

# Narrative Review of Cardiovascular-Protective Phytochemicals

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## ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with atherosclerosis, endothelial dysfunction, oxidative stress, and chronic inflammation as central mechanisms in their pathogenesis. Increasing evidence highlights the role of phytochemicals, non-nutritive bioactive compounds from plants, in the prevention and management of CVDs. This narrative review synthesizes current findings on the cardioprotective effects of major phytochemical classes, including flavonoids, polyphenols, terpenoids, and alkaloids. These compounds exert multiple biological actions, such as antioxidant and anti-inflammatory effects, regulation of lipid metabolism, improvement of endothelial function, and protection against ischemia-reperfusion injury. Clinical studies demonstrate that phytochemical-rich diets, such as the Mediterranean and Nordic diets, are associated with reduced cardiovascular risk, improved lipid profiles, lower systemic inflammation, and enhanced vascular function. Despite promising evidence, variations in dosage, bioavailability, and long-term outcomes underscore the need for well-designed randomized controlled trials to confirm these benefits. Overall, phytochemicals represent a promising, natural, and accessible strategy to mitigate cardiovascular risk and promote long-term heart health.

**Keywords:** Phytochemicals; Cardiovascular diseases; Flavonoids; Polyphenols; and Endothelial function.

## INTRODUCTION

Phytochemicals are substances that the plant kingdom produces during its metabolic processes. Many of these products are secondary metabolites that act as protection agents for the physical integrity of plants. Secondary metabolites belong to different chemical groups, such as flavonoids, terpenoids, alkaloids, carotenoids, organosulphur compounds, and nitrogen-containing compounds. These compounds exert pharmacological actions, including antioxidant, anti-inflammatory, hypocholesterolemic, and vasodilatory effects, which contribute to protection against cardiovascular diseases. The cardioprotective effects of a well-balanced diet are primarily due to an adequate intake of fruits and vegetables, which are rich in phytochemical content. Well-established dietary patterns, such as the Mediterranean diet, Territorial, and Healthy Nordic diets, align with these recommendations. A review of randomized clinical trials that examined the effects of flavonoids, polyphenols, terpenoids, and alkaloids on cardiovascular outcomes found that most substances were effective in controlling dyslipidaemia, especially by increasing total cholesterol and low-density lipoprotein cholesterol. Other endpoints with noteworthy positive results included reductions in triglycerides, body weight, body mass index, low-density lipoprotein, and C-reactive protein, as well as improvements in physical performance. Many studies have also explored the relationships between phytochemical consumption and exercise practice, cardiovascular biomarkers, and diet quality, with the aim of promoting greater protection against cardiovascular diseases. Protective mechanisms were analyzed through in vitro and in vivo experiments, focusing on antioxidant and anti-inflammatory activity and improvements in endothelial function.

### Overviews of Cardiovascular Diseases

**Main Cardiovascular Diseases** The literature review addresses the following cardiovascular diseases (CVDs): coronary heart disease (CHD), including acute myocardial infarction; cerebrovascular disease, including ischemic and hemorrhagic stroke; peripheral artery occlusive disease; heart failure; and cardiac dysrhythmias [1, 4]. Hypertension is included when described as a causal risk factor for the diseases listed above. These CVDs are

leading causes of death worldwide [5]. Their shared etiology, the underlying atherosclerotic process, begins with endothelial dysfunction. The primary risk factors for atherosclerosis are smoking, diabetes mellitus, elevated plasma cholesterol (especially low-density lipoprotein), low HDL cholesterol, and high blood pressure. Other risk factors include obesity, physical inactivity, psychosocial factors, and excessive consumption of alcohol [1, 3].

#### **Phytochemicals: Definition and Classification**

Plant bioactives, also known as non-nutrients or phytochemicals, encompass a large group of exogenous plant molecules in foods and beverages. These compounds have been widely studied for their health-promoting benefits, especially their potential role in the primary and secondary prevention of CVD [6]. Phytochemicals mainly consist of four classes: flavonoids, polyphenols, terpenoids, and alkaloids. Their chemical structures are diverse and include phenolics, sulfur-containing compounds, carbohydrates and derivatives, terpenoids, nitrogen-containing compounds, and alkaloids [4]. The Cambridge Dictionary of Human Nutrition defines a phytochemical as “a non-nutritive component of plants in food that has the potential to affect health”. ECCN outlines eight criteria for classifying phytochemicals: (a) natural product; (b) source in foods that are part of human consumption; (c) chemical structure; (d) metabolism including absorption, modification, and excretion; (e) biological activity in animals, tissues, or cells; (f) multiple biological activities in Ginet; (g) presence in the food chain; and (h) potential impact on human health, both beneficial and detrimental. These criteria are essential for establishing a cause-and-effect relationship between diet and health [7].

#### **Mechanisms of Cardiovascular Protection**

Phytochemicals from different classes provide cardiovascular protection through various mechanisms. Most of them delay the progression of atherosclerosis, enhance the functionality of the endothelium, and reduce systemic inflammation [1]. Recent evidence shows that specific phytochemicals also benefit patients with ischemia reperfusion injury by altering mitochondrial and endoplasmic reticulum calcium balance and reducing the accumulation of reactive oxygen species [2]. The cellular targets underlying the beneficial effects of phytochemicals on cardiovascular health, as reviewed in the following sections, include the following. Oxidative stress triggers endothelial dysfunction, damaging vascular tone regulation, the antithrombotic system, and smooth muscle senescence [4]. It also causes inflammation in the heart. Atherosclerosis involves a disruption of the balance between pro- and antioxidants, and it is exacerbated by the production and release of oxidized low-density lipoproteins (ox-LDL) [5]. These ox-LDLs promote platelet activation and induce the release of proinflammatory mediators. They are also involved in the proliferation and migration of vascular smooth muscle cells, which contribute to plaque formation and atherosclerosis. Antioxidants acting on mitochondria may reduce oxidative stress, which may in turn improve myocardial contractility [3]. Chronic inflammation plays a pivotal role in the pathogenesis and progression of cardiovascular diseases. Patients with myocardial infarction may develop heart failure during the post-infarction period due to a robust and prolonged inflammatory response [7]. Post-infarction heart failure is characterized by cardiac remodeling and dysfunction. Endothelial dysfunction contributes to the initiation and development of atherosclerotic coronary disease and promotes thrombosis in arterioles and veins. Vasodilatory agents are usually produced by a healthy endothelium; when this organ is damaged, a reduced vasodilatory activity leads to an imbalance between vasoconstriction and vasodilation [6]. Improving endothelial bioactivity and regulating blood pressure significantly reduces the risk of cardiovascular disease [5].

