Anti-secretagogue and antiulcer effects of 'Cinnamon'
*Cinnamomum zeylanicum* in rats

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The present study was carried out to evaluate the gastric antisecretory and antiulcer activities of 'Cinnamon' *Cinnamomum zeylanicum* in rats. The aqueous suspension of cinnamon (250 and 500 mg/kg) has been screened using pylorus ligation (Shay) rat model, necrotizing agents and indomethacin-induced ulceration in rats. Histopathological assessment was done on gastric tissue of rats. Gastric wall mucus and nonprotein-sulfhydryl contents were also estimated. Cinnamon suspension pretreatment decreased the basal gastric acid secretion volume and rumenal ulceration in pylorus ligated rats. The suspension effectively inhibited gastric hemorrhagic lesions induced by 80% ethanol, 0.2 M sodium hydroxide, and 25% sodium chloride. The cinnamon suspension also showed antiulcer activity against indomethacin. Pretreatment with cinnamon suspension offered a dose-dependent protection against various histological indices. Treatment of rats with cinnamon replenished the ethanol-induced decreased levels of gastric wall mucus and nonprotein-sulfhydryl concentrations. The gastroprotection of cinnamon observed in the present study is attributed to its effect through inhibition of basal gastric secretion (attenuation of aggressive factors) and stimulation mucus secretion (potentiation of defensive factors); and increase in nonprotein-sulfhydryl concentration probably due to prostaglandin-inducing abilities mediated through its antioxidant property.

**Key words:** Cinnamon, *Cinnamomum zeylanicum*, gastric secretion, antiulcer, histopathological changes.

**INTRODUCTION**

'Cinnamon', *Cinnamomum zeylanicum* Nees (Lauracea), locally known as Qerfah or Darsin is an ancient and important spice with wide applications in flavoring, perfumery, beverages and medicines (Jayaprakasha et al., 2003). In Arabian and Unani systems of medicine, cinnamon has been considered to be an aromatic, astringent, and carminative. Local inhabitants have used cinnamon bark powder to treat nausea, vomiting, flatulence, dyspepsia, abdominal colic, and heart burn. Cinnamon bark is an important component of some Japanese herbal compounds, which have been reported to possess an antiulcer activity (Osawa et al., 2002). Akira et al. (1986) also reported an antiulcerogenic property of Chinese cinnamon. In some earlier studies, an antibacterial effect of cinnamon ethanolic and aqueous extracts against *Helicobacter pylori* has also been reported (Nostro et al., 2005). The essential oil of cinnamon is known to have antibacterial (Jirovetz et al., 2002), antifungal (Misra et al., 2000), ovicidal and antiparasitic activities (Young-Cheol et al., 2005). Earlier, some studies also suggested that cinnamon possesses strong free radical scavenging capacity (Bafna and Balaraman, 2004). Recently, Unlu et al. (2010) reported the antimicrobial and anticarcinogenic properties of an essential oil of *C. zeylanicum* bark.

Since there are no scientific reports available in the existing literature on antiulcer effect aqueous suspension of cinnamon (ASC) (a common dosage form among Unani and Arab traditional medicine). Therefore, the present study was undertaken to investigate anti-secretagogue and antiulcer activities of an aqueous suspension of cinnamon in-vivo test models in rats.
MATERIALS AND METHODS

Plant and preparation of aqueous suspension

Cinnamon bark was purchased from local market in Riyadh, and was identified by an expert taxonomist, bearing voucher specimen number 278 and deposited in the herbarium of the Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia for future reference. The bark was ground to a very fine powder (Mesh number 70 µ) and was used as an aqueous suspension (a known amount of the powder dissolved in the known amount of H2O) for treatment in different experiments.

