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Review Article

# Cinnamon: A potent nutraceutical agent for the protection of the cardiovascular system

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## Abstract

Diseases such as diabetes, atherosclerosis, and hypertension are risk factors for **Cardiovascular** Diseases (CVDs). About 17.3 million deaths worldwide were due to CVDs in 2013 and is anticipated to be 23.3 million by 2030. Common therapies for CVDs are associated with wide side effects. Thus, herbal medicines have been regarded more due to fewer side effects, availability, cultural beliefs, and being cheap. For thousands of years, herbal medicine has been used for bacterial infections, colds, coughs, and CVDs. Cinnamon bark contains phenolic compounds such as cinnamaldehyde and cinnamic acid with protective properties that can reduce the risk of cardiovascular diseases, cardiac ischemia and hypertrophy, and myocardial infarction. Furthermore, cinnamon has antioxidant and anti-inflammatory properties and exhibits beneficial effects on the complications of diabetes, obesity, hypercholesterolemia, and hypertension which cause CVDs. Although the protective effects of cinnamon on the heart have been reported in many studies, it needs more clinical studies to prove the pharmaceutical and therapeutic efficacy of cinnamon on risk factors of CVDs. This review explains the protective effects of bioactive compounds of cinnamon on the cardiovascular system.

## Introduction

Cardiovascular Diseases (CVDs) include ischemic heart disease, congenital and rheumatic heart disease, hypertension, endocarditis, cardiomyopathy, heart failure, and arrhythmias [1] that are the major causes of mortality all over the world [2]. About 1/3 to 1/5 of CVD cases are associated with myocardial infarction and heart failure [3]. Some risk factors for CVDs are smoking, stress, and diseases such as diabetes, atherosclerosis, and hypertension [1]. The application of common therapies for CVDs is associated with side effects, which is why the use of herbal medicines is considered due to the availability of fewer side effects, and being cheap [4]. Herbal medicines have antioxidant, immune regulatory, and anti-inflammatory properties against CVDs [5,6].

Cinnamon belongs to the Lauraceae family; and mainly is found in Asia and Australia [7]. The commercial main species of cinnamon are *Cinnamomum verum, Cinnamomum burmannii, Cinnamomum cassia, and Cinnamomum loureiroi* [8], and the most common species are *Cinnamomum cassia* (Saigon Cinnamon) and *Cinnamomum verum* (Ceylon Cinnamon) [9]. Saigon Cinnamon is the most well-known and is found in Vietnam, China, and Sunda Islands Ceylon Cinnamon as one of the best types of cinnamon is an evergreen tree with 5-7 meters and is native to India, Bangladesh, and Myanmar [9]. Leaves and bark of cinnamon trees have been used as herbal medicine, flavoring, or spice and the most consumed part of the plant is the bark [8]. Bioactive compounds of cinnamon are against inflammation, oxidative stress, diabetes, obesity, hypertension, and high blood lipid [10,11]. In traditional medicine, cinnamon has been used for arthritis, infections, analgesic agents, and wound healing [10]. Poustchi, et al. [12] reported that it may impact the risk of cardiovascular diseases, diabetes, and cancer. The effect of cinnamon on lipid level profiles or plasma glucose indicated promising results [13].



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Due to the use of cinnamon in the food industry and traditional medicine, more clinical research is required in the prevention and treatment of diseases. This review is to highlight the scientific studies revealing the cardiovascular beneficial effects of cinnamon CVDs.

## The bioactive compounds of cinnamon

The main components of cinnamon are cinnamaldehyde and trans-cinnamaldehyde which are linked to fragrance and its biological properties [8]. Catechins and procyanidins; proanthocyanidins or condensed tannins are found in the cinnamon bark which belongs to the flavan-3-ols as important flavonoids [14]. As stated by Vallverdu-Queralt, et al. [15] the most abundant bioactive compounds found in cinnamon are catechin, protocatechuic acid, quercetin, epicatechin, p-coumaric acid, p-hydroxybenzoic acid, syringic acid, rosmarinic acid, caffeic acid, ferulic acid, and chlorogenic acid (Figure 1).

It's reported that cinnamon is rich in cinnamaldehyde, cinnamic acid, cinnamate, and eugenol as the main components [10,16] (Figure 2).

It's reported that amidone, mucilage, tannin, calcium oxalate, sugar, cinnamon, essential oil, and resin also were found in cinnamon [18].

## Extraction procedures of the bioactive compounds of cinnamon

Cinnamic, cinnamyl acetate, cinnamaldehyde, procyanidins, polysaccharides, and catechins are major components in cinnamon bark. A higher concentration of cinnamaldehyde has shown cardiovascular protective properties while cinnamic acid, coumarin, cinnamyl alcohol, and eugenol are used for flavoring and perfumes [19]. The common extraction methods for cinnamaldehyde, cinnamic acid, cinnamate, and eugenol as the main components of cinnamon are steam distillation, hydro distillation, and soxhlet extraction [20,21]. Hydrodistillation is more used because of its low cost, easiness, and lack of solvent residue. But generally, its yields are low (1–2%) [22], thus other extraction methods such as supercritical $CO_2$ extraction, ultrasonic, microwave-assisted extraction, and low-temperature extraction have been performed to increase extraction yields [23,24] (Figure 3).

## Comparison of various methods of extraction

In some research, supercritical fluid extraction is applied to extract cinnamon bioactive compounds [26]. Microwave-assisted extraction provided the best yield of cinnamic acid and cinnamaldehyde in comparison to ultrasonic and reflux extraction [24]. But recently ultrasound-assisted steam distillation was proposed to extract cinnamon essential oil for industrial applications due to high yields of oil and cinnamic aldehydes [27]. Now, Yu, et al. [28] reported that heat breaking of the cell wall by $SO_3$ hydration before hydrodistillation extraction improved the yield of cinnamaldehyde.

