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REVIEW PAPER OPEN ACCESS

A Review of *Cinnamon* as antioxidant in the amelioration of oxidative stress related disorders

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Abstract

Cinnamon is often known as plant of tropical medicine. Its bark is commonly used as a spice in cooking on the daily basis around the world. It also has beneficial medicinal characteristics in the prevention or treatment of different chronic diseases. It is beneficial in oxidative stress, controlling the blood glucose level, blood pressure, blood lipids, and insulin sensitivity. It is used as powdered form, aqueous extract and essential oil. A number of cinnamon constituents have been isolated and are considered responsible for positive health effects. In this article, a brief review of several studies on cinnamon, its constituents and their potential medical uses are critically explained.

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Introduction

Herbs may truly consider as a part of Nature's pharmacy. Herbal remedies are generally gentler and safer in their action and are a major source of many of the drugs used in Eastern as well as Western folk medicine (Vangalapati *et al.*, 2012). Due to the nutritional and pharmaceutical values, the plant materials are being indigenously used as household remedies of various health related issues in the developing and developed countries (Khalid *et al.*, 2014). These plants have been analyzed for their mineral, phenolic and nutritional profile (Rao and Møller, 2011). *Cinnamon* mainly include aroma and cologne and can be used into varieties of perfumes, food products, cosmetics, toiletries and disinfectants used in hospitals (Huang *et al.*, 2007; Urbaniak *et al.*, 2013). The spice is obtained from the brown bark, which forms longitudinal striated quills. Cinnamaldehyde and trans-cinnamaldehyde are the most important components of *Cinnamon* present in the essential oil while catechins and procyanidins have been found in *cinnamon* bark (Yeh *et al.*, 2013). Trans-cinnamaldehyde obtained from the essential oil of *C. zeylanicum* is an antityrosinase (Marongiu *et al.*, 2007; Chou *et al.*, 2013). These procyanidins extracted from cinnamon have antioxidant activities (Peng *et al.*, 2014). The *Cinnamon* plant is native to Sri Lanka, Indonesia, South America, South Eastern India, the West Indies and Sri Lanka produces nearly 90% world's true cinnamon.

Cinnamon is also used as anti-inflammatory, larvicidal of mosquito (Cheng *et al.*, 2004), insecticidal (Cheng *et al.,* 2004), antitermitic (Tung *et al.*, 2010), nematicidal (Kong *et al.*, 2007), anti-mycotic (Dhulasavant *et al.*, 2010; Bandara *et al.*, 2012), anticancer agent (Koppikar *et al.*, 2010; Lu *et al.*, 2010) and used for decrease of perineal pain and refining healing of episiotomy incision (Mohammadi and Oshaghi, 2014).This review provides the antioxidant behavior and some medical uses of cinnamon for controlling the oxidative related diseases.

Historical Background and Traditional Uses

Cinnamon was used as spice for thousands of years. It belongs to botanical Division of Mangnoliophyta, Class Magnoliopsid, Family Lauraceae and many of them are spicy, aromatic, flavouring agent with positive health effects (Lee and Balick, 2005; Timotius *et al.*, 2015). It is mentioned in the Bible, Greek, Roman Theophrast, Herodot, Dioskurides, Galenus and Plinius liturature. Dioskorides delineated five cassia and seven cinnamon species where the cinnamon species were rumoured as possessing diuretic and digestive properties. In the 8th century, cinnamon was introduced in Europe as a delicacy spice. Arabian utilized it around 1275 where, Johannes of Montevino confirmed the existence of cinnamon trees in Ceylon in 1310 (Qin *et al.*, 2010; Najafi and Taherpour, 2014). It was also employed in preserving fluids in Egypt. In Ayurvedic drugs, its natural bark was employed as anti-diarrheal, antiemetic, antiflatulent and common stimulant. The other Portuguese seeing trees of cinnamon growing in Sri Lanka (Ceylon) in the early sixteenth century and thence import cinnamon ensued to Europe during the sixteenth and seventeenth centuries.

The cultivation of cinnamon started around 1765 in Netherlands. The British took over in 1796 and the cinnamon cultivation and mercantilism became a monopoly of the British Eastern-Indian Company. Around 1833, when The Netherlands developed the cultivation of cinnamon in Java and Sumatra, the herb and the volatile oil were introduced into drugs as a stimulant and cardiotonicum. The oil was prepared for the first time by St Amando of Doornyk at the end of the fifteenth century. It was also used traditionally as tooth powder, treat toothache oral micro biota, and breathe problems (Gupta *et al.*, 2012a). In the present time, Sri Lanka is the main regular exporter of cinnamon leaf oils and its bark for food stuff and pharmacological industrialists (Barceloux, 2009).

