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Beneficial Effects of *Cinnamon* on the Metabolic Syndrome, Inflammation, and Pain, and Mechanisms Underlying These Effects – A Review

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Abstract

Cinnamon is one of the most important herbal drugs and has been widely used in Asia for more than 4000 years. As a folk medicine, *cinnamon* has been traditionally applied to the treatment of inflammatory disorders and gastric diseases. After chemical profiling of *cinnamon*'s components, their biological activities including antimicrobial, antiviral, antioxidant, antitumor, antihypertension, antilipemic, antidiabetes, gastroprotective and immunomodulatory were reported by many investigators. As a result, current studies have been performed mostly focusing on the bioactivity of *cinnamon* toward the recently generalized metabolic syndrome involving diabetes. In this review article, we provide an overview of the recent literature describing *cinnamon*'s potential for preventing the metabolic syndrome.

Key words: *Cinnamon*, Spice, Diabetes, Metabolic syndrome, Inflammation, Insulin

Introduction

The genus *Cinnamon* is an aromatic tree belonging to the family Lauraceae, and is one of the most widely studied flowering families, comprising about 250 species. Members of this family are evergreen trees, up to 10-17 m high, that grow in south-eastern Asia, Australia, and South America (Cheng, 1983). The flowers are bisexual, colored yellow with 9 stamens, and the fruits occur mostly as 10-15- mm long black ellipsoids (Cheng, 1983). Traditional uses of Cinnamon throughout Asia, Africa, and Europe have been recorded, where it has been used as a medicine for diarrhea, nausea and chill, or as a spice for seasoning meats. Cinnamon bark (肉桂 ròu guì) is an important source for these purposes, since it contains a great amount of the function-bearing essential oil. The bark-derived cinnamon (termed cinnamon hereafter) contains 45% ~ 65% cinnamaldehyde, 12% ~ 18% eugenol (Cheng, 1983) and small amounts of cinnzeylanine, cinnzeylanol, arabinoxylan, 2'-hydroxycinnamaldehyde, and 2'-benzoloxycinnamaldehyde (Lee, 1999). As a major ingredient, cinnamaldehyde has been well investigated; and its diverse biological activities against central nervous system depression (Harada, 1976) and high blood pressure (Harada, 1975), as well as its analgesic effect (Harada, 1972), have been reported. A water extract of cinnamon was reported to have anti-allergic, anti-inflammatory (Nagai, 1982a; 1982b; 1982c), antipyretic, analgesic (Ozaki,1972) and antithrombotic effects (Terasawa, 1983). Recently,

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the interest of investigators seems to have shifted to become narrowly centered on the verification of cinnamon's potential for preventing the metabolic syndrome (Kannappan, 2006; Blevins, 2007) and diabetes (Anderson, 2004; Chase, 2007; Pham, 2007; Shen, 2010).

This review summarizes the up-to-date and comprehensive information on cinnamon regarding its traditional use, for which modern scientists have solved its pharmacological functions together with its toxicological aspects. Then we discuss a possible trend and scope for future research on cinnamon.

Cinnamon as a traditional medicine

Trees belonging to the genus *Cinnamomum* are one of the major materials used in traditional Chinese medicine. Preparations containing the bark of Cinnamon have been prescribed for more than 2000 years in China, where the first record of its use was described in the Divine Husbandman's Herbal Foundation Canon (see the review introduced by Cheng, 1983). Owing to its roles in dispelling colds (祛寒 qū hán), threading an occluded vasa vasorum, and controlling yin/yang (陰陽 yīn yang) as mentioned in the old Chinese literature, cinnamon has been widely used in China and Japan for the treatment of fever and inflammation as well as for improvement of an appetite depressed by influenza or the common cold (Cheng, 1983). In addition, cinnamon has been used as an aromatic for the preparation of fruit juices, wine, and cakes as well as for cooking meat. Cinnamon extracts have been used for the improvement of or protection against the common cold, diarrhea, and pain (Cheng, 1983). It has also been reported that the cinnamon ameliorates nephritis, purulent dermatitis, and hypertension, as well as potentiates wound healing, even that due to snake or viper bites (Nagai, 1982a; 1982b; Cheng, 1983). However, these effects are not fully supported by experimental or clinical data so far.

