDL cholesterol, preventing blood coagulation and inhibiting platelet aggregation by influencing the process of cell signaling and gene expression, controlling inflammation and improving mood plays a very effective role in the treatment and prevention of cardiovascular diseases [67].

Phenols are one of the natural compounds that can prevent the development of HF heart failure and CVD due to various therapeutic properties such as anti-inflammatory, antioxidant, anti-apoptotic, anti-atherogenic and anti-hypertensive effects. Clinical and animal studies have reported that phenols reduce reactive oxygen species, and malondialdehyde (MDA) in the heart [68]. and induce the expression of enzymes involved in the detoxification system, such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) peroxidase [69]. In addition, phenols inhibit low-density lipoprotein (LDL) oxidation and reduce LDL oxidation-induced cytotoxicity (ox-LDL) in cardiovascular endothelial cells [70]. On the other hand, studies in both ischemic and non-ischemic HF animals have shown that Phenols improved ventricular systolic/diastolic and caused better cardiac function [71, 72].

Carotenoids

A group of pigments for which, in addition to their role in the formation of pigments, antioxidant properties have also been reported. Animals and humans do not have the ability to synthesize them and they must be obtained through the diet and then converted from the carotenoid form to another form. They also play an important role in the formation of vitamin A. Oxidation resulting from reactive oxygen species can cause cell membrane disintegration, damage to membrane proteins and DNA mutation, and the spread of many diseases such as cancer, liver damage, and cardiovascular diseases. Therefore, antioxidants play an important role in the prevention or treatment of diseases related to oxidation or free radicals by inhibiting free radicals [73]. Carotenoids due to antioxidant properties, they protect the body against diseases and prevent the formation of free radicals in the body [74]. Studies have shown that the most abundant carotenoids in the blood are beta-carotene and lycopene, respectively, and the protective effects of high levels of beta-carotene against heart diseases have also been reported [75, 76].

The main storage sites for carotenoids are fat tissue and the liver In tissues that contain large amounts of low-density lipoprotein (LDL) receptors, high levels of carotenoids appear to accumulate, Possibly due to nonspecific uptake of carotenoids by lipoprotein carriers. Diet plays an important role in the prevention of many chronic diseases, including cardiovascular disease (CVD), particularly coronary heart disease (CHD) and stroke [77].

Considering: Oxidative stress is a pathophysiological process involved in atherosclerotic and cardiovascular damage [78]. Carotenoids have powerful antioxidant activity, It is an excellent scavenger of FRs and especially a potent quencher of Radical Oxygen Species (ROS) and Nitric Oxygen Species (NOS). Numerous studies have shown that its unique chemical structure makes it more stable in cell membranes, allowing it to function more effectively as an antioxidant. and intracellular FRs are transferred extracellularly [79].

Lycopene

Lycopene is found in figs, apricots, pomegranates, papayas, watermelons, red peppers, pink grapefruits, and tomatoes. Tomatoes have a large share of lycopene. According to studies, the consumption of sources rich in lycopene has affected many pathological diseases such as cardiovascular diseases, blood pressure and some types of cancer. Lycopene has antioxidant properties and protects the body from carcinogens and biomolecules such as LDL (HMG-COA enzyme inhibition) and it is also very effective in cleaning free radicals. Therefore, lycopene can reduce the risk factors of people suffering from cardiovascular diseases such as arteriosclerosis [80].

Lycopene is a carotenoid with the molecular structure C40H56 and the highest antioxidant potential, It has the ability to moderate inflammation, apoptosis, and cell communication associated with cardiovascular disease [81]. Increased oxidative stress is considered a primary factor in cardiovascular disease, causing myocardial infarction, ischemia/reperfusion, and heart failure [82]. Excessive ROS production contributes to the reduction of nitric oxide and, with vasoconstriction, initiates arterial hypertension [37] and affects calcium handling in the myocardium, Arrhythmias and increased cardiac remodeling are

associated with the induction of signaling hypertrophy and apoptosis. ROS also initiates the formation of atherosclerotic plaques Therefore, dietary compounds, including lycopene, may be able to counteract these changes [83]. Lycopene also plays a role in inhibiting LDL oxidative damage [84]. and improving endothelial function [85].