Cinnamon is also added to flavour chewing gums in addition to its uses as a spice and flavour agent due to its mouth inspirational effects and capability to get rid of bad breath (Jakhetia *et al.*, 2010). Cinnamon can also rally the health of the colon plummeting the danger of colon cancer (Wondrak *et al.*, 2010) and easing intestinal damage (Wang *et al.*, 2015).

Cinnamon is a coagulant and stops bleeding (Hossein *et al.*, 2013). Cinnamon also upsurges the blood circulation towards the uterus and other advances tissue regeneration (Minich and Msom, 2008).

Important compounds in Cinnamon

Different parts of *Cinnamon* including leaves, bark, roots flowers, fruits stalk and buds showed variations in composition. Cinnamon contains a vast variety of viscous compounds, including cinnamic acid, cinnamate, cinnamaldehyde and vital oils. The active phyto-constituents are cinnamaldehyde and eugnols. Singh and Mitra (2007) reported that the spiced taste and scent are due to the occurrence of cinnamaldehyde.

As cinnamon old, it causes blackening in colour; increase the viscous compounds (Singh *et al.*, 2007). Important chemical components of different parts of Cinnamon are provided in the table 1(Vangalapati *et al.* (2012).

Table 1. Important chemical components of different parts of Cinammon.

Part of the plant	Compounds
Leaves	Cinnamaldehyde: 1-5% Eugenol: 70-95%
Bark	Cinnamaldehyde: 65-80% Eugenol: 5-10%
Bark of Root	Camphor: 60%
Fruit	Caryophyllene (90-14%) and Cinnamyl acetate (42-54%)
Buds	Oxygenated terpenoids: 9% alpha-Bergamotene: 27.38% Terpene hydrocarbons: 78% alpha-copaene: 23.05%
Flowers	trans-alpha-Bergamotene: 7.97% (E)-Cinnamyl acetate: 41.98% Caryophyllene oxide: 7.20%

Role as Antioxidant

Animal body is continuously exposed to different type of the toxic substance that produces oxidative stress (Asghar *et al.,* 2016; Khan *et al.*, 2016b). Oxidative stress actually occurs due to the generation of the reactive oxygen species and disturbance in the level with body antioxidant system (Khan *et al.*, 2016). Antioxidants are essential for human body that neutralizes the free reactive oxidant species (ROS). Thus, antioxidants that are present in food materials have an important role in human life as health-saving agents. Antioxidants are also used as key additives in fats, oils and in the food processing industry for the prevention of food from spoilage (Khan *et al.*, 2015; Khan *et al.*, 2015a). However, in the current time, spices and medicinal plants are considered as sources of beneficial antioxidants against a number of different age-related diseases (Gunawardena *et al.*, 2002; Suhaj *et al.*, 2006). Antioxidants are able to react with free radicals and can respond to the damage in metabolism disorders and syndromes (Manosi *et al.*, 2013; Gunawardena *et al.*, 2015).

Cinnamon oil has been reported for potentially exhibiting superoxide dismutase- (SOD) activity as specified by the hang-up of pyrogallol autoxidation.

Cinnamon also has different flavonoids and phenolic compounds that have antioxidant character and free-radical-scavenging capabilities (Rao and Gan, 2014). It also assists as dietary sources of natural antioxidant for refining human nutrition and health (Shobana and Naidu, 2000).

Anti-Inflammatory properties

Chronic inflammation is an important element in a number of age-related problems (Gunawardena *et al.*, 2015). Cinnamon and its essential oils have anti-inflammatory activities (Tung *et al.*, 2010; Kandhare *et al.*, 2013; Manosi *et al.*, 2013). Some examples of important flavonoid compounds isolated with anti-inflammatory activities are hesperidin, gossypin, hibifolin, hypolaetin, gnaphalin, oroxindin, and quercetin (Chou *et al.*, 2013).

Cinnamaldehyde reported to inhibit nitric oxide production which has been implicated in causing inflammation. It also inhibits cyclooxygenase-2 catalyse prostaglandin E2 biosynthesis (Manosi *et al*., 2013). Various components of *C. ramulus* displayed anti-inflammatory activity. This is due to ability to reduce the expression of nitric oxide production (iNOS), nitric oxide (NO) and cyclooxygenase-2 (COX-2) creation in the nervous system. In this manner, *C. ramulus* might be used for the remedial or preclusion of inflammation-mediated neurodegenerative diseases (Kwon *et al*., 2009). In addition, the aqueous extract of cinnamon is helpful in controlling the lipopolysaccharide tempted tumour necrosis factor-α level in the serum (Hong *et al*., 2012). In another study by Du *et al*. (2014), the essential oil of *C. longepaniculatum* has anti-inflammatory activity in dose dependent reduction of the connective tissue injury, paw thickness and the infiltration of inflammatory cell. The production of PGE2, histamine and 5-HT in the exudates of edema paw induced by carrageenan was also significantly reduced by the essential oil. The ethanolic extract of cinnamon (70%) has been effective on acute inflammation in mice (Manosi *et al*., 2013).

