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Cinnamon effects on metabolic syndrome: a review based on its mechanisms

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ABSTRACT

Objective(s): Nowadays, cardiovascular diseases (CVDs) are the major risk factors of death globally. One of the most undeniable reasons of CVDs is metabolic syndrome (MetS). MetS is defined as a complex of diseases including insulin resistance, hyperglycemia, obesity, high blood pressure and dyslipidemia. The use of complementary medicine such as traditional herbal species can be effective in treatment of MetS`s complications. *Cinnamomum verum* (family Lauraceae) is a medicinal global plant which has been used daily by people all over the world. Positive effects of cinnamon in reducing blood pressure, plasma glucose, obesity and ameliorating dyslipidemia which represented in traditional medicine introduced it as probable decreasing MetS`s complications agent. The aim of this review was to investigate the mechanisms of *C. verum* in reducing the MetS`s complications and CVDs risk factors.

Materials and Methods: Various databases such as PubMed, Science Direct, Scopus, Web of Science, Google Scholar and Persian Websites such as www.sid.ir with keywords search of cinnamon, cinnamomum, cinnamaldehyde, atherogenic, hypertension, hyperglycemia, insulin resistance, obesity and dyslipidemia have been included in this search.

Results: Clinical data and mechanisms of action of *C. verum* and its active ingredients that have been shown in this review indicated that cinnamon has protective effects against MetS`s aspects in various ways.

Conclusion: The use of this plant can be effective in reducing MetS`s complications and its morbidity and mortality.

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Introduction

Metabolic syndrome (MetS) is a condition includes insulin resistance and hyperglycemia, central obesity, high blood pressure, dyslipidemia, lower levels of high density lipoprotein cholesterol (HDL-c) and hypertriglyceridemia (1). Numerous definitions of MetS are exist such as definition based on World Health Organization (WHO) and National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) criteria. With WHO criteria each person with type 2 diabetes, glucose/insulin metabolism disturbance or insulin resistance, who are involved with 2 of the following 4 items: [1] hypertension, [2] dyslipidemia, [3] obesity and [4] microalbuminuria, considered to have MetS (Table 1) (2).

Body mass index (BMI) and waist circumference (WC) are routine predictive markers of MetS but nowadays waist hip ratio (WHR) and waist height ratio (WHtR) are better separator of MetS risk factors than BMI and WC. Racial variations in predictive markers suggest that the power of each obesity index differ by ethnic group. For example among Korean adults WHR is better predictor of multiple metabolic risk factors and among adult Iranian population WC is superior to BMI and WHR (3). Based on ATPIII criteria WC cut-off value is 102 cm for men and 88 cm for women. Based on WHO criteria WHR cut-off value is 9.0 in men and 8.5 in women as decisive benchmarks for MetS (4).

Based on National Health And Nutrition Examination Survey [NHANES III], 44% of American with at least 70 years old was suffered from MetS and its prevalence rises with increasing age and BMI, which abdominal obesity (53%), hypertension (40%), and hyperglycemia (39%) were the most frequently occurring risk factors for MetS (1, 5).

Nowadays medicinal plants are considered as preventive and curative agents for their properties such as safety, popularity, easy to earn and less side effects (6). Many studies have been shown that herbal drugs are useful in treatment of MetS (7-12).

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Table 1. Metabolic syndrome: WHO criteria (2)

BMI > 30 or waist-hip ratio > 0.90 (men) or > 0.85 (women)
dyslipidemia: TG ≥150 mg/dL, HDL-c < 35 (men), or < 39 (women)
blood pressure: ≥160/90 mm Hg, with or without medication
microalbuminuria: AER 20–200 ug/min

People with at least 2 of above risk factors with type 2 diabetes, impaired glucose tolerance, or insulin resistance are considered to have metabolic syndrome
AER: average albumin excretion rate, BMI: body mass index, HDL-c: high density lipoprotein cholesterol, TG: triglyceride

Cinnamon

Cinnamomum verum (formerly *C. zeylanicum)* is a medicinal plant belongs to Lauraceae, which is generally called "true cinnamon tree" or "Ceylon cinnamon tree". *C. verum* is a small tropical tree that originated in Sri Lanka, East and Middle Asia (13, 14).

Phamacognostical Characteristics

The *C. verum* tree grows to around 10 m and leaves are leathery, usually opposite, that are lanceolate to ovate, 11 to 16 cm long, with sharp tips. The pallid yellow flowers, which are tubular with 6 lobes, grow in panicles that are as long as the leaves. The fruit is tiny, 1 to 1.5 cm long, and black when ripens (Figure 1) (13).

Chemical Composition

Different parts of cinnamon such as leaves, bark, root bark and fruits have various amount of resinous compounds (Table 2). Cinnamaldehyde, cinnamate and cinnamic acid are the main resinous ingredients found in cinnamon that increase in quantity when cinnamon ages (Figure 2). Cinnamaldehyde is responsible for its spicy taste and fragrance. Essential oils, such as *trans*-cinnamaldehyde, cinnamyl acetate and eugenol are found in cinnamon (15, 16).