Vitamin C

Vitamin C or ascorbic acid is a water-soluble compound that has two hydroxyl groups that can be ionized. Ascorbate anion, which is the dominant form at physiological pH, is a strong reducing agent that converts to ascorbate radical and dehydroascorbic acid DHA.These are two different types of vitamin C and it is a strong antioxidant against H2O radicals [86]. Vitamin C is chemically capable of reacting with ROS and acts as a water-soluble antioxidant. The antioxidant and anti-inflammatory activity of vitamin C plays an important role in preventing heart diseases [87].

The hypothesis that vitamin C may play a role in CVD prevention is also supported by its antioxidant capabilities. Epidemiologic evidence linking fruit and vegetable consumption to reduced CVD risk may be due, at least in part, to antioxidant content, In particular, the role of these antioxidants in preventing oxidative modification of LDL should be explained [88]. Therefore, prevention of LDL oxidation by vitamin C may prevent atherosclerosis, Therefore, it has a potential role in CVD risk reduction. The multiple functions of vitamin C may also support the hypothesis that vitamin C may reduce cardiovascular risk. For example, vitamin C reduces monocyte adhesion to the endothelium and prevents atheroma formation [89]. Vitamin C is also indicated which improves nitric oxide production in the endothelium, which increases vasodilation and reduces blood pressure, atherosclerosis, and CVD [90].

Vitamin A

Research shows that vitamin A in the form of retinal and retinoic acid, as well as retinol and retinyl esters, have no direct antioxidant activity in humans. These review articles concluded that: "Vitamin A's actions in the body include serving as a precursor for ligands for RARs and retinoid X receptors. and also exerts an indirect antioxidant response through the NF-κB and nuclear erythroid 2-related factor 2 (NRF2) The Nrf2 exhibits potential as a promising target for effectively managing CVDs. Significantly, an emerging field of study is around the utilization of natural substances to stimulate the activation of Nrf2, hence facilitating the promotion of cardioprotection. This technique introduces a new pathway for treating CVD [91]. pathways Unfortunately, excessive consumption of vitamin A exclusively in the form of retinol or retinyl ester as food or supplements is already being consumed in sufficient or even high doses in Western countries. It may cause mental disturbances, itching, headaches, an imbalance in the immune response, muscle and bone pain, and other side effects Data suggest that analyzing plasma vitamin A concentrations to determine associations with cardiac disease may be inappropriate [92, 93].

However, studies in rats with severe heart failure after a myocardial infarction (MI) have shown that the plasma concentration of vitamin A has not changed, but there is a significantly decreased hepatic concentration. Therefore, myocardial demand for the antioxidant vitamin A may increase following an oxidative stress event such as MI which can be met without significant changes in plasma concentrations by removal of the vitamin from visceral storage organs such as the liver [94].

Diets rich in vitamin A are effective in reducing oxidative damage in rats, particularly in the heart. Many of these compounds are physiologically important antioxidants that may inhibit the development or progression of heart disease. In addition, it has been shown that carotenoid vitamin A does not provide much oxidative resistance to low-density lipoprotein (LDL) particles. One report showed that dietary vitamin A may mediate the increased activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) induced by a high-fat diet These enzymatic antioxidants have been shown to have a modulatory effect on the pathogenesis of heart disease in a variety of conditions [95].

Lutein

Lutein has been shown to benefit endothelial function by reducing blood pressure, arterial thickness, monocyte migration, and vascular smooth muscle cell migration in one of ten studies. Twelve studies have looked at the anti-inflammatory properties of lutein and have found a significant reduction in pro-inflammatory cytokines. Three animal studies and one clinical trial have shown a beneficial effect of lutein on the lipid profile, although few studies have investigated the antihyperlipidemic effects of lutein.

