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Review

Exploring the potential impact of herbal antioxidants on human cardiovascular diseases

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Abstract: The body's antioxidant system efficiently neutralizes reactive oxygen species, which are intermediates formed during routine metabolic activity. Oxidative stress resulting from an imbalance in this neutralization process is known to be a key factor in many human ailments, including atherosclerosis and various cardiovascular diseases. Observational epidemiological research conducted over the past several decades has shown that consumption of vegetables and fruits rich in vitamins and antioxidants is associated with a reduced incidence of cardiovascular disease. However, it is crucial to exercise caution when considering the use of herbal antioxidants as a treatment for various ailments, including cardiovascular conditions. This caution arises from concerns related to their safety, potentially life-threatening side effects, toxicity, and potential interactions with other medications. Multiple research studies have highlighted these risks associated with antioxidant usage as a form of medical intervention. This overview briefly summarizes cardiovascular disease, associated risk factors, and the role of reactive oxygen species and oxidative stress in its development. Next, delve into some of the most significant plant-based antioxidants, their therapeutic uses, as well as the potential benefits and drawbacks of using them to treat various diseases, with a particular focus on their relevance to cardiovascular disease.

1. Introduction

Cardiovascular disease (CVD) is an encompassing phrase denoting ailments of the heart or blood vessels, where blood flow to the heart, body, or brain can be impeded by a blood clot or the accumulation of fatty deposits in an artery, resulting in the hardening and constricting of the artery. Recent years have seen a significant rise in mortality linked to chronic illnesses, with CVD (hypertension, arrhythmias, myocardial infarction, heart failure, etc.) being one of the primary non-communicable conditions causing a large number of deaths worldwide (1). The number of deaths caused by CVDs increased worldwide, rising from 12.1 million in 1990 to 20.5 million in 2021, as stated in a recent report by the World Heart Federation (WHF). CVDs are prevalent in low- and middle-income countries, accounting for over 80 % of cases and associated fatalities, not solely affecting high-income nations. There are several risk factors for CVDs, which may be categorized as variable and invariable risk factors. Gender, age, ethnicity, and family history are invariable risk factors because there is nothing an individual may do to mitigate them (2). Identifying the mechanisms that lead to

atherosclerosis has advanced significantly in recent years, and one such mechanism is oxidative stress, which is a common finding in individuals with significant CVD risk factors like hypertension, hypercholesterolemia, smoking, and diabetes mellitus (3). Additionally, these risk factors can set off several pathways that collectively result in CVDs including endothelial cell (EC) apoptosis, initiation of proliferation and smooth muscle cell relocation, metalloproteinase actuation, modifications to vasomotor processes, and lipid peroxidation (4). Reactive oxygen species (ROS) are reactive free radicals with oxygen that are chemically unstable and reactive. Examples of these free radicals include lipid radicals, hydroxyl radicals ($OH^{\cdot -}$), and superoxide anion ($O_2^{\cdot -}$). Although ROS, for instance, hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and peroxynitrite ($ONOO^-$), aren't free radicals, they have an oxidizing impact that leads to oxidant stress (5). Comprehensively, a large body of research connects oxidative stress (OS) and ROS to the pathophysiology and physiology of CVD (6). The impact of OS and ROS on the pathogenesis of CVD has been covered in the latter section of this article.

Observational data from epidemiological research point to the possibility that antioxidant supplementation can safeguard against the potentially detrimental consequences of OS on the cardiovascular system, hence halting the progression of atherosclerosis and CVDs (7). Antioxidants provide a variety of health benefits, including the ability to delay the onset of many diseases. Antioxidants produced naturally by an organism may be able to counteract the OS brought on by numerous physiological processes. These include exogenously ingesting naturally occurring antioxidant enzymes viz. vitamin C, E, and A for their protection against ROS. Aside from their ability to neutralize free radical scavenging properties, antioxidants have several essential impacts, including their function in cellular signalling (8). Antioxidants may help hinder medical conditions that arise from cumulative oxidative damage by shielding every cell and membrane in the body from the ravages of daily life (9). Furthermore, the mechanisms underlying the antioxidants' beneficial effects in the prevention of CVDs remain vague and likely complex, as the effects of various antioxidants in various CVD range widely from potentially beneficial to numerous futile to potentially detrimental outcomes. The present review article primarily concentrates on the most important herbal antioxidants, their therapeutic applications, and the potential advantages and disadvantages of utilizing them for the treatment along with how they might aid in preventing certain CVDs.

2. Risk Factors for CVD

Methods The possible contribution of oxidative damage to CVD has been the subject of ongoing research for several decades. In layman's terms, the likelihood of triggering the production of ROS can be further increased by variables that are already known to raise the risk of CVDs, such as diabetes mellitus, ageing, smoking, nitrate intolerance, and hypercholesterolemia (10). Other additional fundamental factors contribute to CVDs. These are an illustration of the principal forces influencing cultural, social, and economic transformation –urbanization, population ageing, and globalization. Hereditary, poverty, and stress events are among other predictors of CVDs (11). Additionally, these risk factors can set off several pathways that collectively result in CVDs (4). Several unavoidable risk factors for cardiac disorders cannot be modified, but there are also a large number of alterable risk factors. The first step in preventing this silent killer is to be aware of potential contributing factors for CVD (12). Some of these variable and invariable risk factors of CVD are given in **Table 1.** The combination of potential risk factors provides an estimate of the total odds of having a stroke or heart attack in the next six years, which is known as 'absolute CVD risk'. Due to the large population and numerous risk indicators for CVD, the Indian subcontinent has a staggering rate of CVD (13).