#### **Antioxidant Activity**

A common feature that hinders the proper functioning of the cardiovascular system is oxidative stress. The generation of pro-oxidants such as superoxide anion, hydrogen peroxide, and hydroxyl radicals is an unwanted accompanying step of the physiological processes that occur in a properly functioning organism [4]. Normally, they are removed by endogenous antioxidant systems or plant-derived exogenous antioxidants, which provide electrons to free radicals. When the accumulation of pro-oxidants surpasses the antioxidant capacity of the individual, irreversible damage may occur to vital biological components (biomolecules, for example) [3]. These can occur directly or indirectly, with the activation of a chain reaction [1]. Using different antioxidant substances in diet and supplement form may be useful in reducing the damage caused by free radicals [1, 3]. Antioxidants are included in a wide range of food elements such as polyphenols, carotenoids, flavonoids, anthocyanins, and vitamins. They are also found in food sources such as herbal products, fruits, vegetables, berries, turmeric, tea, and coffee. Folate-containing foods are important natural folate sources, including green leafy vegetables, legumes, sunflower seeds, oranges, whole grains, and fortified cereals. Antioxidants provided by essential nutrients, in addition to deficiencies in endogenous enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, can cause the rapid accumulation of free radicals, leading to pathological damage and being directly associated with ASCVD [1, 2].

### Anti-inflammatory Effects

Inflammation represents one of the principal components of the complex cascade of vascular and myocardial damage [1]. Preclinical research within cell-culture and animal models has provided extensive evidence of anti-inflammatory properties for all the considered classes of cardiovascular-protective phytochemicals: flavonoids, polyphenols, terpenoids, and alkaloids [1]. Moreover, numerous clinical studies suggest that an appropriate daily phytochemical intake effectively reduces markers of systemic inflammation, including C-reactive protein and pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . While flavonoids have been reported in some clinical trials not to exhibit substantial anti-inflammatory effects, other experiments with different flavonoid compounds and alternative inflammatory markers nonetheless provide some supportive evidence [2]. These field data underscore the pivotal involvement of inflammatory processes in the initial phases of vascular and myocardial damage: the timely supplementation of phytochemical compounds accords a regular modulation of both innate and adaptive immune responses [1].

### Endothelial Function Improvement

Endothelial function is essential for vascular homeostasis, regulating coagulation, immune functions, and inhibition of smooth muscle proliferation and platelet aggregation [1, 2]. Additionally, the endothelium balances the vasodilators and vasoconstrictors released into the subendothelial space, thus controlling smooth muscle tone. An altered endothelial function, represented by the capacity to maximally dilate, is often associated with coronary artery disease. Evidence suggests that flavonoids in foods improve endothelium-dependent functions in both healthy individuals and patients with vascular diseases. Controlled studies provide evidence of the beneficial effect on vascular endothelial function when consuming flavonoid-rich foods, such as grapes, black tea, red wine, cocoa-based products, and olive oil [2]. Red wine constituents improve endothelial dysfunction and accelerate blood flow recovery in ischemic areas, and these protective effects are abolished by the stromal interaction molecule 1 (STIM1) silencing [1,2]. Resveratrol, a polyphenol found in grapes and thus red wine, improves coronary and peripheral vascular function in patients with ischemic heart disease [4]. The consumption of red wine upregulated the expression of STIM1 during ischemia-reperfusion injury and increased the phosphorylation of endothelial nitric oxide synthase (eNOS), which likely contributed to the protection. Functional vascular effects of berries are at least partly explained by an increase in serum nitric oxide, and occurrences of vasodilation have been observed in response to alkaloids from leaves of *Nicotiana tabacum* L. in Wistar rats. Hence, specific flavonoid groups might hold promise for therapeutic strategies aimed at restoring endothelial functioning and preventing the cardiovascular detriments that follow its impairment [1, 5].

### Key Phytochemicals and Their Sources

Although many phytochemical groups are known, this review will focus on the principal groups that have been or are currently being researched for their cardiovascular-protective effects [1]. These groups include flavonoids, polyphenols, terpenoids, and alkaloids [2]. Subsequent sections will begin by individually covering each main phytochemical group, their most common sources, and information from conducted clinical trials. Flavonoids and polyphenols will be addressed first due to the greater number of clinical trials in which they are associated with cardiovascular protection [3].

#### Flavonoids

Flavonoids constitute a major group of phytochemical compounds, primarily found in fruits, vegetables, tea, and red wine. Well-studied examples include quercetin (present in onions, apples, broccoli, olives, cherries, red grapes, berries, and citrus fruits) and catechin or epicatechins (abundant in fruits, cocoa, chocolate, and tea) [1]. Although flavonoids and these representative examples have undergone extensive investigation up to the clinical level, many other phytochemicals warrant similar scrutiny for their therapeutic potential [1]. Numerous clinical studies have examined the effects of different flavonoid groups on cardiovascular diseases (CVDs) [1]. The European Prospective Investigation into Cancer and Nutrition Norfolk cohort study, conducted among 5509 adults without cardiovascular events, found a significant 37% reduction in fatal coronary heart disease risk associated with the highest tertile of flavonoid intake. Similar cardioprotective effects had also emerged from earlier case-control studies. Moreover, a meta-analysis of 14 observational studies, encompassing 462,194 participants and 17,479 CVD events, reported that dietary flavonoid consumption correlated significantly with a decreased CVD risk—78 mg/day intake was linked to a 13% reduction, and 219 mg/day correlated with an 18% decrease [1, 2].