Evidence supports the beneficial effects of lutein on preventing atherosclerosis and reducing some common risk factors for atherosclerosis, including inflammation and endothelial dysfunction. Further studies are needed to determine the effects of lutein on hyperglycemia, lipid profile, blood pressure, and blood coagulation [96]. Some laboratory studies have focused on beta-carotene as the most effective biological carotenoid for protecting against cardiovascular risk. Lutein may be a stronger candidate for cardiovascular health, new evidence suggests [97].

In fact, lutein is a potent ROS scavenger [99, 98], Through activation of the nuclear transcription factor NF-kB, which is a key player in many pathological responses (90). It is a blocker of the degradation of inhibitor kB (I-kB) [100]. When lutein dissociates I-kB from the NF-kB complex, NF-κB can translocate to the nucleus and reduce inducible gene transcription and synthesis of inflammatory markers such as cytokines, chemokines, and iNOS [101]. The final effect of lutein includes not only the reduction of the concentration of TNF-alpha, interleukin 6 (IL-6), prostaglandin 2 (PGE-2), monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 2 (MIP-2) [100]. Oxidative stress is also reduced. However, its antioxidant and anti-inflammatory properties have been shown to not only benefit the eyes but also promote cardiovascular health and reduce the risk of CAD. Recent studies have shown that plasma lutein and oxidized LDL are inversely correlated, which is indicative of its potent antioxidant and anti-inflammatory effects on aortic tissue, which may have protective effects against atherosclerosis [102].

Beta-carotene

There are several nutrients that are readily available in plants and fruits, including vitamin C, folate, flavonoids, and beta-carotene. Several meta-analyses have carefully examined their role in the prevention and control of CVD. Beta-carotene is a provitamin A carotenoid with antioxidant properties and is the most active form of vitamin A. To date, most studies have examined the combined effects of β-carotene with other antioxidants. There are a number of meta-analyses that specifically discuss the effects of beta-carotene treatment on a variety of CVD outcomes. And talking about β-carotene's individual effects on CVD prevention[103, 104].

Natural β-carotene contains several isomers, including all-trans and 9-cis β-carotene. Several epidemiologic studies have shown that high levels of carotenoids in the diet may protect against many diseases, including heart disease and cancer. Also, this carotenoid may enhance immune functions by increasing the proliferation of lymphocytes and have antioxidant capacity. In vitro enrichment of LDL with b-carotene has been shown to decrease LDL sensitivity by reducing the oxidative capacity of LDL [105]. Another interesting mechanism for the prevention of CVD by beta-carotene may be the modulation of vascular NO bioactivity [106].

Selenium

The amount of selenium in plants varies greatly depending on its concentration in the soil. which is related to the geographical area. There are many areas of selenium deficiency around the world, especially in Australia and Asia. Selenium is required as a cofactor for the synthesis of this enzyme, Data show that decreased blood selenium concentrations are associated with increased incidence of CVD and all-cause mortality. Selenium as an antioxidant decreases cardiovascular disease. The amount of selenium in over-the-counter supplements can be much lower. Therefore, the focus seems to be on increasing selenium intake [107].

Selenium significantly reduces LDL cholesterol, insulin levels, and C-reactive protein, while increasing HDL levels, total antioxidant capacity, and glutathione concentration [108]. Because RF is known to increase oxidative stress [109]. This represents a new therapeutic opportunity, especially in patients with low selenium levels, as selenium supplementation has been reported to increase GPx glutathione peroxidase levels in cardiac tissue. As mentioned above, a minimum selenium level of >125μg/L is required for high GPx, which highlights the potential benefits of selenium supplementation in the setting of HF [110].

The mitochondrial matrix protein methionine sulfoxide reductase (MsrB2) is a selenoprotein that is readily regulated by selenium in the diet. MsrB2 has been shown to have anti-inflammatory effects and is required for the induction of up to two anti-inflammatory cytokines, IL-10 and IL-1RA [111].