Solvent extraction is commonly used to extract phenolic components such as proanthocyanidins from *Cinnamomum verum* using ethanol [29]. Ethanol 72%, extraction time 50 min, and 70 °C were proper conditions to extract the phenolic compounds of cinnamon by ultrasound extraction [30]. Some studies concluded the effectiveness of green solvents for the extraction of *trans*-cinnamaldehyde, coumarin, and trans-cinnamic acid from cinnamon [31,32].

## Cinnamon in traditional medicine

According to traditional medicine in Iran and India, the

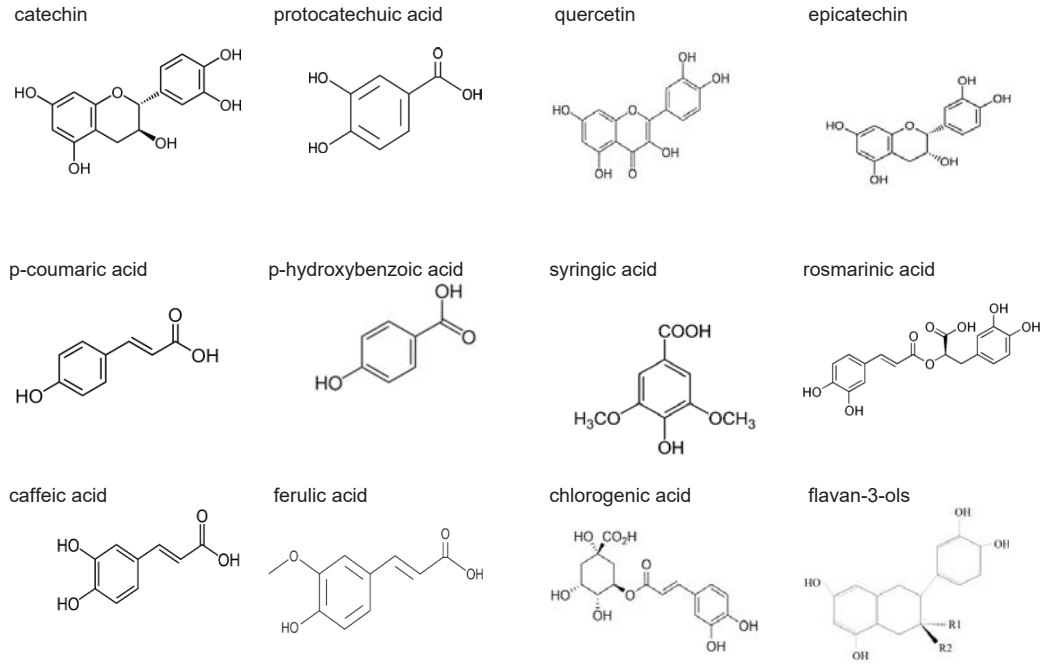


**Figure 1:** Major bioactive compounds in cinnamon bark.



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temperament (mezaj) of Ceylon and Saigon cinnamons is warm and dry [17]. Cinnamon has been used to cleanse the breast, treat coughing, shortness of breath, and thick phlegm, and is used for obsessive-compulsive disorder, panic, insanity, stomach ache, relieving fever, and reduction of joint and back pain. In India and China, it's proven that Ceylon cinnamon's bark is a stimulant for the digestive, respiratory, and kidney and accelerates blood flow. In contrast, Saigon cinnamon is used as a spice due to its flavor. In traditional Far-Eastern medicine, cinnamon has been advised as a stomach booster and sedative, applied for postpartum pain, and increases the body's secretions [17] (Figure 4).

Cinnamon is an anti-clotting agent and prevents atherosclerosis. In addition, it decreases blood cholesterol and insulin resistance, stabilizes blood sugar, and maintains LDL. Cinnamaldehyde dilates blood vessels and helps relieve the tension due to blood pressure. Ingesting 6 g of cinnamon daily lowers triglyceride and total cholesterol in type 2 diabetes. Cinnamon can reduce inflammation that is triggered by obesity [17].

*Cinnamomum zeylanicum* has a blood pressure-lowering effect in rat models [33] as well as in type 2 diabetic and pre-diabetic humans suggesting a NO-dependent mechanism for the antihypertensive effects of *C. zeylanicum* [34]. Nonetheless, outcomes of a placebo-controlled clinical trial showed that cinnamon does not affect BP in type II diabetic cases [16]. Cinnamon affects regulations and mimics, which may have a moderate effect on lowering fasting blood sugar in diabetes. Cinnamon can also keep blood sugar steady throughout the day [25]. Cinnamon reduces the production of the inflammatory molecule of thromboxane A2 in patients suffering from heart diseases. Also, cinnamon's anti-inflammatory properties prevent the release of arachidonic acid (inflammatory fatty acid) that promotes plaque formation in the arteries. Cinnamon is a rich source of flavonoids and antioxidants which are anti-inflammatory and help decrease heart diseases [17]. Cinnamon and cinnamaldehyde have as well as prebiotic effects that may restore the balance of gut bacteria and improve digestive functions [17].

