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Cinnamon: an aromatic condiment applicable to chronic kidney disease

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Cinnamon, a member of the Lauraceae family, has been widely used as a spice and traditional herbal medicine for centuries and has shown beneficial effects in cardiovascular disease, obesity, and diabetes. However, its effectiveness as a therapeutic intervention for chronic kidney disease (CKD) remains unproven. The bioactive compounds within cinnamon, such as cinnamaldehyde, cinnamic acid, and cinnamate, can mitigate oxidative stress, inflammation, hyperglycemia, gut dysbiosis, and dyslipidemia, which are common complications in patients with CKD. In this narrative review, we assess the mechanisms by which cinnamon may alleviate complications observed in CKD and the possible role of this spice as an additional nutritional strategy for this patient group.

Keywords: Chronic renal insufficiency, *Cinnamomum zeylanicum*, Inflammation, Oxidative stress, Spices

Introduction

Cinnamon is a spice used for centuries as a culinary flavoring agent with organoleptic properties in different cultures worldwide. It has been used traditionally as a remedy for respiratory and gastrointestinal complications and has been widely studied because of its potential health-promoting properties [1]. These include antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, and antilipemic properties [2–4].

The anti-inflammatory properties of cinnamon have been suggested to be derived via inhibition of nuclear factor kappa B (NF-κB) expression and consequently reduced production of proinflammatory cytokines, such as tumor necrosis factor (TNF), C-reactive protein (CRP), and interleukin (IL) 6 [5–7]. Cinnamon also promotes the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which upregulates a host of cytoprotective defenses and increas-

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es the synthesis of antioxidant enzymes such as catalase (CAT), heme oxygenase 1 (HO-1), glutathione peroxidase 1 (GPx-1), and NAD(P)H dehydrogenase [quinone] 1 [6–9].

Patients with chronic diseases, including chronic kidney disease (CKD), commonly present with systemic inflammation and oxidative stress, dysregulated glucose and lipid metabolism, variations in blood pressure, and, consequently, a higher risk of cardiovascular disease (CVD) [10]. Furthermore, these patients may present with an altered composition of gut microbiota associated with increased uremic toxin levels in the circulation, exacerbating oxidative and inflammatory burdens [11].

The concept of food as medicine (nutrients and bioactive compounds are obtained from food) has been used to promote health and mitigate the chronic burden of lifestyle diseases [12]. Foods such as turmeric, propolis, Brazil nut, beetroot, berries, and cruciferous vegetables have documented benefits in patients with CKD, including control of inflammation, oxidative stress, and gut dysbiosis [13–19].

Few studies have been conducted on the effects of regular cinnamon consumption in patients with CKD. Therefore, in this narrative review, we summarize the beneficial effects of cinnamon and its possible role as a nonpharmacologic adjuvant therapy for complications associated with CVD, diabetes, obesity, and gut dysbiosis in patients with CKD to explore its medicinal benefits for these high-risk patient groups.

Cinnamon

Cinnamon is an indigenous spice obtained from the inner bark of trees belonging to the genera *Cinnamomum* from the Lauraceae family. It has been used since as early as 3,000 BC in Egypt. The name is of Greek origin (kinnámōmon), which translates as 'sweet wood' [20]. Today, it is used daily in various cuisines worldwide. Despite there being several varieties of cinnamon, only two, Ceylon cinnamon (also known as true cinnamon, which originates mainly from Sri Lanka) and cassia cinnamon (which originates from China, Vietnam, and Indonesia), are available in American and European food markets (Table 1) [2,21].

Cinnamon contains carbohydrates (52%), fibers (33%), protein (3.5%), and fat (4%). This spice is also a source of potassium (134.7 mg/g), magnesium (85.5 mg/g), calcium (83.8 mg/g), phosphorus (42.4 mg/g), manganese (20.1 mg/g), and iron (7.0 mg/g) [22]. The key components of cinnamon are essential oils of trans-cinnamaldehyde, cinnamyl acetate, and eugenol; a range of bioactive resinous compounds including cinnamaldehyde, cinnamic acid, and cinnamate; water-soluble polyphenols such as catechin, epicatechin, procyanidin, quercetin, and kaempferol; and polyphenolic polymers [23,24]. Eugenol is the main compound in the leaves, whereas cinnamaldehyde is predominant in the bark and camphor in the root [2,23,25]. The spicy flavor and fragrance characteristics of cinnamon are due to cinnamaldehyde (known as cinnamic aldehyde). In addition, the aging of cinnamon leads to color darkening due to higher levels of resinous compounds [25].

The daily intake of cinnamon can be considered safe if it does not exceed the tolerable daily intake of coumarin (0.1 mg/kg of body weight) [2], which is a phytochemical with anticoagulant, carcinogenic, and hepatotoxic properties [2,26]. However, coumarin concentration depends on the type of cinnamon, e.g., cassia cinnamon contains significant amounts of coumarin, whereas Ceylon cinnamon contains only trace quantities [2].

Different species of cinnamon may present an array of other oils with diverse characteristics, and their effects have been widely debated. Various studies have used different species and forms of cinnamon supplementation, leading

Table 1. Varieties of cinnamons and origins

Cinnamon variety	Scientific names	Common names	Country of origin	Color	Taste
Ceylon cinnamon	*Cinnamomum zeylanicum or Cinnamomum verum*	Ceylon cinnamon, true cinnamon, Mexican cinnamon	Sri Lanka, southern India	Light to medium reddish brown	Slightly sweetness
Cassia cinnamon	*Cinnamomum burmanni*	Indonesian cassia, Indonesian cinnamon, Korintje cinnamon, Padang cassia	Indonesia, Philippines	Dark reddish brown	Strong spicy
	Cinnamomum loureiroi	Saigon cinnamon, Vietnamese cassia, Vietnamese cinnamon	Vietnam	Dark reddish brown	Spicy and sweet
	Cinnamomum aromaticum	Chinese cinnamon, Chinese cassia, cassia cinnamon	China, Burma	Dark reddish brown	Mild and slightly sweet

to equivocal findings [1,27,28].

Cinnamon: antioxidant and anti-inflammatory actions

High production of reactive oxygen species (ROS) and reactive nitrogen species and reduced antioxidant capacity lead to oxidative stress, which promotes the pathogenesis of several chronic diseases, including diabetes, CKD, and CVD [29,30]. Therefore, modulating antioxidant enzyme production can reduce ROS formation and oxidative stress, slowing chronic disease progression [31]. Various cinnamon extracts, such as *Cinnamomum zeylanicum* Blume essential oil, ethanol extracts of cinnamon bark, cinnamon bark aqueous extract, and methanolic crude extract of *Cinnamomum verum*, display antioxidant activity, which indicates the potential for cinnamon to manage oxidative stress-related disorders [32]. Most cinnamon studies *in vitro* and *in vivo* (Table 2) [9,33–47] demonstrate significant antioxidant activity through multiple mechanisms, including reduction of malondialdehyde level (lipid peroxidation marker), activation of transcription factor Nrf2, and synthesis of antioxidant enzymes such as HO-1, superoxide dismutase, CAT, and GPx [48,49]. Twenty-two chemical ingredients have been isolated from cinnamon in addition to cinnamaldehyde analogues; of these, lignan pinoresinol (PRO) and the flavonol (–)-(2R,3R)-5,7-dimethoxy-3', 4'-methylenedioxy-flavan-3-ol (MFO) display antioxidant capacity [50].

The primary mechanism by which cinnamon (principally the cinnamaldehyde component) acts as an anti-inflammatory is via the downregulation of NF-κB [33,51] and diminution of inflammatory cytokine expression (e.g., TNF, CRP, and IL-6). Cinnamon also appears to reduce the levels of IL-1β and IL-18 by inhibiting the expression of NLR family pyrin domain containing 3 inflammasome and caspase-1 [34].

Additionally, cinnamaldehyde suppresses the expression of cyclooxygenase 2, nitric oxide synthase and prostaglandin E2 (PGE2) [52,53]. It has been implicated in the decreased phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinases (p38 MAPKs) pathways [35]. The role of cinnamon as an antioxidant and anti-inflammatory agent is illustrated in Fig. 1.