Figure 1. *Cinnamomum verum*

Therapeutic Uses and Pharmacological Charactristics

Cinnamon is a very popular culinary spice and is also used in candy, incense, toothpaste and perfumes. Its oil is used in medicine as a carminative, antiseptic and astringent. In traditional medicine cinnamon has been used as antitussive, antiarthritis, antimicrobial, antifungal, anti-oxidant, anti-inflammatory agent and used in treatment of sore pain and dental problems. According to the recent studies, cinnamon may prevent or delay diabetes, colon cancer and bleeding time. Recent investigation in United States National Library of Medicine showed that cinnamon is effective in treatment of diarrhea, emesis, muscle cramps, infections, molds, flu and erectile dysfunction. Also cinnamon has been effective against multiple sclerosis, Alzheimer and human immune deficiency (HIV) infection (17-20).

Purposes

The purpose of this study was to evaluate the aspects of MetS and its complications and the effects of cinnamon on prevention and treatment of it in patients. This has been tried to investigate and show the mechanisms involved and the results of cinnamon uses in this field.

Table 2. Chemical contents of different parts of cinnamon (17)

Parts of cinnamon	Dominant ingredient (s)
Leaves	Eugenol: 70.00 to 95.00%
Bark	Cinnamaldehyde: 65.00 to 80.00%
Root bark	Camphor: 60.00%
Fruit	*trans*-cinnamyl acetate 42.00 to 54.00%
Buds	Terpene hydrocarbons: 78.00% *alpha*-Bergamotene: 27.38%
Flowers	(E)-cinnamyl acetate: 41.98% *trans-alpha*-bergamotene: 7.97%

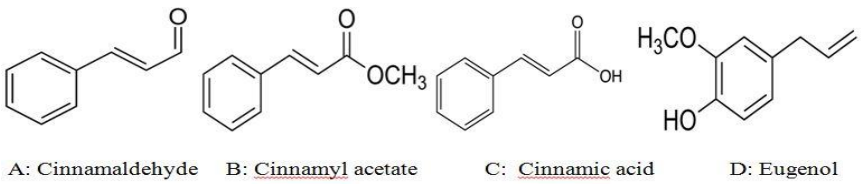

Figure 2. Chemical structure of main ingredients of cinnamon

Table 3. Important liable mechanisms for metabolic syndrome related to cardiovascular diseases

Hypertension	Dyslipidemia	Proinflammatory cytokines	Insulin resistance	Microalbuminuria
Insulin resistance stimulates sympathetic nervous system	Enhancement of lipolysis in adipocytes	Elevation of plasma concentrations of IL-6, TNF-α, C-reactive protein, and resistin	Overabundance of circulating fatty acids by lipolysing of triacylglycerol by insulin	Glomerular hyperfiltration
Insulin resistance mediates hyperadrenergic state	Insulin drives lipogenesis in the liver	Reduction of anti-inflammatory adipokines such as adiponectin	Inhibition of antilipolytic effect of insulin by circulating fatty acids	Over-production of ROS
Insulin resistance stimulates renal sodium absorption	Increase CETP activity and lipolysis of HDL-c		Impairment activation of protein kinase Ce-_ and protein kinase C-by Fatty acids	Insulin resistance, inflammation and altered renal hemodynamics
Insulin can cause upregulation of angiotensin Ⅱ type Ⅰ receptors	Enhancement of triglyceride synthesis in the liver		Defect in insulin stimulated IRS-1 and IRS-2 tyrosine phosphorylation	
Low levels of plasma natriuretic peptides			Activation of protein kinase Ce-_ and c-Jun N-terminal kinase-1.41	
Insulin resistance increases endothelin 1impairment of NO-mediated vasodilation			Fatty acids increase hepatic glucose production and diminish inhibition of glucose production by insulin	
Hyperuricemia Production of endogenous digoxin-like factor			Defect in mitochondrial oxidative phosphorylation	
			Deficient in the endoplasmic reticulum X-box binding protein-1, hyperactivation of c-Jun N-terminal kinase-1 increases serine phosphorylation of IRS-1	

NO: nitric oxide, CETP: cholesteryl ester transfer protein, HDL-c: high density lipoprotein cholesterol, IL-6: interlukin 6, TNF-α: tumor necrosis factor α, ROS: reactive oxygen species, IRS: insulin receptor substrate

Methodology

Various databases such as PubMed, Science Direct, Scopus, Web of Science, Google Scholar and Persian Websites such as www.sid.ir with keywords search of cinnamon**,** cinnamomum, cinnamaldehyde, atherogenic, hypertension, hyperglycemia, insulin resistance, dyslipidemia, etc have been involved in this research. In this review, selected articles were indicated the effects of cinnamon on MetS conditions in a 20 years period of 1995 to 2015. Attempts have been done to make a comparison of related mechanisms and most important of them was highlighted.

Metabolic syndrome and cardiovascular risk

One of the most undeniable reasons of cardiovascular diseases (CVD) is MetS (21). Individuals with MetS were at increased risk for long-term CV outcomes (22). The MetS defined according to the ATPIII criteria was associated with a 2-fold increase in risk of CVD, CV mortality, myocardial infarction and stroke, and a 1.5-fold increase in risk of all-cause mortality. CVDs are the number 1 cause of death globally. It was estimated that 17.5 million people died from CVDs in 2012, representing 31% of all global deaths (23). In Over a 7-year period study, CV mortality was 12% in those with MetS and 2.2% in those without it (22).