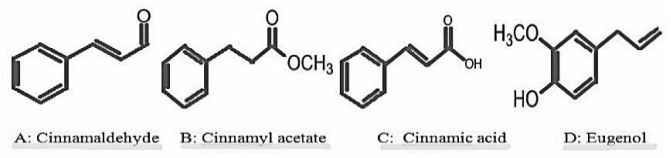


**Figure 2:** The structure of cinnamaldehyde, Cinnamic acid, Cinnamate, and Eugenol in the cinnamon [17].

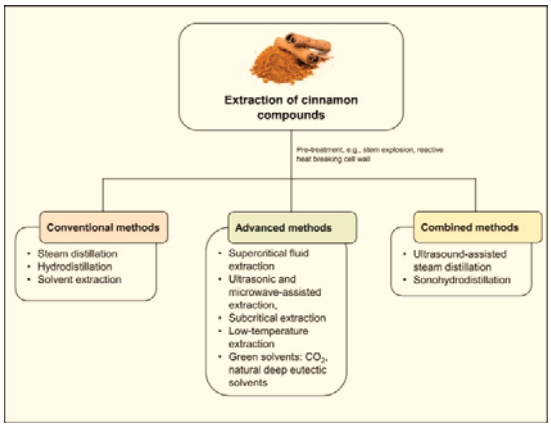


**Figure 3:** Extraction methods for bioactive components of cinnamon [25].

## Daily dosage

Besides many other factors, subspecies, extraction mode, and galenic properties influence the required doses [35]. Cinnamon is generally safe when used in small amounts; Usually, it is used in about 1-6 g depending on the weight. Since Saigon cinnamon contains higher coumarin (5.8 to 12.1 mg) than Ceylon cinnamon, so should reduce its intake [35].

## Cardiovascular protective effects of cinnamon

**Cinnamon and the cardiovascular system:** As explained in the previous parts of the current review, the most important compounds of cinnamon are cinnamaldehyde, cinnamic acid, eugenol, and coumarin [36], out of which cinnamaldehyde is the main bioactive compound (60–75%) [37]. This compound has protective effects on cardiovascular conditions like cardiac ischemia, hypertrophy, and myocardial infarction [38,39]. Using 100 mg cinnamon /kg body weight for two weeks had significant antioxidant ability in reducing the complications related to oxidative stress and increased total antioxidant power by reducing lipid peroxidation. Cinnamon supplementation improves the performance of the heart and increases coronary flow by enhancement of cardiac performance [40].

The consumption of 500 mg cinnamon /kg body weight in type 2 diabetic patients for two months reduced blood sugar and lipid. Using cinnamon along with turmeric, and chili pepper on CVD patients for 11 years showed that cinnamon did not affect blood lipids and CVDs. Daily consumption of 1 g cinnamon powder /kg body weight for 16 months in male diabetic patients reduced diabetes complications [17].

**Figure 4:** Cinnamon plant, bark, and leaves.



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## Cinnamon and atherosclerotic

There is an accumulation of cholesterol and inflammatory cells in the artery wall in atherosclerosis [41]. Atherosclerosis causes cardiovascular diseases such as myocardial infarction, stroke, and ischemic heart failure [42]. Inflammation and oxidative stress play a key role in cardiovascular diseases. It's confirmed that the therapeutic properties of cinnamaldehyde improve oxidative stress-mediated cardiovascular diseases, in atherosclerosis subjects [43]. It's declared that cinnamaldehyde protects smooth muscle cells of vascular against LDL oxidation-induced proliferation [43]. The protective and anti-inflammatory effects of cinnamaldehyde on the oxidative stress induced by $H_2O_2$ in the endothelial cells of the human umbilical vein in Sprague-Dawley rats *in vivo* were proved by Kim, et al. [44]. Moraes, et al. [39], concluded that cinnamaldehyde could inhibit atherosclerotic damage in the aortas due to antioxidant effects in ovariectomized female mice. the effects of cinnamaldehyde on the vascular damage induced by a high-cholesterol diet in rabbits were reported by Nour, et al. [45]. Also, cinnamaldehyde improved atherosclerosis in hypercholesterolemic rabbits by decreasing cholesterol and antioxidant and anti-inflammatory properties. The researchers declared that cinnamon showed preventive effects on the formation of atherosclerotic plaque which inhibits the increase of fibrosis, neutrophils, and hypertrophy and reduce NO concentration [33,46]. Cinnamon leads to the reduction of negative inotropic and chronotropic effects in the heart, the relaxation of the VSM wall, and the improvement of systolic and diastolic failures by reducing the calcium channel activity [47].

## Cinnamon and anti-platelet aggregations

Prolonged use of anti-platelet aggregation drugs has various side effects, therefore natural sources have been considered. Some compounds of cinnamon *C. cassia* such as eugenol, amygdala, cinnamic alcohol, 2-hydroxy cinnamaldehyde, 2-methoxycinnamaldehyde, and conifer aldehyde displayed antiaggregatory activity [25]. The cinnamaldehyde inhibited platelet aggregation induced by collagen and thrombin *in vitro* and platelet aggregation *in vivo* [48]. The administration of cinnamaldehyde to mice inhibits platelet-related thrombosis. Eugenol in cinnamon reduces platelet aggregation by inhibiting thromboxane A2. The administration of cinnamaldehyde to aortic banding mice mitigated the development of pathological cardiac hypertrophy and heart failure [49]. Cinnamon extract has anticoagulant and anti-aggregation properties for the platelets [9]. Administration of cinnamon to hypercholesterolemic rats increased HDL and decreased triglyceride and LDL-cholesterol levels [9]. The cinnamon may prevent the release of arachidonic acid from membrane phospholipids of platelets and reduce the production of thromboxane A2. Also, it decreases triglyceride, LDL, and total cholesterol and increases HDL. Because LDL and Ox-LDL have a high affinity for CD36 that causes platelet activation, thus a reduction in LDL decreases platelet activation [9] Figure 5.

