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Cardiovascular protective effect of cinnamon and its major bioactive constituents: An update

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ABSTRACT

Cinnamon from the bark of *Cinnamomum* species is one of the most important spices used worldwide in food and as a traditional medicine for centuries. It has substantial benefits for human health including its protective role on cardiovascular diseases. This review provides an overview of the cardiovascular protective effects of cinnamon and its major bioactive constituents. Reviewed literature showed sufficient evidence that cinnamon can reduce the risk of cardiovascular diseases, including cardiac ischemia, cardiac hypertrophy, and myocardial infarction. Furthermore, cinnamon exhibited beneficial effects on cardiovascular-related comorbidities like diabetes, and other metabolic disorders, and showed antioxidant and anti-inflammatory effects. Cinnamon contains several bioactive compounds such as phenolics and volatile compounds. Cinnamaldehyde and cinnamic acid are among the main cinnamon compounds with protective effects on cardiovascular diseases through different molecular mechanisms. Although the protective effects of cinnamon and its main compounds have been extensively reported, more preclinical and clinical studies are still required before its use as a biopharmaceutical agent.

1. Introduction

The genus *Cinnamomum* (also known as cinnamon) belongs to the Lauraceae family and is commonly used as a spice and herbal medicine (Jalali, Mahmoodi, Moosavian, Ferns, & Sohrabi, 2020). In contemporary times, cinnamon has been the subject of many ethnopharmacological studies. These reports have pointed out that cinnamon is the source of bioactive compounds with protective properties against inflammation, oxidative stress, diabetes (regulation of insulin, glucose uptake), obesity, hypercholesterolemia, hypertension, and blood lipid profile (Hamidpour, Hamidpour, Hamidpour, & Shahlari, 2015; Mollazadeh & Hosseinzadeh, 2016; Muhammad & Dewettinck, 2017; Ranasinghe et al., 2013; Silva, 2019).

The genus *Cinnamomum* is widely distributed in the world, with around 250 known species and the main species of commercially cultivated cinnamon are *Cinnamomum verum* (Ceylon Cinnamon), *Cinnamomum burmannii* (Korintje Cinnamon), *Cinnamomum cassia* (Saigon Cinnamon) and *Cinnamomum loureiroi* (Royal Cinnamon). Ethnobotanical reports state that the most consumed part of the plant is the bark. The main constituents of cinnamon are cinnamaldehyde and trans-cinnamaldehyde that are present in the essential oil. These compounds besides contributing to the cinnamon fragrance have biological properties (Rao & Gan, 2014). Cinnamon bark is the source of other bioactive compounds like catechins and procyanidins, which belong to the flavan-3-ols sub-group of flavonoids. Flavan-3-ols are characterized by their saturated three-carbon chain with a -OH group in the C3 position (Fig. 1). In nature, they are commonly found as monomers or polymerized as proanthocyanidins, also known as condensed tannins

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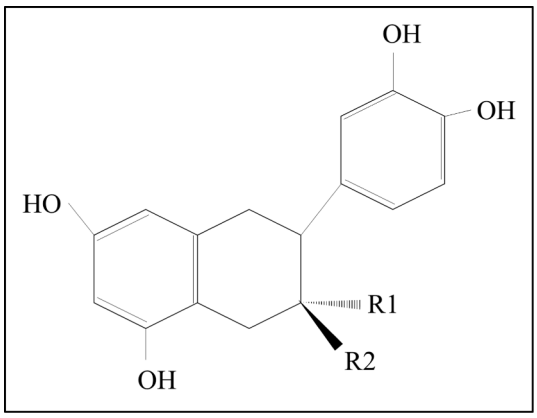

Fig. 1. Graphic representation of the general structure of flavan-3-ols.

(Andrés-Lacueva et al., 2009; Mahmoodnia, Aghadavod, & Rafieian-Kopaei, 2017). These compounds have been extensively studied and popularized by their presence in green tea and attributed antioxidant, anti-inflammatory, and anti-obesogenic properties (Johnson, Bryant, & Huntley, 2012; Suzuki, Pervin, Goto, Isemura, & Nakamura, 2016). Also, studies have shown that some of the most abundant bioactive compounds found in cinnamon are phenolic compounds (Fig. 2) like catechin, protocatechuic acid, quercetin, epicatechin, p-coumaric acid, p-hydroxybenzoic acid, syringic acid, rosmarinic acid, caffeic acid, ferulic acid, and chlorogenic acid (Vallverdu-Queralt et al., 2014). The aim of this review article is to systematize and discuss data from the literature available reporting the cardiovascular protective effects of cinnamon and of its major constituents.

2. Methodology

The review was compiled based on recent scientific literature (2011–2021) from the Scopus and Web of Science databases to identify relevant information on the cardiovascular properties of cinnamon bioactive compounds. The keywords used for the literature search included the terms: cinnamon, *Cinnamomum*, terpenes, essential oils, polyphenols, phenolic compounds, bioactive compounds, cardiovascular, and antioxidants. Research evaluating the activity of cinnamon extracts or supplementations, and cinnamon constituents on the cardiovascular system and related antioxidant, anti-inflammatory, anti-hypercholesterolemic, anti-obesity, and anti-glycemic activities, were considered, using *in vitro*, and *ex vivo*, *in vivo* studies. Data from clinical trials were also considered from original and review articles, meta-analyses, and book chapters.

3. Cardiovascular protective effect of cinnamon

Cinnamon has been evaluated for its beneficial effect on the cardiovascular system, mainly because of its cardiovascular protective properties. Also, comorbidities like diabetes and other metabolic disorders increase the probability of cardiovascular pathologies. Insulin resistance promotes the formation of free radicals contributing to hypertension and endothelial dysfunction. Similarly, low insulin sensitivity is closely related to prevailing metabolic syndrome factors (MetS), such as visceral obesity, hypertension, dyslipidemia, increased pro-inflammatory cytokines, microalbuminuria, increased low-density lipoproteins, and decreased high-density lipoproteins (Mollazadeh & Hosseinzadeh, 2016). The most-reported bioactive compounds in cinnamon with anti-obesogenic activity are eugenol, cinnamaldehyde, and cinnamic acid, which increase glucose uptake and insulin sensitivity. However, *in vitro* models in 3T3-L1 adipocytes indicate that the reported effects are related to the increase in IRβ, GLUT4 and TTP, mRNA levels for GLUT1, GLUT4 translocation, phosphorylation of AMPK and ACC, lipid storage accumulation and fatty acid oxidation, mRNA levels for CPT1α, PGC1α, PPARγ, and CIDEA, expression of PLIN and GPDH, and reduced the levels of mRNA levels for GSK3β, IGF1R, IGF2R, PIK3R1, adiponectin secretion, expression of PLIN and GPDH, C/EBPα, and PPARγ (Lu, Cao, Xiao, Song, & Ho, 2018).

The comorbidities related to type 2 diabetes mellitus (DM2) are mainly macrovascular. Polyphenols isolated from the bark of different species of cinnamon are responsible for lowering blood glucose levels and controlling blood pressure, as well as contributing to other coronary and cardiovascular diseases. In patients with DM2, the possible mechanism of cinnamon is by improving insulin sensitivity and decreasing blood pressure in patients. A meta-analysis on the effects of short-term cinnamon supplementation in patients with prediabetes and DM2 indicates that in addition to lowering glycemic blood levels, it is also linked with a reduction in the systolic blood pressure (SBP) of −5.39 mm Hg, while then in the diastolic (DBP) of −2.6 mm Hg. It should be noted that the effects were shown in patients with hypertension, > 130 mm Hg (SBP) and >80 mm Hg (DBP). On the other hand, the effect was not significant in patients with pressure just above normal (Akilen, Pimlott, Tsiami, & Robinson, 2013). Epicatechin, catechin, and procyanidin B2 are compounds present in cinnamon, which can inhibit the formation of advanced glycation products (AGEs), contributing to the complications of diabetes (Rao & Gan, 2014).

The extracts rich in eugenol and coniferaldehyde of *C.cassia* improve blood circulation; they are also effective in inhibiting platelet coagulation, with effectiveness compared to acetylsalicylic acid (Akram & Rashid, 2017). The mechanisms of action of cinnamon effects on diabetes, obesity, and hyperlipidemic diseases are linked to carbohydrate digestion. The extracts of *C.verum* (Ceylon cinnamon) are inhibitors of α-glucosidase and pancreatic α-amylase. They are also involved in modifying glucose production at a dose of 25 μg/mL, such as the glucose-6-phosphatase (G6Pase) and the phosphoenolpyruvate carboxykinase (PEPCK), which are closely associated to the gluconeogenesis in the liver (Habtemariam, 2019; Rafehi, Ververis, & Karagiannis, 2012). In addition, it influences the adsorption of cholesterol and fatty acids through inactivation of Niemann-Pick c1-like 1 and Cd36 mRNA receptors likewise down-regulates the chylomicron synthesis (Silva, 2019).

Changes at the gene and protein level have been elucidated, proposing mechanisms of action related to the inhibition of tyrosine phosphatase-1 (PTP-1), induction of the activation of the enzyme phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), which is also participated in the manufacture of insulin. Aqueous extracts of *C. burmannii* affect the genes coding for adipokines and glucose transporters (GLUT) in 3 T3-L1 mouse adipocytes. Likewise, it affects the release of insulin in INS-1 cells line, which is related to the protective effect of the β cells of the pancreas. The main cardioprotective and antidiabetic effects are associated with the antioxidant capacity of the hydrophilic extracts of cinnamon. In addition to scavenging reactive oxygen species (ROS) free radicals and reducing malondialdehyde (MDA) levels, they increase the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) enzimes. Cinnamon extracts can also inhibit pro-inflammatory genes and proteins such as IL-1β, IL-6, cytokines, and TNF-α. They also activate transcription factors, peroxisome proliferative-activated receptors (PPARs), which regulate insulin resistance and adipogenesis. It should be mentioned that the responsible compounds are phenolic compounds such as phenolic acids, proanthocyanidins, terpenes, cinnamaldehyde. In particular, the latter has a powerful biological effect and has been observed to be rapidly oxidized (60 %) in cinnamic acid, with a half-life of 6.7 h. As a product of its degradation, benzoic acid is derived and is excreted via the urinary tract (Habtemariam, 2019; Rafehi et al., 2012).