Important liable mechanisms for MetS related to CVDs are summarized in Table 3.

Cinnamon and metabolic syndrome

Based on traditional medicine and recent scientific based evidence cinnamon and its active ingredients such as cinnamaldehyde, cinnamate, cinnamic acid and eugenol in the forms of aqueous and alcoholic extracts have a variety of therapeutic effects. Different aspects of MetS including high blood glucose, dyslipidemia, obesity and high blood pressure are ameliorated with cinnamon extracts. Investigations about cinnamon showed that this plant is a cardiovascular protective agent and has a potential effect in reducing MetS complications due to its anti-diabetic, anti-oxidant, anti-inflammatory and beneficial effects in lipid profile (24-26) (Figure 3 and Table 4).

Insulinotropic and anti-diabetic effects

As mentioned in previous section in Table 3, the main mechanism of MetS complications is insulin resistance. Insulin resistance is a fundamental key

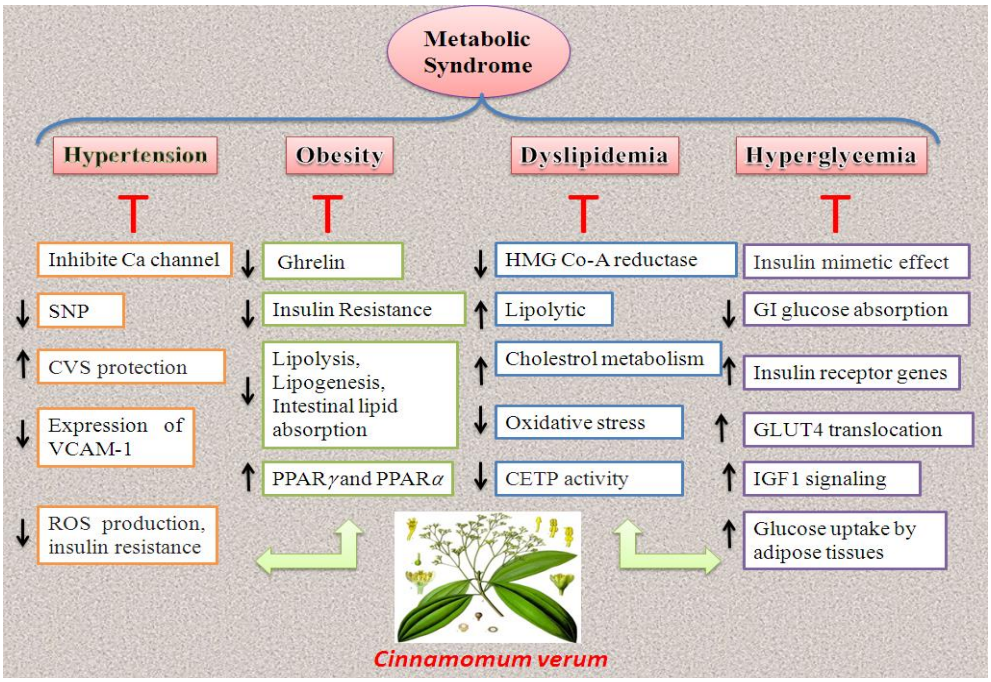

Figure 3. Schematic description for protective mechanisms of *Cinnamomum verum* in ameliorating metabolic syndrome complications

role for other MetS complications including obesity, dyslipidemia and hypertension that summarized in Table 3 (1).

Surely the main characteristic of cinnamon is an insulin mimetic effect (27, 28). The evaluation of beneficial effects of cinnamon on treatment of Type 2 diabetes and insulin resistance began almost 20 years ago. In this time, Khan *et al* extracted an unidentified component from cinnamon and named it as insulin potentiating factor (27). Cinnamon extracts can activate the insulin-receptor-kinases and inhibit insulin-receptor-phosphatases as enhancer of insulin-receptor function and inhibitor of the enzyme that blocks insulin-receptor attachment, respectively. This state causes phosphorylation of the insulin receptors and enhancing its effects (28). The major active components in cinnamon for its anti-diabetic effects are in aqueous extract as water soluble doubly-linked procyanidin type – A polymers. They were able to upregulate glucose uptake, increase glycogen synthesis by activating glycogen synthase and inhibiting glycogen synthase kinase 3β (29), and reducing glucose absorption in the small intestine through increasing in glucosidase enzymes and inhibition of intestinal ATPase (30, 31).