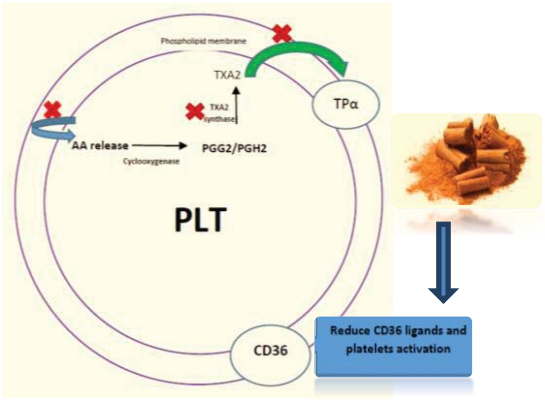


**Figure 5:** The effect of cinnamon on platelets [9].

## Cinnamon and blood lipids

Using one cinnamon extract capsule (250 mg/kg body weight) in type 2 diabetes patients for two months reduced Total Cholesterol, HDL, and LDL [50]. Also, in type 2 diabetes patients, using cinnamon (3 g) reduced HDL and LDL [16]. The practice of 500 mg cinnamon extract /kg body weight for one year had no advantageous effect on Electrocardiogram (ECG) pointers in at-risk diabetic persons [51]. Hyperlipidemia is linked with a high incidence of myocardial infarctions and cardiovascular diseases. The cinnamaldehyde and polyphenols present in cinnamon have antihyperlipidemic effects [43]. A study on the blood lipids of patients with CVDs and cancer during 11 years, proved that cinnamon did not affect CVDs [12]. The use of 300 and 600 mg cinnamon extract/kg body weight alone and with metformin (250 mg/kg body weight) for 30 days in type 2 diabetes rats increased HDL but reduced TC and LDL levels [52]. An alternative study exhibited that 300 mg cinnamon extract /kg body weight for 18 days enhanced HDL and LDL in type 2 diabetes antenatal rats [53]. Daily use of 300 mg cinnamon alcoholic extract /kg along with 20 mg captopril /kg for four weeks reduced TC and LDL, increased HDL, and improved atherogenic index in acute hypertension rats [33]. Supplementation of 100 mg cinnamon extract /kg body weight in metabolic syndrome rats for 12 weeks reduced TC and LDL levels and increased HDL [54]. The use of 200 mg cinnamon alcoholic extract /kg/d for 8 weeks in rats improved cardiac hemodynamics, decreased serum Malondialdehyde, improved hyperlipidemia, and decreased TC, LDL, HDL, and LDL/HDL ratio [40]. Consumption of 500 and 300 mg cinnamon alcoholic extract /kg body weight improved HDL and reduced TC and LDL levels in type 2 diabetes and hyperlipidemia rats [55,56]. It's proved that cinnamon extract in different doses in type 2 diabetes rats reduced Alanine Aminotransferease, Aspartate Aminotransferease, and LDH levels [52]. The different impacts of cinnamon extract on serum parameters are due to differences in the extraction method, the type of solvent, or the dose of cinnamon [57].

According to many studies, cinnamon regulates blood lipids, reduces LDL and TC levels, and improves blood lipids in obese diabetes cases fed with high-fat diets [58]. Although, some studies have declared the protective effects of cinnamon on the heart; however, in some other studies, cinnamon had



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no beneficial effect on the blood lipid [51]. In many studies, cinnamons reduced HDL levels [50], but further studies need to prove the effect of cinnamon on HDL [53,59]. Figure 4 shows the effect of cinnamon on serum levels of sugar, lipids, blood pressure, and cardiovascular tissue changes such as apoptosis, inflammation, and fibrosis Figure 6.

Using 100 mg cinnamon capsule significantly decreased blood TG and total cholesterol but did not change LDL-c and HDL-c and had a small effect on impaired glucose tolerance in diabetic patients [60]. Supplement of 1.5 gm Cinnamon /day for 60 days in type 2 diabetes patients increased HDL and reduced triglyceride and cholesterol [61,62] Figure 7.

The utmost substantial risk pointers for cardiovascular changes are amplified serum cholesterol, TG, LDL, and reduced HDL all of which are linked to oxidative stress. Cinnamon may increase the efficacy of HDL-mediated reverse cholesterol transport, consequently decreasing cardiovascular disease risk [40].

## Cinnamon and blood pressure

Administration of 1–10 mg cinnamaldehyde / kg decreased blood pressure in anesthetized dogs and guinea pigs, due to peripheral vasodilating effects. The hypotensive effects were proved by vasorelaxant action and negative inotropic and chronotropic properties on the heart in anesthetized rats [25]. The vasodilatory action of cinnamaldehyde relaxed the rat aortic rings precontracted with phenylephrine. Tarkhan, et al. [63], showed that cinnamaldehyde elevates methylglyoxal-induced vascular damage in rat thoracic aorta. The aromatic carboxylic acid and cinnamic acid of cinnamon also exhibit vasorelaxant effects in rat thoracic aortas (Kang, et al. 2013) that prove protective effects against myocardial ischemia in Sprague-Dawley rats treated with isoproterenol [64]. According to meta-analyses, the effectiveness of 2 g cinnamon extracts on SBP and DBP for more than 8 weeks was reported [65]. The same effect has been concluded in DM2 patients [66]. The effects on SBP and