Animal stock

Wistar albino rats of either sex (home bred) aged 7 to 8 weeks and weighing 150 to 200 g, were obtained from the Experimental Animal Care Centre, King Saud University, Riyadh, Saudi Arabia. The animals were fed on Purina chow diet and water ad libitum, and were maintained under standard conditions of humidity (55 ± 5%), temperature (22 ± 2°C) and light (12 h light/12 h dark cycle). The rats were randomly assigned to different control and treatment groups (n = 6 animals per group). The conduct of experiments and the procedure of sacrifice (using ether) were approved by the Ethics Committee of the Experimental Animal Care Society, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Determination of anti-secretory activity

The method of Shay et al. (1945) was used to determine the anti-secretory activity. The animals were fasted for 36 h with free access to water. Ligation of the pylorus was done under light ether anesthesia. Care was taken not to bleed or occlude the blood vessels. Aqueous suspension of cinnamon was administered intra-peritoneally, immediately after pylorus ligation. Their stomachs were removed, contents collected, measured, centrifuged and subjected to analysis for titratable acidity against 0.01 N NaOH to pH 7. Each stomach was examined for lesions.

Gastric lesions induced by necrotizing agents

The animals in the test groups were given 1 ml per rat of different necrotizing agents (80% ethanol, 0.2 M NaOH, and 25% NaCl), which are known to produce gastric lesions (Robert et al., 1983). Cinnamon suspension was given 30 min before the necrotizing agents to 36 h fasted rats. Animals were sacrificed under ether anesthesia 1 h after treatment with ulcerogenic agents. The stomach was excised and opened along the greater curvature. After washing with normal saline, the gastric lesions were quantified by an expert using a binocular magnifier. The ulcers were scored and assessed according to the method described by Valcavi et al. (1982).

Gastric wall mucus determination

The modified procedure of Corne et al. (1974) was used to determine gastric wall mucus. The glandular segments from the stomachs were removed and weighed. Each segment was transferred immediately to 1% Alcian blue solution (in sucrose solution, buffered with sodium acetate pH 5), and the excess dye was removed by rinsing with sucrose solution. The dye complexed with the gastric wall mucus was extracted with magnesium chloride solution. A 4 ml aliquot of blue extract was then shaken with an equal volume of diethyl ether. The resulting emulsion was centrifuged and the absorbance of the aqueous layer was recorded at 580 nm. The quantity of Alcian blue extracted/g (net) of glandular tissue was then calculated.

Histopathological assessment

The gastric tissue was fixed in 10% ethanol buffer formalin and was processed through graded ethanol, xylene and impregnated with paraffin wax; sections were made by microtome. After staining with haemotoxylin and eosin stain (Culling, 1974), the sections were examined under a research microscope. The different histopathological indices screened were: congestion, hemorrhage, edema, necrosis, inflammatory and dysplastic changes, erosions, and ulcerations.

Gastric lesions induced by indomethacin

Indomethacin was suspended in 1.0% carboxy-methylcellulose in water (6 mg/ml) and was administered orally to the fasted rats in a dose of 30 mg/kg, body weight (0.5 ml/100 g) (Bhargava et al., 1973). Cinnamon suspension was administered (250 and 500 mg/kg, orally) 30 min before indomethacin. Control rats were treated similarly with an equivalent amount of the vehicle, the animals were sacrificed 6 h after the treatment.

Estimation of nonprotein sulphydryl groups (NP-SH)

Gastric mucosal (NP-SH) was measured according to the method of Sedlak and Lindsay (1968). The glandular stomach was removed and homogenized in ice-cold 0.02 M ethylenediaminetetraacetic acid (EDTA). The homogenate was mixed with distilled water and 50% (w/v) aqueous trichloroacetic acid (TCA) and centrifuged; the supernatants were mixed with phosphate buffer (pH 8), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) was added and the sample was shaken. The absorbance was read within 5 min of addition of DTNB, at 412 nm, against a reagent blank with no homogenates.

Determination of LD50 in mice

Swiss albino mice were divided into various groups and each group was orally treated with cinnamon suspension in the various dose ranges. Following treatments, the animals were observed for 2 continuous hours and thereafter at intervals of 4 to 12 h for up to 72 h. All behavioral changes and death during the observation period were recorded. The percentage of death in each group was then calculated. LD50 was then determined using the methods outlined by Ghosh (1984).

Statistical analysis

Values are given as arithmetic means ± standard error of the mean (SEM). The data were statistically analysed using a one-way analysis of variance (ANOVA), followed by Student’s t-test.