In *in vitro* study performed by Anderson *et al* in 3T3-L1 adipocytes, methylhydroxychalcone polymer (MHCP), the bioactive compound isolated from cinnamon, stimulated the autophosphorylation of the insulin receptor and all pathways listed above were increased by MCHP (32). *In vivo* and *in vitro* studies performed by Qin *et al* showed that aqueous cinnamon extract at dose of 30 and 300 mg/kg body weight of rats for 3 weeks potentiate the insulin effect through up-regulation of the glucose uptake in adipocytes and induced glucose utilization, increased insulin-receptor substrate (IRS)-1 tyrosine phosphorylation levels, skeletal-muscle insulin receptors stimulation and IRS-1 association with phosphatidylinositol (PI) 3-kinase (33). Other polyphenolic compounds of cinnamon like rutin, catechin, quercetin and kaempferol have insulin like activity (34). The polyphenolic content of cinnamom extract is important to induce anti-diabetic activity. The aqueous extract of *C. zeynalicum* containing 45 and 75% gallic acid equivalents (GAE) of polyphenol content was higher officious in lowering blood glucose activity than extract containing 15% GAE in streptozotocin-induced diabetic rats (35). The anti-diabetic effects of cinnamon have been shown in many studies (36-39).

In comparison between cinnamic acid and cinnamaldehyde, Hafizure *et al* showed that cinnamic acid was able to improve glucose tolerance at dose of 10 mg/kg in rats comparable to glibenclamide with dose of 5 mg/kg, but *in vitro* study showed that glucose-stimulated insulin secretion with cinnamic acid was very higher than cinnamaldehyde (36). Cinnamaldehyde was able to up-regulate expression of insulin receptor genes (37). Cinnamaldehyde increases the expression levels of peroxisome proliferator-activated receptor γ (PPARγ) and activates AMP kinase that induces insulin sensitivity (40, 41). Cinnamon can activate insulin-like growth factor 1 (IGF1) signaling in fibroblast, that tend to lowering insulin resistance and improvement in glycemic control but it can down-regulate insulin signaling in adipocytes (42). Modulating mitochondrial physiology and elevation

of cellular metabolism are another anti-diabetic mechanism of cinnamon (43). Cinnamon by modulating the insulin and IGF1 signaling pathways such as mTOR, Cyclic-AMP signaling and autophagy can exhibit anti-diabetic action (44). Alph-amylase inhibition of cinnamon is another anti-diabetic mechanism of it. Hydro-alcoholic extract of cinnamon can reduce activity of pancreatic α-amilase activity in both *in vivo* and *in vitro* study performed by Beejmohon *et al*. This effect was occured without stimulating of insulin secretion (45). Up-regulation of glucose transporter 4 (GLUT4) and translocation in muscle and adipose tissues by cinnamon extract was proved by Shen *et al*. In this study cinnamon stimulated the phosphorylation of AMPK and acetyl-CoA carboxylase. Inhibition of AMPK intended to reduction in glucose uptake by adipose tissues and cinnamon is an AMPK activatore (46). Flavonoid and phenolic compounds such as epicatechin, catechin, and procyanidin B2 isolated from cinnamon. These ingredients have antioxidant activity and entrapping properties of reactive carbonyl species, such as methylglyoxal (MGO), an intermediate reactive carbonyl of advanced glycated end products (AGEs) formation (a marker responsible for diabetic complications) can reduce the risk of progression of diabetes (47).

Above mechanisms were confirmed in Ranasinghe`s study. They evaluated the effect of cinnamon on glucose metabolism in a meta-analysis of 16 *in vitro* and *in vivo* studies (48). A study consist of 109 patients with type 2 diabetes was done in a period of 3 month. 1 g of cinnamon was fed to treated group. After this period hemoglobin A1c (HbA1c) was lower significantly in treated group (49).

Many human and cellular studies showed anti-diabetic, insulinotropic and insulin resistance lowering effect of cinnamon (50, 51). Insulin resistance is important basis of MetS and fundamental aspects of growing its complications. Reducing insulin resistance is the most important mechanism of ameliorating MetS`s complications by cinnamon.

Anti-oxidant activity

Free radicals and oxidative stress are main causes that involved in multiple conditions like MetS. Normal physiological conditions of body systems require balance between oxidant/anti-oxidant mechanisms. Production of reactive oxygen species (ROS) may have a pivotal role in pathogenesis of many disorders such as diabetes, hypertension and CVDs that are main complications of MetS (52, 53). Anti-oxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH), as a none-enzymatic anti-oxidant have a significant role in contrasting ROS and oxidative stress condition. Anti-oxidant enzyme and non-enzymatic anti-oxidant molecules activity in many inflamed conditions were reduced (54). Thus, diminishing these states with anti-oxidant enhancing systems is useful to decrease in MetS complications.

Dietry anti-oxidant such as polyphenols, vitamins A, B, C, and E neutralize the oxidation process by binding to free radicals, chelating catalytic metals and acting as oxygen scavengers (55, 56).

C. zeylanicum has 65.3% anti-oxidant activity and also a very strong free radical scavenging activity and have been shown for many extract such as alcoholic, aqueous and etheric of many parts of plant (57, 58). A recent study compared the anti-oxidant potentiality of several plants, including cinnamon, spinach, chard, Jerusalem artichoke, and red cabbage. Boga *et al* found that extracts of cinnamon had the most potent anti-oxidant effects (59). Phenolic compounds are found in almost all parts of the plants that responsive for anti-oxidant activity of cinnamon and a potent scavenger of hydrogen peroxide, nitric oxide, and lipid peroxide free radicals (60). Cinnamon`s essential oil and its component eugenol both show anti-oxidant activity (61). Use of 75 mg/kg of *C. zeylanicum* for 4 weeks in rats, as an anti-oxidant in food increased SOD, GPX, and CAT that leads to the elimination of ROS as well as decreasing lipoperoxidation (LPO) level and the apoptotic index (62). In addition cinnamon has anti-LPO in vegetable oil that inhibited malondialdehyde (MDA, as a marker of LPO) production at 500, 1000 and 2000 ppm concentration of cinnamon (63). The essential oils and some of the major compounds present in cinnamon, including (E)-cinnamaldehyde, eugenol, and linalool, were investigated in reference to peroxynitrite induced nitration and LPO. Different flavonoids isolated from cinnamon have free-radical-scavenging activities and anti-oxidant properties (64).

