Diverse pharmacological properties of *Cinnamomum cassia*: A review

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**Abstract:** *Cinnamomum cassia* is widely utilized as a spice in different cookeries worldwide, especially in Asian cuisines. This herb is also being used in different forms of traditional medicine (Unani, Ayurvedic, Japanese and Chinese) for managing conditions like dyspepsia, peptic ulcer disease and ischemic brain injury. Recent studies have shown the scientific evidence for the medicinal use of this particular herb in several diseases like *H. pylori* infection, diabetes, brain ischemia and cancers. This article reviews the literature on potential benefits of the herb published within the last 10 years. The authors used MeSH terms "Cinnamomum" with "cassia" or "aromaticum" to filter the PubMed database. To date, no systemic review focusing on medicinal use of *C. cassia* was found in the literature. Various research articles elucidating diverse pharmacological properties of *C. cassia* were identified. The standardised extract of *C. cassia* or the active compounds extracted from the herb might prove to be a novel candidate for early prevention and complimentary management of conditions like diabetes mellitus or *H. pylori*- associated disorders.

**Keywords:** *Cinnamomum cassia*; anti-inflammatory; anti-microbial; anti- *H. pylori*; anti-melanin; anti-cancer; anti-diabetic.

**INTRODUCTION**

*Cinnamomum cassia* (also known as *Cinnamomum aromaticum*, Chinese cinnamon or Chinese cassia) belongs to Laurel (Lauraceae) family of plant kingdom. It is harvested from the bark of its tree and is used as a flavouring agent in various Asian cuisines. Common cultivating countries are India, China, Uganda, Vietnam, Bangladesh and Pakistan. The herb is intensely aromatic and has a sweet taste with a tinge of bitterness. The herb is also used in different forms of traditional medicine. Recently, various studies have reported the medicinal use of this herb in different diseased conditions such as diabetes mellitus, peptic ulcer diseases, and various cancers (Gernot, 2012).

To generate a comprehensive and up-to-date evidence-base for the pharmacological and medicinal use of this herb, studies published within last ten years (2002-2012), including a study from our group, were reviewed and summarised. MeSH terms “Cinnamomum” with "cassia” or “aromaticum” were employed to explore the PubMed and Google Scholar databases. All the studies exploring the effect of this herb were included regardless of outcome of drug on the effect. This study outlines the published uses of this herb to treat diseases along with underlying mechanism if available.

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**Active constituents**

Major active constituents of *C. cassia* are cinnamaldehyde (75-90%), coumarin (7%) and essential oil (4%) (Ng and Wu, 2011). The other constituents present in trace amount include eugenol, benzoic acid, cinnamic acid, salicylic acid, cinnamyl alcohol and the corresponding esters and aldehydes (Ng and Wu, 2011) (fig. 1). The average daily intake (ADI) of cinnamaldehyde permitted by Food and Drug Administration and World Health Organization (FDA/WHO) for an adult male is 1.25mg/kg (Ng and Wu, 2011).

**Properties**

The active chemicals in *C. cassia* has been reported to have anti-inflammatory, anti-oxidant, anti-cancer, anti-fungal, anti-pyretic, antimicrobial, anti-angiogenic and larvicidal activity (Lee et al., 2007; Ng and Wu, 2011). Anti-hepatoma activities of *C. cassia* are also reported and the proposed mechanism may include induction of signalling factors within hepatic cells (Lee et al., 2007). Studies have also examined whether *C. cassia* improves glycemic index, insulin resistance, and glucose tolerance in diabetics. Although various studies have supported the anti-diabetic claim by showing various molecular mechanisms (discussed below), only few have used clinical trials to support this claim (Rafehi et al., 2011; Markey et al., 2011; Mohamed et al., 2011; Lee, 2002, Kwon et al., 2006; Vanschoonbeek et al., 2006).
Cinnamic acid, a constituent of *C. cassia* might act as a depigmenting agent by its effect on melanin synthesis pathway (Kong et al., 2008). *C. cassia* and cinnamon oil has potent nematicidal activity against *Bursaphelenchus xylophilus* (Kong et al., 2007). Guizhi-Fuling-Capsules (GZFLC), a traditional Chinese formulation containing *C. cassia*, has shown to be protective against brain ischemic damage (Li et al., 2007). Also, synergistic effects of *C. cassia* together with several other herbs have been suggested for a polyherbal mixture as a potent anti-oxidant (fig. 2).

**Mechanism of action**

**Anti-bacterial**

*C. cassia* has been shown to have anti-microbial properties against various pathogens. Ethanol extract of *C. cassia* has shown to have strong activity against *Pseudomonas aeruginosa*. Disc diffusion method was employed to demonstrate this effect (Sharma et al., 2009). Agar dilution method was utilized to reveal that pure cinnamaldehyde and its oil extracts are effective against *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, *Vibrio parahaemolyticus* and *Salmonella typhimurium*. The minimum inhibitory concentration (MIC) of cinnamaldehyde was reported to be 75 microg/ml to 600 microg/ml (Ooi et al., 2006).

