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## Beneficial effects of cinnamon and its extracts in the management of cardiovascular diseases and diabetes†

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Cardiovascular diseases (CVDs) and diabetes are the leading causes of death worldwide, which underlines the urgent necessity to develop new pharmacotherapies. Cinnamon has been an eminent component of spice and traditional Chinese medicine for thousands of years. Numerous lines of findings have elucidated that cinnamon has beneficial effects against CVDs in various ways, including endothelium protection, regulation of immune response, lowering blood lipids, antioxidative properties, anti-inflammatory properties, suppression of vascular smooth muscle cell (VSMC) growth and mobilization, repression of platelet activity and thrombosis and inhibition of angiogenesis. Furthermore, emerging evidence has established that cinnamon improves diabetes, a crucial risk factor for CVDs, by enhancing insulin sensitivity and insulin secretion; regulating the enzyme activity involved in glucose; regulating glucose metabolism in the liver, adipose tissue and muscle; ameliorating oxidative stress and inflammation to protect islet cells; and improving diabetes complications. In this review, we summarized the mechanisms by which cinnamon regulates CVDs and diabetes in order to provide a theoretical basis for the further clinical application of cinnamon.

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## 1. Introduction

Cardiovascular diseases (CVDs) and diabetes are the leading causes of death worldwide.<sup>1</sup> According to the statistics of the American Heart Association, the prevalence of heart disease in 2017 was 10.6%, and it is reported that 17.8 million people died from CVDs in this year.<sup>2,3</sup> Diabetes may result in many types of complications, and cardiovascular complications are the main cause of morbidity and mortality in diabetic patients.<sup>1</sup> Currently, various types of Western medicine, such as hypoglycaemic drugs, antihypertensive drugs, statins, and anticoagulants, have been developed. However, the side effects and medication adherence remain concerns.<sup>4,5</sup> In recent years, increasingly more attention has been given to the treatment of

CVDs and diabetes with traditional Chinese medicine. Herbal medicine could improve the surrogate endpoints of CVD, including blood pressure, electrocardiogram changes or left ventricular function and/or drug-related adverse reactions; and Herbal medicine is considered to be a substitute and supplementary method for the primary and secondary prevention of CVD.<sup>6</sup> Traditional Chinese medicine has also been reported to play a more important role in fighting diabetes.<sup>7</sup>

Cinnamon, a common spice, is an herbal medicine and an anti-inflammatory dietary supplement recommended for the primary and secondary prevention of coronary artery disease.<sup>8</sup> Furthermore, cinnamon has been found to decrease fasting blood glucose (FBG) and homeostatic model assessment for insulin resistance (HOMA-IR) level, thus bringing benefits to diabetic patients.<sup>9,10</sup> The genus *Cinnamomum*, also known as cinnamon (Fig. 1), is a small tropical tree of the lauraceae family. There are approximately 250 species of *Cinnamomum*; and the plant was originally grown in Sri Lanka, East and Middle Asia.<sup>11,12</sup> Essential oils made from cinnamon are also widely used in the food and cosmetic industries.<sup>13</sup> A plethora of studies have deeply explored the active ingredients and therapeutic effects of cinnamon. Numerous studies have revealed that cinnamon has neuroprotective, lipid-lowering, antioxidant, anti-inflammatory, and hypoglycaemic effects,

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**Fig. 1** The whole plant of *Cinnamomi Cortex* (a). Traditional Chinese herb Rougui and cinnamon powder (b).

some of which are closely related to the development of diabetes and CVDs.<sup>13–18</sup> In this review, we provide a comprehensive overview of the therapeutic potential and possible mechanisms of cinnamon in treating diabetes and CVDs.

## 2. Chemical constituents and pharmacological features of cinnamon

The German Commission E and the European Scientific Cooperative on Phytotherapy (ESCOP) approved two types of

cinnamon for herbal use: *Cinnamomum* (*C.*): *C. zeylanicum* and *C. cassia*.<sup>19</sup> The bark of cinnamon can be peeled and dried in shade to produce Chinese medicine, which can treat chest pain, abdominal pain and dysmenorrhea. Pharmaceutical manufacturers often use Ceylon cinnamon and Chinese cinnamon to produce cinnamon oil, which is absorbed into the body through the skin or olfactory system to play a therapeutic role, for aromatherapy.<sup>13,20,21</sup> Different types of cinnamon extracts, such as the methanolic crude extracts of *C. verum*, the *C. zeylanicum* Blume essential oil, the ethanol extracts of cinnamon bark, and cinnamon bark aqueous extract, all exhibit antioxidant activity, which indicates the potential of cinnamon to treat oxidative stress-related diseases.<sup>22–25</sup>

More than 80 compounds were separated and characterized from different parts of cinnamon. The major compounds of cinnamon include eugenol, cinnamaldehyde, camphor, cinnamyl acetate, and copane, as well as other minor constituents (Fig. 2). Eugenol has been reported to be a major component of leaf oil; cinnamaldehyde and camphor were found to be the major compounds of stem bark and root bark volatile oils, respectively; and *trans*-cinnamyl acetate was identified as a major compound in fruits, flowers, and fruit stalks.<sup>12</sup>

*C. zeylanicum* bark essential oil can scavenge free radicals, inhibit the oxidation of  $\beta$ -carotene to play an antioxidant role, and has a dose-dependent antiproliferative effect on adipose-derived mesenchymal stem cells, which makes *C. zeylanicum* bark essential oils have the potential to develop medical treatments.<sup>21</sup> Thirteen compounds were extracted from the essential oil of *C. zeylanicum* Blume bark, of which (*E*)-cinnamaldehyde accounted for 97.7%.<sup>26</sup> Cinnamaldehyde has been revealed to exert antioxidation, anti-inflammatory, blood vessel protection and hypoglycaemic and antibacterial effects.<sup>27–30</sup> The main component of cinnamon leaf essential oil is eugenol.<sup>19</sup> Nineteen ingredients were extracted from the volatile oil of *C. zeylanicum* Blume leaves, and eugenol accounted for 87.3%.<sup>26</sup> Eugenol showed very powerful activities of inhibiting peroxynitrite-induced lipid peroxidation.<sup>31</sup> *Trans*-Cinnamaldehyde and *D*-(+)-camphor are the most important compounds in the essential oils extracted from the leaves of two *C. osmophloeum* clones and could be applied as nutraceuticals or antioxidant remedies with their antioxidant effects.<sup>32</sup> *Trans*-Cinnamaldehyde has also been found to possess substantial antimicrobial, anticancer and anti-inflammatory properties.<sup>33,34</sup> *Trans*-Cinnamaldehyde, *T*-cadinol and  $\alpha$ -cadinol obtained from the essential oils of *C. osmophloeum* leaves could strongly inhibit nitric oxide (NO) production and have excellent anti-inflammatory activities, thus having great potential as a source for natural health products.<sup>35</sup> The phenolic constituents extracted from the fruits of *C. zeylanicum* also show antioxidant and radical scavenging activities.<sup>36</sup> Gas chromatographic-mass spectrometry studies showed that the main components of the twig essential oil of *C. osmophloeum* Kaneh are *l*-bornyl acetate (15.89%), caryophyllene oxide (12.98%), gamma-eudesmol (8.03%), beta-caryophyllene (6.60%), *T*-cadinol (5.49%), delta-cadinene (4.79%), *trans*-beta-elemene (4.25%), cadalene (4.19%), and *trans*-cinnamaldehyde



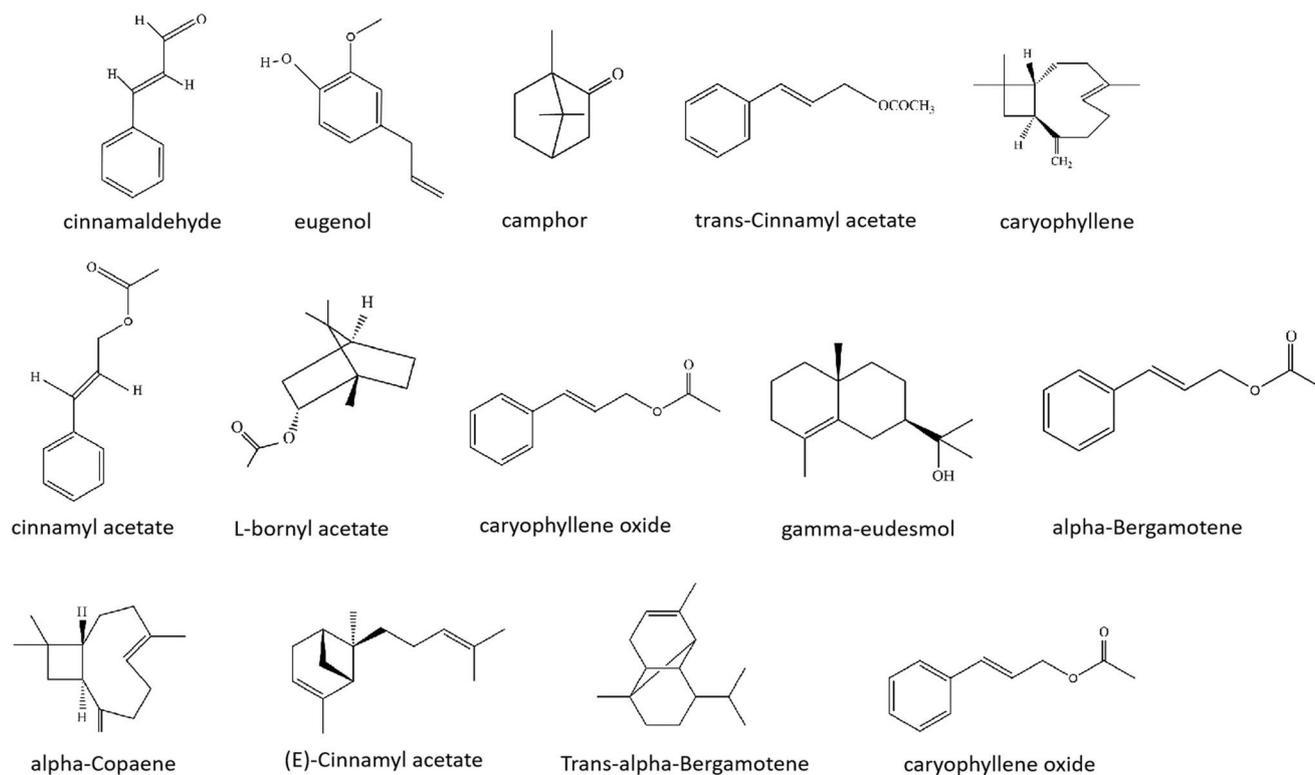


Fig. 2 Chemical structures of relevant isolated components of cinnamon.