Antimicrobial and antifungal properties

A number of studies indicate that cinnamon is a natural antimicrobial agent. Cinnamon and its oils reported for their antimicrobial activities in a number of studies (Becerril *et al*., 2007; Gende *et al*., 2008; Manosi *et al*., 2013). A combination of cinnamon and clove oil shows antibacterial activity against Gram-positive organisms e.g., *Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes* and *Enterococcus faecalis* as well as Gram-negative organisms e.g., *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella choleraesuis Yersinia enterocolitica* (Goni *et al*., 2009). A recent study indicated that the cinnamon extract show antimicrobial activity against oral inhibiting micro flora and its oil has a greater potential than further plant extracts, e.g., *Syzygium aromaticum* and *Azadirachta indica* (Parthasarathy and Thombare, 2013). According to Buru *et al*. (2014) the volatile oils of bark from stem of *C. porrectum C. altissimum*, and *C. impressicostatum* showed a significant antibacterial activity against a varied number of Gram-negative and Gram-positive bacteria. This supports the traditional use of *Cinnamomum* species for the treatment of wound infections. Fratini *et al*. (2014) investigated the antimicrobial activities of *C. zeylanicum* against six bacterial strains.

Urbaniak *et al*. (2013) determined that the cinnamon bark oil has an antibacterial potential and can be used in toiletries and disinfectants, cosmetics, applied in hospital environment as an alternative antimicrobial agent against Gram-negative and Gram-positive bacteria belonging to *Acinetobacter* genera *Staphylococcus* and *Enterococcus*, *Enterobacter* from different clinical specimens. Abd El-Aziz *et al*. (2015) also found the strong antimicrobial and antifungal potential of cinnamon essential oil against fungal growth and aflatoxin production in *A. flavus* and *A. parasiticus*.

Synergic role in Neurological Disorders

Cinnamophilin extracted from cinnamon reported to protective against ischemic injury in brain rat treated at 80mg/kg at the time breaks of 2, 4, and 6 hours after treatment. It has a significant effect (34 to 43%) on shortened brain infarction and further improves the neurobehavioral (Lee *et al*., 2005). Cinnamophilin intensely reduces the oxygen glucose deficiency induced damage of neurons in hippocampus rats (organotypic). Procyanidin type-A trimmer isolated from water-soluble extract of cinnamon showed reduction in cell bulge by amendable the drive of intracellular calcium (Panickar *et al*., 2012). It also significantly relieves the oxygen glucose deprivation-induced damage on uptake of glutamate possibly mediated through effects on the mitochondria (Panickar *et al*., 2012).

Parkinson's disease is second most important neurodegenerative disorder after Alzheimer's disease with an incidence of 2% patients at age of 65 years and older people (Bonifati *et al*., 2004). PARK7 defends cells from harm and additional injury by oxidative stress and therefore this protein might be used for an active therapeutic mediation of Parkinson's disease (Khasnavis and Pahan, 2012).

Sodium benzoate, a cinnamon metabolite, has ability of up regulating DJ^{-1} by controlling the metabolites of mevalonate (Brahmachari *et al.*, 2009; Khasnavis and Pahan, 2012). Jana *et al.* (2013) found cinnamon and sodium benzoate (its metabolite) regulate the neurotropic neurotropic factors derived from brain and neurotrophin-3 (NT-3) in the mouse CNS. Aqueous extract of *C. zeylanicum* also reported to reduce the aggregation and filament formation, most important characteristics of Alzheimer's disease. (Peterson *et al.*, 2009). This indicates the potential of cinnamon for the Alzheimer's disease treatment.

Synergetic role in cancer

Different kind of cancer is usually controlled through the use of the chemical substances including the nanoparticles e.g. the nano-ceria (Khan *et al.*, 2015) silver nanoparticles (Khan *et al.*, 2015a). However, the interest towards the natural substances is increasing due to less deleterious effects (M. S. Khan *et al.*, 2016). The extract (aqueous) and the procyanidins fraction of cinnamon can constrain vascular endothelial growth activities of kinase. Therefore, there is a potential of inhibiting the angiogenesis involved in cancer and hence cinnamon can potentially be used for cancer prevention (Lu *et al.*, 2010).