Cinnamon oil exhibited SOD like activity that evaluated by measuring the inhibition of pyrogallol autoxidation that is catalyzed by the superoxide radical (65). Cardiac and hepatic anti-oxidant enzymes, lipid conjugate dienes, and glutathione (GSH, as non-enzymatic anti-oxidant protein) of rats increased after 90 days of administration of the bark powder of *C. verum* (10%) (57).

In vitro and *in vivo* anti-oxidant studies of *C. tamala* showed that cinnamaldehyde as major constituent of plant can decrease MDA level and increased GSH that be reduced (66). Cinnamaldehyde has potential activity against the production of nitric oxide and it can inhibit the expression of inducible nitric oxide as an enzyme that has a role in oxidative stress (67).

In comparison between the anti-oxidant activities of cinnamon extracts, Roussel *et al* showed that etheric (0.69 mg), methanolic (0.88 mg) and aqueous (0.44 mg) extracts, inhibited the oxidative process in

68%; 95.5% and 87.5% respectively. The butylated hydroxytoluene (BHT) control inhibited 80% oxidation (68). In Pandey study, ethanolic and aqueous extract of *C. verum* showed almost equal capacity to inhibit free radicals in 2,2-Diphenyl-1-picrylhydrazyl test (DPPH) with IC_{50}=13.53 µg/ml and 13.3, respectively. In this study scavenging superoxide radical by ethanolic extract was found to be more potent (IC_{50}=119.7 µg/ml) than aqueous extract and ascorbic acid with IC_{50}=197.8 µg/ml and 237.1, respectively (69). The uses of the aqueous extract of cinnamon in duration of 6 weeks in patients with impaired fasting blood glucose can decrease MDA level and increased plasma thiol content (70).

About anti-oxidant activity of cinnamon 178 articles were found in period of year 1995 to 2015. In all of them that consisting of *in vitro*, *in vivo* and food industry studies, cinnamon showed anti-oxidant activity as increasing in anti-oxidant enzyme activity such as SOD, CAT and GOX, decreasing in MDA, LPO, ROS production and total oxidant index value. These mechanisms can decrease oxidative stress and finally secondary effects of it to all parts of the body.

Effects on cardiovascular diseases and antihypertensive activity

Resistance to the metabolic actions of insulin caused by proinflammatory and pro-oxidative milieu that created by visceral obesity could diminish endothelium functions and induction of vascular rarefaction, reductions in vascular relaxation, and impaired vascular remodeling (71). As mentioned befors insulin resistance is main demonstration of MetS and has system-wide implications for other tissue such as the kidney that affects blood pressure regulation. In addition, the additional autocrine and paracrine activities of adipose tissue, another feature of MetS, contribute to inappropriate activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system that promote kidney microvascular remodeling, stiffness, and sodium (Na^+) retention that in turn promote hypertension (72). Thus, insulin resistance and obesity are two basic causes of hypertension and must be considered in treatment of hypertension.

Short term use of cinnamon can significantly reduce blood pressure especially among those who are prediabetic or type 2 diabetic. In a meta-analyzed performed in 2012 the results of the three clinical trials studies were shown that average drop in systolic blood pressure was 5.39 mmHg, while average drop in diastolic blood was 2.6 mmHg (73). Treatment of 59 subjects who had type-2 diabetes with 1,200 mg of cinnamon per day was shown that systolic blood pressure reduced by 3.4 mmHg on average after twelve weeks (74). Vasorelaxation and decrease in blood pressure are important actions on cardiovascular system by cinnamon. The activation of the chemosensory cation channel (TRPA1) and L-type currents were more potent in ventricular cardiomyocytes (VCM) than in vascular smooth muscle cells (VSMC). This effect may contribute to its vasorelaxing action (75). These effects were confirmed by Nyadjeu *et al* (76). Ankyrin (A) transient receptor potential channel has unitary conductance and slight selectivity for Ca^{2+} versus Na^+. In peripheral arteries TRPA1 agonist such as cinnamon can stimulate these channels and then release of calcitonin gene-related peptide was occurred and vasodilation was seen. Another mechanism was seen in cerebral circulation that TRPA1 in endothelium beds induce hyperpolarization and then vasodilation (77). Renin–angiotensin–aldosterone system and increased free radical formation are two main consequences of insulin resistance state. These phenomena in CVS lead to development of endothelial dysfunction and hypertension (73).