Cinnamon has protective effects against the cardiotoxicity produced by the synthetic compound isoproterenol due to cinnamic acid and cinnamaldehyde (Dorri, Hashemitabar, & Hosseinzadeh, 2018). Extracts rich in proanthocyanidins and phenolic acids from different species of

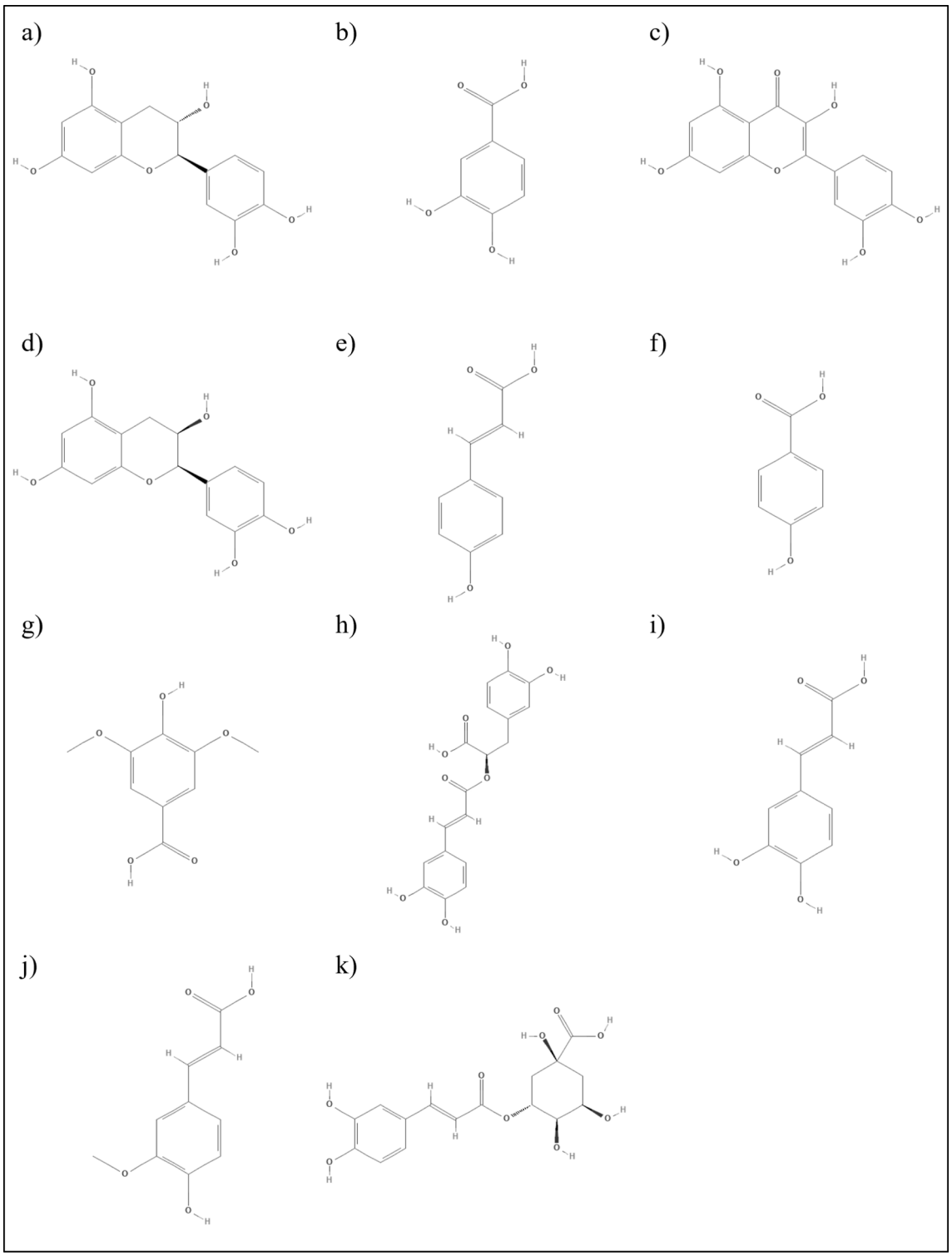

Fig. 2. Most abundant bioactive compounds found in cinnamon bark: a) catechin, b) protocatechuic acid, c) quercetin, d) epicatechin, e) p-coumaric acid, f) p-hydroxybenzoic acid, g) syringic acid, h) rosmarinic acid, i) caffeic acid, j) ferulic acid, and k) chlorogenic acid.

cinnamon such as *C. zeylanicum*, *C. camphora*, *C. cassia*, *C. osmophloeum*, *C. massoiae*, *C. insularimontanum* have shown to interact with the expression of genes and pro-inflammatory proteins, inhibiting or modulating them, such as cyclooxygenase, lipoxygenase, nitric oxide, and cytokines, which act through nuclear factor-kappa B (NF-κB), also mitigating the expression and signaling of these proteins (Gunawardena, Govindaraghavan, & Münch, 2014). Another mechanism associated with cinnamon and cardiovascular health is the inhibition of the release of fatty acids such as arachidonic, which has an inflammatory effect. It also reduces the formation of thromboxane A2. Futhermore, the eugenol identified from methanolic cinnamon extracts has a powerful antioxidant effect that helps inhibit lipid peroxidation and, the generation of ROS (Hariri & Ghiasvand, 2016).

Meta-analyses have shown the effectiveness of cinnamon extracts on SBP and DBP levels, in doses less than or equal to 2 g for a period greater than 8 weeks, this with participants with a baseline body mass index

(BMI) of ≥ 30 kg/m^2 (Hadi et al., 2020). The same effect has been observed in patients with DM2 (Jamali, Jalali, Saffari-Chaleshtori, Samare-Najaf, & Samareh, 2020). On the other hand, the administration of cinnamon supplementation in women with polycystic ovary syndrome affects the absorption of glucose, improving its homeostasis, in the same way, it significantly reduces total cholesterol and LDL levels, as well as triglycerides; improving HDL cholesterol concentrations, compared to control groups (Heydarpour et al., 2020). The effects on SBP and DBP pressure are shown more clearly in low doses but with prolonged periods of administration (>12 weeks) and in people not older than 50 years (Mousavi et al., 2020). Furthermore, cinnamon supplementation can exert an anti-inflammatory effect since it significantly reduces serum C-reactive protein levels (-0.81 mg/dL), in doses of 1.5 g per day, for more than 12 weeks. This effect is associated with a reduction in the probability of suffering from the risk of heart disease (Vallianou, Tsang, Taghizadeh, Davoodvandi, & Jafarnejad, 2019).

Several studies suggest that cinnamon supplementation significantly reduces triglycerides and total cholesterol levels; this may be because the extracts' polyphenols increase glycogen synthesis and decrease glycogenolysis; therefore, glucose absorption is inhibited in the small intestine. Likewise, peroxisome proliferator-activated receptor-alpha and gamma-mediated metabolism are regulated (Maierean et al., 2017). In addition, cinnamaldehyde has a vasodilator effect because it inhibits the invasion and discharges of Ca^{2+}, in this sense, it prevents the appearance of hypertension in type 1 diabetes and DM2 since it reduces vascular contractility. It is important to point out that the main complications of diabetes are cardiovascular diseases and disorders, so cinnamon could help mitigate the appearance or development of both diseases, even if the former is already present (Mahmoodnia et al., 2017). Most clinical studies are on *C. cassia*, which in doses of 3 to 6 g per day could improve glucose metabolism in people with DM2 (Shinjyo, Waddell, & Green, 2020).

Cinnamon supplementation affects different biomarkers related to inflammation and oxidative stress, highlighting its influence on reducing CRP levels, which is linked to the risk of cardiovascular disease. On the other hand, the cytokine IL-6, which is produced in response to wounds or infections, decreases; however, it is also involved in the synthesis of IL-1β, CRP, NF-κ-B, and tumor necrosis factor (TNF-α), which are formed in the existence of circumstances and pathologies such as Crohn's disease, diabetes, cancer, and cardiovascular disease. Cinnamon supplementation also decreases MDA levels, which damages biomolecules caused by lipid peroxidation and damage to their membrane. On the contrary, an increase in total antioxidant capacity (TAC) has been observed, hypothesizing that after consumption, there is lower susceptibility to oxidative damage of the cells, perhaps due to the presence of flavonoids (Zhu et al., 2020). Type-A procyanidin polyphenols extracted from *C. zeylanicum* bark show anti-inflammatory and anti-arthritic activity in rats; moreover, the compound is non-ulcerogenic (Vetal, Bodhankar, Mohan, & Thakurdesai, 2013).

Several studies have shown that supplementation with cinnamon significantly affect the BMI, the bodyweight and the waist-hip ratio (WHR), factors related to obesity, and this in turn is related with cardiovascular complications. These effects are manifested with doses of 2 to 3 g per day, and it is believed that the mechanisms involved have to do with the agonist effects of TRPA1, which acts as delayed stomach emptying, gastrointestinal motility, and release of serotonin from enterochromaffin cells. Likewise reduces visceral fat deposits as it stimulates interscapular brown adipose tissue and thermogenic protein. In addition, it also increases the transport of type 4 glucose, insulin β receptors, zinc finger protein 36 (ZFP36) levels in the adipocytes, and decreases leptin levels (Yazdanpanah, Azadi-Yazdi, Hooshmandi, Ramezani-Jolfaie, & Salehi-Abargouei, 2020).

Food and Drug Administration (FDA) has classified cinnamon supplements as GRAS (Generally Recognized as Safe). The administration of 1 g of Cinnulin PF® per day for six months in patients with prediabetes, did not alter some parameters in electrocardiographic studies (Pender et al., 2018). Table 1 shows the effects of cinnamon on the cardiovascular system and the related biological activities (prediabetes, DM2, antioxidant, anti-inflammatory). It should be mentioned that most of the biological effects have been identified in extracts or supplements obtained from the bark of the different species of cinnamon; however, also other parts such as leaves, flowers, fruits, roots, twig, stem, and branchlets, can potentially exert biological effects because some compounds also isolated from the bark have been identified (Kumar, Kumari, & Mishra, 2019).

3.1. Cardiovascular protective effect of major bioactive constituents

Cinnamaldehyde, cinnamic acid, eugenol, and coumarin are some of the most important compounds of cinnamon (Broadhurst, Polansky, & Anderson, 2000; Shan, Cai, Brooks, & Corke, 2007). These compounds have a vast array of biological activities, namely anti-microbial, anti-inflammatory, antioxidant, antifungal, anti-diabetic, and anti-obesity (Jayaprakasha & Rao, 2011; Khan, Safdar, Khan, Khattak, & Anderson, 2003; Mousavi et al., 2020). Cinnamaldehyde is the main bioactive compound (60–75%), which is extensively applied in the food industry owing to its pleasant taste (Zuo et al., 2017). This compound exhibits beneficial and protective effects on cardiovascular diseases, such as cardiac ischemia, cardiac hypertrophy, and myocardial infarction, among others. (Husain et al., 2018; Moraes, 2020; Yang et al., 2015) (Table 2; Fig. 3). Early in the 1970s, cinnamaldehyde (1–10 mg/kg) decreased blood pressure in anesthetized dogs and guinea pigs (Harada & Yano, 1975), that attributed to its peripheral vasodilating effects. The hypotensive properties were also noticed in anesthetized rats and were justified by its negative inotropic and chronotropic properties on the heart and its vasorelaxant action (Xu et al., 2006). Xue et al. (Xue, Shi, Murad, & Bian, 2011) also investigated the vasodilatory action of cinnamaldehyde, they observed that this compound relaxed the rat aortic rings precontracted with phenylephrine, which was not influenced by the presence or removal of the endothelium. Furthermore, Tarkhan et al. (Tarkhan, Balamsh, & El-Bassossy, 2019), showed that this compound protects against methylglyoxal-induced vascular damage in rat thoracic aorta. The aromatic carboxylic acid, cinnamic acid and, other cinnamon compounds, also displayed vasorelaxant effects in rat thoracic aortas (Kang, Kang, & Shin, 2013). It exhibited protective effects against myocardial ischemia in Sprague-Dawley rats treated with isoproterenol (Song, Li, Sun, & Wang, 2013) (Table 2).