**Anti-fungal**

Cinnamon has demonstrated to have anti-fungal activity against four species of Candida; *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, and *Candida krusei* (MIC: 100 microg/ml to 450 microg/ml), four isolates of molds; three Aspergillus spp. and one Fusarium sp. (MIC: 75 microg/ml to 150 microg/ml) and three isolates of dermatophytes; *Microsporum gypseum*, *Trichophyton rubrum* and *T. mentagrophytes* (MIC: 18.8 microg/ml to 37.5 microg/ml). The MIC was stated after utilizing agar dilution method (Ooi et al, 2006). Another study used mice models and in vitro assay to exhibit the anti-proliferative activity of *C. cassia* on oral candidiasis (*C. albicans*) with cinnamaldehyde as the major compound producing the effect (Taguchi et al., 2010).

**Anti-diabetic**

There is an on-going debate whether *C. cassia* possesses anti-diabetic effect (Rafehi et al., 2011). A clinical trial evaluated *C. cassia* to observe improvement in fasting serum glucose, insulin sensitivity and lipid profile in post-menopausal diabetics (type II) (Vanschoonbeek et al., 2006). The difference compared with a placebo was statistically not significant as cinnamon supplementation did not improve postprandial response to glucose (7.2±0.2 HBA1c for placebo vs. 7.5±0.3 for *C. cassia*, *P*<0.05) and lipids (2.77±0.24 LDL-cholesterol in placebo vs. 2.85±0.16 for *C. cassia*, *P*<0.05) and neither affected appetite (Vanschoonbeek et al., 2006).

**Studies supporting the anti-diabetic claim have proposed several mechanisms.** One study used cinnamaldehyde derived from *C. cassia* to show inhibition of lens aldose reductase, which mediates the polyol pathway on rat model (Lee, 2002). In a non-diabetic individual glucose is not catabolised to sorbitol because of low enzyme affinity. With higher blood glucose levels, the delivery of glucose to tissues such as lens and nerves is increased and is converted by aldose reductase to sorbitol. Sorbitol is not readily diffusible across the membrane and thus accumulates leading to formation of cataract. Inhibition of this enzyme in diabetes can lead to decreased formation of cataracts as the study demonstrates. The author extracted the lens aldose reductase from the mice models and revealed the final results with spectrofluorophotometer (Lee 2002).

**Additional model** exhibits the reversible competitive inhibition of α-glucosidase in streptozotocin (STZ) nourished mice. Dialysis experiment was implemented to ascertain the nature of this inhibition (Mohamed et al., 2011). Carbohydrate metabolism can be impaired with α-glucosidase inhibitors such as acarbose. This study...
compared *C. cassia* with acarbose as a potential inhibitor of α-glucosidase (control). Cinnamon reduced maltose induced post-prandial glucose spike by 86.3% (600mg) as compared to control 54.2% (5mg) (P<0.001 vs. control). The reduction for sucrose induced post-prandial glucose spike was also significant with a reduction of 67.58% for cinnamon (600mg) against 70.71% for control (5mg) (P<0.01 vs. control).

**Fig. 3:** Multiple actions of *Cinnamomum cassia* against *H. pylori* associated pathogenesis. (T4SS: Type IV secretion system, CagA: Cytotoxin associated gene-A, IKK: IκB Kinase, IκB: Inhibitor of Kappa-B, NF-κB: Nuclear Factor Kappa-B, IL-8: Interleukin-8, SHP-2: Src homology phosphatase-2).

Insulin dependent diabetes mellitus (IDDM type I) is characterized by destruction of pancreatic β-cells in the islets. The inflammatory mechanisms involved include inducible nitric oxide synthase (iNOS) and nuclear factor kappa B (NF-κB) expression, nitric oxide (NO) and interleukin production which ultimately results in β-cell dysfunction. One study showed that 1mg/ml *C. cassia* extract (CCE) can completely block iNOS expression and NF-κB activation at mRNA level in streptozotocin nourished mice. iNOS expression was manifested using RT-PCR and western blotting and NF-κB was assayed by using gel mobility shift assays of nuclear extracts. Hence, a protective effect of cinnamon against diabetes is anticipated in humans (Kwon et al., 2006).

Other studies have shown that cinnamon has insulin secretagogue and insulin sensitizing properties. Insulin signalling pathways are up regulated in skeletal muscles leading to increased glucose uptake. This was illustrated by showing increased expression of insulin dependent substrates i.e. IRS-1/PI 3-kinase on mouse models (Qin et al., 2003).