A limited number of studies have described the anti-inflammatory effects of cinnamon in humans, but the results remain inconclusive. Supplementation of 1.5 g/day of *Cinnamomum burmannii* powder in women with rheumatoid arthritis for 8 weeks promoted a reduction in both visual and pain scales, reduced tender and swollen joint counts, and reduced serum CRP and TNF levels [5]. Similarly, cinnamon (1.8 g/day for 2 months) in patients with migraines reduced serum IL-6 and nitric oxide (NO) levels [54]. The frequency, severity, and duration of migraine attacks decreased, suggesting a reduction in the inflammatory process [54]. In contrast, Davari et al. [51] used 3 g/day of cinnamon for 8 weeks in patients with type 2 diabetes (T2D). They found no beneficial effects on NF-κB, sirtuin 1 (SIRT1), or other systemic inflammation markers, including IL-6 and high-sensitivity CRP. The reasons for this outcome disparity remain unclear and may be multifactorial, including differing cinnamon sources, purity, and experimental methodologies.

Diabetes and cinnamon

Diabetes is one of the leading causes of CKD, manifesting as diabetic kidney disease. Several studies (Table 3) [51,55–78] have proposed that cinnamon therapy can improve insulin action and glucose metabolism, with procyanidin type-A polymers and cinnamaldehyde being the primary components associated with the antidiabetic effects [79].

Procyanidin type-A polymers in cinnamon can mimic insulin action as they increase insulin receptor autophosphorylation of β-subunit tyrosine residues and reduce oxidative stress in pancreatic β-cells [80,81]. Moreover, cinnamon extract (*C. zeylanicum*) ameliorated glucose transporter 4 translocation via the adiponectin and intracellular 5' adenosine monophosphate-activated protein kinase (AMPK) signaling pathway [82,83] and through stimulation of liver kinase B1 mediated AMPK phosphorylation [84].

Additionally, inhibition of α-glucosidase and pancreatic α-amylase, which promote postprandial glycemic amelioration, has been attributed to the action of the cinnamon extract [85].

Cinnamon also induces the expression of the peroxisome proliferator-activated receptors (PPAR) alpha and gamma (PPAR-α and PPAR-γ) *in vitro* and *in vivo*. This is notable as these regulate adipogenesis and insulin resistance by

Table 2. Studies involving cinnamon and antioxidant and anti-inflammatory actions

Reference	Study/samples	Intervention	Results
In vitro study			
Uchi et al. (2017) [36]	Human keratinocyte cell line benzo[a]pyrene-stimulated	Cinnamaldehyde (25 μM) or *Cinnamomum cassia* extract (100 mg/mL)	↑ Nrf2 translocation and HO-1 expression ↓ activation of AHR
Kim et al. (2018) [35]	Raw 264.7 murine macrophage cells LPS-induced	Trans-cinnamaldehyde (25, 50, or 100 μM)	↓ TNF-α, IL-1β, and IL-6 and NO synthesis
Schink et al. (2018) [37]	THP-1 monocyte-macrophage cell line TIB-202, LPS-stimulated	Cinnamon compounds (25 μg/mL)	Trans-cinnamaldehyde and p-cymene ↓ IL-8 secretion
Qu et al. (2019) [38]	LPS-stimulated RAW264.7 cells	Cinnamaldehyde (5, 10, or 20 μM) pretreatment	↓ NLRP3 inflammasome, miR-21 and miR-155 ↓ ROS, the phosphorylation of AKT, mTOR, and COX-2 protein level
Cheng et al. (2020) [39]	Human rheumatoid fibroblast-like synoviocyte line MH7A cells IL-1β-induced	Cinnamaldehyde (40, 60, and 80 nM) pretreatment	40, 60, and 80 nM: ↓ TNF-α, IL-6
Chen et al. (2020) [33]	Human osteoarthritis chondrocytes LPS-induced	Cinnamaldehyde pretreatment (10, 20, or 50-μM)	All doses: ↓ IL-6, IL-1β, TNF-α ↓ MMP-13 and ADAMTS-5 Doses of 20 and 50 μM: LPS-stimulated NF-κB expression
Ben Lagha et al. (2021) [40]	The monoblastic leukemia cell line U937 LPS-stimulated	Cinnamon bark aqueous extract (32.5 to 500 μg/mL) pretreatment	250 μg/mL: ↓ IL-6, IL-8, and TNF-α
Vallion et al. (2022) [41]	Human keratinocytes cells	100 μM of cinnamaldehyde	↑ Nrf2 accumulation ↓ IL-1β transcription
Chen et al. (2022) [42]	LPS-induced human osteoarthritis synovial fibroblasts	Pretreatment with cinnamic aldehyde (20 and 50 μmol/L)	↓ IL-1β, IL-6, and TNF-α ↓ TLR-4 and MyD88 expression
Experimental study			
Tuzcu et al. (2017) [9]	HFD rats	Cinnamon polyphenol (100 mg/kg body weight) for 12 weeks	↓ NF-κB p65 expressions ↑ PPAR-α, IRS-1, Nrf2, and HO-1 expressions in the HFD rat livers
Abou El-Ezz et al. (2018) [43]	LPS-induced neuroinflammation mouse model	Trans-cinnamaldehyde (50 mg/kg) intraperitoneally for 1 week	↓ IL-1β levels, MDA, and caspase-3 levels in the hippocampus Activate Nrf2 ↑ Glutathione S-transferase
Liu et al. (2020) [44]	*In vitro*: macrophages (Raw246.7) LPS-induced *In vivo*: arthritis rat model, complete Freund's adjuvant-induced	*In vivo*: cinnamaldehyde (6.25, 12.5, or 25 μM) *In vivo*: cinnamaldehyde (200 mg/kg) orally for 4 weeks	*In vitro*: ↓ IL-1β, NLRP3 (12.5, and 25 μM) ↓ TNF-α and NO (6.25, 12.5, and 25 μM) *In vivo*: ↓ IL-1β in blood ↓ NLRP3 in synovium
Wang et al. (2020) [45]	Leptin receptor-deficient (db/db) mice	Diet containing 0.02% cinnamaldehyde for 12 weeks	↓ ROS generation, preserved NO production ↑ p-eNOS ↑ Nrf2, HO-1 and NQO-1
Ryu et al. (2020) [46]	Mice with cognitive dysfunction induced by d-galactose and aluminum chloride	Trans-cinnamaldehyde (30 mg/kg/day) injected intraperitoneally + treadmill exercise for 5 weeks	↑ Nrf2, NQO-1, HO-1, and SOD-1
Abdel-kawi et al. (2022) [47]	Wistar rats, gastric ulcers ethanol-induced model	2.5 mL/kg of cinnamon oil and omeprazole (20 mg/kg) for 1 week before ulcer induction	↑ CAT, SOD, GPx, and GSH in the stomach ↓ MDA and TNF-α levels
Zou et al. (2022) [34]	Sepsis-induced C57BL/6 J mice	2 g/kg of cinnamyl alcohol by gavage	↓ IL-1β and IL-18 ↓ Expression of NLRP3, caspase-1, and apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain in the liver, heart, lungs, and kidneys

ADAMTS-5, metalloproteinase with thrombospondin motif 5; AHR, aryl hydrocarbon receptor; AKT, protein kinase B; CAT, catalase; COX-2, cyclooxygenase type 2; GPx, glutathione peroxidase; GSH, glutathione; HFD, high-fat diet; HO-1, heme oxygenase 1; IL, interleukin; IRS-1, insulin receptor substrate 1; LPS, lipopolysaccharide; MDA, malondialdehyde; MMP-13, matrix metalloproteinase-13; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; NQO-1, NAD(P)H dehydrogenase [quinone] 1; Nrf2, nuclear factor erythroid 2-related factor 2; p-eNOS, phosphorylated endothelial nitric oxide synthase; PPAR-α, peroxisome proliferator-activated receptors (PPAR) alpha; ROS, reactive oxygen species; SOD-1, superoxide dismutase 1; TLR-4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha.