In addition, selenium may play an important role in mitophagy, the process of removing damaged mitochondria [112]. In addition, selenium has been suggested to facilitate the differentiation of T cells

and the function of other immune cells [113, 114]. This is particularly important because patients with HF have a higher incidence of infection and sepsis [115]. Inflammatory and immune events are associated with endothelial dysfunction observed in HF [116]. Several experimental studies have shown that selenium has a protective role in HF by reducing endothelial dysfunction and inflammation [117]. Selenium levels in immune cells themselves have been shown to affect the half-life of reactive oxygen species (ROS). Because many selenoproteins neutralize ROS through multiple pathways Selenium not only has the potential to help differentiate T cell subsets in HF but also improve the performance of the cells by reducing the intracellular oxidative stress [118]. (Figure 1 shows the effects of antioxidants and the mechanism of action and reversal of the mechanism of action on the heart. Table 1 below lists antioxidants and their mechanism of action.

Table 1 A list of antioxidants and their mechanism of action on the heart

Row	Name	Mechanism	Study done	References
1	Vitamin E	Inhibit the oxidation of LDL cholesterol	Celec P., *et al*., 2012	[29]
		Inhibition of NFκB	Rashidi B., *et al*., 2017	[32]
		Decreased activity of the protein kinase C	Schubert M., *et al*., 2018	[33]
		Decreased levels of prostaglandin (PGE2)		
2	Flavonoids	Inhibit the oxidation of LDL cholesterol	Mendes-Junior L.d., *et al.*, 2013	[44]
		Reduced levels of TNF-α and interleukin (IL)-	Jaffri J.M., *et al*., 2011	[45]
		6 Decrease LDL cholesterol and increase NO	Yamamoto M., *et al*.,: 2008	[46]
3	Phenols	anti-inflammatory	Kutan- Fenercioglu A., *et al*.,	[48]
		Antioxidant	2010	[49]
		Anti-apoptotic	Cheng Y-C., *et al*., 2017	[50]
		Anti-atherogenic	Brito P.M., *et al*., 2008	
		Increased levels of (SOD), (CAT), (GSH)		
		Increase of MDA in the heart		
		Reduction of lipid peroxidation		
4	Carotenoids	Powerful scavenger of ROS and NOS	C Nishida., *et al*., 2004	[58]
		Excellent absorber of the FRs	Pashkow F.J., *et al*., 2008	[59]
		Inhibit the oxidation of LDL cholesterol		
5	Lycopene	Antioxidant	Thies F., *et al*., 2017	[61]
		anti-inflammatory	Senoner, T., *et al*., 2019	[63]
		Anti-apoptotic	He Q., 2015	[65]
		Reduction of ROS, NO	Omidyan R., *et al*., 2020	
		Inhibit the oxidation of LDL cholesterol		
		Endothelial function improvement		
6	Vitamin C	Inhibit the oxidation of LDL cholesterol	Salvayre R., *et al*., 2015	[68]
		Increased Nitric Oxide Production	D'uscio L.V., *et al*., 2003	[70]
		Reduces monocyte adhesion to endothelium and improves endothelial function		
7	Vitamin A	Increased levels of (SOD), (CAT), (GSH)	Robert S., *et al*., 2020	[74]
		Inhibit the oxidation of LDL cholesterol		
		Increased ROS		
8	Lutein	Nuclear transcription factor NF-Kb expression	Jin X.H., *et al*., 2006	[70]
		Reduce inflammatory markers including	Ashino T., *et al*., 2008	[80]
		cytokines, chemokines and iNOS	Osganian S.K., *et al*., 2003	[81]
		TNF-α, IL-6, and prostaglandin-2 (PGE-2) levels are reduced.		
		Inhibit the oxidation of LDL cholesterol		
		Prevent atherosclerosis		
9	Beta-carotene	Inhibit the oxidation of LDL cholesterol	Jialal I., *et al*., 1991	[84]
		Increased nitric oxide levels	Robbins M., *et al*., 2002	
		Reduction of ROS		
10	Selenium	LDL cholesterol significantly reduced	Raygan F., *et al*., 2018	[87]
		Reduction of C-reactive protein	Frustaci A, *et al*., 2012	[89]
		Increased levels of glutathione	Lee B.C., *et al*., 2017	
		Induction of up to two anti-inflammatory cytokines, IL-10 and IL-1RA		