#### Polyphenols

Polyphenols are widely distributed in both plants and the human diet, especially in fruits, vegetables, red wine, and tea [1]. Epidemiological studies have focused on the cardiovascular-protective effects of these dietary components, stemming from the observation that populations with a high intake of polyphenol-rich foods manifest a reduced risk of cardiovascular diseases [3]. The possible protective effect of highly concentrated polyphenol products was also investigated in different clinical trials. Pomegranate juice has been reported to reduce systolic blood pressure,

together with the oxidizability of low-density-lipoprotein (LDL) cholesterol. Green tea intake was shown to improve flow-mediated dilation (FMD) of the brachial artery, though no effects were observed in elderly women with hypertension [5]. Tea's vasorelaxant effect, which likely depends on nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF), has been confirmed both in patients with coronary heart disease and in smokers. In smokers and heavy smokers, an acute decrease in FMD was blunted when the subjects were pretreated with a red grape concentrate powder [1]. Resveratrol, a nonflavonoid polyphenolic compound in grapes and red wine, was found to increase coronary flow reserve and reduce angina pectoris episodes. Among cocoa derivatives, flavanol-rich dark chocolate exerts an important effect on endothelial function [7].

### Terpenoids

Terpenoids represent a class of phytochemicals exhibiting considerable cardiovascular-protective effects [1]. They comprise several isoprene units combined into hemi-, mono-, sesqui, di-, sester-, tri, tetra, and polyterpenes. Among animal-derived terpene-based compounds, retinoids, bile acids, steroid hormones, cardiac glycosides, and coenzyme Q10 possess therapeutic applications in cardiovascular diseases [2]. A dire need exists for more efficient therapies with fewer side effects targeting atherosclerosis and other cardiovascular conditions. Betulinic acid represents a promising compound that ameliorates atherosclerosis risk factors in apolipoprotein E-deficient mice via the suppression of T helper-17 expansion. Natural product research has identified betulinic acid as exerting profound antidiabetic effects [4]. The chemical properties, identification methods, extraction and purification techniques, and pharmacological studies underscoring its anti-inflammatory, antitumor, antiatherosclerosis, antiviral, and antidiabetic actions further indicate its potential in controlling human hypertension [6]. Clinical studies confirm the involvement of dietary terpenoids in reducing cardiovascular disease risk factors. For instance, monoterpenes such as limonene, asarone, linalool, perillyl alcohol, pinene, and citral; diterpenes like cafestol and kahweol, among others, from diverse dietary sources have been linked to beneficial cardiovascular effects [5, 7].

### Alkaloids

Alkaloids, a class of plant secondary metabolites, chiefly consist of nitrogenous compounds, specifically derivatives of amino acids [1]. Structural and chemical distinctions categorize alkaloids into different groups: Tropane and isoquinoline derivatives such as atropine and berberine; purine and pyrrolizidine derivatives exemplified by caffeine and senecionine; and amino acid conjugates, including mescaline, verbascoside, colchicine, solanine, and coniine. Increasing evidence indicates that alkaloids exert several cardioprotective actions, including the suppression of hypertension, cardiac hypertrophy, myocardial infarction, arterial thrombosis, ischemia/reperfusion injury, myocardial apoptosis, inflammation, oxidative stress, and fibrosis, along with the improvement of myocardial function, endothelial function, and lipid profile [3]. Of particular scientific interest is berberine, a natural isoquinoline alkaloid widely distributed in Ranunculaceae and Berberidaceae herbaceous plants, particularly in the genus *Berberis*. Clinical trials probing the cardiovascular effects of berberine provide further insight into its potential health benefits [7].

### Flavonoids and Heart Health

Flavonoids are a large group of water-soluble polyphenolic phytochemicals characterized by a benzo-g-pyrone structure, occurring in fruits, vegetables, herbs, spices, stems, flowers, and beverages such as tea and red wine. Over 4,000 flavonoids have been identified, among which the most studied are anthocyanins, flavones, flavonols, flavanones, and isoflavones [1]. Interest in their cardiovascular-protective role began with the discovery of the "French paradox," which linked red wine consumption to low incidence of coronary heart disease (CHD) despite a high-fat diet. Numerous epidemiological studies have since linked regular intake of foods and beverages rich in flavonoids to reduced risk of CHD and stroke. A reduced risk of fatal CHD, nonfatal CHD, or a combined endpoint has been reported with daily intakes of 10–18 mg of flavonols or up to 180 mg anthocyanins, flavonols, and flavanones [4]. Furthermore, these reduced risks may be more related to the overall intake of flavonoids than to specific compounds or classes [2].

### Sources of Flavonoids

Flavonoids, also called bioflavonoids, are the most extensively researched phytochemicals for their cardioprotective actions [1]. They are widely distributed subclasses of Type III polyphenols that can be found abundantly in numerous fruits and vegetables, including onions, parsley, celery, apples, berries, oranges, lemon, cocoa, red wine, tea, broad beans, and red cabbage, and can also be added to the diet through fruit juices as well as white and red grape wines [4]. Interest in flavonoids is increasing, partly due to their wide distribution in food, but mainly due to epidemiological studies consistently showing an inverse association between the intake of total flavonoids or specific subclasses and cardiovascular disease death in several European populations [5]. Higher intake of anthocyanins and flavanones is also associated with a lower risk of nonfatal myocardial infarction in women. Greater habitual intake of flavonols and flavones is inversely associated with stroke and coronary heart disease (CHD) in men [6].

### Clinical Studies on Flavonoids

Besides epidemiological investigations mentioning the positive correlation between intake of flavonoid-rich beverages and a decrease in CVD incidence, clinical studies are summarized with specific flavonoids, their food sources, dosage, and tested population [1, 7]. Several of these studies have shown that dietary intervention with flavonoid-rich products can improve endothelium-dependent vasodilatation by increasing NO bioavailability in healthy participants or preventing the decrease in plasma NO concentration during high-cholesterol-diet-induced hypercholesterolaemia. Polyphenols reduce vascular cell adhesion molecule-1 (VCAM-1) expression and matrix metalloproteinase-9 (MMP-9) activity in patients with previous myocardial infarction or chronic heart failure. Further evidence from several epidemiological studies suggests a significant inverse association exists between tea consumption and CVD [4]. A recent randomized controlled clinical trial (RCT) additionally supported the positive effect of tea flavonoids on blood pressure and vascular function in patients with early-stage hypertension [5].