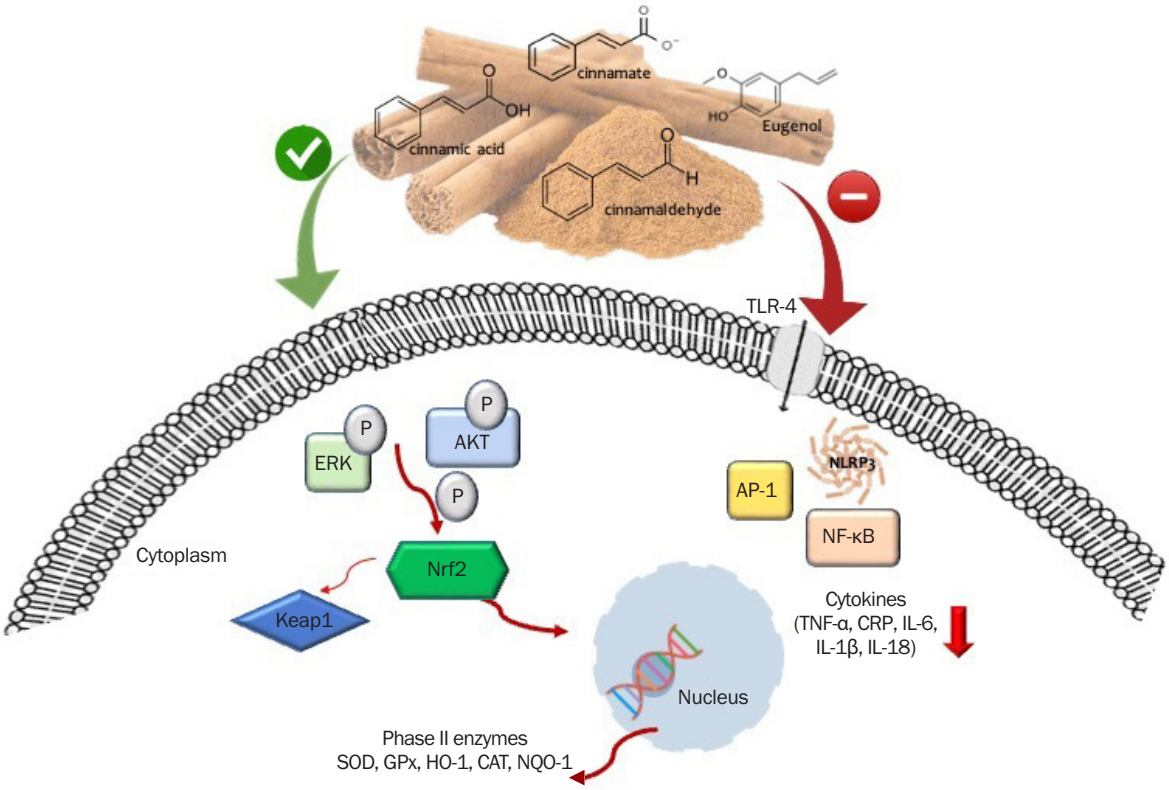

Figure 1. Antioxidant and anti-inflammatory actions of cinnamon in cells. Bioactive compounds from cinnamon may activate the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), leading to the synthesis of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), heme oxygenase 1 (HO-1), glutathione peroxidase 1 (GPx-1), and NAD(P)H dehydrogenase [quinone] 1 (NQO-1). Also, these compounds can inhibit nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and NLR family pyrin domain containing 3 (NLRP3), reducing inflammatory cytokine production.
TLR-4, toll-like receptor 4; ERK, extracellular signal-regulated kinase; AKT, protein kinase B; Keap1, Kelch-like ECH-associated protein 1; TNF-α, tumor necrosis factor alpha; CRP, C-reactive protein; IL, interleukin.

regulating the expression of genes encoding proteins involved in adipokine synthesis, adipocyte differentiation, and lipid and carbohydrate metabolism [86]. Additionally, cinnamaldehyde may stimulate the expression of PPAR-γ and PPAR delta (PPAR-δ) in differentiated adipocytes, promoting insulin sensitivity and fatty acid β-oxidation in adipose tissue and skeletal muscle [87]. Another component of cinnamon extract, the B-type procyanidin C1, has been demonstrated to stimulate preadipocyte differentiation as well as act as a potential insulin sensitizer through the protein kinase B (AKT)/endothelial NO synthase (eNOS): AKT/eNOS pathway in mature adipocytes [88]. The phosphoinositide 3-kinase (PI3K)/AKT pathway participates in glucose uptake by skeletal muscles, adipose tissues, and liver. Cinnamaldehyde treatment (10 mg/kg) has been reported to increase the expression of insulin receptor substrate 1 (IRS-1), PI3K, and AKT2 in diabetic rats, promoting enhanced insulin signaling by the IRS1/PI3K/AKT pathway and reducing insulin resistance and promoting an antidiabetic effect [55].

Despite the salutogenic effects of cinnamon treatment in diabetes, other human-based studies have yielded equivocal results. In one systematic review, no significant benefits were found for cinnamon in reducing glucose and glycated hemoglobin (HbA1c) levels in patients with type 1 diabetes [89]. Conversely, a meta-analysis has reported that intake of whole cinnamon or cinnamon extract lowered fasting blood glucose (FBG) in T2D and prediabetes [90]. In a meta-analysis of 435 patients, Akilen et al. [91] reported that cinnamon doses ranging from 1 to 6 g/day ingested for

Table 3. Studies involving cinnamon and diabetes

Reference	Study/sample	Intervention	Results
Experimental study			
Hafizur et al. (2015) [58]	STZ-induced diabetic rats	5 and 10 mg/kg of cinnamic acid or cinnamaldehyde	Cinnamic acid: ↓ blood glucose, improved glucose tolerance ↑ Glucose-stimulated insulin secretion in isolated islets. Cinnamaldehyde: ↔ glucose-stimulated insulin secretion
Qusti et al. (2016) [59]	STZ-induced diabetic in male albino rats	20% (w/w) cinnamon methanol extract for 28 days	↓ Blood glucose ↓ IL-6 and MDA ↑ CAT and SOD ↓ Urea, Cr, and uric acid
Jawale et al. (2016) [60]	STZ-induced diabetic in rats	10, 20, or 40 mg/kg of cinnamaldehyde for 3 weeks	↓ Blood glucose ↓ TNF-α and IL-6
Hosni et al. (2017) [61]	STZ-induced diabetic in female albino rats with gestational diabetes	20 mg/kg oral dose of cinnamaldehyde with or without fatty-sucrose diet, or normal diet for 8 weeks	↓ Hyperphagia and glucose intolerance ↓ Fructosamine, TC, TG, leptin ↓ TNF-α, MDA, NO ↑ HDL-C, adiponectin, liver glycogen ↑ PPAR-γ gene expression
Taheri et al. (2018) [62]	STZ-induced diabetic in adult male Wistar rats	300 mg/kg cinnamon bark powder for 14 days	↓ CYP2D
Abdelmageed et al. (2019) [55]	STZ-induced T2D in male rats	10 mg/kg of cinnamaldehyde for 2 months	↓ OGTT, ITT, FBG ↓ Insulin and HOMA-IR ↑ HOMA-β ↓ MDA ↑ Aortic GSH, SOD, IRS-1, PI3K-p85, AKT2
Kommula et al. (2020) [63]	Neonatal STZ rat model	3% Cinnamon for 8 months	↓ Fasting and postprandial glucose levels prevented retinal functional abnormalities
Mohammed et al. (2020) [64]	STZ-induced diabetic rats	200 and 400 mg/kg of cinnamon oil emulsion in whey protein concentrate for 1 month	↓ Blood glucose, amylase, ↓ TC, LDL-C, TG ↑ Insulin, HDL-C ↑ Hepatic SOD, GSH ↓ Hepatic MDA
Niazmand et al. (2021) [65]	STZ-induced diabetic rats	Cinnamon extract (100, 200, 400 mg/kg) and metformin (300 mg/kg) orally for 42 days	↓ MDA level, SOD and CAT activities in the liver and kidney
Sampath et al. (2021) [66]	Gastric emptying in obesity-induced diabetic female mice	Cinnamaldehyde 50 mg per body mass per day for 6 weeks	↓ Body weight gain ↓ FBG ↓ HOMA-IR ↑ Reduced/oxidized glutathione ratio
Vijayakumar et al. (2022) [57]	STZ-induced diabetic rats	Ethanolic bark extracts of *Cinnamomum cassia* with different concentrations (300, 400, and 500 mg/kg BW) and glibenclamide (3 mg/kg BW)	↑ Activities of mitochondrial enzymes ↓ Levels of hepatic marker enzymes (AST, ALT, and ALP) ↓ Urea, Cr, and uric acid
Çelik et al. (2022) [67]	STZ-induced diabetic rats	20 mg/kg of BW of cinnamaldehyde by gavage daily for 1 month	↓ FBG ↓ TG, TC, VLDL, LDL-C, and urea levels