Platelets play an important role in normal hemostasis; they are good contributors to thrombotic conditions, particularly cerebral vascular (e.g., transient ischemic attack), ischemic heart (e.g., myocardial infarction), and peripheral vascular diseases. Anti-platelet aggregation drugs can prevent these diseases, but some revealed various side effects after prolonged use, and new products from natural sources have been studied as alternatives. Some cinnamon components presented anti-platelet aggregation effects. Research by Kim et al. (Kim et al., 2010), revealed that among the 13 compounds found in *C. cassia*, eugenol, amygdala tone, cinnamic alcohol, 2-hydroxycinnamaldehyde, 2-methoxycinnamaldehyde, and conifer aldehyde, showed the most anti-aggregatory action. Additionally, the capacity of cinnamaldehyde to inhibit the blood platelet aggregation *in vitro* has long been reported (Matsuda, Matsuda, Fukuda, Shiomoto, & Kubo, 1987; Takenaga et al., 1987). Huang et al. (Huang, Wang, Luo, Xie, & Shi, 2007), demonstrated that this compound inhibited platelet aggregation induced by collagen and thrombin *in vitro* and showed for the first time *in vivo* its inhibitory effects on platelet aggregation. These authors also observed that the administration of this compound to mice prevents platelet-related thrombosis. Eugenol is another cinnamon compound that reduces platelet aggregation by inhibiting thromboxane A2 (Chen, Wang, & Chen, 1996; Raghavendra & Naidu, 2009).

Cardiac hypertrophy is a condition between a normal heart and a progressively failing heart. The development of pathological cardiac hypertrophy and heart failure was mitigated with cinnamaldehyde

Table 1
Protective activities of cinnamon in the cardiovascular system and other related effects (antioxidant, anti-diabetes, improved insulin resistance, anti-obesity, anti-hypocholesterolemic, anti-inflammatory).

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
C. burmannii	Aqueous (tea) (60 g/ 1L water) heated for 30 min at 100 °C.	Phenolics (2286,3 mg/L GAE)	*Clinical trial:* 30 non-diabetic adults (20–53 years). Oral glucose tolerance test (OGTT).	100 mL Oral single dose.	Slightly decreased postprandial blood glucose levels. Significantly lower postprandial maximum glucose concentration.	Could be associated with the action of insulin through the increasing of the insulin receptor-β protein acting beneficially in insulin signaling.	(Bernardo, Silva, Santos, Moncada, Brito, Proença, Singh, & De Mesquita, 2015)
C. burmannii	Standardized extract Herbilogy®	N/S	*In vivo:* 30 male white mice (*Mus musculus*), Swiss Webster strain, feeding with High-Fat diet.	2, 4, and 8 mg/kg B.W, oral, per day for 28 days.	Decreased total cholesterol levels.	N/S	(Pane & Pulungan, 2020)
C. burmannii	Fine powder	N/S	*Clinical trial:* a randomized, double-blind, parallel-group, with 36 women > 18 years with rheumatoid arthritis pre and postmenopausal.	2 g/per day, oral, for 8 weeks.	Significant reduction in serum TNF-α, CRP, diastolic blood pressure tender and swollen joint count, and blood pressure.	The anti-inflammatory effects could be due to cinnamaldehyde, because of its antioxidants capacity. Decreasing ROS generation and NF-κB deactivation and inhibition of pro-inflammatory cytokine	(Shishehbor, Rezaeyan Safar, Rajaei, & Haghighizadeh, 2018)
C. cassia	Aqueous, EtOH, MeOH	Fatty acids, phenolic acids, terpenes.	*In vitro, In vivo, In silico.* Inhibitory activity of α-amylase and α-glucosidase enzymes. *In vivo*: adult Albino Wistar male rats were STZ-induced diabetes.	*In vitro*: 0.2, 0.4, 0.6, 0.8, 1.0 mg/mL. *In vivo*: 300, 400, 500 mg/kg BW. Oral.	The extracts inhibit the enzymes, improve the diabetic state (normalize glucose, insulin, and other marker enzymes), and show a hypolipidemic effect.	The effect is due to the synergistic effects of all the compounds present in ethanolic extract. The stimulating impact of the β-cells and the same drug also has the hypolipidemic effect.	(Vijayakumar et al., 2020)
C. cassia	Standard compounds	Dimer procyanidin B2, and B-type trimer procyanidin C1.	*In vitro:* insulin sensitizer that targets 3 T3-L1 adipocytes.	10 and 20 μg/mL and 0.75, 1.5, 3.1, 6.25, 12.5, 25, 50 and 100 μM.	Improves the differentiation of 3 T3-L1 cells, and promotes insulin-induced glucose uptake.	Procyanidin C1 activates the AKT-eNOS pathway, up-regulated glucose uptake, and enhances insulin sensitivity in mature adipocytes.	(Sun et al., 2019)
C. cassia	Standard compounds	Cinnamic acid and (CD) cinnamic aldehyde (CA)	*In vivo:* 90 male Sprague-Dawley rats, were isoproterenol-induced acute myocardial ischemia.	22.5, 45 and 90 mg/kg/day (CA), and 37.5, 75 and 150 mg/kg/day (CD), during 14 days. Oral.	Both compounds decreased the ST segment elevation induced by acute myocardial ischemia, decreased serum levels of CK-MB, LDH, TNF-α, and IL-6, increased serum NO activity, and SOD decreased MDA content in myocardial tissue.	The protection observed was attributable to antioxidant and anti-inflammatory properties, and increased NO.	(Song et al., 2013)
C. cassia	Bark	N/S	*Clinical trial*: a randomized double-blind, placebo-controlled trial. 99 patients with Diabetes Mellitus Type 2 (T2DM).	1.5 g per day, during 60 days. Oral.	Reduced the HbAIc levels. Reduced plasma glucose, triglyceride, TG/HDL-C ratio, and BP, increased HDL-C levels, and eGFR.	N/S	(Sengsuk, Sanguanwong, Tangvarasittichai, & Tangvarasittichai, 2016)
C. cassia	Aqueous	Cinnamaldehyde, cinnamic acid, cinnamyl alcohol.	*In vitro:* HDAC8 inhibitory effects.	20, 40, 80, μg/mL. Oral.	HDAC8 activity was significantly inhibited at 67 %.	The phytochemicals act synergistically to induce the inhibition of the enzyme.	(Patil et al., 2017)
C. cassia	EtOH	N/S	*In vivo:* Healthy adult male Wistar rats were induced through L-NAME hypertensive (60 mg/kg/100 mL).	300 and 600 mg/kg BW per day, for six weeks. Oral.	No gross abnormalities or mortality. High blood pressures were reduced. Ameliorated hypertension and atherosclerosis in L-NAME-treated rats in a dose-dependent. Increase blood flow, and normalize aortic tissue.	Could be mediated by increased eNOS expression and its anti-oxidative and anti-inflammatory effects.	(Nagarajan et al., 2019)
C. cassia	Aqueous and lyophilized.	N/S		2, 4 g/BW, daily for 30 days. Oral.	4 g/kg BW of extract decreased the weight by4.4 %, food intake	Improves hyperlipidemia, maybe playing a direct role in lipid	

(*continued on next page*)

Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
			In vivo: healthy male Albino rats (n = 30), feeding with a High-Fat diet.		by 1.7, and food efficiency ratio by 22.38 % in hypercholesterolemic adult male rats, the serum total cholesterol by 31.22 %, triglyceride by 24.05 %, and LDL-C by 43.49 % increase levels of HDL-C by 30.16 % decrease in serum total cholesterol, triglycerides, and LDL-C levels and increasing serum HDL-C on day 30.	metabolism, such as inhibiting hepatic β-hydroxy β-Methylglutaryl (HMG-CoA) reductase activity.	(Alsoodeeri, Alqabbani, & Aldossari, 2020)
C. cassia	Spray-dried Aqueous extract of CinSulin®.	4 % type A procyanidin polyphenols.	*Clinical trial*: Human studies (n = 137, W/M from China, mean age 61.3 ± 0.8 years, Fasting Serum Glucose (FSG): >6.1 mmol/L (HG), 56 % overweight CS, 14 % obese).	250 mg twice a day/ two months. Oral.	Reduced fasting insulin, glucose, total and LDL cholesterol, enhanced insulin sensitivity.	Proanthocyanidins act as antioxidants by inhibiting the formation of AGEs and Increased GLUT4.	(Anderson et al., 2016)
C. cassia	Extracts of DCM, EtOAc, EtOH, MeOH, and H_2O.	Phenolic acids, terpenes, and cinnamaldehyde.	*In vitro:* Using RAW 264.7 and J7774A.1 macrophages. Determination of nitric oxide by the Griess assay. TNF-α by ELISA.	1–3 μg/mL	Anti-inflammatory activity inhibiting NO, TNF-α and LPS, IFN-γ in RAW 264.7 and J774A.1 macrophages.	Downregulated the proteins linked to inflammation.	(Gunawardena et al., 2015)
C. cassia	EtOH	Flavonoids, phenolics, triterpenoids, tannins, saponins.	*In vitro:* Lieberman-Burchard reaction.	25–175 ppm	At 150 ppm gave the highest cholesterol decreasing level.	N/S	(Ngadiwiyana et a., 2017)
C. cassia	Aqueous extract of bark and dissolved in DMSO for administration	N/A	*In vivo*: Sixty female Sprague-Dawley rats. Fed and water *ad libitum*	500, 1000, 1500 mg/ kg Orogastric tubes/35 days.	Increases the aortic reactivity in response to the vasoconstrictor and vasodilator agents in rats with T2DM. Reduced iNOS immunoreactivity, oxidative stress, and inflammation.	The extract decreased NO levels by reducing hyperglycemia and consequently iNOS activity.	(Uslu, Gelen, Uslu, & Özen, 2018)
C. cassia	EtOH.	Coumarin, cinnamic acid, cinnamaldehyde, 2-methoxy cinnamaldehyde	*In vivo:* male Kunming mice, cold exposure (4 °C/240 min) after 21 days of administration *In vitro:* the uncoupling effect on mitochondrial was evaluated with Seahorse and fluorescent staining.	90, 180 and 360 mg/ kg/day, during 21 day. Oral.	The BT and energy expenditure was increased in a cold environment. Lipid droplets were reduced, the number of mitochondrial was increased. Increased the non-shivering thermogenesis via up-regulating the expression of the thermogenic protein. Alleviated myocardium injury in the morphology in a cold environment. *In vitro*: the uncoupling effect was along with the decreased mitochondrial membrane potential and ATP production.	The thermogenesis Effect was induced via lipolysis and energy metabolism. The mechanisms were related to lipolysis and activation of brown adipose tissue (BAT).	(X. Li et al., 2021)
C. cassia	Powder cinnamon bark mixed with a High-Fat/high-calorie meal	Polyphenols and<200 ppm coumarin	*Clinical trial:* Human trial, n = 13 (7 M/6 W). 65 years old, BMI 28.0 kg m^{-2}. fasting glycemic 5.4 mmol L^{-1} at the day of study.	3 g, in 4 experimental sessions. Oral.	Reduced glycemic response, postprandial endotoxemia, and C-reactive protein. Increased cholesterolemic response.	Modifying insulin or GLP-1 response.	(Furlan et al., 2019)
C. cassia	MeOH and n-hexane soluble fraction.	2-Methoxycinnamaldehyde (2-MCA).	*In vivo:* Myocardial ischemia and reperfusion injury in adult male Sprague-Dawley rats. *In vitro*: infarct size measurement and	100 μg/kg and 200 μg/ kg. Intravenous. And (1, 10, 20, and 50 M) of 2-MCA, 10 min before reperfusion.	Improved Ischemia/Reperfusion induced myocardial dysfunction. Reduce the expression of the high mobility group. Reduction of neutrophil infiltration and	2-MCA exhibits antioxidant and anti-inflammatory action *in vivo*. Reduced the levels of injury markers mediated by ROS (cTnI,	(J. S. Hwa et al., 2012)