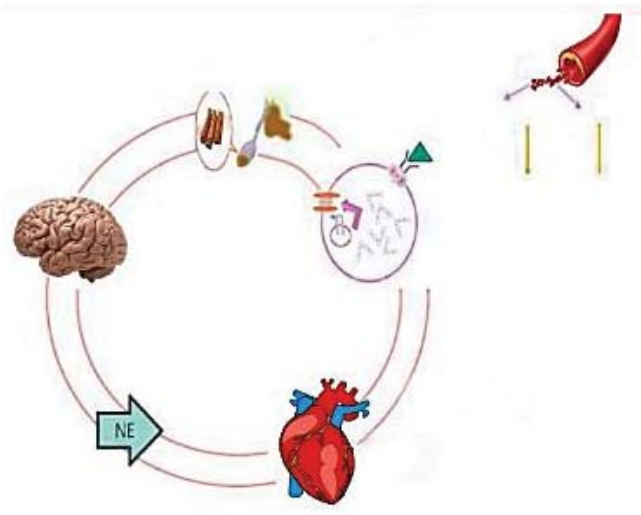


**Figure 6:** The effect of cinnamon on the cardiovascular system [17].

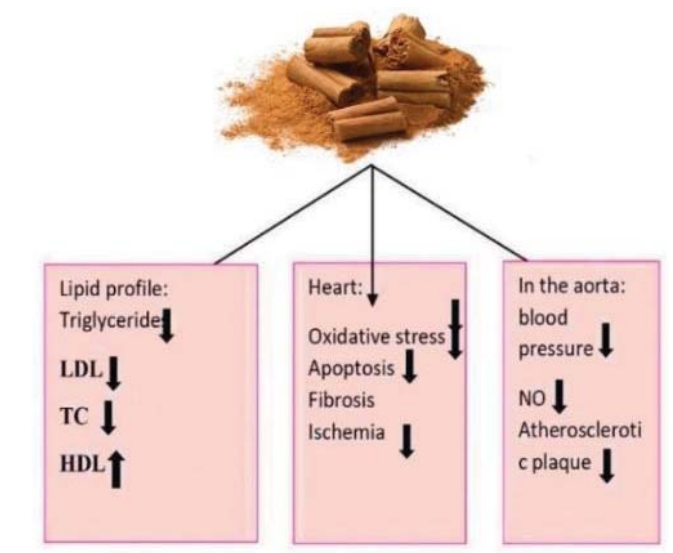


**Figure 7:** The effect of cinnamon extract on blood lipids and the cardiovascular system [17].

DBP pressure in patients not older than 50 years are displayed clearly in low doses and longer periods (>12 weeks) [36]. Another study declared that 1 g of cinnamon per day for three months lowered blood pressure in diabetic patients. High blood pressure causes 2/3 of strokes, and 50% of coronary heart disease, and is linked to premature coronary artery disease (Poorzand. et al. 2019). Using 1500 mg cinnamon capsule for 90 days significantly decreased mean ambulatory SBP and LDL-c, didn't change FBS, and increased HDL-c [67]. Cinnamon powder reduces systolic and diastolic blood pressure [68]. In a study on 59 type 2 diabetes patients, a daily intake of 1200 mg cinnamon for 12 weeks reduced systolic blood pressure by an average of 3.4 mm Hg [34].

## Cinnamon and diabetic

Currently, diabetes is regarded as the most common metabolic disorder in society, and the prevention of cardiovascular issues in diabetic patients is important. The protective effects of cinnamaldehyde against hypertension in streptozotocin-diabetic and fructose-fed insulin-resistant rats reported by El-Bassossy, et al. ( 2011). Furthermore, cinnamaldehyde reduced fibrosis and cardiac inflammation in fructose-fed rats which displayed metabolic syndrome [69]. The antihyperglycemic and antihyperlipidemic function of cinnamaldehyde in insulin-resistant mice was reported after oral administration of cinnamaldehyde. The polyphenols of cinnamon improve regulating blood glucose in humans 70]. The phenolic compounds, catechin, epicatechin, and procyanidin B2 as flavonoids in cinnamon can reduce blood sugar by reducing glycogen synthesis, glycogenolysis, and glucose absorption in the intestine [25]. Furthermore, polyphenols such as rutin, catechin, quercetin, kaempferol, and isorhamnetin in cinnamon can diminish insulin activity and improve glycaemic control [8]. The consumption of 500 mg cinnamon /kg body weight in type 2 diabetes patients for 2 months reduced blood sugar and lipids [71]. Also, using cinnamon extract capsules (250 mg/kg body weight) in type 2 diabetes patients for two months reduced total cholesterol,



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HDL, and LDL. The consumption of cardamom (3 g), cinnamon (3 g), ginger (3 g), and saffron (1 g) for eight weeks reduced HDL and LDL in type 2 diabetic patients. Regarding the research, using 500 mg cinnamon extract /kg body weight for one year in pre-diabetic patients had no beneficial effect in improving Electrocardiogram indicators [17]. It proved that cinnamon significantly reduced FBG and HOMA-IR, in T2DM and pre-diabetes patients compared to placebo [72].