(4.07%); and *trans*-cinnamaldehyde, caryophyllene oxide, *L*-borneol, *L*-bornyl acetate, eugenol,  $\beta$ -caryophyllene, *E*-nerolidol, cinnamyl acetate,  $\alpha$ -terpineol and *p*-allylanisole could inhibit the production of NO by lipopolysaccharide (LPS)-stimulated macrophages, thus exhibiting anti-inflammatory properties.<sup>37</sup> (*E*)-Cinnamyl acetate (36.59%) and (*E*)-caryophyllene (22.36%), which possess good antioxidant activity were found to be major compounds in the volatile oil of *C. zeylanicum* fruit stalks that possess good antioxidant capacity.<sup>38</sup> Several flavonoids obtained from cinnamon also show DPPH radical scavenging activity.<sup>39</sup> The major compounds of the hydrodistilled volatile oil of the *C. zeylanicum* buds are terpene hydrocarbons (78%), alpha-bergamotene (27.38%), alpha-copaene (23.05%) and oxygenated terpenoids (9%).<sup>40</sup> The chemical composition of the flower oil of *C. zeylanicum* was analysed by GC and GC-MS, and it has been reported that (*E*)-cinnamyl acetate (41.98%), *trans*-alpha-bergamotene (7.97%), and caryophyllene oxide (7.2%) are major compounds.<sup>41</sup> The contents and activities of the chemical constituents of different parts of cinnamon are summarized in Table 1.<sup>42–44</sup>

### 3. Side effects and toxicity of cinnamon

Cinnamon is safe to use as a spice and/or flavouring agent. It has been reported that cinnamon has minimal toxic and

adverse effects.<sup>45</sup> Thirty healthy adults in a clinical trial were instructed to take water extracts of *C. zeylanicum* with the dose increased at monthly intervals (85 mg d<sup>-1</sup>, 250 mg d<sup>-1</sup> and 500 mg d<sup>-1</sup>).<sup>46</sup> It has been reported that no serious adverse effects (including hypersensitivity) occurred during the 3-month treatment period or 3-month follow-up period after taking *C. zeylanicum* extract.<sup>46</sup> An *in vitro* study found that indigenous cinnamon (*C. osmophloeum*) twig extracts had no toxicity on 3T3-L1 preadipocytes at 100 mg mL<sup>-1</sup>.<sup>47</sup> Moreover, a plethora of animal and cell experiments have demonstrated that cinnamon and its constituents alleviate the natural toxin-induced and chemical-induced toxicities.<sup>48–56</sup> In MPTP mouse model of Parkinson's disease, daily treatment with cinnamon powder (100 mg per kg body weight, 7 days) protected striatal tyrosine hydroxylase fibers from the toxicity of MPTP and restored the neurotransmitters level.<sup>48</sup> In 3 month old Sprague-Dawley male rats, intragastrical pre-treatment with 2.5 ml per kg body weight *Oleum cinnamomi* 1 h before the ethanol administration protected the stomach, liver and kidney from ethanol-induced damage.<sup>49</sup> In healthy Wistar albino rats, oral administration with aqueous bark extract of *C. zeylanicum* ((2.0 g kg<sup>-1</sup>, 14 days) showed protective effect against doxorubicin induced cardiotoxicity.<sup>50</sup> It was reported that cinnamon diet (25 mg mL<sup>-1</sup>, 10 days) had a marginal protective effect against paraquat in female flies and cinnamon diet (2.5, 25, and 75 mg mL<sup>-1</sup>, 10 days) could extend lifespan in the fly.<sup>51</sup> In male adult Sprague-Dawley rats, both cinnamic acid (50 mg kg<sup>-1</sup>, p.o., 7 days) and cinnamaldehyde (40 mg



**Table 1** The concentration and activities of chemical constituents in different parts of cinnamon

| Parts of cinnamon | Dominant ingredients                            | Activity  | Ref.            |
|-------------------|---|---|-----------------|
| Bark              | Cinnamaldehyde: 65.00 to 80.00%                 | Antioxidant, anti-inflammatory, blood vessel protection and hypoglycemic and anti-bacterial effects | 27–30 and 42–44 |
|                   | Eugenol: 5.00 to 10.00%                         | Antioxidant activity  | 42–44           |
| Leaves            | Eugenol: 70.00 to 95.00%                        | Antioxidant activity  | 31 and 42–44    |
|                   | Cinnamaldehyde: 1.00 to 5.00%                   | Antioxidant, anti-inflammatory, blood vessel protection and hypoglycemic and anti-bacterial effects | 43 and 44       |
| Fruit             | <i>Trans</i> -Cinnamyl acetate: 42.00 to 54.00% | —   | 36 and 42       |
|                   | Caryophyllene: 9.00 to 14.00%                   | —   | 36 and 42       |
| Twigs             | <i>l</i> -Bornyl acetate: 15.89%                | Anti-inflammatory activity  | 37              |
|                   | Caryophyllene oxide: 12.98%                     | Anti-inflammatory activity  | 37              |
|                   | Gamma-eudesmol: 8.03%                           | —   | 37              |
| Fruit stalks      | Cinnamyl acetate: 36.59%                        | Antioxidant activity  | 38              |
|                   | Caryophyllene: 22.36%                           | —   | 38              |
| Buds              | Alpha-bergamotene: 27.38%                       | —   | 40              |
|                   | Alpha-copaene: 23.05%                           | —   | 40              |
| Flowers           | ( <i>E</i> )-Cinnamyl acetate: 41.98%           | —   | 41              |
|                   | <i>Trans</i> -Alpha-bergamotene: 7.97%          | —   | 41              |
|                   | Caryophyllene oxide: 7.20%                      | —   | 41              |

kg<sup>-1</sup>, p.o., 7 days) revealed the ameliorative effects on cisplatin-induced splenotoxicity.<sup>52</sup> In male albino rats, pre-treatment with cinnamon aqueous extract (200 mg per kg per day body weight, 3 times weekly for 50 days) was revealed to ameliorate the Bisphenol A- and octylphenol-induced pathological changes in kidney, brain and testis.<sup>53</sup> Another study showed that erythrocytes suspensions incubated with cinnamaldehyde (40 μM) could reduce the hazardous effects of cyadox, maintain the normal function of the body cells and protect the cells against oxidative injury.<sup>54</sup> In male Wister rats, cinnamon extract (200 mg per kg body weight orally, 8 weeks) was revealed to improve the liver and kidney functions and ameliorate the toxic effect of cadmium.<sup>55</sup> In cultured human lymphocytes, cinnamic acid (0.74, 3.70, 7.40, 14.8, 74.0, 148 mg ml<sup>-1</sup>) was shown to possess antigenotoxic effects against H<sub>2</sub>O<sub>2</sub> induced genotoxicity.<sup>56</sup> Despite this, several studies have identified some side effects that cinnamon may cause in clinical practice. A 13-week repeat-dose oral toxicity study on rats revealed that the use of cinnamon extract in excess of the daily recommended dose, 2000 mg kg<sup>-1</sup>, may increase the weight of the kidney/liver and the total cholesterol (TC) content.<sup>57</sup> *In vitro* mammalian cell micronucleus assays indicated that cinnamon extract (312.5, 625, 1250 μg ml<sup>-1</sup>) was not aneugenic or clastogenic, and *in vivo* bone marrow micronucleus assays demonstrated that cinnamon extract (500, 1000, 2000 mg per kg body weight) was not cytotoxic.<sup>57</sup> A systematic review of cinnamon's adverse effects identified that cinnamon could cause allergic reactions and gastrointestinal disease, which are self-limiting in most cases.<sup>58</sup> A clinical trial involving 15 patients showed that oral administration of 80 mg ethanol extract of cinnamon twice daily for 4 weeks caused stomach aches, nausea, and constipation.<sup>59</sup> In a randomized, controlled trial, one of 54 diabetic patients in the cinnamon treatment group developed a rash after administration with usual care with management changes plus 1 g cinnamon capsules daily for 90

days.<sup>60</sup> We should also be careful when there is repeated exposure to high levels of cinnamaldehyde (100 μM, 20 min) as an *in vitro* study on human induced pluripotent stem cell-derived cardiac myocytes (hiPSC-CMs) revealed that cinnamon may cause progressive electrical remodelling and cardiac dysfunction.<sup>61</sup> In addition, a randomized controlled trial involving 23 females in the cinnamon group found that some females with polycystic ovarian syndrome developed headaches (4), heartburn symptoms (2), menstrual cramps (2), and nausea with diarrhoea (1) after taking 1.5 g of cinnamon powder daily for 6 months.<sup>62</sup> Moreover, seven of the 20 seasonal allergic rhinitis patients who received 200 μg/200 μL cinnamon nasal spray twice a day for 4 weeks developed headaches, coughs, fevers, body aches, and throat irritation.<sup>63</sup> Generally, adverse reactions should be monitored when high doses or long durations of cinnamon are for medical purposes, and further study pertaining to cinnamon's toxicity mechanism is necessary.

## 4 Cinnamon in the treatment of CVDs

### 4.1 Atherosclerosis (AS)

AS, which leads to lumen stenosis or obstruction, is a crucial cause of various CVDs.<sup>64</sup> The occurrence of AS is associated with endothelial dysfunction, elevated blood lipids, imbalanced oxidative stress, dysregulation of the immune response, inflammatory response, growth and mobilization of VSMCs, platelet activity and thrombosis, and angiogenesis.<sup>65</sup> Cinnamon exhibits protective effects against AS by modulating various proatherogenic cellular events (Fig. 3).

**4.1.1. Endothelium protection.** AS is a complex disease characterized by arterial intima damage. Endothelial dysfunction, the primary stage of AS, is accompanied by a decrease in



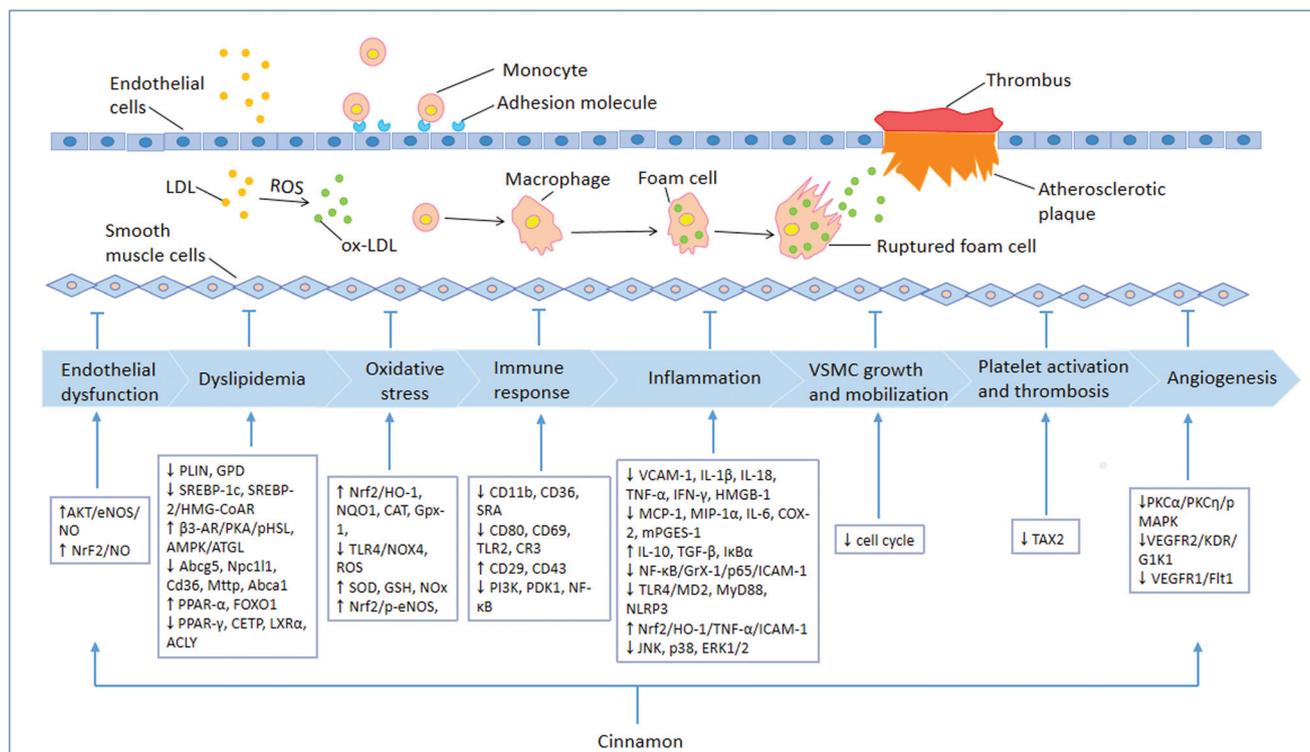


Fig. 3 The anti-atherosclerotic effects by which cinnamon alleviates the development of AS.

endothelial permeability and the expression of cytokines and adhesion molecules; later, lipids and macrophages in the blood tend to deposit in the subendothelial space, which further leads to the formation of foam cells.<sup>66</sup> Endothelium-dependent diastolic dysfunction is also an important cause of aggravation of atherosclerotic disease. Endothelial cells (ECs) attach to the lining of blood vessels and play a significant role in regulating vascular tension and maintaining the vascular smooth surface whose dysfunction is due to decreased secretion of NO and increased levels of endothelin.<sup>67</sup> NO is generated by three isozymes of nitric oxide synthase: endothelial nitric oxide synthase (eNOS), the most important transmitter for EC function; neuronal nitric oxide synthase (nNOS); and inducible nitric oxide synthase (iNOS), which is assumed to be a harmful enzyme and a major contributor to AS in pathological conditions.<sup>68,69</sup> Endogenous NO can adjust vascular tension and inhibit the proliferation of vascular smooth muscle, the aggregation of platelets and the development of inflammation.