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
			stimulation of human umbilical vein endothelial cells.		increased SOD activity in ischemic tissue, reduce serum level of cardiac troponin I. Increased HO-1 induction. Inhibition of VCAM-1 expression. Inhibited NF-κB luciferase activity in TNF-α activated endothelial cells. Inhibited monocyte U937 adhesion to endothelial cells.	CK, LDH in blood and MDA activity).	
C. cassia	Aqueous	Trans-cinnamaldehyde, cinnamic acid, *trans*-cinnamic alcohol, eugenol, coumarin.	*In vitro*: rat aortic VSMCs.	50 μg/mL.	Inhibited the platelet-derived growth factor PDGF-BB-induced VSMC proliferation and suppressed the PDGF-stimulated early signal transduction. Arrested the cell cycle and inhibited positive regulatory proteins. The protein levels of p21 and p27 increased, also the expression of proliferating cell nuclear antigen (PCNA) was inhibited by the cinnamon extract. Inhibited the VSMC proliferation.	These effects were produced through a G_0/G_1 arrest, down-regulated the expression of cell cycle positive regulatory proteins by up-regulating p21 and p27 expression.	(Kwon et al., 2015)
C. cassia	Powder	N/S	*In vivo:* 88 male rats, feed with high fat/high fructose diet.	20 g/kg mixed with feed during 12 weeks. Oral.	Decrease of the glucose infusion rates in rats fed. Improved insulin sensitivity. Also, prevent the reduction of pancreas weight caused by a high fat/high fructose diet.	It has been observed that it increases insulin sensitivity by increasing protein signaling, in addition to activating peroxisome proliferation receptors.	(Couturier et al., 2010)
C. verum	Hydro-alcoholic of barks.	Extracts with 40 % of polyphenols (catechin and epicatechin monomers).	*In vitro:* inhibition of α-amylase.	20, 40, 60, 80, 100 μg/mL.	Inhibition of mammalian α-amylase activity with an IC_{50} of 25 μg/mL.	N/S	(Beejmohun et al., 2014)
C. verum	Hydro-alcoholic	Fatty acids, phenolic acids, terpenes.	*In vitro*: THP-1 monocytes. HEK-TLR2 and HEK-TL4 cell lines, IL-8.	25 μg ml^{-1}	Trans-cinnamaldehyde and *p*-cymene reduced the LPS-dependent IL-8 secretion in THP-1 monocytes. The anti-inflammatory effects increased with the combination of phenolic acids. And mitigated the phosphorylation of Akt and IκBα.	The phenolics acid isolated, inhibit the pro-inflammatory signal transduction of early TL2 and TLR4 signaling events.	(Schink et al., 2018)
C. verum	Hydro-alcoholic	Extracts with 40 % of polyphenols (catechin and epicatechin monomers).	*In vivo*: Wistar Han IGS rats. Admin 7.5 % wheat starch solution at 1.5 g/kg or 20 mL/kg of B.W. Acute starch tolerance test (STT).	Effect on blood glucose: 50 mg/kg of B.W. Insulin response: 6.25, 12.5, 25, 50 and 100 mg/kg B.W. Oral single dose.	Acutely reduce the glycemic response to starch in a dose-dependent in doses of 12.5 mg/kg B.W. Reduced the glycemic response by 20.4 %.	N/S	(Beejmohun et al., 2014)
C. verum	Hydro-alcoholic	Extracts with 40 % of polyphenols (catechin and epicatechin monomers)	*Clinical trial:* monocentric, randomized, double-blind, placebo-controlled, crossover clinical trial. Age 18–45 years old, good physical condition, stable BW n = 18	Two 500 mg capsules of pure extract. Oral single dose.	1 g of pure extract lowered the AUC of glycemic in 14.8% (0–120 min), 21.2% (0–60 min).	N/S	(Beejmohun et al., 2014)
C. verum	Powder of bark.	N/S				N/S	

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
			Clinical trial: randomized clinical trial, 99 women with dyslipidemia.	3 g/per day, 8 weeks. Oral.	Reduced serum levels of total cholesterol, triglyceride, and HDL-cholesterol levels. Decreased the BW, BMI, waist circumference.		(Pishdad, Nadjarzadeh, Abargouei, Nazari, & Papoli, 2018)
C. verum	Powder reconstituted at 100 mg/mL in 100% DMSO.	2.01 % of type A tetramer and 2.83 and 1.64 % of two types A trimers.	*In vitro:* Mouse 3 T3-L1 preadipocytes	10 and 100 μg/mL.	Increases the expression of TTP mRNA levels by up 10-fold, sustained over 16 h. Decreases the expression of VEGF mRNA by 40–50 %. Regulates the expression of multiple other TTP-related genes including in adipocytes (ZFP36L1, ZFP36L3, GM-CSF, COX2, IL6, APP, G-CSF, PAI1.	Increased anti-inflammatory TTP expression. And regulates the expression of multiple other TPP-related genes in adipocytes.	(Cao & Anderson, 2011)
C. verum	EtOH and MeOH bark extracts	Terpenes and cis and *trans*-Cinnamaldehyde.	*In vivo:* 5–6 weeks old collagen-induced arthritic BALB/c mice.	1, 2, and 4 mg/kg BW, for 2 weeks. Oral.	Extracts showed good ameliorative effects, after only 2 days of treatments. The dose more effective was 4 mg/kg BW. Inhibitory effect on NFATc3, TNF-α, CAII, and mCalpin proteins linked in rheumatoid arthritis.	Antioxidative effect of the cinnamaldehyde and protein modulator.	(Qadir et al., 2018)
C. zeylanicum	EtOH.	Cinnamic acid, Methyl eugenol, and cinnamaldehyde.	*In vivo* and *in vitro:* Antioxidant activity, antioxidant enzyme activity, and evaluation of activity against ischemia–reperfusion injury and arrhythmias in rats.	50, 100, or 200 mg/kg, per day for 14 days. Oral.	Improved the ischemia/reperfusion-induced myocardial injury as evidenced by reduction of the infarct size. Decreased ventricular tachycardia and ventricular ectopic beat episodes decreased. Significant elevations in serum SOD and GPx activities. Decrease in serum cardiac troponin I, lactate dehydrogenase, and MDA.	The effects shows probably due to its antioxidant activities.	(Sedighi et al., 2018)
C. zeylanicum	Extract and pure compounds.	Eugenol, cinnamaldehyde.	*In vivo and In vitro:* astrocytes and liver cells of mice to measure insulin signaling and glycogen synthesis. *In vivo:* healthy male mice	4.5 mL/kg BW, per day for 6 weeks. Oral.	Eugenol promoted glycogen synthesis. The extract improved insulin sensitivity and brain activity in mice; the insulin-stimulated locomotor activity was improved. Improved fasting blood glucose, glucose tolerance, and insulin secretion were unaltered. Decreased the triglyceride and increase liver glycogen content and improved insulin action in liver tissues.	The specific effect in improving insulin action in the brain may mediate metabolic alterations in the periphery to decrease liver fat and improve glucose homeostasis.	(Sartorius et al., 2014)
C. zeylanicum	Aqueous	N/S	*Clinical trial:* 28 healthy subjects. Safety evaluation.	85, 250, and 500 mg per day for 3 months. Oral.	No changes in the anthropometric parameters, systolic and diastolic blood pressure reduced significantly. Full blood count, renal function test, liver function, fasting blood glucose, HDL-c, VDL-d, and triglycerides remained in the normal range. Decreased the total cholesterol.	N/S	(Ranasinghe et al., 2017)

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
					No serious adverse effects were noted.		
C. zeylanicum	Powder	N/S	*In vivo:* Zebrafish husbandry.	2 mg/ day, along 4 weeks. Oral.	Ameliorates the genotypic and phenotypic characteristics associated with obesity by lowering BMI, blood glucose, triglyceride levels, lipid levels in the liver, and gene modulation.	Regulated blood glucose levels and lipids, and may exert a blood glucose-suppressing effect by improving insulin sensitivity or slowing the absorption of carbohydrates in the small intestine. The antioxidant capacity attenuated cytotoxicity via inhibition of iNOS, NF-κB activation.	(Kaur et al., 2019)
C. zeylanicum	MeOH and dissolved in DMSO 4 %.	Sterols, polyphenolic, flavonoids, alkaloids, saponins.	*In vivo:* rats induced by intravenous administration of L-NAME acute arterial hypertension.	5, 10, and 20 mg/kg. Intravenously.	Show a long-lasting decrease in blood pressure. Prevented the increase in blood pressure and organs weights, histological tissue damages, and reverse the depletion in NO tissue's concentration. Significantly lower the plasma level of triglycerides, total cholesterol, and LDL-cholesterol, increasing that of HDL-cholesterol, with a significantly low atherogenic index.	Maybe the effects are attributed to the increase in NO production and regulate dyslipidemia.	(Nyadjeu et al., 2013)
C. zeylanicum	Aqueous	Flavonoids, alkaloids, saponins.	*In vivo:* Adult male and female Wistar rats, normotensive, salt-loaded hypertensive rats, L-NAME hypertensive rats, and spontaneously hypertensive rats. *In vitro:* vascular effect on rat aortic ring.	5, 10 and 20 mg/kg intravenous and 1–700 μg/mL (organ bath experiment).	In all the treatments, the extracts show a significant reduction in mean arterial blood pressure. *In vitro* exhibited cumulative vasodilating effects.	The results suggest its possible action through the interferences with both cholinergic and sympathetic transmissions. The possible active vasodilatation effect might be partly mediated by an endothelial l-arginine/NO pathway. And the vasorelaxant effects may be involved the antihypertensive mechanism, increasing the endothelial nitric oxide by activating the KATP channels in vascular smooth muscle.	(Nyadjeu, Dongmo, Nguelefack, & Kamanyi, 2011)
C. zeylanicum	Powder of bark; Aqueous and MeOH extract.	N/S.	*In vivo:* 48 healthy adult male albino rabbits, and hyperlipidemic albino rabbits.	0.25, 0.50, 0.75 g/kg bark powder; Aqueous extract (equivalent to 0.75 g/kg bark powder), MeOH (equivalent to 0.75 g/kg bark powder). 180 days of administration.	Reduction of % in total lipids, triglycerides, total cholesterol, and LDL-cholesterol.	Maybe the inhibition of lipid absorption and augmented cholesterol and bile acids secretion in feces.	(Javed et al., 2012)
C. zeylanicum	Aqueous.	N/S	*In vivo:* 36 healthy male Wistar albino rats, glucocorticoid-induced atherosclerosis in Wistar Rats.	250 mg/mL and 500 mg/mL.	Prevent dyslipidemia, protect the aorta from atherosclerosis, significantly reduce the risk of atherogenicity.	Maybe attributed to the antioxidant activity and strongest action against advanced glycation end products.	(Nagendra Nayak, Rajasekhar, & Jetti, 2017)
C. zeylanicum	Aqueous.	Phenolics.	*In vitro:* DPPH inhibition MDA inhibition	DPPH (0.63–10 mg/mL), MDA inhibition (0.63–10 mg/mL),	Potent inhibitory effect of DPPH radical.	N/S.	(Karthiga, Venkatalakshmi,