## Cinnamon and diabetes complications

Insulin resistance causes the formation of free radicals which lead to hypertension and endothelial dysfunction. Similarly, low insulin sensitivity is associated with visceral obesity, hypertension, dyslipidemia, increased pro-inflammatory cytokines, microalbuminuria, increased LDL, and decreased HDL [10]. According to the studies, the anti-obesogenic bioactive compounds in cinnamon are eugenol, cinnamaldehyde, and cinnamic acid, which increase glucose uptake and insulin sensitivity (Lu, et al. 2018). In type 2 diabetic patients, polyphenols isolated from the cinnamon bark probably improve insulin sensitivity and decrease blood pressure in patients. Short-term supplementation of cinnamon in prediabetes and type 2 diabetic patients lower glycaemic blood [34]. Epicatechin, catechin, and procyanidin B2 in cinnamon can inhibit the formation of advanced glycation products, which leads to diabetes complications [8]. The *C. cassia* extracts are rich in eugenol and conifer aldehyde improving blood circulation and inhibiting platelet coagulation compared to acetylsalicylic acid [73]. The cinnamon effects on diabetes, obesity, and hyperlipidemia are linked to carbohydrate digestion. The Ceylon cinnamon extracts inhibit α-glucosidase and pancreatic α-amylase, modifying glucose production at a dose of 25 µg/mL, and enzymes of the glucose-6-phosphatase (G6Pase) and the phosphoenolpyruvate carboxykinase (PEPCK), which are linked to the liver gluconeogenesis [74].

The supplementation of cinnamon in women with polycystic ovary syndrome affects glucose absorption, improves glucose homeostasis, reduces total cholesterol, LDL, and triglycerides, and improves HDL cholesterol compared to control [75]. Cinnamon administration in doses of 1.5 g per day, for more than 12 weeks can display an anti-inflammatory effect due to reducing serum C-reactive protein which reduces the probability of the risk of heart disease [76]. Cinnamon significantly reduces triglycerides and total cholesterol due to the extracts' polyphenols which increase glycogen synthesis, decrease glycogenolysis, and inhibit glucose absorption in the small intestine [60]. Furthermore, cinnamaldehyde has a vasodilator effect and inhibits the invasion and discharges of $Ca^{2+}$, preventing hypertension in type 1 and 2 diabetes since it decreases vascular contractility. According to most clinical studies, 3 to 6 g *C. cassia* per day could improve glucose metabolism in DM2 people [77] and improve cardiovascular disorders as the main complications of diabetes [14].

Cinnamon consumption also decreases MDA produced by lipid peroxidation which damages biomolecules [78]. Cinnamon affects biomarkers related to oxidative stress and inflammation and reduces CRP levels which are associated with cardiovascular disease risk. The level of cytokine IL-6 which is produced in response to wounds or infections, decreased. An increase in total antioxidant capacity lowers susceptibility to oxidative damage due to flavonoids [78]. Type-A procyanidin polyphenols extracted from *C. zeylanicum* bark has anti-inflammatory and anti-arthritic functions in rats; as well as it is non-ulcerogenic (Vetal, et al., 2013). One g cinnamon daily in prediabetes patients for six months, did not alter electrocardiographic parameters [51]. The most biological effects of extracts or supplements isolated from the cinnamon bark leaves, flowers, fruits, roots, twigs, stems, and branchlets, can potentially exert biological effects [79]. According to a case study, daily consumption of 1 g cinnamon powder /kg body weight for 16 months in male type 2 diabetes patients reduced the complications of diabetes, it caused fluid retention and edema in the knee which probably increased the progressive congestive heart failure [80].

## Cinnamon and obesity

Obesity is strongly linked with cardiovascular diseases. The phytochemicals may be good candidates for anti-obesity drugs due to fewer side effects [25]. The anti-obesity effects of cinnamaldehyde were studied for 8 weeks on mice fed a high-fat diet [37]. Cinnamaldehyde and cinnamic acid have anti-obesity and cardioprotective properties. Also, cinnamaldehyde decreased body weight, fat mass, serum lipid, free fatty acid, and leptin, improved insulin sensitivity, prevented adipose tissue hypertrophy, and induced browning of white adipose tissue in comparison with the control [81]. It decreased hyperlipidemia and the body weight of obese rats on the high-fat diet and protected animals against hypertension and vasoconstriction problems. Supplementations with 2 to 3 g of cinnamon per day significantly impacted body weight, and obesity which is linked with cardiovascular disorders. It delayed gastric emptying, gastrointestinal motility, and release of serotonin from enterochromaffin cells. That reduces visceral fat deposits as it boosts interscapular brown adipose tissue and thermogenic protein. It also increases glucose transport, insulin β receptors, and zinc finger protein 36 in the adipocytes, and decreases leptin amount[82]. Daily use of 3 grams of cinnamon for 8 weeks significantly reduced body fat mass in type 2 diabetes patients [83].

## Cinnamon and oxidative stress

According to the studies, cinnamon increased total antioxidant capacity by reducing the peroxidation of lipids [84]. Ranjbar, et al. [85] reported that the use of 100 mg cinnamon /kg body weight for two weeks causes significant antioxidant ability and might reduce diseases caused by oxidative stress. Consumptions of cinnamon and cardamom in rats fed a high-fat diet improved oxidative stress by reducing the free radical production in heart tissue [67]. Also consuming 200 mg cinnamon extract /kg body weight in gamma radiation exposed rats reduced damage to heart and liver tissue by decreasing necrosis and apoptosis. The protective properties of cinnamon significantly increased when cinnamon was used for longer than 40 days [86]. The use of cinnamaldehyde and allopurinol in metabolic syndrome-induced rats with fructose reduced