(Continued to the next page)

Table 3. Continued

Reference	Study/sample	Intervention	Results
Human study			
Bernardo et al. (2015) [68]	Nondiabetic adults	100 mL of cinnamon tea (*Cinnamomum burmannii bark*) obtained from 60 g sticks of cinnamon soaked into 1,000 mL of water, after OGTT	Slightly ↓ PBG level after OGTT
Sengsuk et al. (2015) [69]	T2D patients	1,500 mg of cinnamon (divided into 3 times a day capsules) or placebo for 2 months	↓ Median glucose, TG, TG/HDL-C ratio, and BP ↑ HDL-C and eGFR
Anderson et al. (2015) [71]	Hyperglycemic adults	1 g (divided into 2 capsules) a day of water extract of cinnamon (CinSulin), or placebo for 2 months	↓ FBG, HOMA-IR ↓ Serum glucose 2 hours after 75 g carbohydrate load ↓ Fructosamine, fasting insulin ↓ TC, LDL-C, HDL-C
Azimi et al. (2016) [56]	T2D patients	3 g/day of cinnamon with black tea for 2 months	↓ ICAM-1 ↔ BP and endothelial function
Gutierrez et al. (2016) [70]	Young, sedentary, obese women	5 g of encapsulated cassia cinnamon bark for 3 separate days (30-, 60-, 90-, and 120-minute following glucose ingestion)	↔ Insulin resistance and sensitivity ↓ Peak blood glucose at 30-time point
Gupta Jain et al. (2017) [72]	Individuals with metabolic syndrome	3 g (divided into 6 capsules) of cinnamon or placebo, for 4 months	↓ FBG, ↓ HbA1c ↓ WC, ↓ BMI improved lipid profile, waist-hip ratio, and BP
Talaei et al. (2017) [73]	T2D patients	3 g of cinnamon (divided into 3 capsules-day), for 2 months	↔ FBG, insulin, HbA1c, HOMA-IR, carboxymethyl lysine, total antioxidant capacity, and MDA
Zare et al. (2019) [74]	T2D patients	1 g of cinnamon bark powder (divided into 2 capsules daily) or placebo for 3 months	↓ BMI, body fat, visceral fat ↓ FBG, HbA1c, fasting insulin, and insulin resistance ↓ TC, LDL-C, and HDL-C
Kizilaslan and Erdem (2019) [75]	Healthy adult individuals	1 g or 3 g or 6 g/day cinnamon peel (*C. cassia*), for 40 days	↔ BMI, HbA1c Difference in pre-prandial blood glucose (6 g/day) Difference in postprandial blood glucose on days 20 and 40 for 1, 3, and 6 g of cinnamon
Davari et al. (2020) [51]	T2D patients	3 g of cinnamon for 2 months	↔ NF-κB, SIRT1, hs-CRP, IL-6, and TNF-α plasma levels
Romeo et al. (2020) [76]	Adults with prediabetes	500 mg cinnamon thrice daily for 3 months	Fasting plasma glucose remained stable only in the cinnamon group ↓ OGTT
Lira Neto et al. (2022) [77]	T2D patients	3 g of cinnamon (capsules daily) for 3 months	↓ HbA1c ↓ Fasting venous glucose
Rachid et al. (2022) [78]	T2D patients	6 g/100 mL of aqueous cinnamon extract (*C. burmannii*) after 30, 60, 90, and 120 minutes	↔ Area under the curve, glucose conc., variation, and maximum glucose conc

AKT, protein kinase B; AKT2, AKT serine/threonine kinase 2; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BW, body weight; CAT, catalase; Cr, creatinine; CYP2D, cytochrome P450; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GSH, glutathione; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment-estimated insulin resistance; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IRS-1, insulin receptor substrate 1; ITT, insulin tolerance test; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; NF-κB, nuclear factor kappa B; NO, nitric oxide; OGTT, oral glucose tolerance test; PBG, postprandial glucose level; PI3K, phosphoinositide 3-kinase ; PPAR-γ, peroxisome proliferated activated receptor gamma; SIRT 1, silent mating-type information regulation 2 homolog 1; SOD, superoxide dismutase; STZ, streptozotocin; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor alpha; VLDL, very-low-density lipoprotein; WC, waist circumference.

between 40 days and 4 months reduced HbA1c and fasting glycemia levels. In 2013, a further meta-analysis including 543 patients reported that cinnamon supplementation (powdered cinnamon and aqueous extract) ranging from 120 mg to 6 g ingested for between 4 and 18 weeks reduced blood glucose, total cholesterol, and triglycerides but did not affect HbA1c level [92]. Costello et al. [80] have shown that cinnamon dietary supplements (doses ranging from 120 to 6,000 mg/day ingested for between 4 and 16 weeks) have clinically meaningful effects on glycemic control (FBG or HbA1c) in patients with T2D.

Additionally, a meta-analysis showed no effect of powdered cassia cinnamon intake (1–2 g) on fasting glucose, HbA1c, triglycerides, low-density lipoprotein (LDL), and total cholesterol levels in patients with T2D. On the other hand, a higher (at least 3 g) rather than a lower dose of cassia bark powder or cassia extract associated with lifestyle and diet protocols was more effective for glucose control in T2D [93].

Analyzing the impact of cinnamon on patients with diabetes is very complex as cinnamon contains several compounds, such as coumarin, cinnamic acid, cinnamaldehyde, cinnamic alcohol, and eugenol, with varied concentrations among species [94]. In addition, results are related to the quality of cinnamon, the type of branches, and manufacturing practices among species and formulations [95].

The effectiveness of cinnamon in glucose control may depend on how well the diabetes was controlled during the study. In addition, previous studies have used different parameters and periods [95]. Therefore, administering cinnamon can be a helpful add-on therapy in integrative medicine for managing T2D. Still, long-term trials are required to establish the efficacy and safety of cinnamon. In addition, the differing contributions of various microbiomes between subjects must be addressed [96].

Cinnamon: benefits in obesity

Obesity is a strong predictor of renal dysfunction and CKD [97]. Some physiological responses of the kidneys to obesity include increased glomerular filtration rate, tubular reabsorption of sodium, filtration fraction, and renal plasma flow [98]. Central obesity and abdominal fat are risk factors for metabolic syndrome, which is also associated with the development and progression of CKD and CVD [99].

Cinnamon has been studied as a potential nutritional strategy for managing obesity and its complications [9]. Cinnamon's antiobesogenic effect may be related to its ability to induce thermogenesis in adipocytes as mediated by uncoupling protein 1 which is expressed in brown and beige tissues and improves metabolism to promote weight loss [100].

Moreover, cinnamaldehyde activates a classic thermogenesis pathway through protein kinase A signaling that phosphorylates p38 MAPK, inducing the transcription of thermogenic genes such as hormone-sensitive lipase and lipid droplet-associated protein perilipin 1 [52]. Additionally, as cinnamaldehyde is the primary natural agonist of the transient receptor potential ankyrin 1 (TRPA1), it may also indirectly influence food intake and weight gain, which can be expressed in gastrointestinal functions such as decreasing ghrelin secretion [101,102]. Other natural compounds present in cinnamon oil, such as cumin aldehyde (cumin), *p*-anisaldehyde (anise), and triglycaldehyde (onion/garlic), can activate human TRPA1 specifically but with lower affinity compared to cinnamaldehyde. Among these compounds, cumin aldehyde demonstrated glucose-dependent insulin secretagogue activity in diabetic rats by TRPA1 stimulation [102].

The AMPK pathway is also relevant to the study of obesity as it is a mediator of cellular energy production, which can improve insulin sensitivity in insulin-sensitive tissues, such as adipose tissue [103]. Cinnamon seems to exert beneficial effects via AMPK activation and enhanced adiponectin concentrations, as demonstrated by Kopp et al. [104]. They evaluated the Gi/Go-protein-coupled receptor 09A, which stimulates adiponectin secretion after binding trans-cinnamic acid from cinnamon.