In isolated rat aortic rings pre-treated with KCl (60 mM), an aqueous extract of *C. zeylanicum* Blume stem bark exhibited cumulative vasodilating effects partially *via* enhancement of endothelial NO production and activation of KATP channels in VSMCs.<sup>70</sup> A study in isolated rat thoracic aortae showed that cinnamaldehyde obviously alleviated the exaggerated contraction, improved endothelial NO production and attenuated detrimental advanced glycation end products (AGEs)-inflicted vascular damage.<sup>71</sup> Cinnamaldehyde also exerts endothelium-

dependent vasorelaxant effects, which are affected by NO; and endothelium-independent vasorelaxant effects by blocking  $Ca^{2+}$  channels in isolated rat aortae.<sup>72</sup> Eugenol enhances the expression of eNOS and the accumulation of intracellular calcium, thus protecting human umbilical vein endothelial cells (HUVECs) from oxidized low-density lipoprotein (ox-LDL)-induced dysfunction.<sup>73</sup> Furthermore, cinnamaldehyde was demonstrated to preserve NO levels *via* endogenous nuclear factor (erythroid-derived 2)-like 2 protein (Nrf2) activation, thus preserving endothelium-dependent relaxation in the endothelium of mouse aortas treated with high glucose.<sup>74</sup> According to the experimental results, cinnamon has a beneficial effect on protecting endothelial function through various pathways.

**4.1.2. Hypolipidemic effect.** Dyslipidaemia is a crucial factor for the occurrence of atherosclerotic CVDs.<sup>75</sup> Low-density lipoprotein (LDL) and other apolipoprotein (apo) B-containing lipoproteins involving very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and lipoprotein (a) [Lp(a)] are retained and accumulate in the intima of the arterial wall, which together with inflammation and the immune response contribute to the formation of atherosclerotic plaques.<sup>76,77</sup> Ox-LDL is closely related to the formation of foam cells whose apoptosis and necrosis result in the release of lipids and the development of AS.<sup>78</sup> It has been reported that plasma high-density lipoprotein (HDL) promotes the outflow of cholesterol, which is inversely associated with the risk of atherosclerotic CVD.<sup>79</sup> Epidemiological and genetic evi-



dence indicates that elevated triglycerides (TGs) are implicated in the development of CVD.<sup>80</sup> TG-rich lipoprotein degradation and uptake into macrophage foam cells in the intima of arteries can lead to inflammation in atherosclerotic CVD.<sup>81</sup>

A clinical study involving 60 diabetic patients demonstrated that daily consumption of 1, 3, or 6 g of cinnamon reduced low-density lipoprotein cholesterol (LDL-C), mean TG, and TC levels.<sup>15</sup> Multiple clinical trials on cinnamon and its constituents have yielded similar results.<sup>46,72–74</sup> Ranasinghe *et al.* investigated the efficacy and safety of cinnamon in healthy adults.<sup>46</sup> Subjects were instructed to take the water extract of *C. zeylanicum* with the dose increased at monthly intervals (85 mg d<sup>-1</sup>, 250 mg d<sup>-1</sup> and 500 mg d<sup>-1</sup>).<sup>46</sup> No significant alteration was observed in HDL-L, VLDL-d and TG levels; and a significant decrease in TC and LDL-C was noted after 3 months of treatment.<sup>46</sup> Azimi *et al.* reported that the consumption of cinnamon (3 g d<sup>-1</sup>) for 8 weeks reduced TC, LDL, and HDL levels in T2D patients.<sup>82</sup> A randomized double-blind control trial evaluated the effect of oral cinnamon consumption (2.5 g d<sup>-1</sup>) on body composition and metabolic parameters in individuals with metabolic syndrome.<sup>83</sup> Serum TC, LDL-C, TG, and HDL-L showed significantly greater improvement in the intervention group.<sup>83</sup> Askari *et al.* conducted a randomized double-blind placebo-controlled trial on fifty patients with non-alcoholic fatty liver disease (NAFLD).<sup>84</sup> After 12 weeks of treatment with cinnamon (1.5 g d<sup>-1</sup>), obvious reductions were observed in TC, TG and LDL-C level.<sup>84</sup> Paradoxically, a single-blind randomized crossover study demonstrated that there was no difference in the TC, HDL, or LDL levels of 9 healthy adults treated with 3 g cinnamon or wheat flour (placebo).<sup>85</sup> A clinical trial by Blevins was designed to observe the effects of cinnamon on patients with type 2 diabetes.<sup>86</sup> The results showed that the lipid levels had no significant change after daily treatment with 1 g cinnamon for 3 months.<sup>86</sup>

Cinnamon and its extract exhibit lipid-lowering effects in animal experiments. Treatment with cinnamic acid reduced TC and LDL-C levels and increased high-density lipoprotein cholesterol (HDL-C) levels in rats.<sup>87</sup> Moreover, the aqueous extract of *C. zeylanicum* significantly prevented dyslipidaemia and protected aortae from the atherosclerotic changes induced by dexamethasone in Wistar rats.<sup>88</sup> *S*-(+)-Linalool, a major constituent of the leaf essential oil of *C. osmophloeum* ct. Linalool, and leaf essential oil resulted in significantly decreased blood TG levels and suppressed lipid accumulation by downregulating 3T3-L1 adipocyte differentiation in mice.<sup>89</sup>

The molecular mechanism by which cinnamon and its extracts improve lipid profiles is mainly involved in regulating enzymes or genes related to the generation, accumulation, transport and degradation of lipids. First, cinnamon reduces lipogenesis. A large number of studies have revealed that cinnamon attenuates lipogenic processes in the liver and adipose tissue. The chronic inclusion of aqueous cinnamon extract improves the lipid profile in the liver and adipose tissue by downregulating the mRNA expression of sterol regulatory element-binding protein-1c (SREBP-1c) and the mRNA

expression of sterol regulatory element-binding protein-2 (SREBP-2) and its target genes 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoAR), cholesterol acyltransferase-1 (ACAT-1) and diacylglycerol *O*-acyltransferase 2 (DGAT2), which are directly involved in lipogenesis.<sup>90</sup> *Trans*-Cinnamic acid plays a positive role in regulating lipid metabolism in a series of adipocyte models. *Trans*-Cinnamic acid was found to reduce the expression of the transcription factors CCAAT/enhancer-binding protein- $\alpha$  (C/EBP- $\alpha$ ) and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) in white adipocytes, which tightly modulate the conversion of preadipocytes to mature adipocytes; and increase their expression in brown adipocytes.<sup>91</sup> Furthermore, *trans*-cinnamic acid stimulated the adiponectin (ADIPOQ) secretion and AMP-activated protein kinase (AMPK) activation involved in Gi/Go-protein-coupled receptors (GPRs) in differentiated 3T3-L1 cells.<sup>92</sup> *Trans*-Cinnamic acid can activate  $\beta$ 3-adrenergic receptors ( $\beta$ 3-ARs) and consequently activate protein kinase A (PKA), thus phosphorylating hormone-sensitive lipase (pHSL); and activate AMPK to increase the levels of pHSL and adipocyte triglyceride lipase (ATGL) to upregulate lipid catabolism in 3T3-L1 adipocytes.<sup>91</sup> In C57BL/Ks db/db mice, lower TG and TC contents and higher HDL-C and HTR levels (HDL-C/TC  $\times$  100) were observed after treatment with *Cinnamomi cassiae* (*Cinnamon bark*) extract due to the enhanced expression of PPAR $\alpha$  in the liver and PPAR $\gamma$  in adipose tissue.<sup>93</sup> Cinnamaldehyde upregulates the expression of HSL and downregulates the expression of glycerol-3-phosphate dehydrogenase (GPD) and adipocyte marker genes, including PPAR- $\gamma$  and C/EBP- $\alpha$ , to increase adipose tissue lipolysis in mature 3T3-L1 adipocytes *in vitro*.<sup>94</sup> In the adipose tissue of fructose-fed rats, cinnamon extract enhanced the mRNA levels of ADIPOQ, a protein with anti-atherosclerotic potential; and inhibited the level of CD36, an ox-LDL scavenger receptor associated with an increased risk of AS in patients with type 2 diabetes and insulin resistance.<sup>95,96</sup>

Cinnamon could also improve the intestinal absorption of fat in food. Microsomal TG transfer protein (MTP) is a microsomal protein that facilitates the conversion of VLDL by catalysing the shift of lipids to nascent apoB-containing lipoprotein particles.<sup>97</sup> A cinnamon extract (cinnulin PF), high in type A polyphenols, may repress postprandial hyper-triglycerides and the overproduction of apoB48 by inhibiting the overexpression of MTP and SREBP-1c mRNA levels in enterocytes isolated from fructose-fed hamsters.<sup>98</sup> Another study on the primary enterocytes of chow-fed rats showed that aqueous cinnamon extract suppresses genes associated with elevated levels of cholesterol, triacylglycerols, and apolipoprotein-B48, including adenosine triphosphate-binding cassette subfamily G member 5 (Abcg5), Niemann-Pick c1-like 1 (Npc111), CD36, microsomal triacylglycerol transfer protein (Mttp), and SREBP-1c; and facilitates adenosine triphosphate-binding cassette transporter-1 (Abca1) expression.<sup>99</sup>

Second, cinnamon could improve the accumulation of lipids. previous research showed that cinnamon reduces lipid accumulation *via* the upregulation of SREBP-1c, SREBP2, forkhead box O1 (FOXO1) mRNA, and LDL receptors (LDLRs) in



adult male zebrafish.<sup>100</sup> Another possible mechanism by which cinnamon alleviates lipid accumulation is regulating the expression of cholesteryl ester transfer protein (CETP), a plasma protein that accelerates the migration of cholesteryl ester from HDL to LDL particles.<sup>101</sup> In high-cholesterol diet (HCD)-fed rabbits, cinnamaldehyde prevents lipid accumulation and decreases the levels of TC, TGs, and LDL-C, which might be related to the lower mRNA expression of CETP.<sup>29</sup> In mouse RAW264.7 macrophage cells, two cinnamic acid derivatives, 4-hydroxycinnamic acid (*L*-phenylalanine methyl ester) amide and 3,4-dihydroxyhydrocinnamic acid (*L*-aspartic acid dibenzyl ester) amide, suppress cellular cholesterol storage and transport by inhibiting the allosteric enzymes acyl-CoA: ACAT-1 and ACAT-2 to demonstrate their anti-atherosclerotic potential.<sup>102</sup> Intake of cinnamon polyphenol significantly decreases the lipid profile specifically by suppressing the expression of hepatic SREBP-1c, liver X receptor- $\alpha$  (LXR- $\alpha$ ), ATP-citrate lyase (ACLY), and fatty acid synthase (FAS) and enhancing PPAR- $\alpha$  expression in the livers of rats fed a high-fat diet (HFD).<sup>103</sup> Studies have demonstrated that the modulatory mechanism of the effect of cinnamon on lipid metabolism has multiple pathways, which are expected to offer new ideas and pharmacological bases for the treatment of AS.