### Polyphenols: A Closer Look

Polyphenols are a category of phytochemicals abundant in plant-derived foods and beverages, such as grapes, olives, soy, berries, coffee, and chocolate. The cardioprotective properties of polyphenol-rich diets have been extensively reported in epidemiological and clinical research [1]. Prospective cohort studies suggest polyphenol supplementation may reduce cardiovascular disease (CVD) risk in otherwise healthy subjects [2]. The cardiovascular benefits of polyphenols have been demonstrated in clinical studies involving both healthy and diseased subjects [7]. Supplementation with polyphenol-rich grape products, for instance, has been shown to lower blood pressure and improve atherogenic lipid profiles in mildly hypertensive individuals. Reduction in inflammatory markers has also been reported following grape polyphenol intake. Additionally, grape polyphenols enhance endothelial function and platelet reactivity, offering further cardiovascular protection [1, 2].

### Sources of Polyphenols

Polyphenols are widely distributed in the plant kingdom and are characteristic components of a widespread variety of foods, mainly fruits such as apples, pears, grapes, and berries; vegetables such as onions and olives; dry legumes such as hazelnuts, walnuts, and chestnuts; cereals, such as cocoa and soy; and beverages such as tea, coffee, and wine [6, 1]. These substances represent an exceedingly large group of phytochemicals, and the amount and type of polyphenols in foods depend on many variables related to plant variety, harvesting seasons, and storage methods. Even though the chemical structure of polyphenol subclasses varies widely, research suggests that many polyphenols can positively influence atherosclerosis and the progression of CVD by means of their antioxidant and/or anti-inflammatory effects; by stimulating nitric oxide production; and by reducing platelet aggregation, endothelial apoptosis, and vascular cell adhesion molecule expression [7]. These mechanisms are reflected in some endpoints of clinical studies on CVD and CVD risk factors [1, 2, 3].

### Clinical Studies on Polyphenols

A clinical study explored the efficacy of polyphenol-rich drops of maqui berry (Delphinol®) combined with metformin in the treatment of type 2 diabetes (T2DM). Randomized, double-blind, and placebo-controlled, the trial included 71 participants with T2DM managed solely with metformin. Over 12 weeks, the intervention group received increasing doses of Delphinol [5]. Results demonstrated that adding Delphinol® to metformin significantly lowered fasting glucose and blood lipids and improved insulin secretion, as well as both systolic and diastolic blood pressure [3]. In an evaluation of an anthocyanin-containing extract from grape and bilberry, 55 non-medicated subjects with elevated high-sensitivity C-reactive protein (hs-CRP) completed an 8-week double-blind, placebo-controlled trial [1]. Participants were randomized to daily consumption of strawberry and black raspberry juice or a sugar-matched placebo. Compared with controls, those who consumed the juice exhibited significantly reduced hs-CRP levels. Additionally, reductions in systolic blood pressure, levels of serum vascular cell adhesion molecule-1 (VCAM-1), and low-density lipoprotein (LDL) cholesterol concentration and LDL oxidation were observed [2].

### Terpenoids in Cardiovascular Health

Natural terpenoids represent a broad class of diverse lipids built from repetitive units of isoprene and comprise the most extensive group of phytochemicals [1]. The two main subgroups are carotenoids and non-carotenoid alcohol-soluble terpenoids. Carotenoids, around 700 identified molecules, are responsible for the yellow, orange, and red hues in plants. Being fat-soluble, they are highly concentrated in both the green leafy parts of plants and in the colorful fruits and vegetables that are part of the human diet [3]. In addition to their antioxidant capacity, carotenoids exhibit anti-inflammatory properties, carotenoid-scavenging nitroxide radicals, and contribute to cholesterol reduction. Although there are numerous terpenoids that have undergone clinical testing for other pathological conditions, only a limited number have been examined for cardiovascular (CV) protective effects. At least five carotenoids, including  $\alpha$ -carotene, astaxanthin,  $\beta$ -cryptoxanthin, lycopene, and lutein, have been shown

to possess CV-protective effects in clinical trials [4]. For example, diastolic blood pressure levels were inversely related to  $\alpha$ -carotene levels in a subgroup of women. Astaxanthin was demonstrated to significantly reduce systolic blood pressure in renal transplant patients. Higher levels of  $\beta$ -cryptoxanthin correlated with a lower risk of hemorrhagic stroke. Recent meta-analyses reported that lycopene supplementation can significantly reduce systolic blood pressure in subjects with baseline blood pressure higher than 120/80 mmHg, and lutein+zeaxanthin consumption decreased systolic blood pressure in a pooled analysis of eight trials [5].

#### Sources of Terpenoids

Terpenoids are a subclass of tertiary metabolites derived from five-carbon units linked to form isoprenes. The subclasses are represented by monoterpenoids, diterpenoids, sesquiterpenoids, and tetraterpenoids. The C30 carotenoids constitute a group of terpenoids found in several plants and some microorganisms [1]. These compounds are important in cardiovascular protection. Clinical studies on terpenoids are usually performed with carotenoids from tomato extracts or from *H. sabdariffa* flowers [2]. The potential cardiovascular protection effect in humans extends to lower obesity-associated cardiac dysfunction, improves lipid and genetic profile, increases antioxidant activity, reduces cardiac injury, and improves post-ischemic reparative processes. Terpenoids' beneficial effects appear to involve antioxidant and inflammatory mediators [3].