RESULTS

Effect on antisecretory activity

Effect on pylorus ligation for 6 h resulted in the
accumulation of basal gastric acid secretory volume, an increase in the titratable acidity, and ulcers which were mainly confined to the forestomach. ASC in doses of 250 and 500 mg/kg produced significant dose dependent decrease in the volume of basal gastric secretion (P < 0.001) and ulcer index (P < 0.001) (Table 1). However, the decrease in the titratable acidity was not significant.

Effect on gastric wall mucus

A gastric wall mucus decrease was observed in the animals treated with 80% ethanol and this depletion of wall mucus was significantly (P < 0.05) reversed by pretreatment with the dose of cinnamon suspension (500 mg/kg) (Figure 2).

Effect on gastric histopathology

Pretreatment with cinnamon suspension was found to protect different histopathological abnormalities (congestion, haemorrhage, edema, necrosis, inflammatory and dysplastic changes, erosions and ulcerations) in the gastric mucosa of ethanol treated rats (Figure 3a to d).

Effect on gastric lesions induced by indomethacin

Administration of indomethacin resulted in the production of gastric mucosal damage mainly in the glandular segment of the stomach. Pretreatment of the animals with cinnamon suspension effectively reduced (P < 0.05) the intensity of ulceration at a dose of 500 mg/kg dose (Figure 4). Although, there was a decrease of the ulcers in the animals that received cinnamon in a dose of 250 mg/kg, but this ulcer prevention was not statistically significant.

Table 1. Effect of an aqueous suspension of cinnamon on the volume of gastric secretion, titratable acidity and the degree of ulceration in 6 h pylorus ligated (Shay) rats.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg, body weight) (IP)</th>
<th>Volume of gastric content (ml)</th>
<th>Titratable acid (mEq/L)</th>
<th>Ulcer index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.0 ml/rat tap water</td>
<td>7.50 ± 0.4</td>
<td>118.33 ± 6.25</td>
<td>1.00 ± 0.26</td>
</tr>
<tr>
<td>ASC</td>
<td>250</td>
<td>2.67 ± 0.70***</td>
<td>83.33 ± 26.47</td>
<td>00***</td>
</tr>
<tr>
<td>ASC</td>
<td>500</td>
<td>2.58 ± 0.42***</td>
<td>80.55 ± 25.91</td>
<td>00***</td>
</tr>
</tbody>
</table>

All values represent mean ± SEM. ***P < 0.001; ANOVA.

Effect on the gastric lesions induced by different necrotizing agents

Lesions induced by various necrotizing agents were grouped in varying sized patches, usually parallel to the major axis of the stomach. Oral administration of ASC significantly (P < 0.001) reduced the severity of these lesions in a dose dependent manner (Figure 1).

Estimation of nonprotein-sulphydryl (NP-SH) groups in the gastric tissue

Gastric mucosal NP-SH contents were significantly decreased following the administration of 80% ethanol. Treatments with cinnamon suspension (500 mg/kg) significantly (P < 0.05) reversed ethanol-induced decrease in NP-SH level (Figure 5).

DISCUSSION

Aqueous suspension of cinnamon showed a significant decrease in basal gastric acid secretion and ulcer protective effects in different experimental models with different etiopathogenesis of ulceration. Pyloric ligation-induced gastric ulcerations are caused by enhanced acid-pepsin secretion leading to autodigestion of gastric mucosa and breakdown of mucosal barrier (Bhattacharya et al., 2006). The etiopathology of ulcer is multifactorial; however, it is generally accepted as an imbalance between aggressive factors and the maintenance of mucosal integrity through the endogenous defense mechanism (Piper and Stiel, 1986). To regain the balance, different therapeutic agents including herbs and spices have been used to inhibit the gastric acid secretion and/or to boost the mucosal defense mechanism by enhancing mucus production (Baggio et al., 2003). The current data clearly demonstrated that cinnamon suspension significantly decreased basal gastric acid secretion and completely inhibited the ulceration in pylorus ligated Shay rats, which concurs with earlier reports of antisecretory and antiulcerogenic actions of two phytoconstituents isolated from Chinese cinnamon (Cinnamon cassia) (Tanaka et al., 1989). In a recent study, Unlu et al. (2010) demonstrated an anti-microbial and anticarcinogenic property of an essential oil.
of *C. zeylanicum* bark.