**4.1.3. Antioxidative effect.** Oxidative stress is a state of imbalance between oxidation and antioxidation. During oxidative stress, the production of reactive oxygen species (ROS) exceeds the scavenging capacity of the antioxidant system, leading to the accumulation of ROS and the main pathological state of oxidative stress.<sup>104</sup> Excessive production of ROS promotes lipid peroxidation and the formation of ox-LDL, which then facilitates the secretion of monocyte chemoattractant protein 1 (MCP-1), a protein that can draw monocytes through the EC space to a lesion from ECs. Furthermore, overproduction of ROS can induce EC apoptosis and smooth muscle cell proliferation and migration to promote the development of AS.<sup>105</sup>

A double-blind placebo-controlled trial involving twenty-two subjects revealed that administration of 250 mg of an aqueous extract of cinnamon (cinnulin PF) for 12 weeks shows increased ferric reducing antioxidant power and decreased plasma malondialdehyde (MDA) levels.<sup>16</sup> Conversely, a single-blind randomized crossover study of nine healthy young adults showed that the use of 3 g cinnamon supplementation following a high-fat meal had no effect on arterial stiffness and oxidative stress.<sup>85</sup>

Positive results were obtained in *in vivo* and *in vitro* experiments. An *in vitro* study in HUVECs demonstrated that eugenol treatment inhibits reactive ROS generation.<sup>73</sup> Experimental data also revealed that new cinnamic acid derivatives possess useful biological activity as anti-atherosclerotic agents with the inhibition of LDL oxidation in mouse RAW264.7 macrophage cells.<sup>102</sup> Furthermore, superoxide dismutase (SOD), glutathione S-transferase (GST), catalase (CAT), glutathione peroxidase (Gpx), haemeoxygenase-1 (HO-1), HMOX1, NAD(P)H dehydrogenase, and quinone 1 (NQO1) are antioxidant enzymes that are conducive to inhibiting the oxidation of LDL. Dietary cinnamate, a phenolic compound

found in cinnamon bark, enhances CAT and Gpx activities and suppresses lipid peroxidation in rats fed a high cholesterol diet.<sup>106</sup> In HFD and streptozotocin (STZ)-induced diabetic rats, eugenol was demonstrated to reduce the level of MDA and increase the serum level of glutathione (GSH). Previous evidence has uncovered that cinnamaldehyde enhances SOD and CAT activities, restores the expression levels of HO-1, and increases aortic NO metabolite (NOx) content in HCD-fed rabbits.<sup>29</sup>

Molecular mechanism studies showed that cinnamaldehyde reversed intracellular ROS production through the Toll-like receptor 4-NADPH oxidase 4 (TLR4-NOX4) pathway in male Sprague–Dawley rats stimulated by LPS.<sup>107</sup> An experiment using db/db mice showed that cinnamaldehyde attenuated oxidative stress status and increased phosphorylated endothelial nitric oxide synthase (p-eNOS) through activating the Nrf2 signalling pathway.<sup>108</sup> Nrf2 can induce the transcription of antioxidant enzymes such as HO-1, HMOX1 and NQO1 by transferring them from the cytoplasm to the nucleus to regulate the adaptive response of cells to oxidative stress.<sup>109</sup> Cinnamaldehyde elevated the cellular protein level of HO-1 and facilitated the translocation of Nrf2 to the nucleus in HUVECs, which indicated that Nrf2/HO-1 may be the pathway by which cinnamaldehyde protects against oxidative stress.<sup>17</sup> In mouse aortas under high glucose conditions, cinnamaldehyde exerts antioxidant effects mediated through Nrf2 activation and the upregulation of downstream target proteins, including HO-1, NQO1, CAT, and glutathione peroxidase 1 (Gpx-1).<sup>74</sup> In short, the anti-atherosclerotic effects of cinnamon can also be explained by its antioxidative properties.

**4.1.4. Regulation of immune response.** Macrophages differentiate from monocytes that migrate under the endothelium engulf ox-LDL to generate foam cells.<sup>110</sup> If the foam cells exceed the clearing ability of HDL, a large number of them will die and contribute to the formation of lipid pools and promote the migration of smooth muscle cells in the middle layer of the artery to the intima.<sup>111</sup> Macrophage scavenger receptors (SRAs) are the main scavenger receptors by which macrophages phagocytose modified LDL. Receptors including CD36 may also be involved in the removal of oxidized LDL particles and the formation of foam cells, and CD11b facilitates monocyte recruitment in atherogenic lesions.<sup>112</sup> In phorbol-12-myristate-13-acetate (PMA)-stimulated THP-1 cells, cinnamon water extract interfered with monocyte differentiation and macrophage scavenger activity by decreasing the expression of costimulatory molecules (CD11b and CD36), the uptake of acetyl LDL, and the expression of SRA associated with mitigated activity of extracellular signal-related kinase 1/2 (ERK 1/2).<sup>113</sup> In addition, Kim's research results showed that cinnamaldehyde has also been demonstrated to regulate monocyte/macrophage-mediated immune responses by attenuating the upregulation of surface levels of CD80 and CD69, Toll-like receptor 2 (TLR2) and complement receptor 3 (CR3) while enhancing the levels of adhesion molecules such as CD29 and CD43 to block cell–cell adhesion.<sup>114</sup> In addition, cinnamaldehyde could be developed as an immunoregulatory



drug to prevent AS by exhibiting the functional activation of monocytes and macrophages due to the inhibition of phosphoinositide-3-kinase (PI3K) and phosphoinositide-dependent kinase 1 (PDK1) and nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation.<sup>114</sup> These research data reveal that regulation of the immune response is also a pivotal part of the mechanism of cinnamon in the treatment of AS.

**4.1.5. Anti-inflammatory activity.** Atherogenesis is a chronic inflammatory reaction.<sup>115</sup> Leukocyte recruitment and proinflammatory cytokines play crucial roles in the early stages of atherogenesis. Activation of the inflammatory cascades in vascular ECs stimulates the biosynthesis of adhesion molecules (vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selection) and chemokines (MCP-1) and promotes the recruitment and retention of circulating monocytes in the intima membrane, which then differentiate into macrophages and aggravate atherosclerotic lesions by transforming into foam cells and secreting plentiful proinflammatory factors.<sup>116,117</sup>

A clinical trial has demonstrated the anti-inflammatory effects of cinnamon. In a randomized double-blind clinical trial involving 36 women with rheumatoid arthritis, the levels of serum inflammatory factors in the cinnamon group and the control group treated with placebo for 8 weeks were compared. Serum CRP and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels in the cinnamon group were significantly lower than those in the placebo group.<sup>118</sup> However, a clinical trial studied 44 adult patients with type 2 diabetes who received either three grams cinnamon supplementation or placebo. The results elucidated that ingestion of cinnamon did not reduce the plasma levels of NF- $\kappa$ B, sirtuin-1 (SIRT1), hs-CRP, interleukin (IL)-6 and TNF- $\alpha$  in type 2 diabetes patients.<sup>119</sup> Furthermore, there was no significant difference in the serum levels of ICAM-1 and VCAM-1 in patients between the groups.<sup>120</sup>

In addition, many *in vitro* experiments have identified the anti-inflammatory effects of cinnamon. The production of adhesion molecules and subsequent attachment of leukocytes to ECs are the key early events in the pathological process of atherogenesis. Liao's research showed that CA and *C. cassia* extracts inhibited the expression of VCAM-1 and ICAM-1 and the TNF-induced adhesion of monocytes to ECs at the transcriptional level in human ECs.<sup>121</sup> A study using endotoxin-injected mice showed that cinnamaldehyde and linalool mitigated the endotoxin-induced levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-18, TNF- $\alpha$ , interferon (IFN)- $\gamma$ , and inflammatory mediator high-mobility group box 1 protein (HMGB-1) in the spleen and mesenteric lymph nodes.<sup>122</sup> In THP-1 monocytes, *trans*-cinnamaldehyde and *p*-cymene were found to decrease the secretion of IL-8 and inhibit the phosphorylation of Akt and inhibitor of NF- $\kappa$ B (I $\kappa$ B $\alpha$ ).<sup>123</sup> Furthermore, Pannee *et al.* reported that the essential oil of *C. cassia* leaves and cinnamaldehyde reduced the levels of MCP-1, macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ), TNF- $\alpha$ , IL-1 $\beta$  and IL-6 and inhibited the expression of cyclooxygenase-2 (COX-2) and microsomal prostaglandin-E synthase-1 (mPGES-1) in LPS-activated J774A.1 cells.<sup>124</sup> Cassia leaf oil and cinnamaldehyde enhanced mRNA expression and

the generation of the anti-inflammatory mediators IL-10 and transforming growth factor- $\beta$  (TGF- $\beta$ ) in LPS-activated J774A.1 cells.<sup>124</sup>

In addition, extensive experimental work has clarified the molecular and cellular pathways of inflammation through which cinnamon promotes AS. Tristetraprolin (TTP) family proteins have anti-inflammatory effects, and cinnamon polyphenol extract was found to enhance TTP and TNF mRNA levels in mouse RAW264.7 macrophages.<sup>125</sup> A plethora of molecular mechanism studies have demonstrated that cinnamon extract can reduce inflammation by modulating NF- $\kappa$ B, which has been regarded as the central mediator of the inflammatory process.<sup>126</sup> NO produced by iNOS plays a crucial role in the pathogenesis of various inflammatory diseases. Experimental data revealed that 2'-hydroxycinnamaldehyde isolated from *C. cassia Blume* bark inhibits NF- $\kappa$ B activation, thus hindering NO production in RAW264.7 cells.<sup>127</sup> Moreover, cinnamaldehyde significantly lowered the levels of TNF- $\alpha$ , and prostaglandin E2 (PGE2) inhibited the expression of iNOS, COX-2, NF- $\kappa$ B, and I $\kappa$ B $\alpha$  in LPS-stimulated mouse macrophages (RAW264.7).<sup>128</sup> Cinnamaldehyde was elucidated to significantly reduce the overproduction of inflammatory cytokines, decrease the expression of matrix metalloproteinase-2 (MMP-2) and achieve an anti-atherosclerotic effect through the I $\kappa$ B $\alpha$ /NF- $\kappa$ B signalling pathway in an HFD-fed ApoE<sup>-/-</sup> atherosclerotic mouse model.<sup>129</sup> In TNF $\alpha$ -treated ECs, cinnamaldehyde inhibits p65 nuclear translocation and ICAM-1 expression by mediating the activity of NF- $\kappa$ B and glutaredoxin-1 (Grx-1).<sup>130</sup> In a study using endotoxin-induced mice, cinnamaldehyde and linalool, two major active components in the essential oil of *C. osmophloeum* leaves, inhibited the activation of NF- $\kappa$ B and caspase-1 activity by decreasing the expression of toll-like receptor 4/myeloid differentiation protein 2 (TLR4/MD2), myeloid differentiation primary response gene 88 (MyD88), nod-like receptor family, pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), and caspase-1 in the spleen and mesenteric lymph nodes to exhibit an anti-inflammatory effect.<sup>122</sup> Cinnamaldehyde elevates the expression of the Nrf2-related gene HO-1, which is associated with the suppressed expression of TNF $\alpha$ -induced ICAM-1, over long-term pre-treatment to elicit anti-inflammatory activity in TNF $\alpha$ -treated ECs.<sup>121</sup> Hong's study showed that treatment with cinnamon water extract reduced serum LPS-induced TNF- $\alpha$  by blocking the degradation of I $\kappa$ B $\alpha$  and the activation of c-Jun NH2-terminal kinase (JNK), p38, and ERK 1/2 *in vivo*.<sup>131</sup> In conclusion, these studies demonstrated that cinnamon extracts may be promising drugs for the treatment and prevention of the inflammatory response in atherogenesis.