Table 1. List of variable and invariable risk factors for CVD.

Sl	Variable	Invariable	Description	Ref
1	Smoking	-	Risk of acute thrombosis due to the onset of atherosclerotic alterations, including vascular lumen constriction and triggering of a hypercoagulable condition.	(14-15)
2	Alcohol consumption	-	Plaque accumulation in arteries, abnormalities in arterial-vascular efficiency, and imbalances in hormones that affect how the body regulates its fluid and blood pressure (through the renin-angiotensin-aldosterone system [RAAS])	(14,16)
3	Sedentary lifestyle	-	Reduces vascular function and insulin sensitivity while elevating sympathetic nervous system activity and decreasing cardiac output	(14,17)
4	Unhealthy diet	-	Meal consumption induces a mild pro-oxidative milieu that elevates circulating levels of the biomarkers for adhesion, inflammation, and endothelial dysfunction. Additionally, elevated cholesterol levels and atherosclerotic cardiovascular disease (ASCVD)	(18,19)
5	Excessive body weight	-	Risk of cardiovascular disease is exacerbated and elevated by insulin resistance, high blood pressure, fluctuations in hormones that cause inflammation, and dyslipidaemia	(20,21)
6	Elevated blood pressure	-	Through artery hardening and a reduction in the amount of oxygen and blood flow reaching the heart, it adversely impacts the heart	(14,22)
8	Socioeconomic	-	Income scale, work status, educational attainment, and community socioeconomic determinants are the four aspects that have consistently been linked to CVD in high-income nations	(14,23)
9	Psychosocial	-	Psychosocial anxiety viz. behaviour, animosity, despair/hopelessness, and workload stress, causes inflammation-induced LDL-cholesterol (LDL-C) oxidation, increased shear stress, and unfavourable catecholamine and reproductive hormone alterations, all of which contribute to further endothelial damage	(14,24)
10	-	Family history	Changes the prospective risk of CVD based on the proportion and maturity of afflicted first-degree kin. Siblings of CVD patients have a 40 % incidence surge, whereas offspring of premature CVD parents experience a 60 % to 75 % incidence surge	(25)
11	-	Age	A surge in RAAS function and angiotensin II concentration, a key RAAS effector, leads to an increase in ROS generation via initiating NADPH oxidase	(26)

12	-	Gender	Numerous genomic alterations are mediated by pathways that include estrogen bound to nuclear receptors of estrogen (ERs), which come in two main varieties: Erα and ERβ	(27)
13	-	Diabetes	Elevated glucose flow via the polyol route, induction of protein kinase C (PKC), rise in advanced glycation end products (AGE), elevated glucose flux via the hexosamine route, and stimulation of the 12/15-lipoxygenase (12/15-LO) route, all of which conduce to higher superoxide generation	(14,28)
14	-	Ethnicity	Social determinant of health (SDOH) is a disorder that predisposes persons of colour (Black, American Indian, Hispanic, Asian, etc.) to poor clinical responses, especially CVD	(29)

3. Impact of ROS and OS on the Pathogenesis of CVD

Free radicals may be present within the body as DNA, lipid, and protein radicals as well as certain ROS ($^{\bullet}OH$, $O_2^{\bullet-}$, $^{\bullet}NO$, and $ONOO^-$). ROS are electron-deficient molecules that are transient and extremely reactive (30). They are a common metabolic by-product of cells (31), and are crucial in the regulation of cell viability, apoptosis, differentiation, cell signalling, and the formation of inflammatory factors (32). ROS, which comprises both free radicals and non-radical species, are distinguished by their resilient reactive chemical properties and are shown in **Table 2** (33).

Table 2. List of ROS determining the radical and non-radical species.

Radical	Non-radical
Hydroxyl (OH-)	Hydrogen peroxide (H2O2)
Peroxyl (RO2-)	Hypobromous acid (HOBr)
Hydroperoxyl (HO2-)	Hypochlorous acid (HOCL)
Alkoxyl (RO-)	Singlet oxygen (Δg)
Superoxide (O2•-)	Ozone (O3)

The risk parameters outlined above can promote ROS production and can also set off several pathways, including EC apoptosis, initiation of proliferation and smooth muscle cells relocation, metalloproteinases actuation, modifications to vasomotor processes, and lipid peroxidation which together can result in CVDs (4). ROS such as $^-O_2$, HO, H_2O_2, and $OONO^-$ have been linked to the onset or development of CVD. ROS generated by enzymatic means includes $^-O_2$ and H_2O_2, which have been linked to the disease's pathologies and physiological signalling. In addition, the superoxide dismutase (SOD) can spontaneously transform $^-O_2$ into H_2O_2 (34). Furthermore, neither HO nor $OONO^-$ are regarded as ROS signalling molecules. Due to their high reactivity, such ROS molecules have been implicated in tissue impairment and OS. HO can be generated by the catalysis of H_2O_2, and glutathione is capable of eliminating it. The $^-O_2$ and NO interaction results in $OONO^-$, which catastrophically affects endothelial tissue because it depletes NO and uncouples the endothelium's nitric oxide synthase (eNOS). This cyclic response then encourages the development of endothelial dysfunction (35). The primary mediators of CVD-ROS are mitochondrial NADPH oxidases (NOX), oxidases (LO), myeloperoxidases (MPO), and xanthine oxidases (XO). In addition, ROS-source-crosstalk has been widely established, with H_2O_2 activating NOX, alongside inducing xanthine dehydrogenase transition to