#### Clinical Studies on Terpenoids

The diverse cardiovascular benefits of terpenoids have prompted clinical studies on their bioactive profiles [1]. Experimental and human studies indicate that d-limonene exerts protective effects against myocardial ischemia through antioxidant and anti-inflammatory actions, with cytoprotective effects on myocardial ischemia/reperfusion injury [2]. A diet enriched with cocoa derivatives, rich in plant metabolites, flavonoids, and the terpenoid theobromine, reduced cardiovascular mortality during a coronary event in patients affected by cardiovascular disease in the Western European EPIC-Norfolk study [3]. The consumption of a theobromine-rich diet diminished postprandial blood glucose and insulin concentrations and increased high-density lipoprotein cholesterol concentration and the size of low-density lipoprotein particles in healthy human adults in a randomised, controlled, double-blind crossover trial. Terpene concentrations have been correlated with immune stimulation, supporting the increased numbers of lymphocytes, T lymphocytes, and natural killer cells found in healthy adults following regular tea consumption. Phytosterols, a category of dietary triterpenoids found in legumes, cereals, nuts, and vegetable oils, are mainly known for their cholesterol-lowering activity. These compounds compete with cholesterol for micellar incorporation in the intestines, thereby reducing its intestinal absorption [5]. A meta-analysis suggests that phytosterols in combination with a hypocholesterolaemic diet are effective for long-term cholesterol reduction, demonstrating dose-dependent effects of between 6.2 and 12.0% in LDL cholesterol levels. A diet rich in Cameroonian spices, a source of provitamin A dietary carotenoids, exerted cholesterol-lowering effects by decreasing LDL cholesterol concentrations in dyslipidemic subjects. Administration of ShenSongYangXin granules, rich in astragalosides from *Astragalus membranaceus*, to patients with paroxysmal atrial fibrillation reduced heart rate and increased heart rate variability in a randomised, double-blind, placebo-controlled trial, thereby exerting cardiovascular-protective and arrhythmia-preventing effects [7].

#### Alkaloids and Their Impact

Alkaloids, an extensive class of structurally and functionally diverse plant-derived compounds, have shown potential as therapeutics in inflammatory and neurodegenerative diseases [3]. Specific alkaloids such as harmine, berberine, aloperine, oxymatrine, tetrandrine, sinomenine, tetrahydropalmatine, and galantamine emerge as promising lead candidates with anti-inflammatory and anti-AChE activities. Further investigation through clinical trials, pharmacokinetic profiling, and safety assessment is critical to advance their medical applications. Given the toxicity of many alkaloids, detailed analysis of their safety profiles remains a priority [3]. Moreover, combination therapies involving alkaloids and FDA-approved agents warrant exploration for the development of enhanced and durable anti-inflammatory and anti-AChE formulations. Plant-derived alkaloids constitute a class of secondary metabolites produced by various species such as Ranunculaceae, Papaveraceae, and Berberidaceae [4]. While a greater diversity of alkaloids is found in dicotyledonous plants, monocotyledons are comparatively less productive. These bioactive compounds exhibit a broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, cardioprotective, anticancer, and antidiabetic effects [6]. The anti-inflammatory and anti-cancer potentials of alkaloids underscore their value for pharmaceutical exploitation, warranting concerted efforts to isolate and characterize novel members of this group with enhanced efficacy and diminished adverse effects [5].

#### Sources of Alkaloids

Alkaloids are a diverse group of nitrogen-containing natural phytochemicals produced by numerous plant families, including Ranunculaceae, Fumariaceae, Papaveraceae, Berberidaceae, Menispermaceae, Annonaceae, Euphorbiaceae, Solanaceae, Scrophulariaceae, Rubiaceae, and Rutaceae, as well as fungi, animals, and bacteria. Notable sources include heads of *Papaver somniferum* (opium poppy), *Aspidosperma* spp., and *Strychnos* spp., from

which alkaloids have been isolated for over a century [3]. An estimated 12,000 alkaloids have been identified, exhibiting wide structural and functional diversity [4]. Characterized by low molecular weight and significant pharmacological activity, many have therapeutic applications for cardiovascular diseases (CVDs), inflammation, arthritis, neurodegenerative disorders, and cancer. Several alkaloids have reached the pharmaceutical market, underscoring their medicinal value [3, 4].

#### Clinical Studies on Alkaloids

A variety of clinical studies have examined the cardiovascular effects of alkaloids, a group characterized by complex cyclic bases. Micheletti et al. [271] reported that caffeine, the most consumed alkaloid, mitigates the risk of stroke. Nimodipine at 30 mg/kg or aspirin at 30 mg/kg can significantly modify paraoxonase, arylesterase activity, and hs-CRP levels in patients with ischemic stroke; however, the modulation of these comorbidity factors by other alkaloids remains uninvestigated [272] [1, 4, 7]. Quinoline alkaloids, specifically two enantiomers isolated from *Evodiae fructus*, induce concentration-dependent vasodilation in thoracic aorta rings with intact endothelium [273]. Berberine administration effectively lowers cholesterol levels in overweight patients [274] [1]. Furthermore, nanoparticle-mediated delivery of bebeerine preserves vascular endothelial function in hypertensive rat models [275]. S-allylcysteine, a water-soluble organosulfur compound derived from garlic, displays an antiapoptotic effect in endothelial cells subjected to oxidative stress, highlighting its antioxidant capacity [276] [1, 2]. Theobromine, prevalent in cacao and chocolate, shows a protective effect against cardiovascular disease risk factors in patients with diabetes [277], while piperine, isolated from black peppercorns, exerts hypotensive effects in hypertensive patients [278]. Dehydrocorydaline derivatives enhance the potencies of warfarin and ticlopidine in myocardial patients diagnosed with thrombosis [279]. Furthermore, vinpocetine demonstrates clinical benefits by modulating the inflammation cascade through NF- $\kappa$ B pathway inhibition, suggesting its potential utility as a preventive agent in patients at high risk of stroke [280] [1].

#### Dietary Patterns and Phytochemical Intake

Certain dietary styles have been identified as being more protective against CVD than others, and the underlying reasons for this may lie in their phytochemical concentrations. Flavonoids, a distinct group of polyphenols, are present in beneficial foods such as tea, cacao, apples, onions, and citrus fruits, as well as in red wine. Various reviews have summarized the health benefits of flavonoids and tea [5]. Polyphenols, widely distributed in the plant kingdom and core constituents of the Mediterranean diet, exemplify the cardio-protective effects of this dietary pattern. Terpenoids in the Mediterranean diet include carotenoids found in citrus and carrots. Other diets, like the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge), which emphasizes fatty fish but also other sources such as olive oil and seeds, provide the cardio-protective alkaloids. Clinical studies supporting a protective role for these phytochemicals in these dietary patterns are further discussed below. Phytochemicals also interact with lifestyle approaches such as increased physical activity and exercise. Acute and chronic exercise cause systemic oxidative stress [6]. Antioxidant supplementation may protect against this; however, antioxidants neutralize reactive species at the same time as they serve as signals to improve exercise performance. While antioxidants are generally protective, in some cases, such as a strenuous bout of exercise, antioxidant-enriched supplements might be harmful. A recent review explored the interactions between phytochemicals and exercise variables, including intensity, duration, and type of training [5].