**4.1.6. Suppression of VSMC growth and mobilization.** Pharmacological effects with antiproliferative and antimigratory properties on VSMCs are conducive to treating AS, given that unlimited proliferation and movement of VSMCs within the arterial wall contribute to plaque expansion and vascular narrowing.<sup>132</sup> Cinnamaldehyde was shown to repress the proliferation and migration of VSMCs and decrease the prolifera-



tive index of injured arteries in Zucker diabetic fatty rats.<sup>133</sup> Another *in vitro* study also indicated that cinnamaldehyde inhibited ox-LDL-induced VSMC proliferation and migration in VSMCs.<sup>134</sup> Platelet-derived growth factor (PDGF) is a potent mitogen and chemoattractant that has been found to promote the proliferation and migration of VSMCs.<sup>135</sup> Previous research reported that cinnamon extracts, including cinnamyl alcohol, cinnamic acid, and eugenol, inhibit PDGF-BB-triggered VSMC proliferation by arresting the cell cycle at G0/G1 phase; down-regulating the expression of cell cycle-positive regulatory proteins by upregulating p21 and p27 expression; and inhibiting the phosphorylation of anti-phospho-phospholipase C- $\gamma$ 1 (PLC $\gamma$ 1), anti-phospho-phosphatidylinositol 3-kinase-linked protein kinase B (AKT), p38, and JNK, which regulate the activation of VSMC proliferation.<sup>136–138</sup> Previous research reported that 2-methoxycinnamaldehyde, a natural compound of *C. cassia*, suppresses PDGF-induced migration of human aortic smooth muscle cells (HASMCs) and inhibits TNF- $\alpha$ -induced proliferation of HASMCs by lowering the cyclin D1, cyclin D3, cyclin-dependent kinase 4 (CDK 4) and CDK6 levels and enhancing the levels of cyclin-dependent kinase inhibitors p21 and p27.<sup>139</sup> Thus, the therapeutic utility of cinnamon in AS has been partly attributed to suppression of VSMC growth and mobilization.

#### 4.1.7. Repression of platelet activity and thrombosis.

Because of circulating haemorrhagic abnormalities or pro-coagulant material upregulation in atherosclerotic lesion areas, platelets are extensively activated and recruited to the damaged endothelium, which initiates the coagulation cascade, thereby inducing a life-threatening acute coronary event, artery thrombosis and vascular occlusion.<sup>140</sup> An experiment using a rat model revealed that administration of cinnamaldehyde significantly prolonged haemorrhage and coagulation times by mitigating platelet aggregation and thrombosis.<sup>141</sup> *In vitro* and in endotoxin-treated normal rats, methanolic extract from Cinnamomi Cortex and cinnamic aldehyde, major essential oily components of methanolic extract, repressed the platelet aggregation triggered by collagen, arachidonic acid and adenosine diphosphate.<sup>142</sup> Eugenol, amygdalactone, 2-methoxycinnamaldehyde, and coniferaldehyde, 4 compounds obtained from *C. cassia*, elicited inhibitory potencies on arachidonic acid-, U46619 (a thromboxane A<sub>2</sub> mimic)-, and epinephrine-induced platelet aggregation in an *in vitro* study.<sup>143</sup> Thromboxane A<sub>2</sub> (TAX2) is the main cyclo-oxygenase derivative of arachidonic acid in platelets and an effective platelet aggregation agent. Cinnamophilin in cinnamon was found to be a TAX2 receptor antagonist that inhibited platelet aggregation in human platelet-rich plasma and rat aortae.<sup>144</sup> According to the findings, it is evident that repression of platelet activity and thrombosis is a crucial constituent of the atheroprotective effects of cinnamon.

**4.1.8. Inhibition of angiogenesis.** Angiogenesis can aggravate inflammatory responses, induce haemorrhages in the plaque, affect the stability of the plaque, and consequently lead to the occurrence of acute cardiovascular events.<sup>145,146</sup> A water extract of *C. cassia* represses vascular endothelial growth

factor (VEGF)-induced angiogenesis in HUVECs by suppressing the tyrosine phosphorylation of VEGFR2 and induces a decrease in VEGF-stimulated microvessel outgrowth in an *ex vivo* angiogenesis model of a rat aortic ring.<sup>147</sup> In HUVECs treated with phorbol ester, cinnamon extract was observed to repress protein kinase C (PKC $\alpha$  and PKC $\eta$ ) mRNA and PKC-dependent phosphorylation of MAPK (pMAPK) in a dose-dependent manner and suppress the mRNA expression of vascular endothelial growth factor receptor 1 (VEGFR1/Flt1) and vascular endothelial growth factor receptor 2 (VEGFR2/KDR/Flk1) to exert inhibitory effects on angiogenesis.<sup>148</sup> Experimental data indicate the potential of cinnamon extracts as a good therapeutic drug for inhibiting angiogenesis to improve AS.<sup>149</sup>

#### 4.2. Hypertension

Hypertension is a common CVD whose continuous progression may lead to a variety of heart, brain, kidney and other complications. Previous research identified that short-term administration of cinnamon shows promising BP lowering potential.<sup>150</sup> In a randomized, placebo-controlled clinical trial, Ziegenfuss *et al.* showed that the cinnamon group (0.5 g d<sup>-1</sup>, 12 weeks) had significant decreases in FBG and systolic blood pressure (SBP), small but statistically significant decreases in body fat and an increase in lean mass, suggesting that cinnamon was effective in lowering BP.<sup>151</sup> Another clinical study yielded similar results.<sup>152</sup> Akilen *et al.* reported that cinnamon (2 g d<sup>-1</sup>) for 12 weeks lowered glycated haemoglobin (HbA1C), SBP and diastolic blood pressure (DBP) in poorly controlled type 2 diabetes patients.<sup>152</sup> A randomized, placebo-controlled clinical trial was designed to evaluate the hypotensive effect of cinnamon. Subjects with type 2 diabetes were instructed to take cinnamon (2.4 g d<sup>-1</sup>) at the first treatment period visit.<sup>153</sup> At the second treatment visit, volunteers were instructed to reduce their intake of cinnamon to 1.2 g d<sup>-1</sup> as a maintenance dose.<sup>153</sup> After a 12-week treatment period, Wainstein *et al.* observed lower blood pressures than the baseline values. However, the by-treatment difference in SBP was a function of a regression to the mean rather than a change related to treatment.<sup>153</sup> Consistent with this, consumption of a water extract of *C. zeylanicum* was reported to significantly reduce SBP and DBP in healthy adults.<sup>154</sup> A single supplement with cinnamon (3 g d<sup>-1</sup>, 16 weeks) was revealed to significantly improve the BP of individuals with metabolic syndrome in a randomized double-blind control trial.<sup>83</sup> In a randomized double-blind clinical trial, DBP was significantly lower after the administration of cinnamon powder (500 mg d<sup>-1</sup>, 8 weeks) in women with rheumatoid arthritis.<sup>118</sup> A meta-analysis showed that cinnamon may play a hypotensive role in adults.<sup>154</sup>

The intake of cinnamon lowered the SBP of spontaneously hypertensive rats consuming sucrose-containing diets. Several studies have shown that cinnamon exerts hypotensive effects through various mechanisms, such as improving endothelial dysfunction, regulating ion channels, and suppressing oxidative stress.<sup>155</sup> The production of NO has a protective effect on the endothelium.<sup>66</sup> Cinnamaldehyde was demonstrated to



improve the relaxation of methylglyoxal (MG)-injured aortas, enhance NO production from isolated aortae, and repress AGE prompted by MG to ameliorate exaggerated vasoconstriction.<sup>71</sup> The methanol extract of *C. zeylanicum* stem bark possesses antihypertensive effects due to the ability to elevate the production of endogenous NO in L-arginine analogues such as N<sup>ω</sup> nitro-L-arginine methyl-ester (L-NAME)-induced hypertensive rats.<sup>156</sup> Another animal experiment revealed that the acute intravenous injection of *C. zeylanicum* Blume stem bark aqueous extract could decrease the mean arterial BP in a rat model partially by increasing endothelial NO.<sup>70</sup> Micelles containing cinnamaldehyde could also induce endothelium-dependent and NOS-dependent relaxations of coronary vascular smooth muscle mediated by NO and H<sub>2</sub>O<sub>2</sub>.<sup>157</sup> Phosphorylated eNOS at serine 1177 (eNOS-Ser1177) plays a key role in producing NO from ECs. Upregulation of eNOS upstream kinases, such as AMPK, AKT, or PKA, promotes eNOS phosphorylation and may improve endothelial dysfunction. *Trans*-Cinnamaldehyde stimulates HUVECs to promote the release of NO by significantly increasing eNOS and AKT phosphorylation and its upstream target PI3K, insulin receptor substrate 1 (IRS1).<sup>158</sup> Angiotensin converting enzyme (ACE), a nonspecific enzyme in vascular ECs, promotes the conversion of angiotensin I to angiotensin II, which then contracts arteries and veins to increase BP. Cinnamic acid is endowed with a strong effect on the regulation of BP by suppressing ACE activity in serum and defending animals against vasoconstriction in HFD-induced obese rats.<sup>159</sup> The function of KATP channels is reduced in hypertension models.<sup>160</sup> *C. zeylanicum* Blume stem bark aqueous extract could activate KATP channels in vascular smooth muscle and reduce BP.<sup>156</sup> An increased intracellular concentration of Ca<sup>2+</sup> would lead to higher vascular wall tension and consequently elevated BP. Cinnamaldehyde has peripheral vasodilatation properties by blocking Ca<sup>2+</sup> channels in mouse ventricular cardiomyocytes and in mesenteric artery smooth muscle cells.<sup>161</sup> In isolated rings of porcine coronary arteries, cinnamaldehyde could relax the coronary arteries by inhibiting the sensitivity of Ca<sup>2+</sup> and influx of Ca<sup>2+</sup> endothelium-independently.<sup>157</sup>

Activation of the transient receptor potential ankyrin 1 (TRPA1) channel can cause peripheral vasodilation and a biphasic blood pressure response.<sup>162</sup> Intravenously injected TRPA1 agonist cinnamaldehyde contributed to a transient hypotensive response and decreased heart rate (HR) dose-dependently, followed by a more sustained pressor response depending on dose.<sup>163</sup> The BP response was lower in TRPA1 KO mice treated with cinnamaldehyde, which showed the involvement of TRPA1 in the modulation of BP.<sup>163</sup> Oxidative stress has been implicated in vascular stiffness and remodelling, which is a crucial process of hypertension.<sup>164</sup> Cinnamaldehyde was demonstrated to regulate oxidative stress. In rats with fructose-induced hypertension, cinnamaldehyde decreased the elevated SBP and DBP; restored the levels of antioxidants such as Gpx, CAT, SOD, and GSH; and lowered MDA levels.<sup>165</sup> These experiments suggested the great potential of cinnamon in treating hypertension.

#### 4.3. Myocardial ischaemia-reperfusion injury (MIRI)

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide.<sup>166</sup> After treatment for acute myocardial infarction, the coronary artery will be reperfused. However, the process of reperfusion can result in cardiomyocyte death, which is known as myocardial ischaemia reperfusion injury.<sup>167</sup> Cinnamon and its extracts have been found to reduce infarct size and bring benefits to the treatment of myocardial infarction through various mechanisms. Administration of *C. zeylanicum* bark extract significantly improved ischaemia/reperfusion (I/R)-induced myocardial injury by reducing the infarct size and exhibited a significant decrease in serum cardiac troponin I (cTnI), lactate dehydrogenase (LDH), and MDA levels in a rat model of regional heart ischaemia.<sup>168</sup> 2-Methoxycinnamaldehyde (2-MCA), an active ingredient of *C. cassia*, could obviously improve I/R-injury myocardial dysfunction and reduce infarct size in adult male rats.<sup>169</sup> The underlying mechanism is that 2-MCA exhibits its antioxidant and anti-inflammatory action through decreasing the expression of HMGB1 and VCAM-1 in I/R myocardium along with increasing HO-1 induction and enhancing SOD activity in ischaemic tissues.<sup>169</sup> Cinnamaldehyde is a TRPA1 agonist, and TRPA1 was found to drive myofibroblast trans-differentiation initiated after MI injury, which is important to maintain ventricular wall integrity and to reduce dilation after infarction remodelling.<sup>170</sup> Thus, TRPA1 may be a possible target for cinnamon to treat MIRI.