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oxidative stress in cardiac tissue. Cinnamon also reduces inflammation and fibrosis in heart tissue by preventing the TGF-β/SMAD cell path [69]. In-vitro studies have proved some vascular protection effects of cinnamon. Moreover, cinnamon improved oxidative stress by increasing the expression of Heme Oxygenase-1, Glutathione Peroxidase-1, Quinone Oxidoreductase-1, and catalase in heart tissue of type 2 diabetes rats. Likewise, cinnamon extract reduces oxidative harm caused by higher glucose in cardiomyocytes via the Transient Receptor Potential Ankyrin subtype 1 (TRPA1)/Nrf2 path [46].Alcoholic extract of cinnamon in doses of 50, 100, and 200 mg/kg body weight decreased the damage of the myocardial infarction in rats and improved protective effects against ischemia-reperfusion injury and arrhythmia due to antioxidant effects [87]. the effects of cinnamaldehyde (22.5, 45, and 90 mg/kg body weight) and cinnamic acid (37.5, 75, and 150 mg/kg body weight) along with propranolol (30 mg/kg body weight) in rats were due to antioxidant properties that inhibited the heart ischemic injury and increased Nitric Oxide and superoxide dismutase activity and reduced the amount of MDA in heart tissue [64]. Using cinnamon improved systolic and diastolic dysfunctions by improving echocardiographic and hemodynamic parameters and cinnamaldehyde reduced cardiac fibrosis and aortic stenosis in rats, that declared cinnamon has obvious antiarrhythmic effects [49]. Consumption of cinnamon bark extract (10%) and cardamom seeds increased the antioxidant enzymes such as glutathione, SOD, CAT, GPX, glutathione S-transferase in the heart and reduced hydrocarbons of conjugated dienes and hydroperoxide in high-fat rats and consequently improved oxidative stress [58]. In many studies, the antioxidant activity of cinnamon has been displayed by inhibiting free radicals and 5 lipoxygenase enzymes [59]. It's proven that cinnamon increases antioxidant activity and decreases apoptosis in the heart tissue [53]. Administration of 0.02% cinnamon for 12 weeks in rats significantly prevented the production of ROS, didn't change the NO production, increased phosphorylated endothelial nitric oxide synthase, and decreased nitrotyrosine [47]. Using 10, 100, and 1000 μM cinnamon dilated the aortic artery and reduced the calcium channel activity, and consequently decreased blood pressure [33]. Negative inotropic and chronotropic effects in the heart tissue of rats were also induced by cinnamon. The protective effects of cinnamon on ventricular cardiomyocytes were more evident than its effect on the VSM cells [88].

The antioxidant capacity of the hydrophilic extracts of cinnamon is linked to phenolic compounds such as phenolic acids, proanthocyanidins, terpenes, and cinnamaldehyde and causes cardioprotective and antidiabetic effects. This property increases the activities of superoxide dismutase, catalase, and glutathione peroxidase as well as scavenging ROS, and free radicals and reducing malondialdehyde concentration [74]. Cinnamic acid and cinnamaldehyde have protective effects against the cardiotoxicity induced by the synthetic isoproterenol [89]. Proanthocyanidins and phenolic acids in *C. zeylanicum*, *C. canephora*, *C. cassia*, *C. osmophloeum*, *C. massive*, and *C. insularimontanum* interact with the gene expression and pro-inflammatory proteins such as cyclooxygenase, nitric oxide, lipoxygenase, and cytokines [90,91]. Cinnamon inhibits the release of arachidonic acid with inflammatory effects and reduces the formation of thromboxane A2. Also, the eugenol isolated from cinnamon methanolic extracts has a strong antioxidant effect that inhibits lipid peroxidation and the production of ROS and consequently maintains cardiovascular health [25,92] Table 1, Figure 8.

**Table 1:** Some studies on the cardiovascular protective properties of cinnamon's bioactive components.

| Cinnamon | Used dose | Case | Results | Reference |
|---|---|---|---|---|
| *Cinnamomum burmannii* 60 g/ 1L water, heated at 100 °C for 30 min | 100 mL per day, oral single dose | 30 non-diabetic cases (20–53 years) | Slightly decreased postprandial blood glucose after 2 hours | [93] |
| *Cinnamomum burmannii* extract Herbilogy® | 2, 4, and 8 mg/kg B.W, orally for 28 days. | 30 male, Swiss Webster mice on a high-fat diet | Decreased total cholesterol | [94] |
| *Cinnamomum burmannii* Fine powder | 2 g/per day, 8 weeks. | 36 women more than 18 years, rheumatoid arthritis pre and postmenopausal | Significant decrease in serum TNF-α, CRP, diastolic blood pressure, swollen joint count, and blood pressure. | [95] |
| *Cinnamomum cassia* Bark | 1.5 g for 60 days | 99 Type 2 Diabetic patients | Reduced HbAlc, glucose, triglyceride, TG/HDL-C ratio, BP, and increased HDL and eGFR | [61] |
| *Cinnamomum cassia* Spray-dried Aqueous extract | 250 mg twice a day, two months | 137 Chinese, mean age 61 years, Fasting serum glucose: >6.1 mmol/L | Reduced fasting insulin, glucose, total cholesterol, and LDL, improved insulin sensitivity | [50] |
| *Cinnamomum cassia* bark <200 ppm coumarin | 3 g in 4 experimental sessions | 13, 65 years with a high-fat meal, fasting glycaemic 5.4 mmol. l at the first | Reduced glycemic response, postprandial endotoxemia, and C-reactive protein. Increased cholesterolemic response | [96] |
| *Cinnamomum verum* bark Powder | 3 g/per day, 8 weeks | 99 women with dyslipidemia | Reduced total cholesterol, triglyceride, and HDL, BW, BMI | [97] |
| *Cinnamomum zeylanicum* | 50, 100, or 200 mg/kg, 14 days | Antioxidant activity, antioxidant enzyme activity, and evaluation of activity against ischemia-reperfusion injury and arrhythmias in rats. | Improved the ischemia/reperfusion-induced myocardial injury by reduction of the infarct size. Decreased ventricular tachycardia and ventricular ectopic beat episodes.increased SOD and GPx activities. Decreased cardiac troponin I, lactate dehydrogenase, and MDA of serum | [87] |