It is a close association between glycemic indicators (fasting plasma glucose or HbA_{1c}) and systolic and diastolic blood pressure levels (24, 74). Also, decrease in level of MDA by cinnamon linked with blood pressure regulation (68). The reduction of blood pressure by 12.5%, 26.6% and 30.6% in rats at the doses of 5, 10 and 20 mg/kg of *C. zeylanicum* methanolic extract, respectively was seen in Nvadjeu`s study. In this study increase in NO tissue's concentration was the main mechanism of antihypertensive effects of extract (78).

The effect of cinnamon on blood pressure was greater with higher baseline systolic blood pressure. Cinnamon is independently associated with blood pressure levels than sodium intake (74). Cinnamon with dose of 50 mg/kg for 2 weeks was given to dogs. Among this period systolic blood pressure and heart rate in treated dogs was lower significantly than normal group. QT and PR interval was longer in treated group. R wave amplitude in treated group was shorter and may contribute to lowest blood pressure in this group. In this study decrease in blood pressure was hypothesized on decrease in vascular resistance and decrease in cardiac stroke volume (79).

The normalization of vascular contractility via restoration of normal Ca^{2+} influx parallel to its insulinotropic effect are main mechanisms to prevent development of hypertension in patients with insulin deficiency and insulin resistance (80).

Hyperuricemia is one of the causes of an increased risk for incident hypertension. 450 mg/kg or higher doses of *C. cassia* oil reversed serum and hepatic levels of uric acid to the same level as normal in control mice by inhibiting those liver enzymes responsible for converting purines to uric acid (81, 82). Insulin resistance in MetS condition induces directly and

indirectly increasing in markers of adrenergic state such as resting tachycardia, increased sympathetic nerve traffic and high plasma norepinephrine values (72). Thus, the effects of cinnamon on any of the above issues resulted in hypotensive effects of it. The insulinotropic effect of cinnamon was discussed already.

The CVS protective effects of cinnamon were shown in many studies (18, 83). The antiathrosclerotic effects and preventive vascular diseases of cinnamon resulted from inhibition of vascular smooth muscle cell proliferation through blockade of thromboxane A2 (TXA2) receptors mediated proliferation by cinnamon (84). Cinnamophilin, a lignin isolated from *C. philippinense*, inhibited *in vitro* human platelet aggregation, alongside [3H] inositol monophosphate formation, thromboxane B2 (TXB2) content and intracellular Ca^{2+} was decreased and prostaglandin E1 (PE1) formation was increased. Cinnamophilin was a potent TX inhibitor. These results were shown in rats and guinea pigs (85).

The induction of hemeoxygenase (HO) by 2-methoxycinnamaldehyde (2-MCA), a component isolated from *C. cassia*, amended the ischemia/reperfusion (I/R) injury. 2-MCA also can decrease the expression of vascular cell adhesion molecule-1 (VCAM-1) in TNF- activated endothelial cells. This effect was shown in rats precisely (86, 87).

Effects of 200 mg/kg cinnamon bark extract on myocardial hemodynamic parameters in rats was investigated by Badalzadeh *et al*. In this study, hemodynamic parameters such as left ventricular systolic and diastolic pressures, ventricular contraction and relaxation, left ventricular developed pressure, work index of the heart and coronary flow were measured during the 8 weeks period of training. In this study, exhausted animals were compared in these parameters with animals receiving cinnamon. The results showed that treated group had better consequences with enhanced cardiac force and contractility, positive inotropic effect, improved heart performance, increased coronary flow, better myocardial contractility and cardiac work (88).

Anti-inflammatory activities

Inflammation and rise in proinflammatory cytokines are common features of the MetS. Adipocytes and macrophages within fat secrete numerous hormones and cytokines that may contribute to the characteristic pathophysiological changes seen in the MetS, and local inflammation within adipose tissue may be the sentinel event that causes systemic insulin resistance and systemic inflammation, two of the cardinal features of the MetS (24). Circulating cytokines have similar metabolic effects on muscle, liver, and endothelium. Adipose tissue-derived cytokines, such as interlukin 6 (IL-6) and leptin induce endothelial cell activation and inflammation that causes atherosclerosis in the vascular beds and tend to mortality (89).