#### 4.4. Viral myocarditis

Viral myocarditis is a disease of inflammatory destruction of the myocardium after myocardial virus infection and is a common cause of sudden cardiac death and dilated cardiomyopathy.<sup>171</sup> Research has shown that cinnamon may have the potential to treat viral myocarditis. Previous research demonstrated that  $\alpha$ -bromo-4-chlorocinnamaldehyde, synthesized by cinnamaldehyde, dose-dependently decreased the viral titers and alleviated cardiac pathological changes in a coxsackie virus B3-induced viral myocarditis model.<sup>173</sup> The underlying mechanism might be inhibiting inflammatory signalling as BCC inhibits the secretion of inflammatory cytokines such as TNF- $\alpha$ , IL- $\beta$  and IL-6 in cardiomyocytes; suppresses the activation of NF- $\kappa$ B and the degradation and phosphorylation of I $\kappa$ B $\alpha$ ; and reduces the protein level of TLR4 in hearts.<sup>172</sup>

#### 4.5. Heart failure

Myocardial fibrosis accelerates the development of heart dysfunction and eventually leads to heart failure.<sup>173</sup> Cinnamaldehyde was identified to improve cardiac fibrosis, which exhibited possible benefits for the treatment of heart failure.<sup>174</sup> Cinnamaldehyde was revealed to inhibit NLRP3 inflammasome activation by blocking CD36-mediated TLR4/6-IL-1R-associated kinase 4/1 (IRAK4/1) signalling to protect rats from fructose-induced cardiac inflammation and fibrosis.<sup>174</sup>



#### 4.6. Arrhythmias

There are few studies on the effect of cinnamon on arrhythmias, which needs further study. The only study we retrieved demonstrated that myocardial ischaemia rats after oral administration of *C. zeylanicum* bark extract showed reduced ventricular tachycardia and ventricular ectopic beat episodes, smoother ST segment changes, shorter QTc, lower R-wave amplitude, and increased heart rate during ischaemia compared to the control group.<sup>168</sup>

## 5. Cinnamon in the treatment of diabetes

Diabetes mellitus (DM) is closely related to CVD, which is the most common cause of morbidity and mortality in diabetic patients.<sup>175</sup> DM has been shown to independently exacerbate the initiation and progression of AS and blunt the regression of lesions following lipid lowering.<sup>176</sup> DM is characterized by chronic hyperglycaemia due to insufficient insulin secretion and/or insulin dysfunction.<sup>177</sup> Long-term metabolic disorder of carbohydrates, fat and protein will result in damage to the eyes, kidneys, nerves, heart, blood vessels and other tissues and organs. Furthermore, it was estimated that diabetes prevalence, deaths and health care expenditures attributable to diabetes would cause a large burden on society, finance and the health system worldwide.<sup>178</sup> Cinnamon and its extracts have been demonstrated to have therapeutic effects on diabetes mellitus and its cardiovascular complications. The effects of cinnamon on improving diabetes may be achieved in a variety of ways.<sup>179–185</sup>

### 5.1. Enhancement of insulin sensitivity and insulin secretion

Multiple studies have reported that cinnamon and its extracts possess the capacity to enhance insulin sensitivity and insulin secretion.<sup>186</sup> Administration of *C. cassia* and *zeylanicum* extracts was found to increase plasma insulin in rats.<sup>187</sup> Polyphenols from cinnamon restored pancreatic weight and alleviated mesenteric white fat accumulation related to improved insulin sensitivity in high fat/high fructose (HF/HF)-fed rats.<sup>188</sup> Polyphenols from cinnamon have been shown to improve insulin sensitivity in HF/HF-fed rats.<sup>188</sup> The influence of cinnamon on insulin sensitivity and its secretion is achieved by a variety of signalling pathways. Insulin-like growth factor 1 (IGF-1), produced by the liver, could promote glucose uptake in peripheral tissues, increase insulin sensitivity, and inhibit the release of glucose in the liver.<sup>189,190</sup> Previous research reported that encapsulated cinnamon oil emulsion (COE) improved the concentrations of glucose, insulin and amylase and enhanced IGF-1 mRNA expression in diabetic rats.<sup>191</sup> Insulin receptor- $\beta$  (IR- $\beta$ ) is auto-phosphorylated and plays a role in phosphorylating insulin receptor substrates. HPLC-purified cinnamon polyphenols increased the levels of IR $\beta$  in 3T3-L1 adipocytes.<sup>192</sup> NO was found to promote the uptake of insulin-mediated glucose in muscle and play an important

role in peripheral tissue uptake of glucose.<sup>193,194</sup> The pathway involving IR $\beta$ , IRS1, PI3K and eNOS has been reported to account for important physiological actions of insulin in facilitating the production of NO.<sup>195,196</sup> In HFD-fed rats, cinnamon extract prevented insulin resistance, enhanced the tyrosine phosphorylation levels of IR- $\beta$  and IRS-1, and strengthened the association between IRS1 and PI3K by improving NO production.<sup>197</sup> Additionally, the decreased AKT signalling is closely related to hepatic insulin resistance.<sup>198</sup> Previous research reported that cinnamaldehyde upregulates the IRS1/PI3K/AKT2 signalling pathway to induce its hypoglycaemic effect in a STZ-induced T2D rat model.<sup>199</sup> Cinnamaldehyde was revealed to induce the activation of PPAR $\delta$ , PPAR $\gamma$  and retinoid X receptor (RXR) to enhance insulin sensitivity.<sup>200</sup> *In vivo* and *in vitro* studies have identified that cinnamic acid dose-dependently improved glucose tolerance and obviously enhanced insulin secretion in isolated islets.<sup>201</sup> Cinnamon extracts suppressed the expression of glycogen synthase kinase 3 beta (GSK3B), insulin-like growth factor receptor (IGF1R), IGF2R, and phosphatidylinositol 3-kinase regulatory subunit 1 (PIK3R1), which encodes insulin signalling pathway proteins in adipocytes that exhibit antidiabetic activity.<sup>202</sup> It is well known that protein tyrosine phosphatase 1B (PTP1B) alleviates the signalling pathways of insulin and leptin receptors. Indigenous cinnamon (*C. osmophloeum*) twig extracts were found to inhibit PTP1B activity and exhibit great potential as natural health products.<sup>47</sup> ADIPOQ is known to improve insulin resistance. In 3T3-L1 adipocytes, treatment with *trans*-cinnamic acid increased the level of ADIPOQ, which is involved in stimulated GPRs.<sup>203</sup> In 3T3-L1 adipocytes, cinnamaldehyde was revealed to improve insulin sensitivity, possibly by activating the TRPA1 pathway.<sup>204</sup>

### 5.2. Regulation of the enzyme activity involved in glucose

The regulation of enzyme activities related to glucose metabolism by natural products has attracted much attention.<sup>205</sup> In db/db mice, cinnamon extract was revealed to decrease the activity of small intestinal  $\alpha$ -glycosidase, which converts carbohydrates into glucose and slows the absorption of carbohydrates in the small intestine.<sup>206</sup> Cumulative findings have produced similar results.<sup>207</sup> Cinnamon bark extracts were found to inhibit intestinal  $\alpha$ -glucosidase and pancreatic  $\alpha$ -amylase and exhibited potential in reducing postprandial glucose.<sup>208</sup> Another *in vitro* study revealed that cinnamon may inhibit lipase,  $\alpha$ -amylase and  $\alpha$ -glucosidase digestive enzymes.<sup>209</sup> In rat hepatoma cells, aqueous cinnamon extract was also found to decrease the gene expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), which regulate hepatic gluconeogenesis, to reduce FBG.<sup>210</sup>

### 5.3. Regulation of glucose metabolism in liver, adipose tissue and muscle

The liver plays an important role in glucose metabolism by converting glucose into liver glycogen for storage. Cinnamon extract could increase liver glycogen content, improve insulin



action in liver tissues, reduce liver fat and improve glucose homeostasis.<sup>211</sup> The upregulation of glucose transporter 2 (GLUT2) expression may increase the hepatic glucose output to the circulatory system.<sup>212</sup> SREBP-1c increases the level of GLUT2 mRNA in a primary hepatocyte model.<sup>213</sup> Increased FAS mRNA expression is associated with restricted conversion of glucose into fatty acids. PEPCK mRNA is a limiting gene in gluconeogenesis.<sup>214</sup> COE dose-dependently decreased hepatic GLUT2, FAS, SREBP-1c and PEPCK gene expression in diabetic rats.<sup>191</sup> GLUT-1 could facilitate the transport of glucose into cells.<sup>215</sup> Cinnamon extract was reported to upregulate the expression of GLUT1 mRNA levels in adipocytes.<sup>202</sup> Reduced activity of pyruvate kinase (PK) in the liver tissue of diabetic rats is associated with reduced glycolysis and amplified gluconeogenesis. Cinnamaldehyde was found to enhance PK levels and alleviate PEPCK levels in diabetic rats.<sup>216</sup>

Glucose can be converted into fat stored in adipose tissue or converted into muscle glycogen in muscle. Cinnamon was revealed to facilitate the uptake of glucose in adipose tissue and muscle. GLUT4, the main transporter for glucose removal from the circulatory system, works after insulin stimulation. Uncoupling protein-1 (UCP-1) promotes the uptake of glucose by brown adipose tissue. An aqueous cinnamon extract upregulated UCP-1 and GLUT4 in brown adipose tissues and muscles of STZ-induced diabetic rats.<sup>217</sup> Serum levels of retinol binding protein 4 (RBP4) and the expression of RBP4 were increased in IR mice, and serum RBP4 levels were negatively correlated with the expression of adipose tissue glucose transporter 4 (GLUT4).<sup>218,219</sup> Previous research reported that cinnamaldehyde displays outstanding antidiabetic efficacy by decreasing serum RBP4 levels and enhancing the expression of tissue GLUT4 protein.<sup>220</sup> In 3T3 adipocytes, treatment with a cinnamon extract increased glucose uptake but inhibited the secretion of the antidiabetic hormone ADIPOQ to levels that were nondetectable.<sup>221</sup> In C57BLKS db/db mice, cinnamaldehyde upregulated the mRNA expression of GLUT-4 and the protein expression of p-Akt in skeletal muscle, which suggested that cinnamaldehyde could regulate the stimulation and translocation of GLUT4 to exert antidiabetic effects.<sup>222</sup> In 3T3-L1 adipocytes and C2C12 myotubes, cinnamon extract stimulated the LKB1-AMPK signalling cascade, consequently leading to increased glucose uptake.<sup>223</sup>

#### 5.4. Protection of islet cells

Cinnamon polyphenols have been shown to ameliorate the pathological damage of pancreatic beta cells in STZ-diabetic mice.<sup>175</sup> In addition, cinnamon methanol extract ameliorated pancreatic functions and restored them to a normal state due to the antioxidant activity acquired by their phenolic phytochemicals in diabetic rats.<sup>224</sup> Oxidative stress and the inflammatory response may lead to islet  $\beta$  cell injury.<sup>225,226</sup> Attenuating oxidative stress and anti-inflammation are crucial ways for cinnamon to treat diabetes. Previous research demonstrated that camphor could enhanced the activity of Gpx, CAT, SOD, and the GSH content in the pancreatic tissues of alloxan-induced diabetic rats.<sup>227</sup> Consistent with this is that STZ-

induced diabetic rats treated with *C. tamala* leaf oil experienced reduced blood glucose levels and increased plasma insulin levels, which may be attributed to the antioxidant effect of *C. tamala* leaf oil.<sup>228</sup> COE improved the histological picture of the liver and pancreas by enhancing antioxidant capacity.<sup>191</sup> Trimer procyanidin oligomers in cinnamon extracts protected pancreatic  $\beta$ -cells by increasing cell viability and reducing ROS accumulation in H<sub>2</sub>O<sub>2</sub>-treated  $\beta$ -cells.<sup>229</sup> Previous research demonstrated that pre-mating treatment with cinnamaldehyde alleviated the levels of leptin, TNF- $\alpha$ , MDA and NO while enhancing the levels of GSH and CAT activity at term pregnancy in fatty-sucrosed diet/STZ (FSD/STZ)-induced gestational diabetic rats.<sup>230</sup> Leaf essential oil from indigenous cinnamon was reported to enhance the activities of SOD and GSH and ameliorate pancreatic levels of IL-1 $\beta$ , TNF- $\alpha$  and NO, thus protecting pancreatic  $\beta$  cells.<sup>231</sup> Human islet amyloid polypeptide (hIAPP), a 37 residue peptide hormone, aggregates and causes dysfunction of pancreatic  $\beta$ -cells.<sup>232,233</sup> Proanthocyanidins in cinnamon water extract repressed the amyloid formation of hIAPP and obviously improved the membrane damaging and cytotoxic effects due to hIAPP aggregation.<sup>234</sup> Moreover, cinnamon oil was demonstrated to promote the immunoreactivity of pancreatic islet  $\beta$ -cells in type 2 diabetic mice.<sup>235</sup>