#### Mediterranean Diet

The Mediterranean Diet (MedDiet) has endured as a salient paradigm for healthy eating in many of the world's populations since its characterization in the Seven Countries Study by Ancel Keys and colleagues. Observational studies demonstrate substantial positive associations with improved cardiovascular outcomes among persons exhibiting greater dietary adherence. The PREDIMED trial recently provided conclusive evidence that a MedDiet can protect high-risk men and women against cardiovascular disease (CVD) [5]. The completely plant-based diet consists of vegetables, legumes, participatory fruits, nuts, cereals, virgin olive oil, a regular but low intake of fish and seafood, moderate amounts of fermented dairy products, and small quantities of wine alongside limited consumption of meat and poultry [6]. Several pathways are suggested for therapeutic activity, including a reduced list of inflammatory and oxidative stress biomarkers, favorable modulation of lipid parameters, enhanced insulin sensitivity, direct microscopic improvements, as well as antiatherosclerotic and antithrombotic capacities. Recent clinical trials often report cardiovascular benefits for prevalent lifestyle evaluations incorporating MedDiet trends among both male and female participants, regardless of other environmental determinants. High virgin olive oil consumption associates with approximately a 35% reduction in cardiovascular risk in multiple epidemiological analyses, and comparable decreases in all-cause mortality linked to higher total polyphenol intake [7]. The preferential use of virgin olive oil over nut and seed oils appears especially promising, with the most comprehensive investigations conducted in Greece and Italy. Improved dietary control is advisable in order to elucidate the individual contributions of particular constituents within complex culinary orders. Nutritional

recommendations continue to highlight olive oil, legumes, fruits and vegetables, nuts, whole grains, and moderate wine, respectively, as their administration affects virtually all of the underlying mechanisms of CVD risk modulation [5, 6].

### **Plant-Based Diets**

Plant-based diets emphasize foods derived from plants, including fruits, vegetables, nuts, seeds, oils, whole grains, legumes, and beans [7]. Studies associate these diets with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality. They help lower lipid profiles and reduce atherosclerosis [7]. Phytochemicals in plant-based foods affect macrophage cholesterol efflux, further influencing atherosclerosis development. Consuming a plant-based diet may contribute to improved cardiovascular health and increased longevity.

### **Phytochemicals and Lifestyle Modifications**

Cardiovascular disease is the main cause of death worldwide, accounting for 17.9 million deaths in 2019. In 2020, cardiovascular deaths accounted for 30% of global deaths [4]. Lifestyle changes or ageing increase the risk of mortality from cardiovascular diseases. External factors such as air pollution and second-hand tobacco smoke may contribute to morbidity and mortality, so it cannot be ruled out that phytochemicals can confer cardiovascular protection against these external factors. Therefore, it is difficult to clarify the efficacy of phytochemicals in cardiovascular protection with consideration for the impact of their bioavailability and interaction with other nutrients on the results of intervention studies. However, the combination of exercise and phytochemicals may compensate for the modest effects of phytochemicals alone [3]. Thus, it is essential to recommend moderate exercise and the intake of phytochemicals to maintain a healthy lifestyle. Previous studies have shown an inverse association between the amount of flavonoids consumed and the risk of all-cause mortality, cardiovascular events, and cerebrovascular disease. Physical inactivity is one of the most critical risk factors for cardiovascular disease and mortality. Exercise improves mitochondrial integrity and function, regulating the synthesis of mitochondrial enzymes, coenzymes, and cofactors involved in oxidative phosphorylation. Exercise improves cardiovascular health by improving antioxidant capacity and maintaining mitochondrial morphology and viability [2]. Exercise is effective in stimulating the transmission of intercellular signals, such as superoxide, which is necessary to maintain the physiological and adaptive phase of the cardiovascular system. Flavonoids, as well as the intake of several nutrients such as vitamins C, E, and some minerals, especially selenium and zinc, show antioxidant properties. However, diverse phytochemicals can communicate complex biological effects that cannot be mimicked by the simple presence or absence of one antioxidant. In addition to their antioxidant properties, they play an essential role in regulating various cellular functions, including metabolic parameters and inflammatory signaling [1]. The lifelong intake of flavonoids appears to be the key step to improving and maintaining health; the long-term intake should be combined with physical activity to provide real cardiovascular protection. Even during physical inactivity intervention, polyphenols were capable of attenuating blood pressure declines and preventing the decreases in endothelium-dependent, flow-mediated dilation induced by sedentary behaviour. However, exercise appears to rescue the vascular dysfunction induced by acute hyperglycaemia, and hence, the combination of exercise and phytochemicals may compensate for the modest effects of flavonoids alone [1].

### **Exercise and Phytochemical Absorption**

Exercise enhances gastric motility, potentially accelerating the movement of flavonoid-rich foods through the stomach; however, the impact on intestinal absorption remains unclear [1]. Phytochemical co-ingestion with specific nutrients can significantly influence their pharmacokinetics [6]. For example, timing the intake of grape polyphenols relative to staple foods affects plasma levels of hippuric acid, a polyphenol metabolite. Studies have demonstrated a dose-dependent increase in the diazepam-metabolite nordazepam following pure flavonoid consumption when co-administered with carbohydrates. Co-consumption of polyphenols with vitamin C alters pharmacokinetic behavior compared with polyphenols ingested alone, and the presence of ethanol in red wine modifies the absorption of key polyphenols like resveratrol [1]. These observations underline the importance of considering metabolite composition, co-ingested foods, and individual gut microbiota when evaluating the protective biological activity of phytochemicals against cardiovascular disease [1].