Other protective effects ascribed to cinnamon appear to result from a reduction of hepatic expression of the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c) and NF-κB, in conjunction with upregulation of PPAR-α, a cluster of differentiation 36 (CD36), fatty acid synthase, carnitine palmitoyltransferase I, and Nrf-2 [105]. Studies of obese rats with hepatic steatosis caused by a high-fat diet suggest enhancement of hepatic beta-oxidation and inhibition of hepatic lipogenesis, oxidative damage, and inflammation resulting from cinnamon intake.

Aqueous extract of *Cinnamomum cassia* bark has been linked to neurochemical and behavioral effects in rats by decreasing food intake through augmentation of 5-hydroxy tryptamine in the brain [106].

Only a few studies have reported a relationship between cinnamon and antiobesogenic effects in humans. Yazdanpanah et al. [107] have conducted a systematic review and meta-analysis to investigate the effects of cinnamon on fat and body mass, body mass index (BMI), waist circumference, and waist-hip ratio. In total, 21 randomized controlled trials (RCTs) with 1,480 participants were included, and it was reported that cinnamon supplementation decreased obesogenic parameters. In agreement with the studies discussed, a systematic review and dose-response meta-analysis suggested that cinnamon supplementation could improve obesity measures, particularly in obese subjects aged <50 years at dosages of ≥2 g/day for at least 12 weeks [108]. More recently, Keramati et al. [109] evaluated the effects of cinnamon on obesity rates in humans through an umbrella meta-analysis, which indicated that cinnamon supplementation reduced BMI. The effects of cinnamon were more pronounced at doses of ≥3 g/day and in patients with polycystic ovary syndrome. Table 4 [52,72,105,110–123] lists these associated experimental and clinical studies on the effects of cinnamon on obesity.

Cinnamon and cardiovascular disease

Patients with CKD have a high risk of developing premature CVD due to a combination of traditional risk factors, including diabetes, obesity, dyslipidemia, hypertension, and a toxic uremic milieu [124]. Cinnamon may benefit cardiovascular health; indeed, studies have shown hypotensive effects, control of dyslipidemia, and protection of the endothelium and vascular smooth muscle cells (VSMC). As already discussed, cinnamon has anti-inflammatory and antioxidant properties, which can reduce the progress of atherosclerosis [56]. However, postulated hypotensive effects ascribed to cinnamon remain inconclusive [125]. Ghavami et al. [126] evaluated the effects of cinnamon supplementation on blood pressure through a systematic review and meta-analysis of RCTs. Eight studies, including 582 participants, suggested that cinnamon supplementation had beneficial effects only on diastolic blood pressure.

Components of cinnamon, such as catechin, epicatechin, procyanidin B2, and phenolic polymers, can act as agonists of PPARs, inhibiting the formation of advanced glycation end products to reduce oxidative stress and increasing the bioavailability of vasodilator NO [108,125].

Furthermore, cinnamon improves the lipid profile and reduces lipid oxidation and the risk of vascular blockage, mitigating potential hypertensive conditions [127]. Flavonoids and phenolic acids found in cinnamon inhibit pancreatic lipase, which is necessary for forming chylomicrons [110]. Cinnamon ameliorates lipid profiling by suppressing the expression of transcription factor SREBP-1c and liver X receptor alpha enzymes, such as ATP-citrate lyase and NF-κB p65. Furthermore, it upregulates PPAR-α expression to enable modulation of lipid metabolism [9]. Additionally, cinnamon has been reported to inhibit the secretion of proatherogenic apolipoprotein B 48 CD36, and the class A macrophage scavenger receptor, as well as the uptake of acetylated LDL, again suggesting that cinnamon can act as a preventive medicine [128,129].

Despite these promising results, the evidence remains inconclusive. Krittanawong et al. [130] have systematically reviewed the literature and evaluated cinnamon consumption and cardiovascular risk. A meta-analysis that included 23 studies (1,070 subjects) concluded that there was no association between cinnamon consumption and differences in LDL-cholesterol, high-density lipoprotein cholesterol, and HbA1c levels. Studies on cinnamon *in vitro*, in animals, and in humans are listed in Table 5 [9,45,131–144]. Again, allowance for different exposome features, such as microbiota composition, may be pertinent here [145].

Does cinnamon benefit the gut microbiota?

Microbiota dysbiosis is a disruption to the normative microbial community driven by host-related exposome factors such as diet, resulting in perturbations to its composition and function [145,146]. Dysbiosis is associated with many chronic diseases, such as metabolic syndrome, inflammatory bowel disease, and CKD, which present a typical proinflammatory phenotype. Increased permeability in the gut with age and condition enables the entry of microbial metabolites, pathobionts, or endotoxins such as lipopolysaccharides (LPS) into the circulation [147,148]. It also presents a loss of symbiotic microbes.

Table 4. Studies involving cinnamon on obesity

Reference	Study/sample	Intervention	Results
Experimental study			
Lopes et al. (2015) [111]	Adult male Wistar rat	400 mg/kg BW/day of cinnamon aqueous extract (*Cinnamomum zeylanicum*), for 25 days	↔ Food intake and serum lipid profile ↓ Body mass gain ↓ Relative mass of WAT Leptin mRNA expression in the WAT ↑ Protein content
Lee et al. (2016) [112]	3T3-L1 preadipocytes cells	50, 100, 200 μg/mL of cinnamon extract (*Cinnamomum cassia*)	↑ Lipid storage in white adipocytes, ↑ Fatty acid oxidation capacity ↑ PGC-1α, CPT-1α, PPARγ, C/EBP-α, and C/EBP-β genes expressions
Khare et al. (2016) [113]	3T3-L1 preadipocytes cells *In vivo*: male Swiss albino mice	10, 20, and 40 μM of cinnamaldehyde: *in vitro* 5 mL/kg and 10 mL/kg BW of cinnamaldehyde with a normal or HFD: *in vivo*	↑ HPL ↓ Expression of perilipin and GPD ↓ PPARγ and C/EBP-α prevented the increase in visceral fat pad weight regulated leptin/ghrelin ratio ↑ Anorectic gene expression in hypothalamus (POMC, BDNF, UCN, CARTPT, and CCK) ↓ Glycerol and free fatty acid levels ↑ Expression levels of lipolysis-promoting genes: HSL, PNPLA2, and MGLL ↓ IL-1β, COX, MCP1, TNF-α, and IL-6 ↑ Anorectic and lipolytic gene expression
Jiang et al. (2017) [52]	Primary preadipocytes from and human adipose-derived stem cells	200 and 400 μM of cinnamaldehyde	↑ Thermogenesis: ↑ UCP1, FGF21, PKA, phosphorylation of HSL and PLIN1 ↑ Lipid metabolism: Pdk4
Kwan et al. (2017) [114]	3T3-L1 preadipocytes and *Ex vivo*: subcutaneous adipose tissue from db/db mice and *in vivo/ex vivo* DIO mice	80 μg/mL (*in vitro*) and 500 mg/kg BW (*in vivo*) cinnamon extract (*C. cassia*)	Induced browning in white adipocytes: ↑ UCP1 expression; ↑ Prdm16, Cidea, PPARγ, PGC, Cpt1 Induced browning in subcutaneous adipocytes in db/db mice: UCP1 protein and mRNA Cidea and Prdm16 DIO mice: ↑ UCP1 expression in the subcutaneous adipose tissue; ↓ BW
Kang et al. (2019) [115]	3T3-L1 and HIB1B preadipocytes cells	10–200 μM of trans-cinnamic acid of bark (*C. cassia*)	Induced browning in white adipocytes activation of β3AR-PKA-AMPK, TRPA1, and GPR signaling pathways ↑ Fat oxidation ↓ Adipogenesis and lipogenesis
Neto et al. (2019) [116]	Lactating dams (Wistar rats) were supplemented, and adult male offspring were evaluated at 180 days old	400 mg/kg BW/day of cinnamon aqueous extract (*C. zeylanicum*) during lactating period	↑ Visceral obesity Hepatic metabolic dysfunction and ↑ lipid accumulation ↓ Glycogen content in the liver, hyperleptinemia and hyperinsulinemia
Neto et al. (2020) [117]	Adolescent rat model of obesity programmed by early overnutrition	Cinnamaldehyde 40 mg/kg of body mass per day for 29 days	↓ Visceral adipose tissue mass
Ataie et al. (2021) [118]	Adult male Wistar rats with HFD-induced	Cinnamaldehyde 20 mg/kg of body mass per day for 16 weeks	↓ Plasma nitrate and nitrate ↓ Islet insulin secretion ↓ iNOS activity