#### 5.5. Modulating gut microbiota

Several animal experiments have identified that PTPBs could reduce blood glucose by altering the composition of the gut microbiota. Previous research reported that treatment with polyphenol-containing extracts from cinnamon bark significantly improved the insulin resistance index in mice fed a HFD, which was achieved by modulating the microbiota composition and reducing inflammation.<sup>236</sup> Cinnamaldehyde intervention was demonstrated to significantly increase *Lactobacillus johnsonii* in T1DM mice, suggesting that cinnamaldehyde could protect against STZ-induced T1DM by interfering with gut microbiota.<sup>237</sup>

#### 5.6. Improvement of diabetes complications

Cinnamon also shows prospects for improving diabetic complications. AGEs are a stable and heterogeneous group of compounds that are involved in the pathogenesis of diabetic complications.<sup>238</sup> *C. burmanii*, *Vietnamese*; *C. loureirii* and *Ceylon*; *C. zeylanicum* showed great potential to suppress the formation of AGEs.<sup>239</sup> In diabetic rats, cinnamon and its active component procyanidin-B2 (PCB2) inhibited AGE accumulation and ameliorated AGE-mediated pathogenesis of diabetic nephropathy.<sup>240</sup> It has also been reported that the procyanidin-B2 fraction has the physiological significance of delaying diabetic cataracts by repressing AGEs in diabetic rats.<sup>241</sup> Cinnamic aldehyde was reported to ameliorate common metabolic disorder symptoms related to diabetes, improve renal function and minimize pathological alterations by activating Nrf2.<sup>242</sup> Moreover, multiple substances, including nonpolar sesquiterpenoids, in the bark of *C. cassia* were reported to exhibit renoprotective effects by suppressing the expression of



fibronectin, MCP-1 and IL-6 in high glucose-induced mesangial cells, which provided evidence for clinical applications of cinnamon in diabetic nephropathy prevention and treatment.<sup>243</sup> Consistent with this, administration of cinnamon oil was revealed to blunt oxidant stress-induced renal injury in alloxan-induced diabetic rats due to its antioxidant and insulin interaction properties.<sup>244</sup> Furthermore, cinnamaldehyde treatment prevents the elevation of BP in insulin deficiency and insulin resistance by normalizing vascular contractility in rats.<sup>245</sup> Cinnamaldehyde was also revealed to improve behavioural deficits in diabetic rats by enhancing brain ChE activity and neurotransmitter levels and reducing IL-6 and TNF- $\alpha$  levels.<sup>246</sup> Administration of cinnamic acid was revealed to significantly improve dose-dependent memory in STZ-induced diabetic mice by alleviating oxidative stress and cholinergic dysfunction.<sup>247</sup> In obese/T2D female mice, cinnamaldehyde has been shown to possess potential therapeutic value for the management of diabetic gastroparesis, which may be related to modulating key regulating detoxifying enzymes by Nrf2-mediated gastric estrogen receptors (ERs) and nNOS function.<sup>248</sup> In addition, the topical application of cinnamon increased fibroblast proliferation and glucose uptake in keratinocytes and consequently accelerated wound healing during diabetes by enhancing the antioxidant capacity and the expression of cyclin D1, GLUT-1 and IGF-1.<sup>249</sup>

## 6. Clinical trials of cinnamon and its extracts in DM

Multiple clinical trials revealed that cinnamon improved glycaemic indicators [fasting plasma glucose (FPG), two-hour postprandial glucose (2hpp), HbA1c, fasting insulin, and insulin resistance] and clarified the hypoglycaemic properties of cinnamon. Khan *et al.* conducted a randomized, placebo-controlled study on 60 subjects with T2DM.<sup>15</sup> After 40 days of treatment with cinnamon (1, 3, or 6 g d<sup>-1</sup>), an improvement was observed in the mean fasting serum glucose levels (18–29%).<sup>15</sup> A triple-blind placebo-controlled randomized clinical trial was conducted in patients with T2DM to investigate the efficacy of cinnamon.<sup>250</sup> After consuming 500 mg capsules of cinnamon bark twice daily for 3 months, subjects exhibited improved glycaemic indices including FPG, 2hpp, HbA1c, fasting insulin, and insulin resistance.<sup>250</sup> Crawford compared the effects of cinnamon capsules (1 g d<sup>-1</sup>) plus usual care with management changes or usual care with management changes for 90 days in type 2 diabetes patients.<sup>60</sup> After the treatment period, the cinnamon group showed lower HbA1c than the usual care alone group.<sup>60</sup> Similarly, Mang *et al.* showed that aqueous cinnamon extract (3 g d<sup>-1</sup>) reduced fasting plasma glucose levels.<sup>251</sup> The effects were more obvious in subjects with a higher initial plasma glucose level, which showed the potential of cinnamon for treating diabetic patients with poor glycaemic control.<sup>251</sup> Lu *et al.* reported that cinnamon extract (120 and 360 mg d<sup>-1</sup>) decreased HbA1c and FBG levels in a randomized, double-blinded clinical study.<sup>252</sup>

A randomized, placebo-controlled, triple-blind clinical trial was designed to evaluate the effects of cinnamon (3 g d<sup>-1</sup>) for 90 days in people with type 2 diabetes.<sup>253</sup> The cinnamon group exhibited statistically significant reductions in HbA1c and fasting venous glucose compared with the placebo group.<sup>253</sup> Consistent with this, supplementation with cinnamon decreased the HOMA index and FBG in patients with NAFLD.<sup>84</sup> Despite this, studies have demonstrated that cinnamon does not contribute to glycaemic control and has no preventive or ameliorating effect on metabolic diseases.<sup>254</sup> Altschuler *et al.* conducted a prospective, double-blind, placebo-controlled study on 72 adolescent type 1 diabetic subjects.<sup>255</sup> After 90 days of treatment with cinnamon (1 g d<sup>-1</sup>), no significant differences were observed in the final A1C, change in A1C, total daily insulin intake, or number of hypoglycaemic episodes.<sup>255</sup> A double-blind, randomized, placebo-controlled clinical trial evaluated the hypoglycaemic effects of cinnamon (3 g d<sup>-1</sup>, 8 weeks) in patients with T2DM.<sup>256</sup> No significant changes were observed in the levels of FBG, insulin, haemoglobin bA1c, or HOMA-IR between the cinnamon supplementation group and the placebo group.<sup>256</sup>

## 7. Conclusion and future perspectives

In conclusion, a large amount of literature has shown that cinnamon and its components possess great potential in treating diabetes and CVDs, including AS, hypertension, MIRI, viral myocarditis, heart failure, and arrhythmias (Fig. 4 and 5). The potential of cinnamon has been tested in a number of clinical trials, animal and cell experiments (ESI Tables 1 and 2†). Generally, cinnamon's therapeutic capacity for CVDs is attribu-

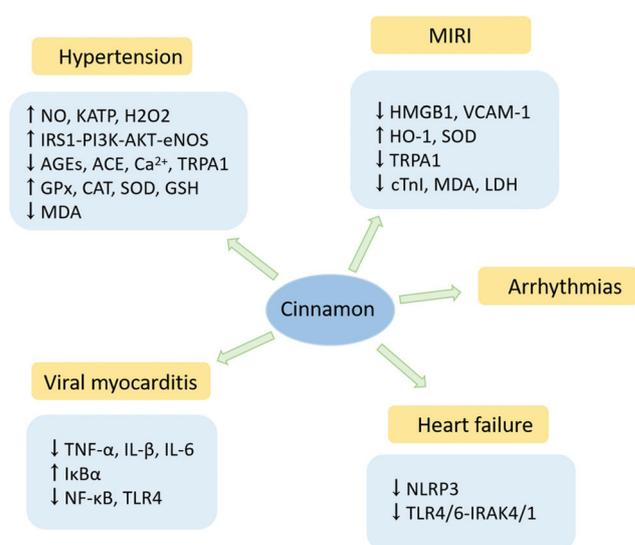


Fig. 4 Molecular mechanism underlying cinnamon protects against hypertension, MIRI, viral myocarditis, heart failure and arrhythmias.



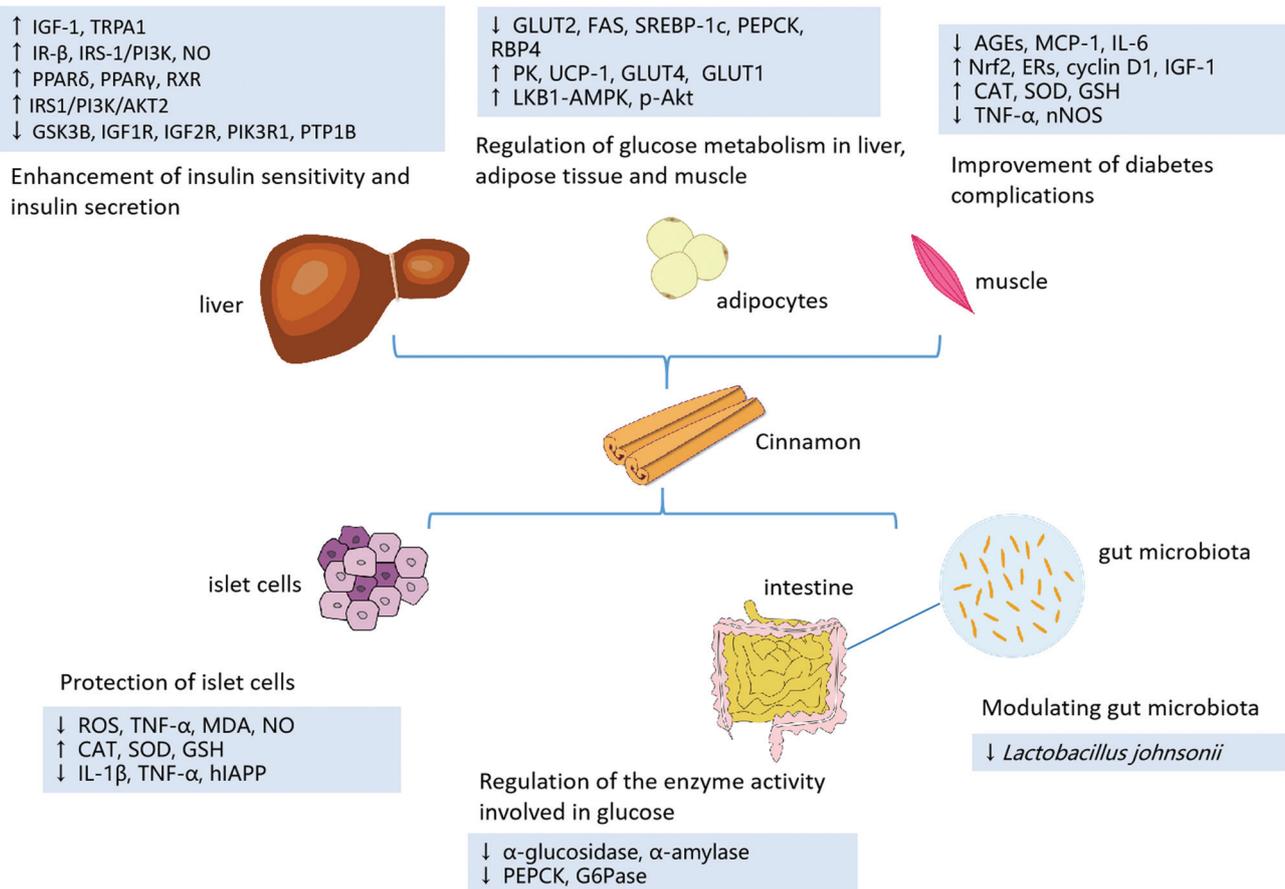


Fig. 5 Molecular mechanism of cinnamon on diabetes.