XO; $OONO^-$ inducing $^-O_2$ formation; and, perhaps most intriguing, mitochondria and NOX interacting with one another, resulting in an oxidative cycle (36-37). ROS detoxification is crucial for every cell's viability. To survive in oxygen-rich cellular conditions, biological organisms have acquired several protective mechanisms that establish an equilibrium amid the production and eradication of ROS. The disparity across the systemic formation of ROS and cells' ability to rapidly metabolize reactive intermediates or recover the resulting dysfunction is commonly referred to as "oxidative stress" (OS) (38). In the past couple of years, OS markers have become more often used in patients with cardiac failure. 8-hydroxy-20-deoxyguanosine (8-OHdG), one of the most common types of free radical-induced oxidative DNA lesions, is one of the indicators that has drawn more attention (39-40).

4. Antioxidant Defense System

The term "antioxidant" refers to a molecule that safeguards the cell's lipids, protein, DNA, RNA, and carbohydrates from damage caused by oxidation by blocking or scavenging reactive radicals that include RNS (reactive nitrogen species) and ROS. Numerous antioxidant elements are thought to be crucial for the body's defensive mechanisms to minimize the damage caused by free radicals, which have been linked to the progression of CVDs. A lower risk of cardiovascular disease is reportedly attributed to diets abundant in fruits and vegetables, which include antioxidants such as vitamin C, vitamin E, and β-carotene (41). Those liable for retaining transition metal ions, which in their liberated form facilitate the synthesis of hydroxyl radicals, can be called preventive antioxidants; these include the iron-binding protein transferrin, the copper-binding protein caeruloplasmin, and albumin (1). Antioxidants are classified according to their catalytic activity, which might be enzymatic or nonenzymatic. The enzymatic antioxidants are extremely selective for substrate-reactive molecules and have particular cofactors. Examples of enzymatic antioxidants include CAT, GPx, and SOD. However, those nonenzymatic antioxidants are different from the former since they lack a particular substrate and may thus counteract the damaging impacts caused by both ROS and RNS (42).

4.1 Enzymatic Antioxidant

The antioxidant defense system's enzymatic constituents include a plethora of antioxidant compounds, (43) that are listed in **Table 3**. The antioxidant enzymes in the cell carefully control redox equilibrium, which is essential for regulating cellular homeostasis and protecting against OS by degrading ROS (43,44). Enzymatic antioxidants, which comprise catalase, SOD, and glutathione peroxidase (GSHPx), facilitate the depletion of oxidants throughout cells (1). SOD is the sole enzyme capable of catalyzing the conversion of superoxide anion to oxygen and hydrogen peroxide among numerous enzymatic compounds. Three distinct isoforms have been identified thus far: manganese SOD (MnSOD) found in the mitochondrial matrix, extracellular SOD (ECSOD), which is present in extracellular fluids, and copper-zinc SOD (Cu/ZnSOD) found in the cytoplasm and nuclei (45,46). The peroxisome's chloramphenicol acetyltransferase (CAT) breaks down H_2O_2 into water and oxygen. Nearly all human tissues contain GSHPx, which may be found both intracellularly and extracellularly. The enzyme GSHPx exhibits potent anti-H_2O_2 and anti-fatty acid hydroperoxide activity. Peroxynitrite ($ONOO^-$), organic hydroperoxides, and H_2O_2 are all reduced by an enzyme called peroxyredoxin. The complicated nature of ROS biology is revealed by the various expression patterns, subcellular sites, and substrates of the enzymes that neutralize them. Undoubtedly, antioxidant enzymes are essential for preventing damage due to oxidation (47).

4.2 Non-enzymatic Antioxidant

Non-enzymatic antioxidants are widely present across all compartments within cells. Non-enzymatic antioxidants suppress free radical chain reactions, in contrast to enzymatic antioxidants. The intended effect

of antioxidants is not to fully eradicate free radicals but to keep them at an optimal level as ROS is known to play in various redox signalling processes, in addition to response against specific pathogens (47,48). Non-enzymatic antioxidants are classified into two types: natural antioxidants and synthetic antioxidants as shown in **Table 3**. However, because the subject of this article is confined to natural herbal antioxidants, this article focuses mostly on natural non-enzymatic antioxidants, which are covered under the section titled *plant-derived antioxidants*.

Table 3. List of antioxidant defence in biological systems (1,42,49).