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
			Anti-inflammatory activity Pancreatic lipase inhibitory activity.	Anti-inflammatory effect (0.5 mL), pancreatic lipase inhibitory (1 mL).			Vadivel, & Brindha, 2016)
C. zeylanicum	Extracts of DCM, EtOAc, EtOH, MeOH, and H_2O.	Phenolic acids, terpenes, and cinnamaldehyde.	*In vitro:* Using RAW 264.7 and J7774A.1 macrophages. Determination of nitric oxide by the Griess assay. TNF-α by ELISA.	1–3 μg/mL.	Anti-inflammatory activity inhibiting NO, TNF-α and LPS, IFN-γ in RAW 264.7 and J774A.1 macrophages.	Downregulated the proteins linked to inflammation.	(Gunawardena et al., 2015)
C. zeylanicum	Raw dried powder bark.	N/A	*In vivo*: 40 adult Wistar male albino rats. Fed and water *ad libitum.* G4 (HFD + CG).	15% w/w (15 g/100), eight weeks. Oral.	Alleviate testicular damage (histological, ultrastructure, and biochemical parameters) in obese rats.	Flavonoids, polyphenols, and cinnamaldehyde eliminate ROS, improving spermatogenesis and testosterone levels, by increasing Leydig cells and affecting Sertoli cells.	(Arisha, Sakr, & Abd-Elhaseeb, 2020)
C. zeylanicum	MeOH.	N/A	*In vivo*: 30 male Wistar rats. Diet and tap water *ad libitum*. All the groups performed a session of exhaustive exercise.	200 mg/kg/day during 8 weeks. Oral.	Significantly decreased serum levels of total cholesterol, low-density lipoprotein, and increased high-density lipoprotein level. Reduced MDA level elevation induced by exhausting exercise.	Cinnamon may increase the efficacy of HDL-mediated reverse cholesterol transport. Scavenging and delaying the accumulation of ROS.	(Badalzadeh, Shaghaghi, Mohammadi, Dehghan, & Mohammadi, 2014)
C. zeylanicum	Dried and solid milled barks.	Alkaloids, Carbohydrates, Coumarins, Flavonoids, Phenols, Saponins, Steroids, Tannins.	*In vivo:* adult male Wistar rats induced diabetes through a single intraperitoneal injection of alloxan at the dose of 15 mg/kg.	5 % rate (Cinnamon powder/standard feed, 28 days. Oral.	The extract blocked the increase of blood glucose. The restored activity of SOD, CAT, and GPx. Improved lipid profiles and protection against the damage of oxidative stress in a diabetic state.	The phenolic compounds regenerate the damaged β-cells. Decreasing lipid peroxidation and normalizing the antioxidant system.	(Beji, Khemir, Wannes, Ayari, & Ksouri, 2018)
C. zeylanicum	Powder cinnamon bark.	N/S.	*Clinical trial*: Double-blind randomized controlled clinical trial: 84 women with polycystic ovary syndrome.	Three capsules of 500 mg/daily for 8 weeks. Oral.	Significantly increased serum total antioxidant capacity. MDA decreased. Improved serum level of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.	The phenols act as free radical scavenger actions, inhibiting the intestinal absorption of cholesterol with subsequent hypocholesterolemic activity.	(Borzoei et al., 2018)
C. zeylanicum	Powder cinnamon bark	N/S.	*In vivo:* n = 32 male hamsters, with high cholesterol diet.	2 and 8 %, Oral, 4 weeks.	Reduction in serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol. Up-regulated LDL-R gene expression in the liver.	May increase LDL-R, gene expression in the liver. The supplementation with cinnamon can reverse hepatic steatosis and have a protective effect against hypercholesterolemia.	(Kassaee, Goodarzi, Roodbari, & Yaghmaei, 2017)
C. zeylanicum	Aqueous.	Cinnamaldehyde and other phenylpropanoids, fatty acids, and procyanidins.	*In vivo:* Male adult Wistar rats.	400 mg of extract per kg/25 days. Oral.	No changes in the food intake, serum lipid profile. Decreased body mass gain, a mass of white adipose tissue, high protein content. Lower leptin mRNA expression reduced serum leptin levels. Lower mRNA expression of SREBP1c, in the WAT and the liver, lower mRNA expression of SRWBP2, HMGCoA reductase, ACAT1, DGAT2 in the liver.	Reduced esterified cholesterol and triacylglycerol content were detected in this tissue. Attenuates lipogenic processes, regulating the expression of the key enzymes and transcriptional factors and their target genes, which are directly involved in lipogenesis.	(Lopes et al., 2015)
C. zeylanicum	MeOH, unboiled and boiled.	N/S	*In vitro:* Inhibition of DPPH radical and lipase, amylase, and glucosidase.	1 mg/mL	The boiled extract was active against lipase, amylase, glucosidase, and DPPH radical.	The boiled extracts change the number and amount of bioactive compounds and increase the activity against enzymes.	(Fernando et al., 2019)
C. zeylanicum						N/S	(Im et al., 2014)

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
	Hydro ethanolic and spray dried.	Polyphenol content 45.4% (ProcynZ-45) GAE. Procyanidin type A trimer, tetramer, catechin, epicatechin, procyanidin trimer, a tetramer of double linked procyanidin type-A.	*Clinical trial:* 15 human volunteers (males, age 33–45 and BMI −28 ± 2). 115–130 mg/dL^{-1} fasting blood sugar.	250 mg per day for 30 days. Oral.	Significant reduction of fasting plasma glucose FPG, postpandrial glucose PPG levels, and postprandial blood sugar, and reduces the TBARS values. Increase the SOD, GSH, and CAT enzyme levels.		
C. zeylanicum	Hydro ethanolic and spray dried	Polyphenol content 45.4% (ProcynZ-45), 75.6% (ProcynZ-75), Aqueous standard extract, 15.8 % GAE. Procyanidin type A trimer, tetramer, catechin, epicatechin, procyanidin trimer, a tetramer of double linked procyanidin type-A.	*In vivo:* 36 adult Wistar rats induced diabetes by single intraperitoneal injection of STZ (45 mg /kg BW).	200 mg/kg B.W. Once a day for 30 days. Oral.	Significantly improved weight loss, improvements in blood sugar, serum insulin, lipid profile (reduced hypercholesterolemia and hypertriglyceridemia), liver enzymes, and reduced damage in glomeruli, interstitial cells, and pancreatic islets, with ProcynZ.45 and ProcynZ-75.	Insulin sensitizing and enhancing effect by the polyphenol extract.	(Im et al., 2014)
C. zeylanicum	Hydro ethanolic and spray dried.	Polyphenol content 45.4% (ProcynZ-45), 75.6% (ProcynZ-75), Aqueous standard extract, 15.8 % GAE. Procyanidin type A trimer, tetramer, catechin, epicatechin, procyanidin trimer, a tetramer of double linked procyanidin type-A.	*In vitro:* inhibition of radicals DPPH, SO, ABTS, FRAP, and ORAC.	N/A	Standard extract inhibits IC_{50} DPPH (42 ± 4.4 μg mL^{-1}), Superoxide radical (130 ± 8.1 μg mL^{-1}), ABTS 20 ± 2.2 μg mL^{-1}), FRAP (337 ± 1.52 μM), ORAC (3200 ± 320 μmol TE g-^{1}). ProcynZ-45 inhibits IC_{50} DPPH (2.45 ± 9.13 μg mL^{-1}), Superoxide radical (23 ± 2.5 μg mL^{-1}), ABTS 2.7 ± 0.27 μg mL^{-1}), FRAP (300 ± 3.21 μM), ORAC (6900 ± 270 μmol TE g-^{1}). ProcynZ-75 inhibits IC_{50} DPPH (14.25 ± 0.91 μg mL^{-1}), Superoxide radical (19 ± 1.4 μg mL^{-1}), ABTS 5.5 ± 0.67 μg mL^{-1}), FRAP (500 ± 5.03 μM), ORAC (8800 ± 180 μmol TE g-^{1}).	Polyphenols scavenge these radicals.	(Im et al., 2014)
C. zeylanicum	Aqueous and lyophilized.	N/S	*In vivo*: ovariectomized adult female Wistar rats (n = 40). With MetS (high serum cholesterol LDL, TG, large waist circumference, and FBG. The rats were initially in the endurance training program.	100 mg/kg for 12 weeks. Intraperitoneal.	Reduction in serum glucose, low-density lipoprotein, homeostasis in insulin resistance, and TNF-α. Reduced WNT5A.	The cinnamon extract and exercise, reduce inflammation that may occur via inhibition of TNF-α secretion from visceral fat. Increase in Glut4, glucose uptake, and glycogen synthesis. SFRP5 probably inhibits the non-canonical WNT5A pathway to improve insulin sensitivity.	(Fayaz, Damirchi, Zebardast, & Babaei, 2019)
Cinnamon (USA origin)	Aqueous.	0.74% of a type-A tetramer, 2.30%, 0.72%, 0.22% and 0.12% of four type A trimer isomers.	*Ex vivo:* Male Wistar rats (n = 30) were sacrificed to isolate enterocytes to investigate apolipoprotein-B48 secretion by immunoprecipitation.	10 and 100 μg/mL	Decreased the amount of apolipoprotein-B48 secretion, inhibited the mRNA expression of genes of the inflammatory cytokines, interleukin-1β, interleukin-6, and tumor necrosis factor-α, induced the expression of the anti-inflammatory gene Zfp36. Increased the mRNA expression of genes to increased insulin sensitivity (Ir, Irs1, Irs2, Pi3k, and Akt1), and decreased	The extract regulates multiple metabolic pathways involved in the intestinal lipoprotein metabolism of small intestinal primary enterocytes.	(Qin, Dawson, Schoene, Polansky, & Anderson, 2012)