Another study demonstrated altered body composition in association with improved insulin sensitivity. In this study, high fat/high fructose (HF/HF) diet was fed to rats and then divided into groups with one receiving cinnamon. Pancreatic weight was reduced in HF/HF diet as compared to HF/HF + cinnamon diet (p-value <0.01). Also Cinnamon increased glucose infusion in HF/HF as compared to rats that were only given HF/HF diet without cinnamon (Jain et al., 2011).

**Anti-oxidant**

*C. cassia* ethanol extract has significant anti-oxidant properties (Boga et al., 2011). The underlying mechanism probably includes inhibition of NO production, a potent free radical, via inhibition of NF-κB by cinnamaldehyde. NO activity was assayed *in vitro* using Griess reagent, western blotting and gel electrophoresis (Lee et al., 2005). Cinnamon is used along with several herbs to formulate an herbal tea preparation to lower nitric oxide and oxygen derived free radicals preventing cardiovascular diseases, cancers, arthritis etc. The authors used DPPH free radical scavenging activity, NO scavenging activity and superoxide radical scavenging activity (Jain et al., 2011).

**Anti-cancer**

Cinnamon has been extensively studied for its anti-neoplastic activity. It has anti-proliferative and apoptotic activity affecting variety of cancers including colorectal cancer, human promyelocytic leukemia, hepatoma, cervical cancer, lymphoma and melanoma through several pathways as exemplified using *in vitro* experiments (Lee et al., 2007; Ng and Wu, 2011, Ka et al., 2003). In most cases the most toxic factor for cancer growth was found out to be cinnamaldehyde (Ka et al., 2003).

*In vitro* analysis revealed that CD95 (APO-1/CD95) and p53 pathway is affected by cinnamaldehyde in hepatoma cells. p53 is the guardian of genome as it identifies DNA damage and stops replication cycle allowing the cell to repair its damaged content. If the condition is irreversible, p53 directs the cell to undergo apoptosis by increasing Bax (pro-apoptotic) expression while inhibiting Bcl-xl (anti-apoptotic) expression. p53 is induced by cinnamomum thus increasing apoptosis of hepatoma cells (Ng and Wu, 2011). Cinnamaldehyde induces oxygen radicals to cause disruption of mitochondrial membrane and leakage of cytochrome-c, which prompts program cell death in human promyelocytic leukemia cells (Ka et al., 2003). Her-2 gene is down regulated by *C. cassia* in cervical cancer along with mitochondrial membrane disruption, which results in cell death (Koppikar et al., 2010). Anti-melanoma effects of cinnamon extract are produced by NF-κB and AP-1 inactivation, stimulation of pro-apoptotic factors, and modulation of angiogenesis and cytotoxic T lymphocytes. Anti-apoptotic factors including Bcl-2 and Bcl-xl were found to be suppressed by cinnamaldehyde in the mice-melanoma model (Kwon et al., 2010). The activation of Nrf-2 (nuclear factor-E2-related factor 2) dependent anti-oxidant pathway by cinnamon extract in colon cells has been implicated as chemo-preventive activity for colorectal cancers (Wondrak et al., 2010). Cinnamaldehyde further, inactivated AP-1 transcription factor in colon cancer cells,
which is a source for potential oncogenes (Lee et al., 2007).

**Anti-H. pylori and gastro protective**

Under the traditional Unani medicinal system of Pakistan, the herb has been consumed for curing gastric complaints of diarrhoea, flatulence and vomiting (Zaidi et al., 2009). *H. pylori* is one of the common causes of dyspepsia and various other gastric ailments (Muhammad et al., 2012). Although *H. pylorus* is a non-invasive organism, it stimulates a robust inflammatory and immune response. Bacterial colonization, persistence and virulence, and resulting innate and adaptive host immune responses are all important in the pathogenesis of *H. pylori* related diseases (Muhammad et al., 2013).

An *in vitro* study performed revealed that ethanol extract of Cinnamon has weak anti-*H. pylori* activity by blocking the enzyme urease which is involved in the pathogenesis of *H. pylori* infection of the gut, however, methylene chloride extracts displays a strong anti-*H. pylori* activity, the mechanism of which was not mentioned (Tabak et al., 1999). Human gastric epithelial cells infected with *H. pylori* exhibits reduced IL-8 secretion when treated with *C. cassia*. The concentrations of 50µg/ml and 100µg/ml show the most potent effect and almost totally block the *H. pylori* induced IL-8 secretion. Furthermore, the similar anti-inflammatory effect is also shown in TNF-α (tumour necrosis factor-alpha) stimulated cells, which represent non-infectious inflammatory factors (Zaidi et al., 2012). Furthermore, we also found the inhibition of hummingbird morphology, a characteristic feature of *H. pylori*-infected cells, by *C. cassia* and its major constituent, Cinnamaldehyde, in AGS gastric epithelial cells (data not published) (fig. 3).