Functional components in *Cinnamomum* plants

Cinnamaldehyde is a major constituent (45~65% of the essential oil in cinnamon bark) of the plants belonging to genus *Cinnamomum* (Cheng, 1983). Eugenol is contained as a second major constituent; and cinnzeylanine, cinnzeylanol (Isogai, 1977), arabinoxylan (Gowda, 1987), 2'-hydroxycinnamaldehyde, and 2'-benzoloxycinnamaldehyde (Lee, 1999) are also detected. Chemical structures of these compounds

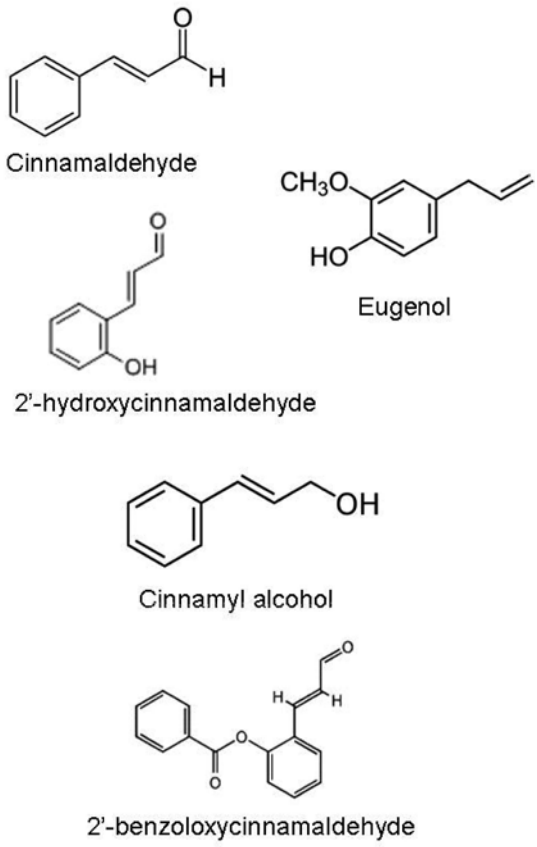

Figure 1. Compounds found in the Cinnamon barks

are shown in Fig. 1. A hot-water extract of cinnamon sticks (dried barks of cinnamon trees) yields 8.5 mg/ml cinnamaldehyde and 3.6 mg/ml cinnamyl alcohol (Shen, 2010).

Pharmacological effects of cinnamon

In vitro and *in vivo* studies on cinnamon extracts or its components (mainly cinnamaldehyde) revealed that these substances exhibit a wide variety of pharmacological effects, such as antifungal, anti-cardiovascular, anticancer, antiinflammatory, antiulcer, antidiabetes, antiviral, antihypertensive, antioxidant, and cholesterol- and lipid-lowering ones. Some of the relevant literature on these therapeutic effects is summarized in Table 1, and some of the observations made are discussed in the following sections.

Antifungal effect

The antifungal activity of cinnamaldehyde, which is used as a vapor to treat respiratory tract mycoses, has been reported. Cinnamon tree power (we usually call it "cinnamon") acts against infectious fungi including *Aspergillus niger*, *A. fumigatus*, *A. nidulans*, *A. flavus*, *Candida albicans*, *C. tropicalis*, *C. pseudotropicalis*,

Table 1. Pharmacological activity of cinnamon and its compounds

Pharmacological activities	Plant species	Material/compound	References
antifungal	---	cinnamaldehyde (vapour)	Lima, 1993; Quale, 1996 ; Singh, 1995
Improvement of bronchoconstriction, arrhythmia	*C. philippinense*	cinnamophilin	Su, 1999 ; Yu, 1994a; 1994b
anticancer, immunomodulatory	*C. cassia*	extracts, cinnamaldehyde	Abraham, 1998; Ka, 2003; Koh, 1998; Lee, 1999; Nishida, 2003; Schoene, 2005
antiulcer	*C. cassia* *C. zeylanicum*	water extract	Keller, 1992
antiinflammatory	*C. cassia*	water extract	Nagai, 1982a; 1982b
antioxidant	*C. zeylanicum*	essential oil, water and alcoholic extracts	Chericoni, 2005; Dragland, 2003; Khan, 2003; Kim, 2006a; Mancini-Filho, 1998; Okawa, 2001; Shobana, 2000
cholesterol and lipid-lowering	*C. cassia*	plant	Khan, 2003; Kim, 2006a
antidiabetis	*C. cassia* *C. zeylanicum*	plant, water extract cinnamaldehyde	Anderson, 2004; Altschuler, 2007; Berrio, 1992; Blevins, 2007; Broadhurst, 2000; Cao, 2007; Chase, 2007; Imparl-Radosevich, 1998; Jarvill-Taylor, 2001; Kannappan, 2006; Khan, 1990; Kim, 2006a; 2006b; Kreydiyyeh, 2001; Lee, 2011; Mang, 2006; Onderoglu,1999; Pham, 2007; Qin; 2003; 2004; Roffey, 2006; Shen, 2010; Subash, 2007; Suppapitiporn, 2006; Taher, 2004; Talpur, 2005; Vanschoonbeek, 2006; Verspohl, 2005; Wang, 2007
antivirus	*C. cassia*	extract, cinnamaldehyde	Hayashi, 2007; Premanathan, 2000
antihypertension	*C. cassia* *C. burmannii*	acetic acid extract	Chen, 1981; Preuss, 2006; Zhou, 1995
Improvement of central nervous system, depression	*C. cassia*	water extract	Harada, 1972; Iwasaki, 2008
gastroprotection	*C. Cassia*	ethanol and methylene chloride extracts	Tabak, 1999