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
					Pten expression. Inhibited genes associated with elevated cholesterol levels, triacylglycerols, and apolipoprotein-B48 levels (abcg5, Npc1l1, Cd36, Mttp, and Srebp1c, and facilitated Abca1 expression. Stimulated the phospho-p38 mitogen-activated protein kinase, cJun, N- terminal kinase, and extracellular-signal-regulated kinase expression.		
Cinnamon (Chinese origin)	EtOH, and partitioned successively with petroleum ether and ethyl acetate.	5-hydroxyethyl salicylate, syringaldehyde, hydroxybenzoic acid, is vanillic acid, protocatechuic acid, protocatechualdehyde, vanillin, vanillic acid, trans-cinnamaldehyde, cinnamyl alcohol, cinnamic acid, cinnamaldehyde, litseachromolaevanes A, 4–hydroxy–1,10-seco-muurol-5-ene-1,10–dione, pinoresinol, syringaresinol,coumarin, 4-hydroxymellein, kaempferol, (-)-(2R,3R)-5,7-dimethoxy-3′,4′-methylenedioxy-flavan-3-ol, decumbic acid, and β-sitosterol.	*In vitro:* Hepa 1c1c7 murine hepatoma cells, human breast carcinoma MDA-MB-231 cells, and normal human lung epithelial Beas-2B cells. NAD(P)H: quinone reductase assay, dual-luciferase reporter gene assay (Beas-2B cells), Glutathione assay, ROS detection, acridine orange, ethidium bromide staining, annexin V-FITC/Pi double staining.	6.25–200 μg/mL and 6.25–200 μM.	Improved intracellular antioxidant capacity. The compounds are Nfr2 activators protecting tissues against oxidative stress in Beas-2B cells.	Activated Nrf2-dilated antioxidant response, and protected human lung epithelial cells against sodium arsenite [As (III)]-induced oxidative insults.	(A.-L. Li et al., 2019)
Cinnamon (Korean origin)	Aqueous.	Cinnamaldehyde and terpenes.	*In vitro:* ferric reducing ability potential assay, inhibitory activity against copper-mediated LDL oxidation, apoA-I glycation, cholesteryl ester transfer assay.	Ferric reducing ability potential assay (10 μg/mL), apoA-I glycation (10 μg/mL), cholesteryl ester transfer assay (0.01 mL).	Showed potent anti-glycation activity, has a strong reducing ability in FRAP assay, and DPPH assay. Have a potent inhibition against LDL oxidation.	Potent activities suppress the incidence of diabetes and atherosclerosis via strong antioxidant potential.	(Jin & Cho, 2011)
Cinnamon (Korean origin)	Aqueous	Cinnamaldehyde and terpenes.	*In vivo:* hypercholesterolemic zebrafish.	10% wt of powder/wt of tetrabit, during 5 weeks. Oral.	Potent cholesteryl ester transfer protein (CETP) inhibitory activity. Hypolipidemic activity.	strongest reducing ability and radical scavenging activity *in vitro* and *in vivo*.	(Jin & Cho, 2011)
Cinnamon (Iranian origin)	Powder.	N/S.	*Clinical trial:* Randomized, double-blind, controlled clinical trial. 39 patients with type 2 diabetes, with body mass index (kg/m2) 27.70.	3 g /per day/ 8 weeks. Oral.	No remarkable effects in reduction of NF-kB, SIRT1, hs-CRP, IL-6, and TNF-α plasma levels.	N/S.	(Davari et al., 2020)
Cinnamon (Indian origin)	Raw powder cinnamon bark.	N/S.	Randomized, double-blind placebo controlled trial. 116 individuals with MetS. Abdominal obesity men > 90 cm, woman > 80 cm. triglycerides > 150 mg/dL, Low HDL-C man < 40 mg/dL, woman < 50 mg/dL, dysglycemia > 100 mg/dL and hypertension > 130/>85 mmHg).	6 capsules (3 g) per day during 16 weeks. Oral.	A significantly greater decrease in fasting blood glucose, glycosylated hemoglobin, waist circumference, and body mass index. Reduced the prevalence of MetS in the intervention group.	The cinnamon probably inhibits the enzymes pancreatic α-amylase and α-glucosidase, stimulation of cellular glucose uptake by membrane translocation of GLUT-4, stimulation of glucose metabolism and glycogen synthesis, inhibition of gluconeogenesis, stimulation of insulin release, and enhancing insulin receptor activity. Inhibition of differentiation of	(Gupta Jain, Puri, Misra, Gulati, & Mani, 2017)

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Table 1 (*continued*)

Species	Extract	Compounds	Study type	Doses	Highlighting Results	Mechanism of action	Reference
						adipocytes, modify intestinal lipid absorption, induction of fatty acid oxidation, and antagonism at cannabinoid receptors.	
Pure Compounds							
N/S	N/S	Cinnamaldehyde.	*In vivo:* 32 C57/BL6 mice, were pressure overload-induced cardiac hypertrophy.	50 mg/kg BW, per day, along 7 weeks. Oral.	Ameliorate of systolic and diastolic abnormalities. Cardiac fibrosis in AB mice was decreased. Normalization in gene expression of hypertrophic and fibrotic markers.	Via blocking ERK signaling pathway.	(Yang et al., 2015)
N/A	N/S	Cinnamaldehyde, cinnamyl alcohol, cinnamic acid, and cinnamyl isobutyrate.	*In vitro:* Caco-2 cells.	0.3–3000 μM	Decrease fatty acid uptake, increase serotonin release in Caco-2 cells.	Cinnamaldehyde is a transient receptor potential channel A1-dependency in the decrease of fatty acid uptake.	(Hoi et al., 2019)
N/A.	N/A.	Cinnamaldehyde.	*In vitro:* TNF-α induced inflammatory response in human umbilical vein endothelial cells (HUVECs,). *In vivo:* 25 male Sprague-Dawley rats, used to evaluate the anti-inflammatory effect of cinnamaldehyde	20 μM.	Increased the cellular protein level of heme oxygenase-1 (HO-1) and promoted the translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) to the nucleus. Cinnamaldehyde inhibited the adhesion of U937 monocytic cells to HUVECs by decreasing the expression level of vascular cell adhesion protein 1 (VCAM-1). The anti-inflammatory effect shows in the *In vivo* model.	Cinnamaldehyde-mediated Nrf2/HO-1 activation protected the HUVECs from H_2O_2– induced oxidative stress, which promotes apoptosis. HO-1 depletion by siRNA attenuated the cinnamaldehyde mediated cell-protective against oxidative stress.	(N. Y. Kim, N. T. Trinh, S. G. Ahn, & S. A. Kim, 2020)
N/A.	N/A.	Cinnamaldehyde.	*In vivo:* male ApoE atherosclerotic and C57BL/6 mice, fed with HDF.	5, 10, and 20 mg/kg for 8 weeks. Oral.	Serum levels of LDL-C, TG, and TC were elevated. HDL-C level was increased. Decreased inflammatory cytokine (TNF-α, IL-6, NO, and MCP-1), serum lipid levels, MMP-2 expression and attenuated the phosphorylation level of IκBα and p65 NF-κB. Downregulated the MDA levels in serum. Reduced the atherosclerotic plaque area.	Cinnamaldehyde may achieve the anti-atherosclerotic effect via the IκBα/NF-κB signaling pathway.	(W. Li et al., 2019)

W = Woman; M = Man; FSG = Fasting Serum Glucose; CS = Chinese Standards; HG = Hyperglycemic; AGEs = Advanced glycation end Products; G4 (HFD + GD) = Group 4 (High fatty diet to produce hyperlipidemia) plus cinnamon group (standard diet + cinnamon powder); N/D = No Determinate; N/S = No Studied. TA = Thoracic aorta; iNOS = Nitric Oxide Synthase. MDA = Malondialdehyde. B.W = Body Weight. WNT5A = Wingless-type mammary tumor virus integration site family member 5A. FBG = Fasting Blood Glucose. HFD = High Fat Diet. BT = Body Temperature. SREBP1c = Sterol regulatory element-binding protein 1c).

Table 2
Selected studies reporting the cardiovascular protective effects of cinnamon bioactive constituents.

Compound	Effect/Main findings	Model	Dose	Reference
Cinnamic acid	Vasorelaxant effects	Rat thoracic aorta	0.1–2 mM	Kang et al. (2013).
	Protective effects against myocardial ischemia	Myocardial ischemia induced by isoproterenol in Sprague-Dawley rats	22.5, 45, 90 mg/kg/d	Song et al. (2013).
	Anti-obesity and cardioprotective	High fat diet-fed rats	30 mg/kg/day for 7 weeks	Mnafgui et al. (2015)
Cinnamaldehyde	Inhibits platelet aggregation and prevents platelet-related thrombosis	*In vitro* and *in vivo* on experimental models of thrombosis in mice and rats	250, 500 mg/kg orally and 50, 100 mg/kg i.p.	Huang et al. (2007)
	Prevent the development of hypertension associated with diabetes	Rat models of insulin deficiency and insulin resistance	20 mg kg/day orally by gavage	El-Bassossy et al. (2011)
	Vasodilatory effect	Isolated rings of rat aorta	10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} g/mL.	Xue et al. (2011)
	Vasorelaxant effect	Isolated rat aorta	1 μM	Yanaga et al. (2006)
	Vasorelaxation effect	Rat aortic rings and isolated mouse heart		Alvarez-Collazo et al. (2014)
	Delay the progression of cardiac hypertrophy and fibrosis	Cardiac hypertrophy induced by aortic banding in mice	50 mg/kg b.w./day during seven weeks	Yang et al. (2015)
	Protect endothelial dysfunction under high glucose conditions	Mice aortic rings and HUVECs	10 μM	Wang et al. (2015)
	Vasculoprotective effects in hypercholesterolemic rabbits	Rabbits subjected to a high-cholesterol diet	10 mg/kg/day	Nour et al. (2018)
	Vasculoprotective effects	Isolated rat aortae subjected to vascular damage by methylglyoxal	10–100 μM	Tarkhan et al. (2018)
	Prevent the development of atherosclerotic lesions	LDL receptor knockout (LDLr-/-)-ovariectomized mice	20 mg/kg b.w./day orally oral gavage for 8 weeks	Moraes (2020)
	Cytoprotective and anti-inflammatory effects	Human umbilical vein endothelial cells (HUVECs) And Sprague-Dawley	50 mg/kg i.p.	Kim et al. (2020)

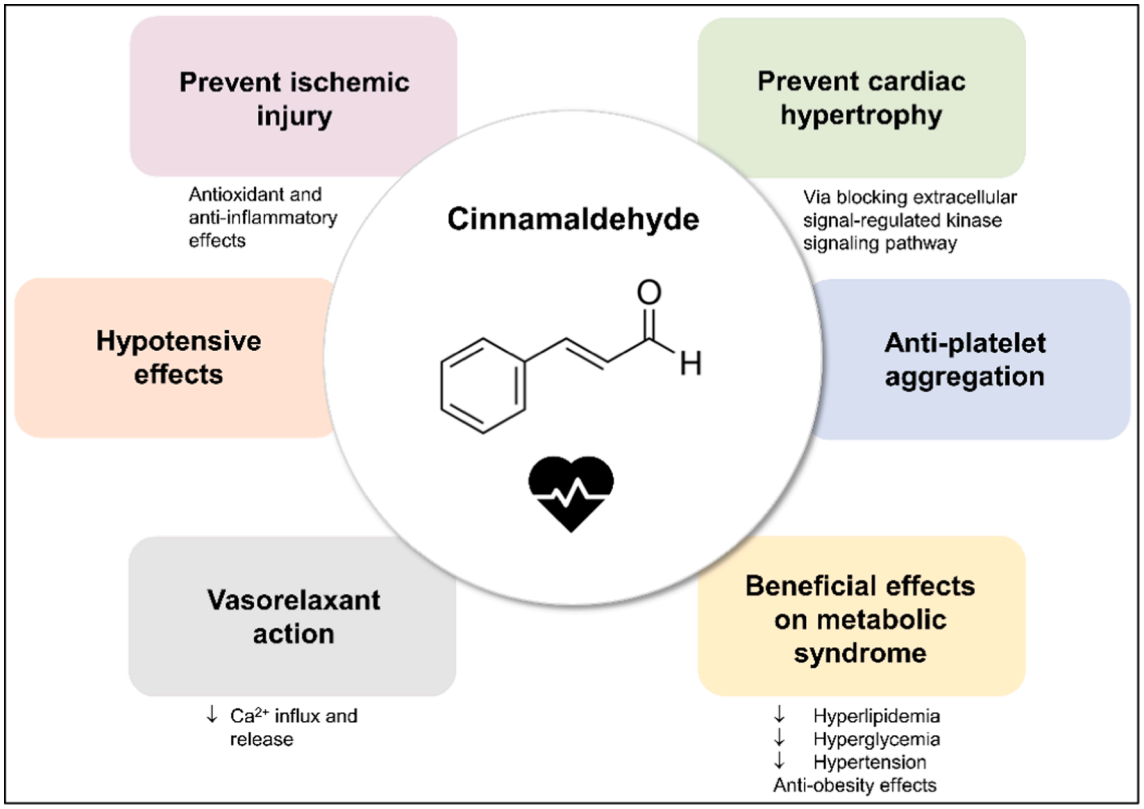

Fig. 3. Main cardiovascular protective effects of cinnamaldehyde.