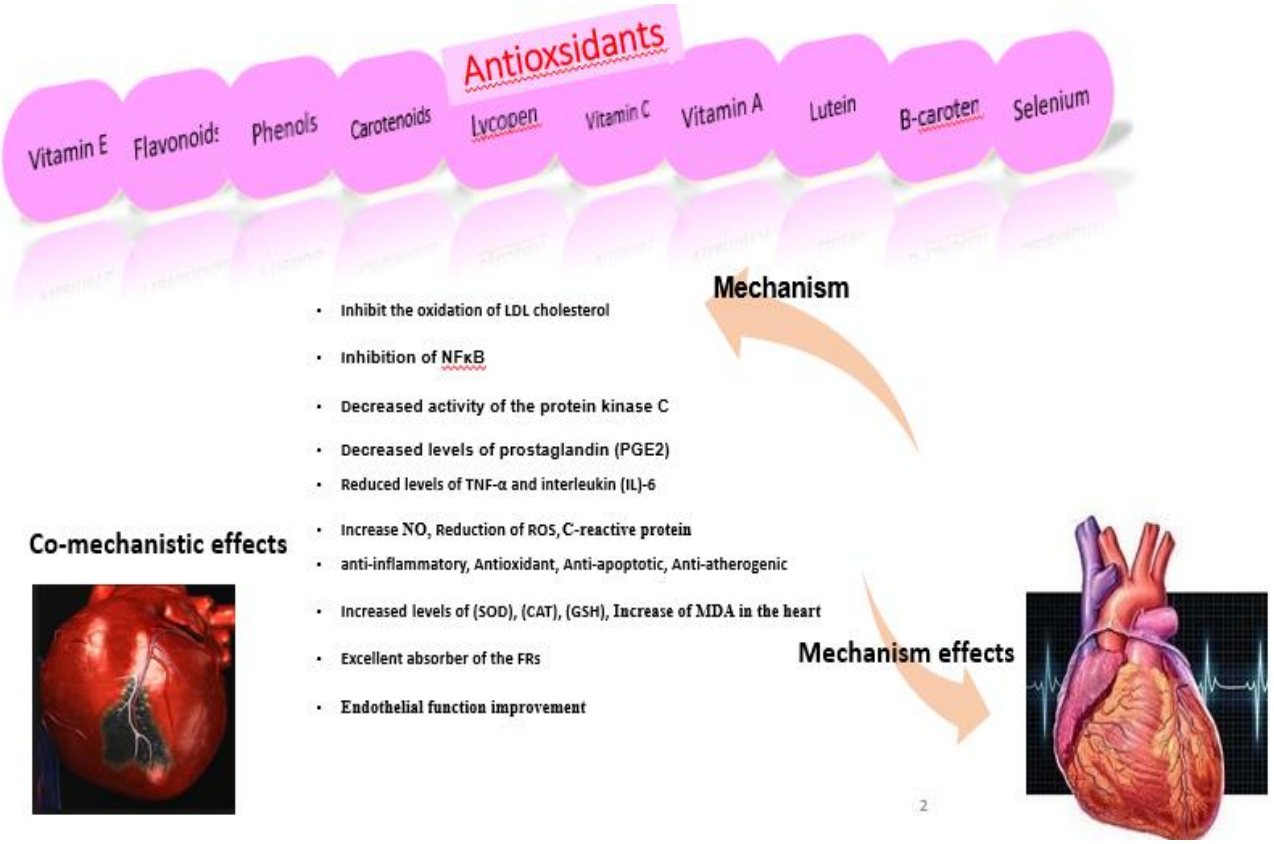

Fig. 1 Protective effects of antioxidants against cardiovascular diseases. These effects are due to the inhibition of LDL oxidation, increase of HDL, reduction of inflammatory factors and the reduction of interleukins, reduces oxidative stress, increases nitric oxide and vasodilation, increases anti-apoptotic activity, and increases the antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase and improve endothelial function and mitophagy properties of mitochondria.

DISCUSSION

The present study states that active oxygen species or oxidants that are free or combined with vital components such as the structure of the cell membrane, lipids, proteins and cell DNA react and cause serious oxidative damage in them. These injuries become a prelude to many chronic and non-chronic, inflammatory and cardiac diseases, etc. Antioxidants are compounds in both synthetic and natural forms. There are many natural antioxidants in fruits and vegetables that neutralize reactive oxygen species, but one should be careful in the dosage and duration of their use.