and *Histoplasma capsulatum* (Singh, 1995; Lima, 1993; Quale, 1996). In these cited studies, the following data were reported: the minimum inhibitory concentration (MIC), minimum lethal concentration (MLC) and exposure duration for its fungicidal action at MIC and higher doses, as well as incubation temperatures for expression of its fungitoxicity. The inhalation of cinnamaldehyde appears to be an ideal chemotherapy against respiratory tract mycoses.

Effects on cardiovascular system and gastrointestinal tract

Cinnamophilin in cinnamon was found to be a thromboxane A_2 (TXA_2) receptor-blocking agent; and therefore its antagonistic effect was shown in TXA_2-induced human platelet aggregation, rat aortic ring contraction, and contraction of guinea pig tracheal rings (Yu, 1994a). Intravenous administration of arachidonic acid (50 μg/kg body weight) to a guinea pig induces bronchoconstriction, whereas when cinnamophilin is pre-administered (0.1 mg/kg body weight, *i.v.* at 1 min before arachidonic acid), the bronchoconstriction is abolished (Yu, 1994a). Cinnamophilin (1-15 μM) also possesses a voltage-dependent Ca^{2+} channel-blocking action, which was judged from its antagonism toward high K+(60 mM)- and Bay K 8644 (0.1 μM)-induced contraction of rat thoracic aorta (Yu, 1994b). Su *et al*. demonstrated that the inhibition of sodium inward current, calcium inward current, and transient outward currents of both may contribute to the anti-arrhythmic activity of cinnamophilin against ischemia-reperfusion arrhythmia (Su, 1999).

Anticancer and immunomodulatory activities

An early study on water-soluble extracts of cinnamon showed that it increases the glutathione *S*-transferase (GST) activity in mice administered urethane, a carcinogenic substance, and prevents carcinogenesis (Abraham, 1998). Furthermore, an aqueous extract of cinnamon reduces cellular proliferation and blocks the cell cycle of Jurkat, Wurzburg, and U937 cells at the G2/M phase (Schoene, 2005). Cinnamaldehyde or its source *C. cassia* powder is reportedly a potent inducer of apoptosis in human promyelocytic leukemia cells, in which the aldehyde stimulates an apoptotic cascade leading to the activation of caspase-3 (Ka, 2003, Nishida, 2003). 2'-Hydroxycinnamaldehyde and 2'-benzoloxycinnamaldehyde isolated from the bark

of *C. cassia* show cytotoxicity against several human solid tumor cells such as HCT-15 and SK-MEL-2 cells (Lee, 1999). Koh *et al*. (1998) reported that both of these compounds inhibit lymphocyte proliferation and modulate T-cell differentiation *in vitro*.

Antiulcerative activity

The antiulcerative effect of a cinnamon extract has not yet been clarified, but the effect of a water extract of cinnamon on serotonin-induced gastric lesions in mice was studied. A palliative effect is observed after oral administration of the extract at a dosage of 5–10 mg/kg body weight (Keller, 1992).

Antiinflammatory activity

Nagai *et al*. (1982a, 1982b) proved that complement-dependent reactions including reversed passive cutaneous anaphylaxis, Forssman cutaneous vasculitis, nephrotoxic serum nephritis classified as type II, and the Arthus reaction classified as type III are clearly inhibited by an aqueous extract of *C. cassia*. However, this extract does not affect the nephritis caused by the F(ab')2 portion of the nephrotoxic IgG antibody. The aqueous extract of *C. cassia* at a high concentration (200 mg/kg body weight) inhibits the immunological hemolysis and the chemotactic migration of neutrophils caused by activated serum complement as well as the generation of chemotactic factors. They also showed that the type IV reaction found in contact dermatitis is not affected by the aqueous extract of *C. cassia* but that the production of hemolytic plaque-forming cells is slightly inhibited by it. Their findings suggest that an aqueous extract of *C. cassia* has an anti-complement activity and inhibits complement-dependent allergic reactions.