**Anti-nematodes**

To the best of our knowledge, only one study has reported nematicidal use of cinnamon extracts against *Bursaphelenchus xylophilus*, which infects pine trees and causes pine wilts. Cinnamaldehyde was found to be the most potent chemical derived from Cinnamon (Kong et al., 2007). More studies performed on animal models or human trials with different nematodes are required to extrapolate and support the nematicidal effect.

**Anti-ischemic and neuroprotective**

Guizhi-Fuling-Capsules (GZFLC) is one of the traditional Chinese medicines composed of five different herbs including *cinnamomum cassia*. In an *in vivo* rat model experiment, this formulation has been shown to have anti-ischemic effect preventing brain infarction. IL-1β (interleukin-1β) and TNF-α, potent inflammatory mediators, are suppressed whereas IL-10 and IL-10 related inflammation negating cytokines are expressed considerably (Li et al., 2007). Further, research could be carried to find out which herb has the best possible aforementioned effect. Experiments carried out on rat model have shown that cinnamon avoids neuronal cell loss tempted by glutamate by hindering of Ca"" influx mechanism (Shimada et al., 2000).

**Anti-inflammatory**

Mous emacrophages were treated with lipopolysaccharide (LPS) endotoxin obtained from *E. coli* to cause inflammation. As a result NO levels were increased in these macrophages which are drastically reduced when macrophages are treated with LPS and cinnamaldehyde with a dose dependent response. The underlying mechanism of this suppression is directly related to inhibition of iNOS, COX-2 (cyclooxygenase-2), 1xBα (NF-kappa-B inhibitor alpha), and NF-κB. LPS also induces TNF-α, which in turn lead to increased expression of IL-1β and interleukin-6 (IL-6). Cinnamaldehyde also blocked TNF-α and Prostaglandin E2 (PGE2) (Liao et al., 2012).

Within the same study, carrageenan was introduced in mouse model to cause paw edema. The edema was shown to be limited by cinnamaldehyde infusion by suppressing NO, TNF-α, and PGE2. This suppression by cinnamaldehyde is due to inhibition of iNOS, COX-2, and NF-κB. Moreover, cinnamic aldehyde also showed anti-oxidant properties by enhancing the enzymes including catalase, super oxide dismutate, and glutathione peroxidase activities (Liao et al., 2012). The above mentioned study was also supported by another study which used the cinnamon extract to block NO, TNF-α and PGE2 in LPS induced inflammation in murine macrophages. The study also reveals a direct blocking of Src (spleen tyrosine kinase) / Syk kinase action to mediate NF-κB action (Yu et al., 2012).

**Anti-melanin**

Guinea pigs were exposed to ultraviolet-B radiation to increase pigmentation of their skin. Cinnamic acid was then applied topically to reduce the pigmentation. Results revealed that cinnamic acid when applied topically reduced skin melanin by 29% without any adverse reactions. Cinnamic acid blocks tyrosinase enzyme to mediate its action, but does not show appreciable activity against dopachrome tautomerase (Kong et al., 2008). Therefore, Cinnamon might be used in cosmetics and beauty products to enhance skin whitening by its effect on melanin bio-synthetic pathway in skin cells. Studies are required to explore possible effect on alpha-melanocyte stimulating hormone and microphthalmia transcription factor (Mitf) expression for de-pigmenting pathway.

**Anti-allergy**

Allergic diseases related to mucosal mast cells, such as food allergies, are thought to be treated by cinnamaldehyde. Inhibitory effects of cinnamaldehyde on phospholipase C (PLC) signalling pathway in human
embryonic kidney cells have been shown (Kim et al., 2008). Similar pathways are thought to play a major role in intracellular mobilization of Ca$^{2+}$ ions in mucosal mast cells. Yahara et al. confirms this by showing inhibition of mucosal mast cell activation via suppression of PLCγ1 signalling pathway (Yahara et al., 2011).

**Pregnancy and lactation**

Although adverse reactions of cinnamon in pregnancy and lactation have not been reported, however, to the best of our knowledge, no study is available to establish a relationship between the herb and its safety and efficacy during pregnancy and lactation.

**CONCLUSION**

Cinnamon has been broadly studied for its anti-microbial, anti-inflammatory, anti-cancer, anti-diabetic, anti-melanin and anti-oxidant effects. Hereby we review these effects with the underlying pathophysiological mechanism and type of study involved. The anti-diabetic effects need to be explored and should be studied extensively as we believe that the data available in this regard is scarce. The emerging multiple mode of actions of cinnamon against H. pylori-related pathogenic pathways also demands for in vivo experiments and clinical trials. In view of all the pharmacological properties discussed above, the therapeutic applications of cinnamon are quite vast and the potential for unveiling more benefits is tremendous. Clinical trials on a large scale would provide a better insight and the true relationship between the molecular, chemical and physical properties.

**REFERENCES**