administration to mice subjected to aortic banding (Yang et al., 2015). In atherosclerosis, there is an accumulation of inflammatory cells and cholesterol in the artery wall (Li et al., 2018). The development of cardiovascular diseases as myocardial infarction, stroke, and ischemic heart failure can be a consequence of atherosclerosis (WHO, 2017). Both oxidative stress and inflammation play important roles in cardiovascular diseases. Some studies demonstrated that cinnamaldehyde has therapeutic properties for oxidative stress-mediated cardiovascular diseases, as is the case of atherosclerosis. The pathology of vascular smooth muscle cells augmented the development of atherosclerosis. Li et al.,

2019 (Li et al., 2018), demonstrated that cinnamaldehyde protects vascular smooth muscle cells against ox-LDL-induced proliferation and migration. Additionally, Kim et al. (Kim, Trinh, Ahn, & Kim, 2020) recently demonstrated the protective effects of cinnamaldehyde alongside the oxidative stress persuaded by the action of H_2O_2 in the endothelial cells of the human umbilical vein and also its anti-inflammatory effects in these cells and *in vivo* in Sprague-Dawley rats.

Reduction in estrogen levels in postmenopausal women is regarded as a risk issue for the expansion of atherosclerosis. Thus, Moraes et al. (Moraes, 2020), evaluated the effects of cinnamaldehyde in ovariectomized LDLr-/- female mice, a model of atherosclerosis with low estrogen levels. It was observed that the administration of this compound could prevent atherosclerotic lesions in aortas related to its antioxidant effects. The role of cinnamon and its components, particularly cinnamaldehyde, cinnamic acid, and polyphenols, in managing metabolic syndrome has been extensively investigated (Cicero & Colletti, 2016; Mollazadeh & Hosseinzadeh, 2016; Zhu et al., 2017). Currently, diabetes is considered as among the most common metabolic disorders prevalent in society, and the prevention of cardiovascular complications in diabetic patients is of utmost importance. El-Bassossy et al. (El-Bassossy, Fahmy, & Badawy, 2011), reported the protective effects of cinnamaldehyde against hypertension in streptozotocin-diabetic and fructose-fed insulin-resistant rats. This compound also protected endothelial dysfunction under high glucose conditions by Nrf2 activation (Wang et al., 2015). Moreover, cinnamaldehyde decreased cardiac inflammation and fibrosis in fructose-fed rats displaying metabolic syndrome (Kang et al., 2016).

Hyperlipidemia is one among the most significant risk issues that are connected with a high incidence of myocardial infarctions and cardiovascular diseases. Li et al., 2019 (Li et al., 2012), reported the antihyperglycemic and antihyperlipidemic actions of cinnamaldehyde in insulin-resistant mice after oral administration. More recently, Nour et al. (Nour, Shehatou, Rahim, El-Awady, & Suddek, 2018), evaluated the effects of cinnamaldehyde against high-cholesterol diet-induced vascular damage in rabbits. This compound relieves the development of atherosclerosis in hypercholesterolemic rabbits by reducing cholesterol, antiinflammatory, and antioxidant effects. In addition to the antihyperlipidemic effects of cinnamaldehyde, polyphenols present in cinnamon also influence lipid metabolism (Li et al., 2013). As a good natural source of polyphenols, cinnamon has been reported to aid in regulating blood glucose in humans in the systematic review of randomized controlled trials (Medagama, 2015).

Several constituents of cinnamon as phenolic and flavonoid complexes such as catechin, epicatechin, and procyanidin B2 are well-known to be able to diminish the blood sugar level through their capability to reduce the glucose absorption in the intestine as well as glycogen synthesis enzymes and glycogenolysis (Solomon & Blannin, 2007). Additionally, cinnamon polyphenols as rutin, catechin, quercetin, kaempferol, and isorhamnetin can mimic insulin activity and improve glycemic status (Rao & Gan, 2014).

Obesity is a global health concern that is strongly associated with many disorders, including cardiovascular diseases. Several investigations indicated that phytochemicals could be good candidates for conventional anti-obesity drugs with fewer side effects. The anti-obesity effects of cinnamaldehyde administered via gavage for 8 weeks were evaluated on mice fed a high-fat diet (Zuo et al., 2017). In comparison with the control group, this compound reduced body weight, fat mass, food intake, serum lipid, free fatty acid, and leptin levels, improved insulin sensitivity, inhibited adipose tissue hypertrophy, and induced browning of white adipose tissue. These results indicated that this compound has therapeutic potential against obesity. The anti-obesity and cardioprotective properties of cinnamic acid, another compound found in cinnamon, have also been reported (Mnafgui et al., 2015). It reduced the body weight of obese rats and hyperlipidemia caused by a high-fat diet and protected animals against vasoconstriction and hypertension problems.

3.2. Molecular mechanism of action of major bioactive constituents on the cardiovascular protective effect

Cinnamaldehyde is one of the major active pharmaceutical ingredients of cinnamon bark having vital actions in the cardiovascular system like vasorelaxation and reduction in blood pressure. Studies by Yanaga et al. (Yanaga et al., 2006), suggested that the vasorelaxant effects of cinnamaldehyde resulting from endothelium-dependent effects influenced by nitric oxide and from endothelium-independent relaxation influenced by the blocking of Ca^{2+} channels. Posteriorly, Xue et al. (Xue et al., 2011), proposed that the vasodilatory action of this compound in rat aorta rings was independent of endothelium and is associated with its capacity to inhibit Ca^{2+} influx and release. Also, Raffai et al. (Raffai et al., 2014), observed that this compound caused vascular relaxation in the porcine coronary arteries by hindering the Ca^{2+} sensitivity and Ca^{2+} influx via an endothelium-independent mechanism. Later Alvarez-Collazo et al. (Alvarez-Collazo et al., 2014), showed that the relaxation in vascular smooth muscle cells and ventricular cardiac myocytes induced by cinnamaldehyde is linked with the inhibition of the L-Type Ca^{2+} channel. These investigations also prove that TRPA1 is not a specific target of this compound. Afterward, studies from Tarkhan et al. (Tarkhan et al., 2019), showed that this compound protects against methylglyoxal-induced vascular damage in rat thoracic aorta by enhancing vasodilation and stimulating aortic nitric oxide (NO) production, and lowering the negative effects of the formation of advanced glycation end products (AGEs). Furthermore, cinnamaldehyde exerts protection against cardiac hypertrophy development through targeting the extracellular signal-regulated kinase (ERK) signaling pathway (Yang et al., 2015).

Oxidative stress and inflammation have crucial roles in the progression of cardiovascular disorders. Song et al. (Song et al., 2013) studied the protective effects of cinnamaldehyde on ischemic injury induced by isoproterenol and attributed the cardioprotective action of this compound to its antioxidant and anti-inflammatory effects. The treatment with this compound reduced pro-inflammatory cytokines (TNF- and IL-6), enhanced serum NO and SOD amounts on the heart, and reduced ST-segments generated by myocardial ischemia. Recently, Kim et al. (Kim et al., 2020), observed that this compound protected human umbilical vein endothelial cells from the oxidative stress induced by H_2O_2 via stimulation of the nuclear factor erythroid 2-related factor signaling pathway and the consequent induction of HO-1. This compound also inhibits monocyte adhesion to endothelial cells by reducing the expression level of vascular cell adhesion protein 1. Overall, these results indicate that this compound can be utilized as a therapeutic agent for atherosclerosis and other cardiovascular disorders mediated by oxidative stress.

Several risk factors stimulate vascular damage associated with cardiovascular diseases collectively defined as metabolic syndrome, including hypertension, hyperglycemia, and hyperlipidemia. Cinnamaldehyde prevents the progression of hypertension in insulin deficiency and insulin resistance via normalization of vascular contractility due to its insulinotropic properties in insulin deficiency (El-Bassossy et al., 2011). Shen et al. (Shen et al., 2014), suggested that the beneficial properties of cinnamon on lipid profile are related to the ability of this compound to stimulate the lipolysis through stimulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), which conducts to the inhibition of fatty acid synthesis. AMPK is implicated in maintaining lipid and cholesterol homeostasis and, through phosphorylation, reduces acetyl-CoA carboxylase activity (Shen et al., 2014). Additionally, this compound enhanced the lecithin cholesterol acyl transferase activity, contributing to the regulation of blood lipids (Medagama, 2015).

Moreover, the antioxidant effects of cinnamaldehyde and the preservation of NO amounts are involved in its capacity to protect the relaxation of the endothelium in the aortic rings of hyperglycemic mice. Its antioxidant mechanism involves the upregulation of the endogenous

antioxidant enzyme NF-E2-related factor 2 regulating ROS production (He et al., 2011; Wang et al., 2015). A meta-analysis by Maierean et al. (Maierean et al., 2017), reviewed several randomized, placebo-controlled clinical trials that evaluated the impact of cinnamon on blood lipid concentration and concluded that cinnamon supplementation substantially decreased blood triglycerides and total cholesterol amounts. In addition, polyphenols in cinnamon decrease glucose absorption the of (Medagama, 2015; Solomon & Blannin, 2007) and regulate peroxisome proliferator-activated receptor alpha and gamma-mediated metabolism (Kim & Choung, 2010).

Among cinnamon compounds, cinnamaldehyde is the most recognized for its protective effects on cardiovascular diseases. Nevertheless, other components like cinnamic acid, cinnamic aldehyde, eugenol, and polyphenols are also reported as active components implicated in the cardiovascular protective effects of cinnamon. Studies from Kang et al. (Kang et al., 2013), indicated that the vasodilation effect induced by cinnamic acid in rat thoracic aorta involves the nitric oxide–cGMP–PKG-mediated pathway, that stimulates Ca^{2+}-activated K^{+} channels lowering cytosolic Ca^{2+} level. Furthermore, the treatment with cinnamic aldehyde and its derivative cinnamic acid, have decreased the inflammatory markers and biochemical (CK-MB and LDH) of the myocardial ischemia (TNF-α and IL-6) and have increased the NO levels in a rat model of ischemic myocardial injury (Song et al., 2013); this caused a reduction of cardiac histological abnormalities which is partially attributed to the increase of NO synthesis and the antioxidant effects of this compound. Cinnamic acid and cinnamaldehyde reduce complications of acute myocardial ischemia, influencing serum levels of creatine kinase (CK)-MB, lactate dehydrogenase (LDH), TNF-α, NO, and interleukins such as IL-6. It also inhibits the thrombin-induced conversion of fibrinogen to fibrin in rats fed a diet high in hydrogenated fats. Moreover, 2-methoxycinnamaldehyde (2-MCA), protects against myocardial ischemia/reperfusion injury; this may be mediated by heme oxygenase (HO)-1 induction (Sobhani, Nami, Emami, Sahebkar, & Javadi, 2017).