(Continued to the next page)

Table 4. Continued

Reference	Study/sample	Intervention	Results
Li et al. (2022) [105]	Adult male Wistar rat obesity HFD-induced	Cinnamon powder 50 or 100 mg/kg BW orally for 12 weeks	↓ Hepatic levels of oxidative and inflammatory biomarkers ↓ Serum levels of glucose, liver enzymes, insulin, and lipid profiles ↓ Hepatic expression of SREBP-1c and NF-κB ↑ PPAR-α, CD36, CPT-1, and Nrf-2
Neto et al. (2022) [119]	Adolescent rat model of obesity programmed by early overnutrition	Cinnamaldehyde 40 mg per kg of body mass per day for 30 days	↓ Adipocyte hypertrophy ↑ Oxidative pathways (PGC1α, FGF21) in WAT ↑ Increased BAT thermogenesis markers (PPARα, FGF21, UCP-1) ↓ WAT adipocyte size
Miah et al. (2022) [120]	Adult Swiss albino mice hyperlipidemia and obesity Butter enriched HFD-induced	10% butter with cinnamon 200 mg, 400 mg, or 600 mg powder per liter drinking water for 10 weeks	↓ TC, LDL-C, and glucose levels ↓ ALT and AST and fat deposition in the liver
Human study			
Gupta Jain et al. (2017) [72]	Adults with metabolic syndrome	3 g/day (6 capsules) of cinnamon for 16 weeks	↓ BW, WC, waist-to-hip ratio ↓ % Body fat
Borzoei et al. (2017) [121]	Polycystic ovary syndrome in overweight or obese women	1.5 g cinnamon extract (3 capsules) for 8 weeks	Improved glucose metabolism and lipid profile, ↓ insulin
Khedr et al. (2020) [110]	Overweight /obese adults	1.2 g of Ceylon cinnamon capsules and 120 mg of Orlistat for 15 weeks	↓ BMI ↓ Lipase activity ↓ Lipid profile
Wang et al. (2021) [122]	Normal and overweight/obese individuals	1/2 cup dry instant oatmeal with milk prepared with or without 6 g of cinnamon (Korintje cinnamon, from cassia bark), acute intake (4 hours)	↓ Postprandial insulin response in overweight/obese individuals ↓ Postprandial glucagon levels, glucagon and C-peptide response in normal weight participants
Huang et al. (2022) [123]	Overweight adults	6 g of cinnamon meal on 4 separate visits at least 3 days apart	↓ Postprandial glycemia

ALT, alanine aminotransferase; AMPK, adenosine monophosphate-activated protein kinase; AST, aspartate aminotransferase; BAT, brown adipose tissue; BDNF, brain-derived neurotrophic factor; BMI, body mass index; BW, body weight; C/EBP-α, CCAAT/enhancer-binding protein alpha; C/EBP-β, CCAAT-enhancer-binding protein beta; CARTPT, cocaine amphetamine-related transcript; CCK, cholecystokinin; CD36, cluster of differentiation 36; Cidea, DFFA-like effector A; COX, cyclooxygenase; CPT-1, carnitine palmitoyl transferase 1; CPT-1α, carnitine palmitoyltransferase 1 alpha; DIO, diet-induced obesity; FGF21, fibroblast growth factor 21; GPD, glycerol-3-phosphate dehydrogenase; GPR, G-protein-coupled receptor; HFD, high-fat diet; HSL, hormone-sensitive lipase; IL, interleukin; iNOS, inducible nitric oxide synthase; LDL-C, low-density lipoprotein cholesterol; MCP-1, monocytechemotactic protein 1; MGLL, monoglyceride lipase; NF-κB, factor nuclear kappa B; Nrf-2, nuclear factor erythroid 2-related factor 2; Pdk4, pyruvate dehydrogenase kinase 4; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PKA, protein kinase A; PLIN1, lipid droplet-associated protein perilipin 1; PNPLA2, patatin phospholipase domain containing 2; POMC, proopiomelanocortin; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; Prdm16, PR domain containing 16; SREBP-1, sterol regulatory element-binding transcription factor 1; TC, total cholesterol; TNF-α, tumor necrosis factor alpha; TRPA1, necrosis factor receptor-associated protein 1; UCN, urocortin; UCP-1, uncoupling protein 1; WAT, white adipose tissue; WC, waist circumference; β3AR, β3 adrenergic receptor.

Beyond typical treatments to mitigate dysbioses, such as pro-, pre-, or symbiotics, some bioactive compounds can be effective in modulating the gut microbiota [149,150]. Studies of the benefits of cinnamon in this capacity have been increasing [150,151].

Cinnamon compounds, such as polyphenols, reach the colon and serve as substrates for bacterial metabolism [152]. Normative gut microbiota is dominated by anaerobic bacteria from the Firmicutes and Bacteroidetes phyla. Dysbiosis is characterized by a loss of microbial diversity and symbionts and an increased representation of pathobionts [96,153]. Cinnamon effectively enriches gut microbiota by reducing Proteobacteria and increasing Bacteroidetes [154].

The essential oil in cinnamon contributes to the growth of salutogenic bacteria capable of short-chain fatty acid

Table 5. Studies involving cinnamon on cardiovascular health

Reference	Study/sample	Intervention	Results
Experimental study			
Kwon et al. (2015) [131]	Rat aortic vascular smooth muscle cells	Extract *Cinnamomum cassia* bark – 10, 30, and 50 μM	↓ PLCγ1, Akt, and P38 ↑ Percentage of G0/G1 phase cells ↓ PCNA expression
Panickar et al. (2015) [132]	Mouse brain endothelial cells	Cinnamtannin D1 – 10^{-2} and 10^{-3} mg/mL	↓ OGD-induced swelling ↓ Cell swelling in presence of MCP-1 ↓ Mitochondrial ROS ↓ OGD-induced fluorescence
Chen et al. (2016) [133]	Mice with ischemia/reperfusion-induced brain injury	10, 20, and 30 mg/kg trans-cinnamaldehyde, an essential oil in cinnamon powder 60 minutes before ischemia surgery	↓ Infarction area and neurological deficit score ↓ iNOS, COX-2, NF-κB, mRNA, TNF-α
Kang et al. (2016) [134]	Male rats with metabolic syndrome with cardiac oxidative stress	20, 40, and 80 mg/kg cinnamaldehyde for 5 weeks	↓ HW/BW, TGF-β, p-Smad 2/3 and Smad4 ↑ GSH/GSSG
Tuzcu et al. (2017) [9]	Rats given high-fat feed	100 mg/kg cinnamon polyphenol extract for 12 weeks	↓ Expression of hepatic SREBP-1c, LXRs, ACLY, FAS, MDA, NF-κB ↑ PPAR-α, IRS, Nrf2, HO-1, SOD, CAT ↓ TG, TC, LDL-C ↓ BW, visceral fat
Nayak et al. (2017) [135]	Mice with dexamethasone-induced atherosclerosis	500 mg/kg and 250 mg/kg cinnamon extract for 12 days	↓ TG, TC, LDL-C ↑ HDL-C ↓ Atherosclerotic change of aorta
Sedighi et al. (2018) [136]	Rats with ischemia	*Cinnamomum zeylanicum* bark extract – 50, 100, or 200 mg/kg – 2 weeks before ischemia	↓ Infarct size ↓ Ventricular tachycardia, ventricular ectopic beats episodes ↓ R-wave amplitude ↑ Heart rate during ischemia ↓ MDA, cardiactroponin I, LDH ↑ SOD, GPx
Pulungan and Pane (2020) [137]	Mice (Mus musculus) given high-fat feed	2, 4, and 8 mg/kg cinnamon extract for 2 weeks	↓ TC
Alsoodeeri et al. (2020) [138]	Rats given high-fat feed	2 and 4 g/kg cinnamon powder for 4 weeks	↓ TG, TC, LDL-C ↑ HDL-C
Wang et al. (2020) [45]	Leptin receptor-deficient mice	Diet containing 0.02% cinnamaldehyde for 12 weeks	↑ Nitrotyrosine, NO, NRF2, HO-1, NQO-1 ↓ ROS, p-eNOS
Moreno et al. (2022) [139]	Rings from male Wistar rat thoracic aorta pre	Cinnamon extract (0–380 μg/mL)	Induced concentration-dependent vasodilation
Tian et al. (2022) [140]	Male, cardiac hypertrophy model C57BL/6	Trans-cinnamaldehyde daily at a dosage of 50 mg/kg or 100 mg/kg via oral gavage for 2 weeks	Inhibited induced cardiac hypertrophy
Human study			
Ranasinghe et al. (2017) [141]	Healthy adults	85 mg, 250 mg, and 500 mg of *C. Zeylanicum* (water extract) for a period of 3 months, with dose increased at monthly intervals	SBP, DBP ↔Renal and liver function, fasting blood glucose, HDL-C, VLDL, and TG ↓TC and LDL-C
Mirmiran et al. (2019) [142]	Type 2 diabetes patients	3 g cinnamon extract capsules, for 2 months	↓ICAM-1 and VCAM-1 in both cinnamon and placebo groups, but not between groups