ted to its multifactorial functions. Cinnamon and its extracts, especially cinnamaldehyde, increase the production of endothelial NO by activating the Nrf2 signalling pathway and enhancing pAKT-Ser473 and eNOS-Ser1177, thereby protecting ECs. Cinnamon and its extracts, in particular cinnamaldehyde and *trans*-cinnamic acid, might attenuate lipogenic processes, improve the intestinal absorption of fat in food and lower the accumulation of lipids to regulate lipid metabolism, thus reducing the risk of CVD. In addition, cinnamon and its extracts could blunt the production of ROS and ameliorate the level of antioxidant enzymes to mitigate the formation of ox-LDL, thereby preventing the occurrence of AS. Cinnamaldehyde can regulate oxidative stress in a TLR4-NOX4- and Nrf2-dependent manner. Furthermore, cinnamon and its extracts have strong roles in modulating immune responses and inflammatory responses. Moreover, cinnamon extracts, such as cinnamaldehyde, cinnamyl alcohol, cinnamic acid, and eugenol, can suppress the growth and mobilization of VSMCs by regulating the cell cycle. Cinnamon and its extracts also repress platelet activity and thrombosis and inhibit angiogenesis, which are helpful in protecting against CVDs.

The impact of cinnamon on diabetes is ambiguous. Some clinical studies have yielded conflicting results on whether cinnamon improves glucose metabolism. Several mechanisms

could be responsible for the supposed positive effects of cinnamon on diabetes, including enhancing insulin sensitivity and insulin secretion; regulating the enzyme activity involved in glucose; regulating glucose metabolism in the liver, adipose tissue and muscle; ameliorating oxidative stress and inflammation to protect islet cells; and improving diabetes complications.

Evidence for cinnamon and its extracts as a natural product to prevent and counteract CVDs and diabetes is increasing.<sup>257</sup> Nevertheless, most experiments were conducted in animals and *in vitro*, and the clinical effect and metabolic impact in humans need to be further determined. Concluding that intake of cinnamon or its extracts is a useful way to ameliorate the pathological process of CVDs and diabetes is probably premature. Long-term, large-sample, randomized and controlled trials are required to clarify the role of cinnamon in the control of CVDs and diabetes.

## Abbreviations

|          |  |
|----------|--|
| 2-MCA    | 2-Methoxycinnamaldehyde                  |
| HMG-CoAR | 3-Hydroxy-3-methylglutaryl-CoA reductase |
| AMI      | Acute myocardial infarction              |



|                 |   |                       |  |
|-----------------|---|-----------------------|--|
| Abcg5           | Adenosine triphosphate-binding cassette sub-family G member                     | HFD                   | High-fat diet  |
| Abca1           | Adenosine triphosphate-binding cassette transporter-1                           | HMGB-1                | High-mobility group box 1 protein                            |
| ATGL            | Adipocyte triglyceride lipase   | HOMA-IR               | Homeostatic model assessment for insulin resistance          |
| ADIPOQ          | Adiponectin   | HASMCs                | Human aortic smooth muscle cells                             |
| AGEs            | Advanced glycation end products   | hiPSC-CMs             | Human induced pluripotent stem cell-derived cardiac myocytes |
| AMPK            | AMP-activated protein kinase  | hiAPP                 | human islet amyloid polypeptide                              |
| ACE             | Angiotensin converting enzyme   | HUVECs                | Human umbilical vein endothelial cells                       |
| AKT             | Anti-phospho-phosphatidylinositol 3-kinase-linked protein kinase B              | IRAK4/1               | IL-1R-associated kinase 4/1                                  |
| PLC $\gamma$ 1  | Anti-phospho-phospholipase C- $\gamma$ 1  | iNOS                  | Inducible nitric oxide synthase                              |
| ASC             | Apoptosis-associated speck-like protein containing a caspase-recruitment domain | I $\kappa$ B $\alpha$ | Inhibitor of NF- $\kappa$ B                                  |
| AS              | Atherosclerosis   | IRS1                  | Insulin receptor substrate 1                                 |
| ACLY            | ATP-citrate lyase   | IR- $\beta$           | Insulin receptor- $\beta$                                    |
| cTnI            | Cardiac troponin I  | IGF-1                 | Insulin-like growth factor 1                                 |
| CVDs            | Cardiovascular diseases   | IGF1R                 | Insulin-like growth factor 1 receptor                        |
| CAT             | Catalase  | ICAM-1                | Intercellular adhesion molecule-1                            |
| C/EBP- $\alpha$ | CCAAT/enhancer-binding protein-alpha  | IFN- $\gamma$         | Interferon- $\gamma$   |
| ACAT-1          | Cholesterol acyltransferase-1   | IL-1 $\beta$          | Interleukin-1 $\beta$  |
| CETP            | Cholesteryl ester transfer protein  | IDL                   | Intermediate-density lipoprotein                             |
| C.              | Cinnamomum  | I/R                   | Ischaemia/reperfusion  |
| JNK             | c-Jun NH2-terminal kinase   | LDH                   | Lactate dehydrogenase  |
| CR3             | Complement receptor 3   | LDLRs                 | LDL receptors  |
| CDK 4           | Cyclin-dependent kinase 4   | LPS                   | Lipopolysaccharide   |
| COX-2           | Cyclooxygenase-2  | [Lp(a)]               | Lipoprotein (a)  |
| DM              | Diabetes mellitus   | LXR- $\alpha$         | Liver X receptor- $\alpha$                                   |
| DGAT2           | Diacylglycerol <i>O</i> -acyltransferase 2                                      | LDL                   | Low-density lipoprotein                                      |
| DBP             | Diastolic blood pressure  | LDL-C                 | Low-density lipoprotein cholesterol                          |
| COE             | Encapsulated cinnamon oil emulsion  | MIP-1 $\alpha$        | Macrophage inflammatory protein-1 $\alpha$                   |
| ECs             | Endothelial cells   | MMP-2                 | Matrix metalloproteinase-2                                   |
| eNOS            | Endothelial nitric oxide synthase   | MG                    | Methylglyoxal  |
| ERs             | Estrogen receptors  | mPGES-1               | Microsomal prostaglandin-E synthase-1                        |
| ERK 1/2         | Extracellular signal-related kinase 1/2   | MTP                   | Microsomal TG transfer protein                               |
| FBG             | Fasting blood glucose   | Mttp                  | Microsomal triacylglycerol transfer protein                  |
| FPG             | Fasting plasma glucose  | MCP-1                 | Monocyte chemotactic protein 1                               |
| FAS             | Fatty acid synthase   | MyD88                 | Myeloid differentiation primary response gene 88             |
| FSD/STZ         | Fatty-sucrosed diet/STZ   | MIRI                  | Myocardial ischaemia-reperfusion Injury                      |
| FOXO1           | Forkhead box O1   | NQO1                  | NAD(P)H dehydrogenase, and quinone 1                         |
| GPRs            | Gi/Go-protein-coupled receptors   | nNOS                  | Neuronal nitric oxide synthase                               |
| GLUT2           | Glucose transporter 2   | Npc1l1                | Niemann-Pick c1-like 1                                       |
| GLUT4           | Glucose transporter 4   | NO                    | Nitric oxide   |
| G6Pase          | Glucose-6-phosphatase   | NOx                   | NO metabolite  |
| Grx-1           | Glutaredoxin-1  | NLRP3                 | Nod-like receptor family, pyrin domain containing 3          |
| Gpx             | Glutathione peroxidase  | Nrf2                  | Nuclear factor (erythroid-derived 2)-like 2 protein          |
| Gpx-1           | Glutathione peroxidase 1  | NF- $\kappa$ B        | Nuclear factor- $\kappa$ B                                   |
| GST             | Glutathione S-transferase   | L-NAME                | N $\omega$ nitro-L-arginine methyl-ester                     |
| HbA1C           | Glycated haemoglobin  | ox-LDL                | Oxidized low-density lipoprotein                             |
| GPD             | Glycerol-3-phosphate dehydrogenase  | PPAR $\gamma$         | Peroxisome proliferator-activated receptor $\gamma$          |
| GSK3B           | Glycogen synthase kinase 3 beta   | PMA                   | Phorbol-12-myristate-13-acetate                              |
| HO-1            | Haemeoxygenase-1  | PIK3R1                | Phosphatidylinositol 3-kinase regulatory subunit 1           |
| HR              | Heart rate  | PEPCK                 | Phosphoenolpyruvate carboxykinase                            |
| HF/HF           | High fat/high fructose  | PI3K                  | Phosphoinositide-3-kinase                                    |
| HDL             | High-density lipoprotein  | PDK1                  | Phosphoinositide-dependent kinase 1                          |
| HDL-C           | High-density lipoprotein cholesterol  |                       |  |



|               |   |
|---------------|---|
| p-eNOS        | Phosphorylated endothelial nitric oxide synthase                                |
| pHSL          | Phosphorylating hormonesensitive lipase   |
| pMAPK         | Phosphorylation of MAPK   |
| PDGF          | Platelet-derived growth factor  |
| PCB2          | Procyanidin-B2  |
| PGE2          | Prostaglandin E2  |
| PKA           | Protein kinase A  |
| PKC           | Protein kinase C  |
| PTP1B         | Protein tyrosine phosphatase 1B   |
| PK            | Pyruvate kinase   |
| ROS           | Reactive oxygen species   |
| RXR           | Retinoid X receptor   |
| RBP4          | Retinol binding protein 4   |
| SRAs          | Scavenger receptors   |
| SIRT1         | Sirtuin-1   |
| SREBP 1c      | Sterol regulatory element-binding protein 1c                                    |
| SREBP 2       | Sterol regulatory element-binding protein 2                                     |
| STZ           | Streptozotocin  |
| SOD           | Superoxide dismutase  |
| SBP           | Systolic blood pressure   |
| ESCOP         | The german commission E and the european scientific cooperative on phytotherapy |
| TAX2          | Thromboxane A2  |
| TLR2          | Toll-like receptor 2  |
| TLR4/MD2      | Toll-like receptor 4/myeloid differentiation protein 2                          |
| TLR4-         | Toll-like receptor 4-NADPH oxidase 4  |
| NOX4          |   |
| TC            | Total cholesterol   |
| TGF- $\beta$  | Transforming growth factor- $\beta$   |
| TRPA1         | Transient receptor potential ankyrin 1  |
| TGs           | Triglycerides   |
| TTP           | Tristetraprolin   |
| TNF- $\alpha$ | Tumour necrosis factor- $\alpha$  |
| 2hpp          | Two-hour postprandial glucose   |
| UCP-1         | Uncoupling protein-1  |
| VCAM-1        | Vascular cell adhesion molecule-1   |
| VEGF          | Vascular endothelial growth factor  |
| VEGFR         | Vascular endothelial growth factor receptor                                     |
| VSMC          | Vascular smooth muscle cell   |
| VLDL          | Very low-density lipoprotein  |
| $\beta$ 3-ARs | $\beta$ 3-adrenergic receptors  |

## Author contributions

CS, HC-L and XQ-F wrote the main text. HC-L and XQ-F contributed equally to this work. CS, HC-L, XQ-F, YL-W, ZL-J, YQ, MX, ZH-S and LY-X reviewed the literature available; JL-G, YD-L and XN-C revised the manuscript.

## Conflicts of interest

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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