In a double-blind study conducted on 2002 patients with coronary atherosclerosis in England, 800 and 400 units of vitamin E were given to the case group and placebo to the control group. Treatment with vitamin E significantly reduced the risk of heart disease and heart attack. The death rate was 36 people in the case group and 27 people in the placebo group, which difference was not significant. Finally, it was concluded that treatment with vitamin E for one year is beneficial and reduces the possibility of heart attack [119].

In a double-blind study, 40 patients in two groups were examined for one year. The first group was given 500 mg of vitamin C and 400 mg of vitamin E once every two days, and the second group was given a placebo. All patients received pravastatin. In the period of one year, the intima increased by 8% in the placebo group. From the results, it seems that the use of antioxidants C and E reduces the early progression of coronary atherosclerosis [120].

In a review study in 2006, Siekmeier considers antioxidants C, E and beta-carotene to be effective in preventing atherosclerosis based on in vitro studies. Also, based on clinical and epidemiological studies, the use of antioxidants (vitamin E, beta-carotene) in healthy people, especially in large amounts, is known to be harmful [121].

Early studies in the UK reported the opposite, linking fresh fruits and vegetables have antioxidant properties and reduce the risk of cardiovascular diseases [122]. Verlangieri *et al* showed the opposite and they show the inverse relationship between the

consumption of antioxidants and the reduction of heart diseases [123].

A study by Ginther *et al*. in the United States, it has been shown that vitamin C intake is associated with reduced mortality [124]. A study by Gey *et al* showed an inverse relationship between vitamin E levels and cardiovascular disease in 11 European countries [125]. The study by Riemersma *et al* showed that there is a significant relationship between the consumption of vitamin E and angina, but there is no significant relationship between selenium and vitamin A [35]. A study by Ramirez *et al* showed that there is an inverse relationship between blood ascorbic acid and heart disease [126].

A study by Kok *et al* reported no significant association between vitamin A, vitamin E and subsequent vascular mortality [127]. Finally, a study by Street *et al* reported a significant inverse association between p-carotene in frozen samples and subsequent risk of myocardial infarction [128].

In the end, it can be concluded that due to the increase in the number of cardiovascular diseases and the death caused by it and the importance of antioxidants in the health of the heart and blood vessels, it is recommended to pay more attention in this field and it is necessary to inform the society about the importance of antioxidants, and to educate people about the consumption of natural and nutritious substances that contain these antioxidants. In people who are at risk (such as people with low intake of these antioxidants or high serum levels), it is necessary to control and take supplements by a doctor. Furthermore, there are numerous other plants with high level of antioxidant activity [129,130]. The positive effects of these plants also should be examined in cardiovascular complications.

CONCLUSION

We conclude that free radical damage contributes to many chronic health problems. These include cardiovascular and inflammatory diseases, cataracts, and cancer. Antioxidants prevent tissue damage caused by free radicals by preventing their formation, destroying them, or promoting their degradation. Recently, it has been reported that artificial antioxidants are dangerous to human health. Therefore, the search for effective and non-toxic natural compounds with antioxidant activity has been on the rise in recent years. In addition to endogenous antioxidant defenses, dietary and plant-derived antioxidants appear to be a viable alternative. The main sources of antioxidants are diet and other plant compounds. Antioxidants have protective effects against cardiovascular diseases such as CVD, atherosclerosis, and HF. These effects are due to the inhibition of LDL oxidation, the increase of HDL, the reduction of inflammatory factors and the reduction of interleukins, the Reduces oxidative stress, the increase in nitric oxide and vasodilation, increased anti-apoptotic activity, and increases in the antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase and improve endothelial function and mitophagy properties of mitochondria.

Declarations

Acknowledgements

Not applicable.

Funding

The authors received no funding for this project from any organization.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for Publication

Not applicable

Competing Interests

The authors declare that they have no conflict of interest.

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