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Table 5. Continued

Reference	Study/sample	Intervention	Results
Shirzad et al. (2021) [143]	Stage 1 hypertension patients	Cinnamon capsules, 1,500 mg/day, for 2 months	Moderate clinical decrease in mean ambulatory SBP ↑ HDL-C ↓ LDL-C levels
Zhang et al. (2022) [144]	Patients with mild stroke or transient ischemic attack	Aspirin-cinnamon group (100 mg/day aspirin + 5 g of cinnamon granules) and aspirin-placebo group (100 mg/day aspirin + placebo granules) for 2 months	Aspirin-cinnamon group: ↓TG, LDL-C, fasting plasma glucose, HbA1c, Lp-PLA_2, and hs-CRP ↑ HDL-C ↓ Carotid atherosclerosis

ACLY, ATP-citrate lyase; Akt, protein kinase B; BW, body weight; CAT, catalase; COX-2, cyclooxygenase type 2; DBP, diastolic blood pressure; FAS, fatty acid synthase; GPx, glutathione peroxidase; GSH/GSSG, glutathione/oxidized glutathione ratio; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HO-1, heme oxygenase 1; hs-CRP, high-sensitivity C-reactive protein; HW/BW, heart-to-body weight; ICAM-1, intercellular adhesion molecule 1; iNOS, inducible nitric oxide synthetase; IRS, insulin receptor; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, plasma lipoprotein-related phospholipase A_2; LXRs, liver X receptor; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; mRNA, messenger RNA; NF-κB, nuclear factor kappa B; NO, nitric oxide; NQO-1, NAD(P)H dehydrogenase [quinone] 1; NRF2, factor erythroid nuclear factor 2 related to factor 2; OGD, oxygen-glucose deprivation; P38, anti-phospho-p38; PCNA, antiproliferating cell nuclear antigen; p-eNOS, phosphorylated endothelial nitric oxide synthase; PLCγ1, anti-phospho-phospholipase C gamma 1; PPAR-α, peroxisomeproliferator-activated receptor alpha; p-Smad 2/3, phosphorylated Smad2/3; p-Smad4, phosphorylated Smad4; ROS, reactive oxygen species; SBP, systolic blood pressure; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element-binding proteins; TC, total cholesterol; TG, triglyceride; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1; VLDL, very-low-density lipoprotein.

production. These can produce butyrate, acetate, and propionate, which not only serve as the substrate for the host cells but also regulate inflammation [154,155]. Cinnamon oil may improve microbiota diversity and downregulate inflammatory processes [154]. Moreover, cinnamon oil can protect against LPS-induced intestinal injury through upregulation of epidermal growth factor, claudin-1, occludin, alkaline phosphatase (ALP), and pregnane X receptor expression, improving gut barrier integrity [156]. The evidence supports cinnamon or cinnamon compounds as nutritional adjuvants for maintaining intestinal integrity [156,157].

An experimental study conducted with early-weaned rats, highly susceptible to intestinal stress and alterations, has shown that treatment with 100 or 200 mg/kg body weight/day cinnamaldehyde for 2 weeks improved the gut barrier and was accompanied by an increase in mucin production, reduced inflammation, and improved microbiome diversity [158]. These authors suggested that the beneficial effects were due to inhibition of NF-κB activation; upregulated expression of mucin 2, trefoil factor 3, and tight junction proteins; and reduced IL-6 and TNF-α expression, potentially mediated by increased in gut microbe diversity [158].

Another recent study has supported this assertion, indicating that the microbiota in ovariectomized mice displayed improved diversity after treatment with cinnamic acid. This result was accompanied by an elevation in transforming growth factor beta levels in bone marrow cells, which induced osteoblast differentiation and increased the expression of osteogenic markers [159].

Based on these data, cinnamon usage is encouraged not only to manage diseases influenced by microbiota, such as CKD but also for general health. The role of the microbiota in the health of the general population has recently been exemplified by a report linking poor renal function with accelerated aging and an imbalanced diet [160]. These data are pertinent to the treatment and management of CKD, as well as other diseases of aging.

Cinnamon: could it be of benefit in chronic kidney disease?

Although studies evaluating the effect of cinnamon on the kidneys are scarce, the salutogenic effects suggested by the literature (as shown in Fig. 2) suggest an overall benefit [161]. CKD is a significant cause of mortality globally, and its prevalence is growing in low-middle-income countries, where social deprivation amplifies its effects [145]. The reenvisioning of the Hippocratic concept of 'food as medicine' champions the use of natural bioactives as potential therapeutics to tackle the emerging diseasome of aging [12].