Enzymatic	Non-Enzymatic	
	Natural	**Synthetic**
Superoxide dismutase	Vitamin C	*Butylated hydroxytoluene*
Catalase	Vitamin E	*Butylated hydroxyanisole*
Glutathione peroxidase	Carotenoids	-
Glutathione transferase	Glutathione	-
Glutathione reductase	Bioflavonoids	-

5. Plant-derived Antioxidants

Although conventional medications (beta-blockers, diuretics, calcium channel blocker, anticoagulant, ACE inhibitors etc.) have been used to treat cardiovascular diseases, their effectiveness has been constrained by side effects such as kidney dysfunction, liver enzyme elevation, elevated blood potassium levels, bradycardia etc., hence, forcing a search for alternatives (50). As a result, the search for new cardioprotective agents is shifting toward natural sources. Enzymes such as GSHPx, SOD, catalase, and reduced glutathione are part of the antioxidant defence system in humans. However, exogenous antioxidants like vitamin E and ascorbic acid can enhance the benefits of the endogenous antioxidant system (51). Antioxidants have recently acquired popularity due to their numerous health advantages. They have been demonstrated to reduce the risk of CVD (52). Plants are enriched with antioxidant phytochemicals. The use of natural antioxidants as a preventative measure against cardiovascular issues such as ischemia-reperfusion has recently gained more attention. Cardioprotective attributes of medicinal plants have been found to reduce harm to macrophages and monocytes, cardiomyocytes, vascular smooth muscle cells, and endothelial cells (53). Plants are the primary source of the perpetual need for novel medications with fewer side effects and lower costs. As a result, there is an urgent need for therapeutic candidates that are safe, effective, eco-friendly, and cost-effective (54). Some of the most important antioxidants derived from plants are addressed further below.

5.1 Vitamin C

Vitamin C, also known as ascorbic acid, ascorbate, or L-ascorbate, is a water-soluble natural vitamin that serves as a free radical scavenger and a cofactor in various enzyme activities, including catecholamine production (55). It is synthesized in mitochondria and transported to another cell through proton–electron chemical gradient or through facilitated diffusion. Additionally, it can scavenge a wide variety of free radicals Its antioxidant activity is derived from its non-enzymatic reduction of O2 •-, hydroxyl (HO•), alkoxyl (RO•), peroxyl (ROO•), and other radicals (56). When Vitamin C scavenges free radicals in lipid membranes, it combines with the radical tocopheroxyl, which originates from Vitamin E oxidation, regenerating vitamin E (57). Vitamin C acts by detoxifying both external and endogenous ROS, as well as the modified proteins and lipids formed by the ROS. Studies have demonstrated that vitamin C can regulate smooth muscle-mediated vasodilation, endothelial cell proliferation, and apoptosis, both of which are crucial in the pathophysiology of cardiovascular disorders (58). The absorption, distribution, and metabolism of vitamin C are complex, in

contrast to those of the majority of molecules with low molecular weights. The sodium-dependent vitamin C transporter family of proteins is primarily responsible for its absorption and distribution in tissues (59). The variable expression of these transporters between tissues results in nonlinear pharmacokinetics of vitamin C under physiological conditions, with highly compartmentalized distribution (60). Ascorbic acid can fight against chronic diseases, such as cardiovascular diseases and certain types of cancer. The main sources of ascorbic acid are fruits (orange, grapefruit, kiwifruit etc.) and vegetables (rep pepper, green pepper, broccoli etc) (61).

5.2 Vitamin E

Vitamin E is the primary lipid-soluble antioxidant. It is a common name for eight compounds known as trocochromanols among which four are tocopherols and four are tocotrienols. Since the human body is unable to synthesize this vitamin, it needs to be obtained from the diet (62). As shown in the equation, vitamin E (-tocopherol) 1 intercepts lipid peroxyl radicals (LOO•) and terminates the lipid peroxidation chain reactions as seen in Equation 1.

$$LOO^{\bullet} + \alpha\text{-tocopherol–OH} \rightarrow LOOH + \alpha\text{-tocopherol–O} \qquad \textbf{Equation 1}$$

The resulting tocopheroxyl radical is comparatively stable and, under normal conditions, not sufficiently reactive to start lipid peroxidation on its own, which is a crucial requirement for an effective antioxidant (47). Vitamin E also inhibits superoxide production by impairing the assembly of NOX enzymes. Experimental studies have shown that vitamin E can reduce the risk of coronary heart disease (CHD) and cardiovascular consequences. A meta-analysis of 400,000 patients found that consumption of vitamin E and C reduced the risk of coronary heart disease (63). However, the antioxidant effects of each Vitamin E isoform are complex, and their mechanism is still unknown. Researchers believe that vitamin E may protect essential cell components by decreasing free radicals and interrupting the chain reaction of lipid peroxidation. Thus, cell membranes are protected by lipid repair and replacement (64). However, due to the lack of approved findings, the American Heart Association does not advise vitamin E supplementation to prevent CVD. Instead, it suggests consuming foods high in antioxidant vitamins, particularly fruit and vegetables (65).