A compound isolated from *C. cassia*, 2-methoxycinnamaldehyde, reduces the vascular cell adhesion molecule-1 expression in the TNFα-activated endothelial cells, which indicates that the ischemia/reperfusion damage is alleviated as a consequence of the induction of hem-eoxygenase- (HO-1) (Hwa et al., 2012). Although some reports describe the cardiovascular protective effects of cinnamon components, clinical studies about the cinnamon effects with isolated compounds are scarce.

4. Main extraction procedures of the major bioactive constituents

The extraction of bioactive compounds with pharmaceutical interest is an important step that must be accurately optimized and can comprise several aspects like sample preparation, pre-purification, and clean-up. The main compounds found in cinnamon bark are cinnamic acid, cinnamyl acetate, cinnamaldehyde, procyanidins, polysaccharide, catechins, among others (Ranasinghe et al., 2013). Among these, cinnamaldehyde is found in higher amounts of essential oil and exhibits several health benefits including cardiovascular protective effects, as discussed in the previous sections. Other important components are cinnamic acid and eugenol (used in perfumes and for flavoring). The conventional extraction methods used to extract these compounds are steam distillation, hydrodistillation, and soxhlet extraction (Conde-Hernández, Espinosa-Victoria, Trejo, & Guerrero-Beltrán, 2017; Kallel, Hadrich, Gargouri, Chaabane, Lassoued, Gdoura, Bayoudh, & Ben Messaoud, 2019) (Fig. 4). Hydrodistillation is the most commonly used methods because of its easiness, low cost, and absence of solvent residue. However, this method generally allows low yields (1–2%) (Baseri, Haghighi-Asl, & Lotfollahi, 2010; Wang, Wang, & Yang, 2009), and thus new extraction methods (Fig. 4) have been applied in the last years to improve extraction yields and to overcome the limitations of

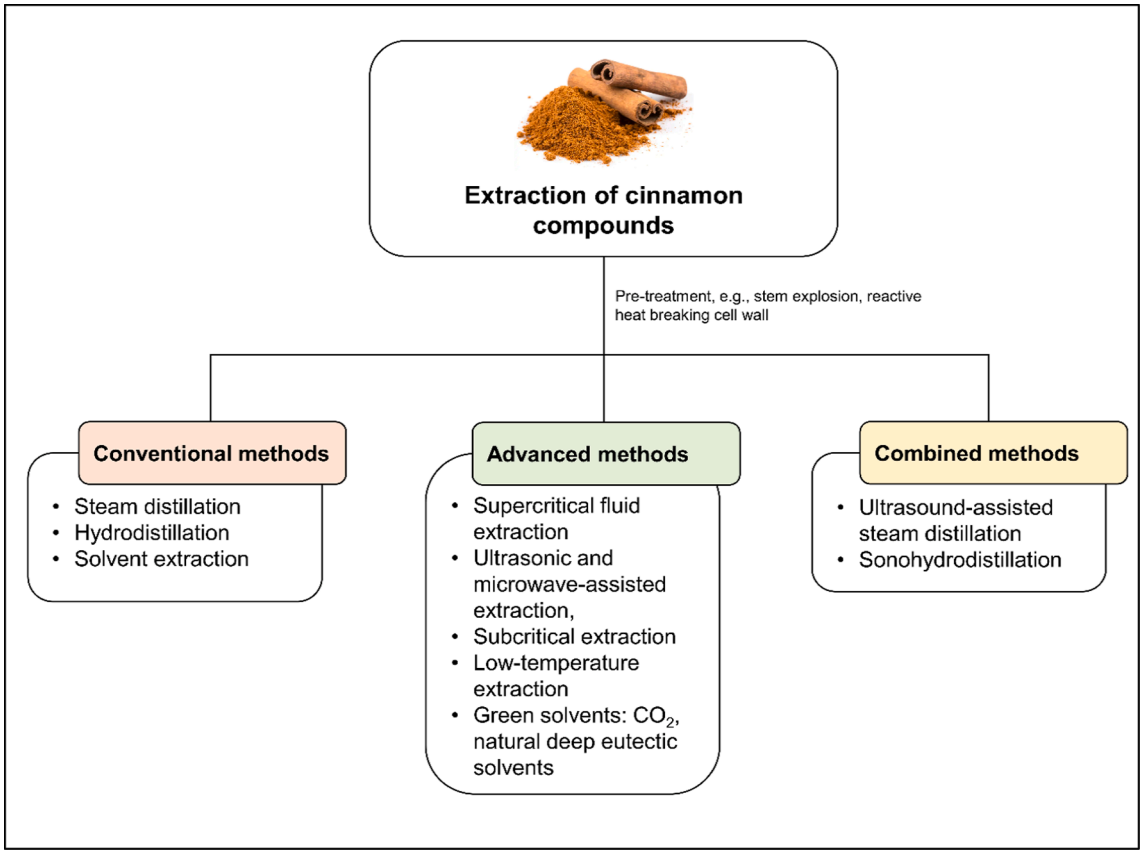

Fig. 4. Examples of extraction methods used to extract the major cinnamon compounds.

conventional extraction techniques (Gonçalves & Romano, 2021). These include supercritical fluid CO_2 extraction, ultrasonic and microwave-assisted extraction, and low-temperature extraction (Chen, Du, Zu, Yang, & Wang, 2016; Jeyaratnam et al., 2016; Lee, Jo, Ameer, & Kwon, 2018; Masghati & Ghoreishi, 2018; Nenov et al., 2011).

Some studies describe the use of supercritical fluid extraction to extract compounds from cinnamon (Baseri et al., 2010; Baseri, Lotfollahi, & Asl, 2011; Marongiu et al., 2007; Masghati & Ghoreishi, 2018; Miller, Poole, & Chichila, 1995; Zhao & Liang, 2006). Masghati and Ghoreishi, (Masghati & Ghoreishi, 2018); used response surface methodology to optimize the operating conditions to obtain cinnamaldehyde and eugenol from cinnamon by supercritical CO_2 extraction, using methanol as a co-solvent. Optimized conditions allow average extraction recoveries of 54 ± 1% and 38 ± 1.5%, respectively for cinnamaldehyde and eugenol. The extraction of several flavoring compounds from cinnamon (coumarin, cinnamic acid, cinnamaldehyde, and cinnamyl alcohol) by subcritical extraction was also recently optimized by response surface methodology (Cha, Kim, Kim, & Cho, 2019).

Lee et al. (Lee et al., 2018) compared the efficiencies (extraction yield, time and energy consumption, and CO_2 emission) of three green extraction methods (ultrasonic and microwave-assisted extraction, and reflux extraction) to extract cinnamic acid and cinnamaldehyde from cinnamon powder. The optimization of extraction conditions to obtain the maximum target response was performed by response surface methodology. Results showed that microwave-assisted extraction provided the best results (total yield: 0.89%, cinnamic acid: 6.48 mg/100 mL, and cinnamaldehyde: 244.45 mg/100 mL) in comparison to the other two techniques, and thus it was proposed as the most adequate for green extraction of cinnamic acid and cinnamaldehyde. On the other hand, ultrasound-assisted steam distillation was recently recommended as the preferable procedure to isolate essential oil from cinnamon for industrial applications, since in comparison with steam distillation and microwave-assisted steam distillation, this method allows high yields of extracted oil and the highest content of total cinnamic aldehydes (Yu, Yao, Qi, & Wang, 2020).

Sonohydrodistillation, a combination of ultrasound and hydrodistillation, was recently applied to enhance the extraction of cinnamon oil from cinnamon bark (Modi, Parikh, & Desai, 2019). Results demonstrated that this method improved the extraction efficiency compared to hydrodistillation alone and reduced the energy consumption and carbon emission emerging as a green substitute and an effective tactic for extracting essential oils from cinnamon. Recently Yu et al. (Yu et al., 2021) showed that using *in situ* reactive heat breaking cell wall by SO_3 hydration as pretreatment of hydrodistillation extraction, improved cinnamaldehyde extraction. This treatment destroys the cell wall, which is a crucial factor restricting the extraction of essential oils, facilitating the diffusion of cinnamaldehyde.

Solvent extraction is the commonly used method to extract phenolic compounds from plant matrices. In this procedure, several parameters can be optimized to increase the extraction efficiency and reduce the degradation of compounds, such as the type of solvent, the solid: solvent ratio, particle size, temperature, pH, and extraction time. De Souza et al. (de Souza et al., 2021), recently studied the extraction kinetics of proanthocyanidins from *C. verum* using aqueous ethanol as a solvent; they demonstrated that a solid: solvent ratio of 1:7.5 during 30 min at 60 °C provided the maximum yield (99%). Using response surface methodology and a fuzzy modeling approach; Cebi et al. (Cebi et al., 2019), found that ethanol 72%, extraction time of 50 min, and 70 °C are the optimal conditions to obtain the highest phenolics recovery from cinnamon by ultrasound-assisted extraction. The extract recovered contained cinnamic acid (41 mg/g) and p-coumaric acid (2 mg/g) as the two major compounds. More recently, some reports described the effectiveness of green solvents as natural deep eutectic solvents for the extraction of bioactive compounds (e.g., *trans*-cinnamaldehyde, coumarin, and trans-cinnamic acid) from cinnamon (Ahmad, Arifianti, Sakti, & Saputri, 2020; Aryati, Nadhira, Febianli, & Fransisca, 2020; Sakti, Saputri, & Mun'im, 2019).

5. Conclusions and recommendations

There is sufficient evidence that cinnamon can reduce the risk of cardiovascular diseases and might be used to treat cardiovascular ailments as it showed to reduce biomarkers in several cardiovascular and cardiovascular-related comorbidities like metabolic syndrome disorders. Cinnamaldehyde and cinnamic acid are the main cinnamon compounds with protective effects on cardiovascular diseases through different molecular mechanisms. It should be considered that several factors could influence the phytochemical composition of cinnamon. Among these factors are the presentations, modes, doses, and routes of consumption, as well as the species, environmental conditions of growth, conservation and storage methods, previous processing, type of extraction, solvents used, as well as other variables of the obtaining procedure of the extracts or supplements. The next step for using cinnamon as a biopharmaceutical agent is the determination of the effective dose. Thus, more preclinical and clinical studies are needed.

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Author statement

Jk Patra conceptualized the whole concept. G Das, JK Patra, JB Heredia, and S Gonçalves wrote, review, and edited the manuscript. A Romano, LA Jiménez-Ortega, EP Gutiérrez-Grijalva, HS Shin helped in the collection of literature, review, and editing of the manuscript. All authors read and approved the manuscript.

Ethics Statement

All authors affirm that the manuscript has not previously been published or not under consideration for publication in another journal. In addition, all authors agree to submit this paper to your journal considering the quality and the reputation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2022.105045.

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