### **Synergistic Effects with Other Nutrients**

Phytochemical compounds, such as polyphenols and flavonoids, interact synergistically with nutrients and trace elements, such as omega-3 fatty acids (n-3 FA), magnesium, and niacin, dietary components known to protect cardiovascular health, thereby improving their bioavailability [1]. These synergisms may change the gastroesophageal transit profile and absorption and metabolism of phytochemicals and nutrients [1]. For example, a phytochemical found in the diet, such as curcumin, modulates lipid metabolism in combination with n-3 FA. Quercetin enhances the plasma concentration/concentration of n-3 FA and high-density lipoprotein (HDL) cholesterol, demonstrating nutrient-nutrient synergistic effects. A similar mechanism of behavior is also noticed

with flavonoids and magnesium [2]. Dietary curcumin interacts synergistically with lipid metabolism-down-regulating nutrients, such as niacin, in relation to fatty liver, which is considered a cardiovascular risk factor. Vitamin E shows interaction against vitamin K within the body and helps the anticoagulation process; therefore, it may be advisable to use supplements combining both. Nutrient interactions also exist through the modification of metabolic enzymes by phytochemicals; the metabolism of n-3 FAs by cytochrome P-450 is modulated by naringenin and quercetin. The lipoxygenase (LOX) pathway is inhibited by quercetin and naringenin, which otherwise metabolize n-3 FA to anti-inflammatory derivatives. The cascade of vitamin C and flavonoids further influences catecholamine oxidative metabolism, thereby contributing to anti-inflammatory activities. Epidemiological studies demonstrate enrichment of antioxidant vitamins, such as vitamin C, in phytochemical-rich foods; such a combination may provide additional cardiovascular protection through reduction in the reactive oxidative species (ROS) [3].

### Challenges in Research

Although clinical studies have demonstrated the protective effect of flavonoids and other phytochemicals, several aspects warrant further attention to better understand their contribution to cardiovascular health. Flavonoids represent a broad group of compounds with varied CVD-protective mechanisms; however, when categorizing specific flavonoids, only certain subgroups have been extensively examined clinically [7]. Overall, most studies affirm the positive cardiovascular effects of phytochemicals. The heterogeneity of phytochemicals and recent discoveries necessitate further clinical investigation [3]. Bioavailability is a critical factor for all phytochemicals. High concentrations of active compounds are often required to enhance antioxidant and anti-inflammatory capacities, improve endothelial function, and induce cardioprotection. Factors such as low pH and enzymes in the gastrointestinal tract can degrade these compounds, leading to poor bioavailability [2]. Additional considerations include differences in experimental models and the dietary or lifestyle context of phytochemical intake, both of which substantially influence clinical outcomes. For instance, combinations with other nutrients, exercise, and unhealthy dietary habits may affect efficacy [1]. The content of phytochemicals in food and dietary supplements also varies within and across foods. Hence, dietary patterns rich in flavonoids have yielded more positive clinical results compared to specific, isolated flavonoid groups.

### Bioavailability Issues

Phytochemicals are species-specific secondary metabolites constituted mainly by polyphenols, carotenoids, phytosterols, organosulphur compounds, and nitrogen compounds, which play ROS scavenging and antioxidation roles in plants and also provide beneficial activities for humans [4]. Setting a phytochemical-rich diet appears to be effective in the management of cardiovascular disease risks through different protection mechanisms, including antioxidation, anti-inflammation, anti-platelet, blood pressure-lowering effects, and lipid profile improvements. The combined intakes of these phytochemicals adopted in Mediterranean, Nordic, and traditional Japanese diets provide effective protection against CVD risk. Although cardiovascular-protective phytochemicals have often been suggested in many reviews, the importance of their bioavailability and content in fruit, vegetables, and plants is frequently neglected [5]. By considering this topic, it emerges that several trials have also been designed with a different approach, trying to verify whether these compounds do have a protective effect on CVD. The most representative of these studies is presented here. Most of them are randomized clinical trials and deal with CVD cohorts or parameters (body weight, plasma lipid profile, etc.). As regards clinical trials, an attempt has been made to include recent studies on different groups of phytochemicals, such as polyphenols, flavonoids, terpenoids, and alkaloids [7].

### Variability in Phytochemical Content

Evidence obtained from clinical trials with phytochemicals and plant food extracts shows that consuming these molecules daily is associated with beneficial effects on cardiovascular health. However, the results are not entirely compatible because the epidemiological and interventional study evidence is often conflicting [2]. Three main research topics have emerged in the phytochemicals CVD relationship that can explain the diverse effects of the same phytochemical: bioavailability differences of the phytochemicals, insufficient understanding of phytochemical biological activity, and the differences in phytochemical content in foods [5]. Phytochemical contents in different plant-based products and in the same products but from different origins and producers differ substantially. Furthermore, phytochemical contents in the final product depend on the processing method used. These variations can lead to inconsistent study results. When considering variations found in plant products, berries, grapes, and green tea represent some of the best examples of such effects. For example, blueberries are sold on the market in different varieties, with yearly differences; they are often grown in closed conditions in a greenhouse, and the industry processes them into many products (fresh, frozen, dried, in jellies, jams, juices, powder, fiber products, fertilizers, and by-products for the pharmaceutical industry). These issues make it difficult to determine what the real phytochemical intake is among those in the intervention group of clinical trials related to these fruits [6].

### Future Directions in Research

In addition to classical antioxidant and anti-inflammatory mechanisms, emerging interest focuses on less-explored phytochemical groups with potential cardiovascular-protective properties [3]. Glycosides, for example, have been found to reduce intima thickness and support macrophage activity, highlighting their antiatherogenic and immunomodulatory roles [4]. Proteins may reinforce genetic and metabolic regulation of the cardiovascular system, while phytosterols have demonstrated efficacy in lowering serum lipid levels. The accelerating pace of nanoparticle research points toward an increasing role for nanoformulated natural compounds, which offer potential advantages in delivery and bioactivity. Incorporating diversity and bioavailability parameters into clinical trial design should clarify differential effects among individual polyphenols and other phytochemicals. Achieving personalized diets based on analyses of gut microbiota and genomic profiles would represent a significant advance for cardiovascular-protective nutrition [5, 4].