5.3 Carotenoids

Carotenoids are a class of over 600 fat-soluble compounds that are found in plants. Around 50 of them are found in the human diet (66). The carotenoids that are found most abundantly in the food are β-carotene, lutein, lycopene, β-cryptoxanthin, astaxanthin, and zeaxanthin (67). It is crucial to remember that carotenoids (a-carotene, β-carotene, cryptoxanthin) are precursors of vitamin A and that astaxanthin is one of the most notable carotenoids that has been identified as a ROS scavenger (68). Based on their ability to quench singlet oxygen and their significant antioxidant characteristics, these compounds possess a high potential for promoting healthy life. They may suppress free radicals by the following mechanisms: (1) electron transfer, which results in the creation of carotenoid cation radicals, (2) addition, which results in radical adduct formation, and (3) hydrogen atom transfer (69). They protect the plasma lipoprotein structure against oxidative alterations. They prevent the generation of oxidized LDL (ox-LDL), which possesses proatherogenic characteristics. Free radicals lead to hypertension by raising the level of F2-isoprostanes, which leads blood vessels to constrict. Thus, by scavenging free radicals, antioxidants may prevent the rise in blood pressure. In addition, since carotenoids are antioxidants, they may prevent the development of advanced oxidation protein products (AOPPs), whose elevated level is linked to increasing common carotid artery intima-media thickness (CCA-IMT) (70,71). Furthermore, astaxanthin's preventive efficacy against I/R damage and

thrombotic disorders was shown in preclinical research in animal models (68). Additionally, it has been demonstrated that astaxanthin lowers blood pressure in spontaneously hypertensive rats (72)

5.4 Glutathione

GSH is a tripeptide (cysteine, glycine, and glutamic acid) that is abundant in the mitochondria and cytoplasm of most of the cells. It is produced in the cytoplasm by the sequential addition of cysteine to glutamic acid, followed by the addition of glycine. GSH is a cofactor for the enzyme GSH peroxidase, serves as a substrate for the enzyme GSH S-transferase, and keeps exogenous antioxidants within range (73,74). It also acts as an antioxidant, a free radical scavenger, and a detoxifying agent. As an antioxidant, GSH lowers ROS in both enzymatic and nonenzymatic reactions. In addition to repairing lipids harmed by peroxidation processes and maintaining the reduced form of sulfhydryl moieties in proteins, it regenerates other oxidized antioxidants including vitamin C and E (75,76). The sulfhydryl group of cysteine is required for GSH activity because it contributes to reduction, oxidation, and conjugation processes [30]. To maintain an intracellular reducing environment and prevent the overproduction of damaging ROS, GSH works in collaboration with three groups of enzymes. These enzymes are glutathione reductase (GR), glutathione oxidase (GOx), and GSHPx. GSHPx is a selenium-containing enzyme that catalyzes the reduction of peroxides by utilizing GSH as a sacrificial reductant (77). This antioxidant exists in two states: reduced (GSH) and oxidized (GSSG); in the reduced state, the cysteine's thiol group can donate an electron to unstable molecules such as ROS; by donating this electron, the GSH oxidizes and reacts with another GSH to produce GSH disulfide (GSSG). As a result, the ratio of GSH/GSSG represents the redox status of the cells (78).

5.5 Flavonoids

A wide class of polyphenolic chemical substances known as flavonoids may be identified by their benzo-y-pyrone configuration (79). Flavonoids are considered low molecular phenolics that are classified into numerous subclasses, including flavones, flavanones, isoflavones, anthocyanins, and flavanols (80). The configuration of functional groups based on structure determines the antioxidant properties of flavonoids. The arrangement and total quantity of hydroxyl groups have a significant impact on how the antioxidant property acts (81). Flavonoids, which are commonly present in vegetables and fruits, are said to have a variety of biological impacts, including the ability to scavenge free radicals (82). Based on an analysis of over 250 observational research studies Veer *et al*. (83), claimed that vegetables and fruits can reduce cancer and CVD. The participation of chelating metal ions, like iron or copper, represents the mechanisms that explain the safeguarding actions of flavonoids on DNA. Iron or copper-complexed flavonoids inhibit the production of ROS (84-86). In addition to mitigating malaria, flavonoids also have antibacterial, antifungal, and anti-LDL oxidation inhibitory properties (80). The potential of flavonoids to increase vasodilation and inhibit apoptotic events in the endothelium, on the other hand, is another favourable impact on the cardiovascular system (87).

6. Clinical Applications of Herbal Antioxidants in CVD

Historically, either as pure active chemicals or as traditional extracts, herbs, and plants have been a significant source of pharmaceuticals. Contrasting to their pharmaceutical derivates, the phytochemical substances found in the natural plant material are highly effective and have fewer adverse effects. A wide range of plants and their bioactive phytoconstituents are widely recognized for their low toxicity, offering alternative treatment possibilities for heart disorders (88). The benefits of using antioxidant natural compounds and their active ingredients to reduce the risk of CVD events have been the subject of several clinical studies. So, the following is a summary of how various natural products can protect against CVDs

6.1 Vegetables and CVDs

Dietary optimization must be viewed as a crucial aspect of lifestyle modification for the control of pre-existing CVD and its mitigation since dietary parameters have a significant influence on the onset and advancement of the disease (89). A poor diet substantially raises the probability of developing serious diseases. 70 % of all fatalities globally are caused by persistent illnesses such as diabetes, cancer, chronic respiratory diseases, and CVD (90). Numerous pathways may work to prevent CVD when minerals and phytochemicals are consumed in plant-based meals. These consist of regulating blood pressure, managing lipid and glucose metabolism, modulating enzyme activity, changing the expression of genes and signalling mechanisms, influencing antiplatelet activity, antioxidants, and anti-inflammatory; influencing endothelial function, and reducing myocardial injury (91-92). Additionally, several studies demonstrated beetroot's strong hypotensive effectiveness, which was linked to its excessive nitrate concentration. For instance, research showed that pregnant hypertensive women who had 70 mL of juice from beetroot had their (diastolic blood pressure) DBP levels dramatically reduced (93). A randomized controlled study (RCT) demonstrated that patients with hypertension and a high risk of CVD saw a reduction in DBP and mean arterial pressure after taking 213 mg of tomato extract daily for 4 weeks (94). Also, stressed individuals with stage 1 hypertension or normal-high blood pressure who regularly consumed 1.2 g of aubergine powder had a significant improvement in their blood pressure and mental health (95). According to the findings presented, increased vegetable consumption may have the greatest positive effects on cardiovascular health when cruciferous and leafy green vegetables are consumed (90)