According to a study by Kwon *et al.* (1997), cinnamaldehydes from cinnamon has a potential as inhibitor against angiogenesis disorder. Jeong *et al.* (2003) stated that a chemical substance which can be produced from 2-hydroxycinnamaldehyde derived from cinnamaldehyde, called CB403, can prevent tumour growth. Overall, many *in-vivo* and *in-vitro* studies show that cinnamon can be used as an anticancer agent due to the antitumor and growth inhibitory potential of CB403. Fang *et al.* (2004) stated the anticancer effect of trans-cinnamaldehyde obtained from the source of *C. osmophloeum*, verdict that trans-cinnamaldehyde presented potential effects in restraining growth and produces the apoptosis. *C. zeylanicum* aqueous extract can persuade apoptosis in the human myelocytic leukaemia cell line (Assadollahi *et al.*, 2014); whereas the oils from *C. cassia* extracted prevent alpha melanocyte stimulating hormone's persuaded melanin production, thereby overwhelming murine B16 melanoma oxidative stress (Chou *et al.*, 2013).

Glycaemic control

Diabetes is a disorder of metabolism. Millions of people around the globe are affecting day by day. Therefore, new drugs or functional foods that contain selective α-glucosidase inhibitors are required (Kongstad *et al.*, 2015). A substance "insulin-potentiating factor" has been isolated from cinnamon. The studies showed the anti-diabetic activities of cinnamon bark in streptozotocin-induced diabetic rats. Numerous studies have also discovered that cinnamon extracts lower blood glucose as well as cholesterol levels (Blevins *et al.*, 2007; Crawford *et al.*, 2009).

The studies showed that water soluble polyphenol enhanced extracts of *C. zeylanicum* Gallic acid equivalents of polyphenol content had better antioxidant potential and significant decrease in glucose and lipids and other biochemical parameters. Furthermore, 'procynz-45' containing 45% GAE polyphenols at a dose level of 125 mg twice per day for 30 days administered to fifteen volunteer humans with elevated fasting blood glucose levels and were not taking any medications, lowered blood glucose levels and ameliorated oxidative stress. Cinnamaldehyde extracted from cinnamon has been found to have insulinotropic effect in insulin deficiency (El-Bassossy *et al.*, 2013). Cinnamon extract has also affect the insulin action in the brain and brain activity during locomotion, which shows that cinnamon, can mediate metabolic changes in the periphery to decrease liver fat and improve glucose homeostasis (Sartorius *et al.*, 2014).

Cardiovascular and related Diseases

Heart diseases are common around the world with huge number of causalities (Khan *et al.*, 2016). Large number of studies has stated the defensive effects of cinnamaldehyde on the cardiac system (Hwa *et al.*, 2012). A study by Song *et al.* (2013) studied the possible effects of two compounds, cinnamic aldehyde and cinnamic acid,

isolated from C. *cassia* against ischemia (Song *et al*., 2013). Cinnamophilin have the potential of thromboxane synthase inhibition and helpful in disorders such as platelet aggregation and cancers (MA *et al*., 2006; El-Bassossy *et al*., 2013).

Toxicity of Cinnamon

Cinnamon no doubt has positive health effects against many chronic diseases but its uses with other medications and overdose can cause serious negative effects. It should be taken carefully and one should know the species and the components present in that particular species. According to U S department of health the recommended dose of cinnamon is six grams per day for about six weeks. High dose of cinnamon can damage liver due to presence of Coumarin (5%) that is dangerous to human body. In pregnant woman, cinnamon can induce premature labour pain and uterine contraction. Cinnamon can cause allergy especially in children, the symptoms of allergy may be running of nose, soreness of eyes, watery eyes and shortness of breath. Cinnamon oil causes skin irritation especially in young ones and cinnamon powder produces allergy to the touching hands. Cinnamon acts as an antibiotic so while taking other antibiotic, the use of cinnamon should be stopped as high level of antibiotics disturb metabolism (Civitello, 2011). Frequent and over use of cinnamon also produces body heat like alcohol, black pepper, lobster and coffee. Like cinnamon oil that burns the skin directly where it is applied, the candy and gum that contain cinnamon can also irritate the tissues inside the mouth.

Conclusion

This review concluded that Cinnamon can be effectively used in prevention and treatment of chronic diseases. It is also effective in controlling of the oxidative stress, blood glucose level, blood pressure, blood lipids, and insulin sensitivity. A number of cinnamon constituents have been isolated to date that are considered responsible for positive health effects. A daily used in feeding can reduce the chance of oxidative stress related disease.

It is further revealed that, the compounds isolated are of medical importance and can be used in the future medicine of plant origin.

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