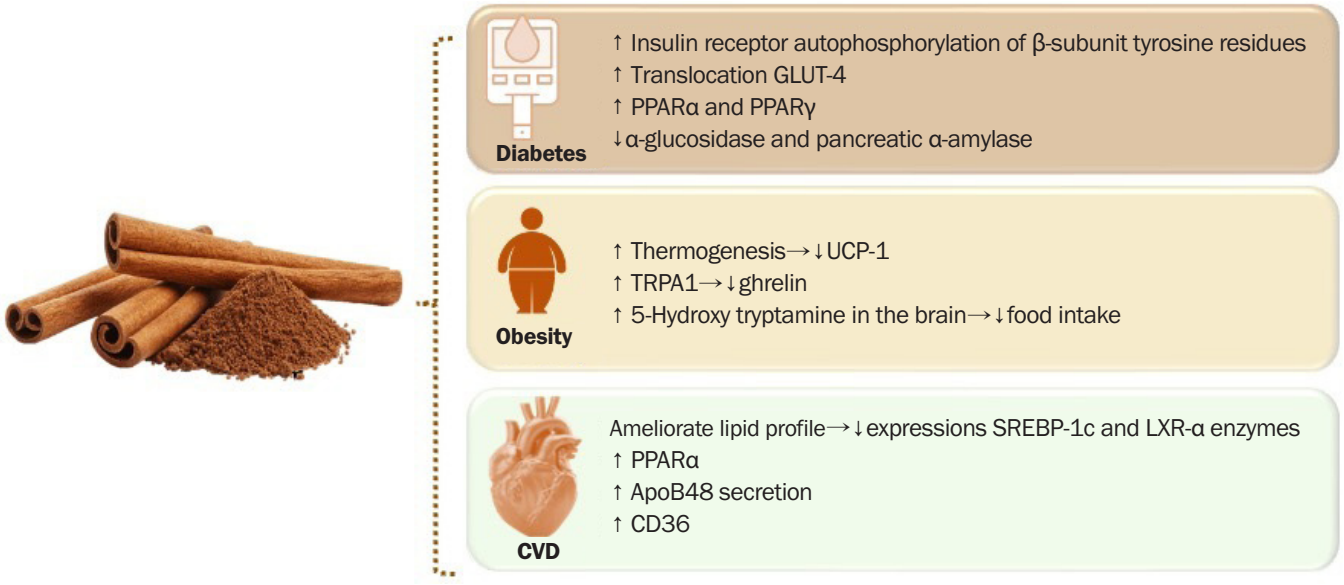

Figure 2. The potential benefits of cinnamon to patients with diabetes, obesity, or CVDs. Cinnamon can provide physiological benefits by mimicking insulin action through insulin receptor autophosphorylation of the β-subunit of tyrosine and promoting glucose transporter (GLUT) translocation via the 5' adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. Cinnamaldehyde has antidiabetic activity through upregulation of the insulin signaling pathway, induction of peroxisome proliferator-activated receptors (PPARs), and inhibition of α-glucosidase and pancreatic α-amylase. Cinnamon may increase the expression of uncoupling protein 1 (UCP-1), promoting thermogenesis. It can also reduce hepatic expression of sterol regulatory element-binding protein-1c (SREBP-1c) and nuclear factor kappa B (NF-κB) and upregulate PPAR-α, fatty acid synthase, carnitine palmitoyltransferase I (CPT-1), and nuclear factor erythroid 2-related factor 2 (Nrf-2) to promote cytoprotective effects and reduce inflammation. Cinnamaldehyde might act as a natural agonist of transient receptor-ankyrin receptor 1 (TRPA1), reducing ghrelin secretion and food intake. Cinnamon may decrease SREBP-1 and cluster of differentiation 36 (CD36) expression and increase expression of PPAR-γ, reducing oxidative stress, inflammatory burden and, therefore, cardiovascular risk.
LXR-α, liver X receptor alpha; CVD, cardiovascular disease.

The use of cinnamon is merited for evaluation to be included in the physician's and nutritionist's armamentarium.

Common pathways underpin the salutogenic effects of cinnamon in CKD, including the inactivation of the ERK/JNK/p38 MAPK pathway leading to reduced renal interstitial fibroblast proliferation and hypertrophy [162]. Nrf2 pathway stimulation, promoting attenuation of renal damage and preservation of renal function, is also a key element in this mechanism [8,163–165]. Other reported benefits of cinnamon are the inhibition of peroxynitrite-induced nitration and lipid peroxidation and its influence on the production of NO and PGE2 [166,167].

Patients with CKD experience premature and accelerated aging [145], and cinnamon may also benefit in mitigating the effects of cellular aging. In support of this, it has been reported that cinnamaldehyde attenuates cellular senescence in the kidney through PI3K/AKT pathway-mediated autophagy via downregulation of microRNA-155 [168].

Cinnamon is a promising candidate in the dietetic management of CKD, as it can mitigate complications such as dyslipidemia and diabetes. Studies have suggested possible improvements in kidney function through dietetic approaches aimed at upregulating antioxidant and anti-inflammatory defenses [12,169]. However, despite the known properties of cinnamon, its effect on patients with CKD has not been explored, and most studies are experimental (Table 6) [65,168,170–173]. This highlights the need for further investigations.

Toxicity caused by cinnamon

Contrary to popular belief, herbal medicines are not entirely safe and may have adverse effects. The available data suggest that cinnamon is safe for use as a spice, and mod-

Table 6. Experimental studies involving cinnamon on kidney diseases

Reference	Study/sample	Intervention	Results
Hussain et al. (2019) [170]	Administration of acetaminophen in BALB/c mice	Pretreatment with 200 mg/kg/day i.g. of cinnamon bark aqueous extract for 2 weeks	Prevention against elevation in serum ALT, AST, Cr, urea Prevention against macroscopic and histological alterations in liver and kidney Improvement of oxidative balance
Niazmand et al. (2021) [65]	STZ-induced diabetic rats	100, 200, or 400 mg/kg of cinnamon extract for 6 weeks	↓ MDA level, SOD and CAT activities in the liver and kidney ↑ GSH and total thiol contents and NO production
Alshahrani et al. (2021) [171]	Male Wistar rats with nephrotoxicity induced by acetaminophen	50, 100, and 200 mg/kg of cinnamon oil with 2 g/kg of acetaminophen, for 15 days	Improvement in serum biochemical markers and oxidative parameters: Protected cellular injury in kidney tissue ↓ IL-1β, IL-6, and caspase 3 and 9 ↑ GSH level and ameliorates antioxidative enzymes (SOD, CAT, GR, and GPx in kidney tissue)
Atsamo et al. (2021) [172]	Male Wistar rats with gentamicin-induced nephrotoxicity	200 and 400 mg/kg/day of *Cinnamomum zeylanicum* stem bark aqueous extract for 2 weeks concomitantly with gentamicin administration	Prevention of alterations in body weight, serum total proteins, calcium level, kidneys' relative weight, Cr, urea, and uric acid ↓ MDA, and TNF-α, IL-1β, and IL-6 and nitrites ↑ GSH, SOD, CAT Prevention of histological alterations
Elshopakey and Elazab (2021) [173]	Broiler chickens with copper-induced nephrotoxicity	200 mg/kg of *C. zeylanicum* alone or plus probiotic for 6 weeks	Both supplementations: ↓ Urea, Cr, and uric acid In renal tissue: ↓ MDA ↑CAT, and GSH, ↓ Copper ↓ TNF-α, IL-2, Bax, and COX-II in kidneys ↑ IL-10 and Bcl-2
Xiao (2022) [168]	Sprague-Dawley rats (male) kidney senescence model D-galactose-induced	40 mg/kg/day of cinnamaldehyde for 6 weeks	↓ Blood urea nitrogen and Cr In the kidneys: the contours of the proximal and distal convoluted tubules were improved, ↓ the number of nuclear pyknosis, ↓ hyperemia ↑ Ratio of p-P13K to P13K and the ratio of p-Akt to Akt

Akt, protein kinase B; ALT, alanine transaminase; AST, aspartate transaminase; Bcl-2, B-cell lymphoma 2; CAT, catalase; COX-II, cyclooxygenase; Cr, creatinine; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; IL, interleukin; MDA, malondialdehyde; NO, nitric oxide; p21, p21/WAF-1Cip1; PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor alpha.

erate ingestion has several health benefits, as previously reported. However, its use for medicinal purposes in high doses or over a long duration may lead to adverse effects, such as gastrointestinal disturbances and self-limiting allergic reactions that should be clinically monitored [174]. Yun et al. [175] have reported that cinnamon extract (2 g/kg body weight/day for 13 weeks) might result in nephrotoxicity and hepatotoxicity in rats due to high doses of coumarin. In animals, despite all the extracts tested showing possible antioxidant activity *in vitro*, they showed acute dose-dependent toxicity (1,000, 2,000, 3,000, 4,000, and 5,000 mg/kg body weight) *in vivo*, with increased levels of aspartate transaminase, alanine transaminase ALP, urea, and creatinine reported in animals treated with the highest dose [57].

In a systematic review of the adverse effects of cinnamon, the authors report that most studies did not identify the cinnamon species responsible for these effects. Knowing that different cinnamon species contain other components, such as coumarin, studies on herbal medicines should be standardized to include their exact identification, dose, and duration of treatment [174]. Recently, Gu et al. [176] evalu-

ated the safety of cinnamon in humans through a study using relevant meta-analyses and systematic reviews of RCTs and concluded that there are no adverse effects caused by cinnamon.

There is no exact recommendation for the daily intake of cinnamon. Still, studies recommend approximately 1 to 4 g per day, and attention should be paid to the amount of coumarin in different types of cinnamon and symptoms such as diarrhea, nausea, and vomiting [161].

Conclusion

Cinnamon compounds have several beneficial effects for consideration for inclusion in a 'food as medicine' strategy to treat CKD. These reside in inherent antioxidant, anti-inflammatory, cardioprotective, antiobesogenic, and antidiabetic properties. Additionally, they may reside in the ability of cinnamon to influence the composition of the gut and microbiota. Though most reported studies are preclinical, they indicate that human clinical studies are merited. Therefore, different clinical trials need to be planned regarding the dose and period of supplementation, the types of cinnamon species, and other populations. This review highlights the need for further studies on patients with CKD who suffers from several comorbidities, in which the use of cinnamon supplementation has demonstrated potential advantages.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: LSGM, ISCB, DCMVR, LT, TRC, ME, LFMFC, PS, DM
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Supervision: PS, DM, PGS
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