6.2 Fruits and CVDs

Numerous clinical studies have revealed a detrimental relationship between fruit intake and the risk of CVDs. An RCT demonstration found that guava pulp significantly enhanced lipid composition by reducing TG (triglycerides), TC (total cholesterol), and LDL-C (low-density lipoprotein cholesterol) levels while increasing HDL-C (high-density lipoprotein cholesterol) levels (96). In a different RCT, 100 g of soursop fruit was shown to substantially decrease DBP, SBP (Systolic blood pressure), and serum uric acid levels in pre-hypertensive participants as compared to the control group when ingested twice daily for three months (97). A controlled nonrandomized clinical trial also showed that healthy women who sipped 300 mL of orange juice for two months experienced improvements in their insulin sensitivity, blood glucose, LDL-C, and gut microbial metabolism (98). In addition, a cross-over research revealed that following the ingestion of 200 mg or 400 mg of the anthocyanin obtained from haskap berry (*Lonicera caerulea* L.), BP levels in subjects between the ages of 62 and 81years were dramatically lowered (99). According to Swedish women and men's cohorts, eating 3.1 servings of total fruits per day reduced overall stroke risk by 13 % as compared to eating 0.4 servings per day (95 % confidence interval (CI): 0.78–0.97) (100). Thus, eating fruits like guava, oranges, soursop, etc. is a useful strategy for managing and preventing CVDs.

6.3 Nuts and CVDs

Nuts are foods that are nutrient-dense and have intricate matrices that are high in unsaturated fatty acids as well as additional bioactive substances, including l-arginine, beneficial minerals, fibre, vitamin E, polyphenols, and phytosterols. Nuts are believed to have a positive impact on cardiovascular health due to their distinct makeup. Studies on the epidemiology of disease have linked nut intake to lower rates of coronary heart disease (CHD) in both sexes and diabetes in women particularly (101). An RCT indicated that eating almonds, which included 15% energy, significantly reduced total body fat and truncal as well as DBP in persons who are obese or overweight (102). Intake of walnuts significantly decreased body weight, waist

circumference, body mass index, TC, SBP, and LDL-cholesterol, according to the results of another 6-month RCT (103). The randomized clinical trial of PREvencio'n con DIeta MEDiterra'nea (PREDIMED) evaluating a long-term nutritional treatment in participants at high risk for cardiovascular disease stipulated first-class data demonstrating that consistently consumption of nuts has been associated with a 50 % decrease in diabetes-related events and, more significantly, a 30 % decline in CVD. It is worth noting that the risk of stroke was decreased by approximately 50 % in individuals assigned to a Mediterranean diet supplemented with a daily portion of mixed nuts (7·5 g almonds, 15 g walnuts, and 7·5 g hazelnuts) (101). In addition, studies have shown that eating a variety of nuts, such as almonds, hazelnuts, cashews, pecans, macadamia nuts, Brazil nuts, pistachios, peanuts, and walnuts, can reduce CVD risk factors by regulating blood sugar and fat levels without harming lipids (104).

6.4 Spices and CVDs

Culinary spices and herbs have been identified to have bioactive components that may have positive effects on health in CVD-risk individuals (105). Spices are abundant in antioxidants, and research indicates that they additionally serve as powerful regulators of inflammation and injury to tissues brought on by excessive sugar in the blood and circulating lipid levels. Spices are a solid source of antioxidants and other possible bioactive substances in the diet since they have a relatively small calorie percentage and are reasonably affordable (106). In an RCT, the concentrations of TC and LDL-C in obese or overweight prediabetic women were considerably reduced after receiving 3 g of cardamom twice daily for two months, despite DBP, SBP, serum lipid, and glycemic indices levels in the cardamom group did not change substantially from the group receiving placebo (107). Another study on individuals suffering from Type 2 diabetes found that cinnamon intake at 1-1.5 g/d and *Dichrostahys glomerata* (DG) intake at 0.8 g/d significantly reduced fasting glucose levels, SBP, DBP, LDC-C, HbA1c, and TG while increasing HDL-C in cinnamon and significantly lowering overall cholesterol levels. Fenugreek intake at 10g/d dosages reduced fasting blood glucose and overall cholesterol levels significantly. *Nigella Sativa* (NS) at dosages of 1-3 g/d reduced LDL-C, and total cholesterol, and improved HDL-C, and TG. Ginger at dosages of 1-2 g/d dramatically decreased fasting levels of glucose, MDA, lipid concentration, and Apo B while considerably increasing Apo A-1 (105,108). Furthermore, regular use of *Satureja hortensis* L. enhanced the lipids balance of individuals with symptoms of metabolic syndrome via decreasing TG, TC, and LDL-C while boosting HDL-C (109). In addition, cumin and garlic had a considerable hypotensive impact on type 2 diabetic patients (110). Consequently, these advantages include the potential for them to offer safeguards against CVD and other ailments