The anti-inflammatory activities of cinnamon and its essential oils indicated in many studies (90, 91). The inhibition of nuclear factor kappa B (NF-κB) was seen by Lee *et al* by 2`-hydroxycinnamaldehyde isolated from *C. cassia* bark that tended to inhibition of production of nitric oxide (92). Also NF-κB suppression by cinnamaldehyde was seen in Muhammad *et al* study. In this *in vitro* study on AGS/MKN-45 cells, cinnamaldehyde inhibited production of IL-8 secretion/expression from *Helicobacter pylori*-infected cells and degradation of I- κB was reduced by use of cinnamaldehyde (93). Reducing the activation of Src/spleen-tyrosinekinase- (Src/Syk-) as an inflammatory signaling cascades, is another anti-inflammatory mechanism of cinnamon with its ethanolic extract (94). Tumor necrosis factor-α (TNFα) levels were decreased with aqueous extract of cinnamon in *in vivo* and *in vitro* model of lipopolysaccharide-induced TNFα rising. *In vitro* inhibition of TNF-α gene by cinnamon water extract was seen in Lee`s study via the modulation of JNK, p38, and ERK1/2 activation and IκBα degradation (95). In another study performed by Hong *et al* cinnamon water extract (CWE) inhibited expression of TNF-α in *in vitro* and *in vivo* model. In this study degradation of IκBα and MAP kinase phosphorylation induced by lipopolysaccharide in macrophages was strongly inhibited by the polyphenol-rich CWE fraction. The results of this process tended to inhibition of TNF-α and IL-6 production. This strong anti-inflammatory effect of CWE was related to high polyphenolic content of extract. Procyanidins, catechin, epicatechin and ellagic acid are the main ingredients of CE with anti-inflammatory effect (96). Also, CWE prevented anti-CD3-stimulated T cells from secreting IFN-γ (95). Cinnamon polyphenols induced the expression of the pro-apoptotic protein, Bax and suppressed the expression of the anti-apoptotic protein, Bcl-xl, in OGD treated cells. Cinnamon polyphenols reduced OGD-induced inflammatory factors including TNF-α and phospho-NF-κB p65 and also induced sirtuin1 expression as a negative regulator of NF-κB activity through the deacetylation of the p65 lysine 310 (97). Interleukin-1 beta (IL-1β) suppressing production was showed with Chao *et al*. In this study eugenol was the main ingredient of cinnamon to do this (98). Eugenol could also inhibit 5-lipoxygenase enzyme in polymorphonuclear leukocytes and it can inhibit inducible nitric oxide synthesis (iNOS), cyclooxygenase-2 (COX-2), and nitric oxide (NO) production (99). Inhibition of NO production by E-cinnamaldehyde and o-methoxycinnamaldehyde with IC_{50} values with RAW 264.7 cells of 55±9 μM and 35±9 μM, respectively; was

shown in another study performed by Gunawardena *et al* (100). Cinnamon extract with doses of 50, 100, and 200 mg/kg was used for evaluation of anti-inflammatory effects on rats. All aspects of models of inflammation such as paw volume, weight loss, and paw edema and cotton pellet-induced granuloma were ameliorated and significant reduction in elevated serum TNF-α concentration was seen. Also cinnamon inhibited cytokines (IL-2, IL-4, and IFNγ) release from concanavalin-stimulated lymphocytes in *in vitro* (101). Inhibition of angiogenesis by cinnamon extract through blocking of vascular endothelial growth factor 2 (VEGF2) signaling and diminishing of endothelial cell proliferation, migration and tube formation which seen in *in vitro* study are the other main anti-inflammatory mechanisms of cinnamon (102).

Effects on dyslipidemia

Insulin resistance and obesity are two factors that each one can stimulates another one in the progression of MetS. Obesity and increased adipocyte mass are accompanied by angiotensinogen, TNF-α, leptin, resistin, and plasminogen activator inhibitor 1 (PAI-1) elevation in plasma. Plasma concentration of adiponectin is actually decreased in obesity, as well as in the type 2 diabetes mellitus. TNF-α and resistin are correlated with insulin-resistant state (103, 104). The role of insulin resistance in dyslipidemia was mentioned in Table 3.

Cholesterol- and lipid-lowering effects of cinnamon were shown in many studies (105, 106). In Khan *et al* study, cinnamon with doses of 1, 3, and 6 g per day caused a reduction triglyceride (TG), total cholesterol, and LDL-c cholesterol levels in humans (107). In streptozotocin-induced diabetic rats fed with 5% cinnamon for 8 weeks HDL-c significantly increased, while cholesterol, LDL-c and TG were significantly decreased. Also increase in adiponectin and decrease in leptin were seen (108). The lipid lowering effect of cinnamon was evaluated by Javed *et al.* In this study *C. zeylanicum* bark powder at doses of 0.50 g/kg, 0.75 g/kg and methanol extract equivalent to 0.75 g/kg powder produced a reduction in triglycerides total cholesterol LDL-c and increase in HDL-c (109).

Inhibiting hepatic HMG Co-A reductase enzyme is the main hypolipidemic mechanism of cinnamon. Reduction in oxidative stress by cinnamon through inhibition of 5-lipoxygenase enzyme is another mechanism that reduces lipid peroxidation. Cinnamon extracts have lipolytic activity. The enhancement of hepatic antioxidant enzyme activity is a critical role in hypolipidemic characteristics of cinnamon (110).

Cinnamon has the strongest inhibition of activity against copper-mediated LDL-c oxidation, LDL-c phagocytosis by macrophages and has potent cholesteryl ester transfer protein (CETP) inhibitory activity (111).

Badalzadeh *et al* study showedthat 200 mg/kg CBE significantly decreased serum levels of total cholesterol, LDL-c, and increased HDL-c level and HDL-c/LDL-c ratio as compared to control group in an 8 weeks test period (83).

Effects on obesity

One of the most important causes of CVD is obesity. Obesity is a source of proinflammatory cytokines and increase in oxidative stress condition (112). Insulin resistance is a major cause of the obesity while it can also be caused by obesity. Alteration in endocrine and paracrine hormones such as ghrelin is another cause of obesity (113).