Antioxidant activity

Mancini-Filho *et al*. (1998) demonstrated the antioxidant activity of cinnamon extracts by using an oxidative β-carotene/linoleic acid system, and they suggested that the cinnamon extracts can be used not only for improvement of food palatability but also for prevention of food oxidation.

Cinnamon bark extracts prepared with water and alcohol as well as its essential oil were tested in two different *in vitro* systems, i.e., peroxynitrite-induced nitration and lipid peroxidation. The essential oil and its component eugenol both show antioxidant activity in these systems (Shobana, 2000; Dragland, 2003; Khan, 2003; Chericoni, 2005; Kim, 2006a).

Cinnamon barks from *C. zeylanicum*, *C. cassia* or other cinnamon species are reported to exhibit antioxidant and free radical-scavenging activities, some of which were measured by using 1,1-diphenyl-2-picrylhydrazine (DPPH; Mancini-Filho, 1998; Shobana, 2000; Okawa, 2001; Dragland, 2003).

Cholesterol- and lipid-lowering effects

Administration of cinnamon to mice increases their HDL-cholesterol level and decreases their plasma triglyceride one (Kim, 2006a). Khan *et al*. (2003) reported that cinnamon improves the blood glucose, triglyceride, total cholesterol, HDL cholesterol and LDL cholesterol levels in patients with type 2 diabetes.

Antidiabetes effect

Recently, the anti-diabetic effect of cinnamon has been studied intensively by many investigators (Anderson, 2004; Chase, 2007; Pham, 2007; Shen, 2010). They commonly found that cinnamon improves insulin resistance and glucose metabolism *in vitro* and *in vivo* (Subash, 2007; Kannappan, 2006; Kim, 2006a; Berrio, 1992; Broadhurst, 2000; Cao, 2007; Imparl-Radosevich, 1998; Jarvill-Taylor, 2001; Khan, 1990; Kim, 2006b; Kreydiyyeh, 2000; Lee, 2011; Roffey, 2006; Taher, 2004; Talpur, 2005; Onderoglu, 1999; Qin; 2003; Qin, 2004; Verspohl, 2005). Among the components of cinnamon, cinnamaldehyde significantly and dose-dependently decreases the plasma glucose concentration of streptozotocin-induced diabetic rats (Subash, 2007). Regarding the mechanism underlying these effects, Shen *et al*. (2010) reported that cinnamon extracts promote the transportation of glucose by glucose transporter 4 in brown adipose tissue and muscles. Clinical research studies support the positive effects of cinnamon on both types 1 and 2 diabetes mellitus (Mang, 2006; Suppapitiporn, 2006; Vanschoonbeek, 2006; Altschuler, 2007; Blevins, 2007; Wang, 2007).

Conclusions

As has been reported, cinnamon, as forms of bark, bark powder, extracts or its isolated components, has multifunctional activities promoting the health of human beings. Different from therapeutic drugs, cinnamon can be used daily in our diet without ill effect. Therefore, it may be preventive especially against the lifestyle-related illness or metabolic syndrome.

Although we did not mention in this review on cinnamon that it is also a representative agonist of the transient receptor potential A1 (TRPA1) cation channel

(Iwasaki, 2008), many of the pharmacological activities of cinnamon might be exhibited via this receptor; e.g. the effects on cardiovascular and gastrointestinal systems might be regulated more or less by nervous systems via TRPA1. The anticancer and anti-inflammatory activities could also be explained partly by sympathetic nerves stimulated via TRPA1.

Taking the self-protective antifungal and antioxidant activities of cinnamon into account, cinnamaldehyde, cinnamophilin, and other components possess both direct and indirect activities; i.e., the antifungal and antioxidant activities occur by direct action on fungus or oxidant, whereas the antidiabetic, anticancer, and antiinflammatory ones occur indirectly via some yet undefined receptor-mediated mechanisms.

The remarkable health benefits of cinnamon prompt us to explore derivatives of cinnamon that might be much more useful structures for overcoming the metabolic syndrome.

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