6.5 Tea and CVDs

The nutritional content of teas has received a lot of attention since they are the second-most popular beverage in the world. Tea is believed to have a positive impact on endothelial health and blood pressure reduction, and the outcomes of various research indicate that tea could play an integral role in CVDs (111). Determinants of Myocardial Infarction Onset Study found that those who consumed at least two servings of black tea on average per day experienced a reduction in overall and cardiovascular-related mortality following 3.8 years of follow-up in comparison to individuals who consumed minimal tea (112). Another instance shows that supplementing with green tea extract, a substance that contains 1,315 mg of catechins, might considerably enhance postmenopausal women's lipid profiles by lowering the concentrations of LDL-C, non-HDL-C, and TC (113). According to JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk), heavy coffee intake was linked to an elevated risk of CVD mortality among individuals with extreme hypertension, but not among those having grade 1 hypertension or those who refrain from hypertension. Contrarily, among all BP groups, drinking green tea was not linked to an elevated risk of CVD mortality (114).

Additionally, results from the Multi-Ethnic Study of Atherosclerosis, which involved white, black, Hispanic, and Chinese-American populations, indicated that routine tea use (≥1 cup per day) might slow the development of coronary artery calcification which resulted in a reduction in the incidence of cardiovascular events, and when contrasted to different ethnicity/race groups, the Chinese-American population consumed more tea and had a less frequent occurrence of events related to CVD (115). Furthermore, in a randomized controlled trial of 19 hypertensive individuals, black tea had outstanding endothelium protective benefits. In this study, participants sipped black tea (150 mg polyphenols) or a placebo twice per day for eight consecutive days. The findings showed that black tea might increase the quantity of circulating angiogenic cells and alleviate acute oral fat load-induced endothelial cell dysfunction (116).

6.6 Other Plants and CVDs

Other natural commodities, such as herbs, grains, and legumes, have also been shown to protect cardiovascular health (117). Various medicinal plants widely recognized for treating CVD are - *Terminalia arjuna*, *Tinospora cordifolia, Daucus carota*, *Amaranthus Viridis, Mucuna pruriens*, *Bombax ceiba, Salvia miltiorrhiza, Nerium oleander, Ginkgo biloba, Hydrocotyle asiatica, Picrorhiza kurroa,* and *Andrographis paniculate*. These plants include flavonoids, a plant sterol, terpenoids, polyphenols, plant sulfur compounds, and other active phytoconstituents. The prevention of LDL oxidation, which encourages vasodilatation, is a common flavonoid mode of action. By lowering blood cholesterol absorption, plant sterols reduce CVD (118). For example, stage 1 hypertension patients' blood pressure was successfully lowered by consuming two cups of *Hibiscus sabdariffa* in the early hours of the day (119). In a 3X3 complete randomized repeated measures design research, it demonstrated that using 25 or 45 g of soy flour daily in the form of dosa in postmenopausal women experiencing pre-hypertension and prediabetes was shown to have an impact on DBP, glycaemic management, and insulin resistance (120). A dosage of 1 mg/kg of *Dioscorea deltoidea* can also prevent the onset of arterial hypertension (SBP decreases by 9.7 % ($p < 0.05$) and DBP (lower by 8.2 %), as well as 1.75 times, lessen the coefficient of endothelial dysfunction in the presence of hypoestrogenic conditions (121). In a clinical experiment, normal and moderately hypercholesterolemic participants were used to examine the lipid-lowering ability of oat noodles in place of a partial staple diet (rice noodles or wheat). Oat noodle has been shown to significantly enhance the health state of all participants, particularly hypercholesterolemic patients, and hence minimise the CVD risks (122). As a result, clinical trials involving subjects with varying conditions demonstrated that several antioxidant natural substances might promote cardiovascular conditions and minimize the potential risk of CVDs, which may be associated with lowering BP, maintaining serum lipid levels, minimising blood sugar levels, and reducing total body weight.

7. The Extent of Reliance on Antioxidant Supplementation: Are we on Solid Ground?

Antioxidants are compounds that prevent free radical damage and maintain the well-being of the host's cells within the body, and supplements containing antioxidants include amplified forms of these molecules (123). Phytochemicals like carotenoids and polyphenols, as well as alkaloids, flavonoids, phenolic acids, glycosides, lignans, and saponins, are found in herbal products derived from seeds, roots, gums, bark, leaves, berries, or flowers. These phytoconstituents are regarded to impart health advantages. Higher consumption of dietary flavonoids may lower the risk of chronic illnesses, such as certain malignancies and CVD, according to epidemiological research (124). However, there is mounting research suggesting that antioxidants tend to be more potent when they come from a whole meal instead of when they are isolated from a diet (125). Supplements containing antioxidants at high doses may occasionally be dangerous. For instance, the findings