### Emerging Phytochemicals

In the search for new pharmacological agents with potential applications for disease prevention and treatment, already known natural compounds with new biological activity for the cardioprotective mechanism continue to emerge [5]. Numerous phytochemicals with the potential to influence cardiovascular risk have been identified in edible plants, but it is important to evaluate the scientific data and weigh the risks associated with their consumption to use them in a new pharmaceutical form, which will be efficient, thermostable during transportation, and resistant to gastric digestion. Among these potentially cardioprotective agents are cyclooxygenase inhibitors such as synthunin and salicin, antiplatelet agents such as curcumin, and vasodilating agents such as nitrite and nitrate [1]. An ideal plant-derived cardioprotective agent would achieve its effect at low concentrations and cause no adverse effects. In addition, the stability of these compounds during transportation or administration is important. Based on these criteria, phytochemical constituents with potential cardiovascular protection should be evaluated for scientific evidence supporting their relevance in the prevention and treatment of cardiovascular diseases. Although different groups of compounds can exert their effects through various mechanisms, some known agents known for their important activity on the cardiovascular system should be mentioned [4, 1].

### Personalized Nutrition Approaches

Personalized nutrition is an approach designed to provide dietary advice tailored to individuals or groups based on specific characteristics [1]. For instance, the relevant parameters for nutritional therapy differ in young or elderly individuals, athletes or sedentary people, and apparently healthy subjects or patients with a specific medical condition. Additional factors, such as Body Mass Index (BMI), gender, food preferences, cultural background, and geographical location, can also be considered. In particular, precision nutrition considers genomic, transcriptomic, metabolomic, and microbiomic data to provide the optimal dietary pattern that maximizes human metabolic potential, allowing for accurate prevention and treatment of diseases. The personalized profile can influence phytochemical intake [2]. Furthermore, lifestyles affect the level of oxidative stress and inflammation, modulating phytochemical needs. The intestinal absorption of phytochemicals is another relevant aspect. Among the main groups, alkaloids are more efficiently absorbed, while flavonoids need to be, at least partially, biotransformed by the gut microbiota; terpenoids and polyphenols are absorbed at different levels depending on their chemical structures [4].

### Public Health Implications

The burden of cardiovascular diseases (CVDs) and the multifaceted pathophysiology of these diseases require ongoing interventions to address residual risks [1]. Clinical and experimental evidence suggests that certain phytochemicals and a healthy diet can contribute to reducing CVD risk. The consistently demonstrated link between diet and cardiovascular health has led to research on diet-based interventions aimed at promoting cardioprotective lifestyles [7]. Given the global transition in dietary patterns, the initiation of public policies targeting the population's eating habits is crucial. Chronic non-communicable diseases significantly affect the population and pose a challenge to public health. Their growth aligns with the epidemiological and demographic transition in the aging process and the adoption of a pro-inflammatory lifestyle [5]. The association between aging, lifestyle, and disease has attracted attention from governments, public health, and health-promoting organizations, which strive for the sustainable development of healthy, economically productive societies. Scientific interest in older adults and the promotion of a healthy aging process is growing. Consequently, the identification of natural food components capable of modulating oxidative and inflammatory conditions is relevant. Phytochemicals possessing antioxidant and anti-inflammatory properties may prevent chronic diseases, including CVDs and neurodegenerative diseases [1].

### Policy Recommendations

Policymakers face limited strategies to improve cardiovascular health and promote phytochemicals that can prevent cardiovascular diseases. A strategic prevention framework is urgently needed [1]. The NIH and the American Heart Association recommend improved monitoring, research, community-based and other preventive interventions, collaborative efforts through private, public, and academic institutions, and expansion of awareness campaigns to decrease incidence, morbidity, and mortality associated with cardiovascular diseases [6]. For example, increased intake of fruits and vegetables is crucial because most are rich in phytochemicals, vitamins, and minerals. Current investment in behavioral and social science research aimed at understanding and improving dietary and physical activity behavior can be encouraged. Intensified research on quantifying phytochemical content of fruits, vegetables, grains, nuts, seeds, and other plant-based foods will guide consumers and health professionals in adopting a phytochemical-rich diet to combat age-related chronic diseases. Ultimately, the search for cardiovascular-protective phytochemicals holds great promise for promoting a healthier and longer life [1].

### Community Education Efforts

Community education is a key public health strategy to reduce the impact of heart disease and promote the adoption of healthful behaviors [1]. Most efforts to educate the layperson on cardiovascular diseases connect risk factors such as smoking, obesity, physical inactivity, and unhealthy diet choices. These efforts convey fundamental heart anatomy and functions, the various forms of cardiovascular diseases, and the resultant human symptoms associated with these conditions. Community-based programs deepen the understanding of heart-healthy habits for at-risk populations as well as the general high-risk population. Prevention and management of heart disease are crucial focuses of programs such as the Arizona Department of Health Services public community website, the American Heart Association, and Million Hearts®, among others. Although many of the initiatives concerning heart health include information on natural remedies and related vascular effects of phytochemicals, none are designed exclusively for informing the public about these agents [1, 7-10].

### CONCLUSION

Phytochemicals play a pivotal role in cardiovascular protection through diverse mechanisms that target oxidative stress, inflammation, lipid metabolism, and endothelial function. Among them, flavonoids, polyphenols, terpenoids, and alkaloids have shown the strongest evidence for reducing the incidence and progression of cardiovascular diseases. Diets rich in fruits, vegetables, tea, coffee, cocoa, herbs, and whole grains, natural sources of phytochemicals, are consistently linked with favorable cardiovascular outcomes. However, the effectiveness of these compounds depends on their bioavailability, dietary patterns, and individual variability. To establish clear dietary recommendations and therapeutic applications, further large-scale, long-term clinical studies are required. In the meantime, promoting phytochemical-rich diets represents an effective, low-cost, and sustainable approach to cardiovascular disease prevention and overall health promotion.

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