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| | | | | |
|---|---|---|---|---|
| *Cinnamomum zeylanicum* | 85, 250, and 500 mg aqueous for 3 months | 28 healthy subjects | reduced systolic and diastolic blood pressure and cholesterol. Renal and liver function, fasting blood glucose, HDL-c, VDL-d, and triglycerides were in the normal range, No changes in the anthropometric parameters, | [98] |
| *Cinnamomum zeylanicum* bark Powder | Three capsules of 500 mg/daily for 8 weeks | 84 polycystic ovary syndrome women | increased total antioxidant capacity and Malondialdehyde decreased. Improved total cholesterol, HDL, and LDL | [99] |
| Iranian *Cinnamon* Powder | 3 g / day/ 8 weeks | 39 type 2 diabetes patients, body mass index 27.7 | No significant effect in reduction of NF-kB, SIRT1, hs-CRP, IL-6, and TNF-α | [100] |
| Cinnamic acid | 30 mg/kg/day for 7 weeks | rats fed High fat | Anti-obesity and cardioprotective | Mnafgui, et al. (2015) [81] |
| Cinnamaldehyde | 20 mg/ kg/day orally | Rat with insulin deficiency and resistance | Prevent hypertension due to diabetes | El-Bassossy, et al. (2011) |
| Cinnamaldehyde | 50 mg/kg for 7 weeks | Cardiac hypertrophy-induced mice by aortic banding | improve cardiac hypertrophy and fibrosis | Yang, et al. [49] |
| Cinnamaldehyde | 10 mg/kg/day | hypercholesterolemic rabbits | Vasculoprotective effects | Nour, et al. [45] |
| Cinnamaldehyde | 10–100 μM | Isolated rat aortae subjected to vascular damage by methylglyoxal | Vasculoprotective effects | Tarkhan, et al. [63] |
| Cinnamaldehyde | 20 mg/kg b.w. orally for 8 weeks | ovariectomized mice, LDL receptor knockout | Prevent the development of atherosclerotic lesions | Moraes [39] |
| Cinnamon powder | 1000 mg/kg, 16 months | type 2 diabetes cases | preventing cardiac ischemia | Crawford, et al. 2018 [80] |
| Cinnamon extract | 500 mg/kg, 2 months | type 2 diabetes cases | decreased TC, HDL, LDL | Anderson, et al. [50] |
| Cinnamon powder | 1 g/day, 3 months, | type 2 diabetes cases | Decreased blood pressure | Zamani, et al. [68] |
| Cinnamaldehyde | injection of 10, 100 1000 micro m, 6-8 hours | healthy rats and mice, | induced negative inotropic and chronotropic effects in the heart, | Tuzco, et al. 2017 [88] |
| Cinnamon extract | 300 and 600 mg/kg, 30 days | STZ-induced diabetes rats, | Decreased ALT, AST, LDL, and LDH increase of HDL | Ashoor, et al. 2016 [52] |
| Cinnamon | 0.02%, 12 weeks | mice, healthy heart, | Decreased ROS and nitrotyrosine, maintained NO, improved phosphorylated endothelial nitric oxide synthase and fibrosis | Wang. et al. 2020 [59] |

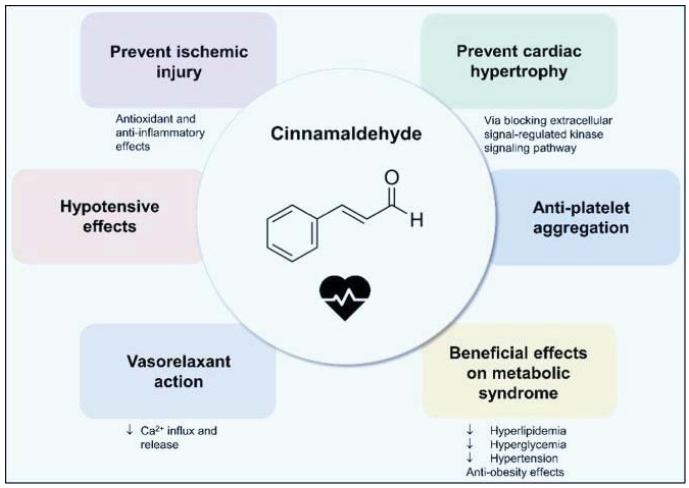


**Figure 8:** Main protective effects of cinnamaldehyde on the cardiovascular system [25].

## Conclusion

The effectiveness of cinnamon and its various bioactive compounds in preventing and treating CVD is declared in most human and animal studies. Cinnamaldehyde and cinnamic acid are the main compounds with protective effects on cardiovascular diseases. Previous studies have reported the beneficial effects of cinnamon on lipid profiles, fasting glucose, blood pressure, cardiovascular disease, diabetes, and consequently mortality. Cinnamon is influential in preventing and treating CVDs by lowering blood lipids and blood pressure and improving the oxidants: antioxidants balance. It's concluded that cinnamon consumption may need to exceed 3 g/d to improve insulin resistance. Therefore, cinnamon has protective effects on the cardiovascular system by reducing oxidative stress and increasing HDL, reducing ischemic damage such as apoptosis in heart tissue, reducing blood pressure, and having anti-arrhythmic effects. More preclinical and clinical studies are needed to prove the efficacy and the effective dose of cinnamon as a biopharmaceutical agent and its protective effect on CVDs.

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