Cinnamaldehyde as an agonist of TRPA1 in epithelial mouse stomach cells reduced cumulative food intake and gastric emptying rates. Also, it up-regulated expression of TRPA1 and insulin receptor genes in parallel with increase in insulin sensitivity was seen in cinnamaldehyde *in vitro* incubation model. Reduction in ghrelin secretion was another consequence of this *in vitro* model (37). Cinnamon water extract in Sartorius *et al* study reduced insulin resistance, lowered blood glucose, and serum lipid level and ameliorated obesity-related type 2 diabetes in mice due to activation of both PPAR*γ* and PPAR*α* (114).

Polyphenolic compounds with anti-obesogenic effects are abundant in cinnamon species. *In vitro* studies showed that differentiation of adipocyte could be inhibited by polyphenolic compounds; also they inhibited lipolysis (115), lipogenesis (116) or intestinal lipid absorption (117) that they tend to lowering weight. Polyphenolic compounds are inducers of fatty acid oxidation (116) or antagonist at cannabinoid receptors (118) and attenuate the inflammatory changes (119).

In a double blind, randomized, placebo controlled clinical trial led on 44 patients with type 2 diabetes, Vafa *et al* showed that consumption of 3 g/day cinnamon after 8 weeks could decreased significantly the levels of fasting blood glucose, HbA1c, weight, triglyceride, body fat mass and BMI in contrast to the baseline but these differences were not significant when compared with placebo groups (120).

In summary and according to the contents expressed above, the antiobesity effect of cinnamon was due to its insulin sensitivity, cardiovascular protection and immunomodulatory effects.

Conclusion

This review article expressed the main aspects of metabolic syndrome and protective mechanisms of cinnamon and its active ingredients in reducing and ameliorating complications of metabolic syndrome. Features of metabolic syndrome including dyslipide-

mia, hyperglycemia, hypertension and obesity are under the influence by cinnamon that be proven by *in vivo* and *in vitro* studies that be shown in this article. It has been concluded that cinnamon has potential therapeutic use in metabolic syndrome and can prevent morbidity and mortality due to cardiovascular diseases.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Table 4. Most important mechanisms of cinnamon in reducing metabolic syndrome complications

Effect	Mechanisms	Reference
	Insulin mimetic effect	(28)
	Activating glycogen synthase, inhibiting glycogen synthase kinase 3β	
	Reducing glucose absorption in the small intestine through increasing in glucosidase enzymes and inhibition of intestinal ATPase	(29)
	Up-regulating the expression of insulin receptor genes	
	Activating the PPAR γ and AMP kinase	(30)
	Activating IGF1 signaling in fibroblasts	(37)
	Modulating mitochondrial physiology and elevation of cellular metabolism	(40)
Anti-diabetic	Modulating the insulin and IGF signaling pathways such as mTOR, Cyclic-AMP signaling and autophagy	(42)
	Inhibition of Alph-amylase	(43)
	Up-regulation of GLUT4 translocation in muscle and adipose tissues	
	Phosphorylation of AMPK and acetyl-CoA carboxylase and inhibition of AMPK intended to	(43)
	reduction in glucose uptake by adipose tissues	(45)
	Anti-AGEs formation	(46)
		(46)
		(47)
	Increasing conjugate dienes and glutathione	(55,57)
	Free radical scavenging activity	(58)
Anti-oxidant	Increasing SOD, GPX, and CAT	(62)
	Decreasing lipoperoxidation	(63)
	Inhibiting expression of inducible nitric oxide	(67)
	Reducing in free radicals production and insulin resistance	(58)
	Reducing sympathetic nerve traffic	(72)
	Activation of the chemosensory cation channel	(75)
	Release of calcitonin gene-related peptide	(77)
	Restoration of normal Ca^{2+} influx and vasorelaxation	(80)
	Reducing plasma uric acid	(81)
	Cardiovascular protective effects	(83)
Antihypertensive	Blocking of thromboxane A2 receptors	(84)
	inhibition of platelet aggregation, alongside [3H] inositol monophosphate formation, thromboxane B2 content and Intracellular Ca2+ prostaglandin increasing in PE1 formation	
	Activating hemeoxygenase enzyme	(85)
	Reducing the expression of VCAM-1	(86)
		(87)
	Inhibition of NF-κB activity	(93)
	Reducing the activation of Src/spleen-tyrosine kinase	(94)
Anti-inflammatory	Inhibition of TNF-α gene, IL-2, IL-4, and IFNγ	(95)
	Induction of sirtuin expression	(97)
	Decrease IL1β concentration	(98)
	Inhibition of 5-LPO, COX2 and iNOS enzymes	(99)
	Inhibiting hepatic HMG Co-A reductase enzyme, lipolytic activity and increasing hepatic anti-oxidant enzymes activity	(110)
Antihyperlipidemic	Inhibition of activity against copper-mediated LDL-c oxidation	
	and potent CETP inhibitory activity	(111)
	Agonist of TRPA1 and reduction in ghrelin secretion	(37)
	Activation of both PPARγ and PPARα receptors	(114)
	Reduction in insulin resistance	(1,104)
Antiobesity	Inhibition of lipolysis	(115)
	Inhibition of lipogenesis and fatty acid oxidation	(116)
	Inhibition of intestinal lipid absorption	(117)
	Antagonist at cannabinoid receptors	(118)

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