of certain research studies have connected high doses of supplements containing beta-carotene to a higher probability of lung cancer in people who smoke and high doses of vitamin E supplements to an elevated risk of both prostate cancer and hemorrhagic stroke (a kind of stroke brought on by bleeding in the brain) (126-127). Shie *et al*. (128), performed the analyses of 13 trials that involved 1956 participants following cardiac surgery, and the results revealed that vitamin C substantially lowered the prevalence of postoperative atrial fibrillation (POAF) and the possibility of undesirable events. The researchers concluded that vitamin C use, both on its own and in conjunction with other therapies, may mitigate POAF in individuals experiencing cardiac surgery, and it ought to be advised to patients to minimize the risk of POAF. Also, there is a direct correlation between the physiological effects of vitamin E and C. Ingesting supplements with 2 g of vitamin C and 600 mg of vitamin E significantly augmented endothelium-dependent vasodilatation in the radial circulation in patients with coronary artery disease (CAD) (129). On the other hand, resveratrol is a non-flavonoid stilbenoid that has a wide range of therapeutic advantages, notably antioxidant and anti-inflammatory capabilities, anti-platelet, immuno-modulator, anti-hyperlipidemic, neuroprotective, vasorelaxant, and cardioprotective activities (130). An assessment of the resveratrol studies over the past ten years revealed that moderate and repeated doses of the supplement are preferable to a single, greater dose. A daily dose of 1 g or higher is considered safe and effective, although up to 5 g of resveratrol is considered safe (131). On the other hand, plants contain tens of thousands of flavonoids in a variety of concentrations and compositions. Currently, the weight of scientific research points to a possible link between long-term intake of foods high in flavonoids and a reduced risk of both lethal and non-lethal ischemic heart disease (IHD), cerebrovascular disease, and overall CVD (132).

However, doses below 1 mg/adult/day are being suggested for people as a precautionary. Flavonoids are capable of acting as mutagens, pro-oxidants that develop free radicals, and regulators of crucial enzymes associated with hormone metabolism when consumed in greater doses (133-134). Bergström *et al*. (135), also added that if antioxidant nutrients or vitamins are ingested at levels much higher than those advised for dietary consumption, they may serve as pro-oxidants or harmful "oxidants." In the context of carotenoids, various epidemiological research has demonstrated an association between increased dietary consumption of carotenoids and the reduction of CVD (136). Toti *et al.* (137), have thus recommended a safer dosage of β-carotene (2-4 mg/day) and non-provitamin A carotenoids (up to 20 mg/day) for lutein and (75 mg/day) for lycopene. However, in enormous-scale prospective randomized studies, major adverse effects of β-carotene have been documented: Smokers and asbestos-exposed employees who took 20 to 30 mg of β-carotene supplements daily for four years had an elevated incidence of CVD and lung cancer (138). Based on data from numerous clinical trials, Coenzyme Q (CoQ10), another antioxidant, has a safety level of 1200 mg/day/person, indicating that it is incredibly safe for consumption as a nutritional supplement (139) and that diseases linked to CoQ10 deficiency benefit from CoQ10 dietary supplement, that involve mitochondrial diseases, diabetes mellitus, and CVD (140). Jorat *et al.* (141), indicated the results of eight studies' analyses, which included 267 subjects, suggested that individuals with CAD who received CoQ10 had considerably less overall cholesterol and higher HDL-C ratios. It is currently difficult to determine which sort of supplementation with antioxidants will have the greatest impact on CVD. The effects of various antioxidant products on various cardiovascular conditions vary widely, from possible benefits to numerous ineffective adverse responses to certain negative consequences. The varying outcomes might be attributable to a variety of variables, such as the varying concentration used—keeping in mind that excessive quantities have detrimental consequences. Furthermore, because some supplements have no clinical evidence or data from small studies, it is critical to investigate patient-relevant events (142). Antioxidant supplements, like any other nutritional supplements, may interfere with certain drugs. There is contradictory information about the benefits of ingesting vitamins with

antioxidants throughout cancer therapy; some research indicates that taking them may be useful, while others indicate suggesting it may be detrimental. The National Cancer Institute advises anyone receiving cancer treatment to see their doctor before using supplements (143).

8. Conclusion

The pathophysiology of CVD is thought to involve oxidative stress as a significant component. A lot has been reported on how OS plays a part in the onset of cardiovascular events as well as the inception and advancement of atherosclerosis. Even though numerous research investigations have shown that employing antioxidants to reduce OS is advantageous, the efficacy of antioxidant therapy is debatable for several reasons. It has also been hypothesized that dietary or food-based sources of antioxidant vitamins and minerals may be more therapeutically efficacious than traditional non-food-derived supplements of vitamins. Herbal antioxidants have attracted growing emphasis in the prevention and management of different cardiovascular diseases. According to current research, several natural products that are antioxidants and their active substances might be turned into functional meals or medications for the treatment and prevention of CVDs. Additionally, it must be noted that depending on the OS levels, OS may play diverse roles in various disease phases. Therefore, it is essential to monitor the levels of OS indicators before administering antioxidant therapy. Additionally, not every antioxidant has the ability to alter the impact of cardiovascular-related risk aspects and different dose approaches are used in clinical studies for the same disease. As a result, it is unsafe to offer these natural remedies as complementary medicines. The role of various medicinal plants and their fundamental mechanisms in the light of CVDs must therefore be investigated through better-designed studies and upcoming clinical trials with greater sample sizes. These trials should also focus on the toxicity and safety of these natural remedies as well as the synergistic impacts of numerous bioactive elements found in plants.

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