On the other hand, cinnamon suspension has shown to protect gastric lesions induced by noxious chemicals (ethanol, sodium hydroxide, and sodium chloride); these agents are known to promote oxygen free radicals (Halliwell, 1991), reduce gastric mucosal non-protein sulphydryl levels (Szabo, 1988), and stimulate the formation of leukotriene C4 (LTC4), a lipoxygenase derived...
Figure 3a. Section through gastric mucosa of control rat showing normal appearance. Haematoxylin and Eosin stain × 100.

Figure 3b. Section through gastric mucosa of rat treated with ethanol (80%, 1 ml) showing mucosal ulceration with intramucosal haemorrhage. Haematoxylin and Eosin stain × 100.
**Figure 3c.** Section through gastric mucosa of rat treated with *C. zeylanicum* (250 mg/kg) and ethanol (80%, 1 ml) showing superficial and focal mucosal erosions. Haematoxylin and Eosin stain × 100.

**Figure 3d.** Section through gastric mucosa of rat treated with *C. zeylanicum* (500 mg/kg) and ethanol (80%, 1 ml) showing intramucosal vascular congestion and submucosal edema. Haematoxylin and Eosin stain × 100.
metabolite of arachidonic acid (Hua et al., 1985). Constriction of submucosal values with subsequent stasis of blood flow in mucosal microcirculation as well as plasma leakage from the vascular bed could contribute to the wide spread mucosal injury (Trier et al., 1987).

In this study, rats pre-treated with ASC showed a significant reduction of necrotizing agents-induced gastric lesions. Furthermore, cinnamon suspension offered a significant effect in replenishing the NP-SH concentration and preventing the decreased level of wall mucus contents induced by ethanol. Thus, sulphydryl seemed to be involved in gastroprotection mechanism by enhancing prostaglandin synthesis. Improvement in gastric wall mucus by cinnamon suspension offers protection against
gastric damage by stimulation of mucus secretion, thus strengthening the gastric mucus-bicarbonate barrier (Wallace and Whittle, 1986). This is considered important to prevent damage as well as to facilitate repair (Alqasoumi et al., 2008; Alqasoumi et al., 2011). Hence, the enhanced gastric NP-SH and mucus levels may contribute to the cinnamon antulcer activity by its antioxidant potential (Mathew and Abraham, 2006). Furthermore, it has also been reported that glutathione (GSH) is the most abundant non-protein thiol in mammalian cells and involved in defense against oxidative stress as a scavenger of reactive oxygen species (ROS). GSH also plays an important role in maintaining cellular redox homeostasis, scavenging lipid peroxides detoxifying reactive intermediates of noxious chemicals (Udeanu et al., 2011).

Histopathological assessment further support that ASC possesses the ability to prevent ethanol-induced various pathological indices in rat stomach. Conventional non-steroidal anti-inflammatory agents are well recognized to produce gastric mucosal damage due to their capacity to inhibit cyclooxygenase-1 (COX-1) and the synthesis of gastroprotective PG (Guo et al., 2005); a reduction in the local blood flow, topical irritation and an interference with restitution and tissue repair. The current study on indomethacin-induced gastric damage showed inhibition of gastric lesions by ASC; suggested that the ability of the cinnamon suspension to prevent ulceration is at least partly through prostaglandin biosynthesis mechanism (Rujjanawate et al., 2004).

The chemical constituents of cinnamon responsible for its antiulcer activity are not known. However, the volatile oil of cinnamon and its constituents are known to offer protection against gastric damage caused by aggressors in animal models that might be through antioxidant properties (Tanaka et al., 1989). The principal constituents of cinnamon bark are volatile oil, tannins, mucilage, gum, resins, and coumarins. The cinnamon oil contains cinnamaldehyde as its major component. Other constituents include eugenol, cinnaldehyde, caryophyllene and safrol (Leung, 1980), which are known to possess antioxidant properties (Schimdt et al., 2002). The current data suggested that the active principles are responsible, at least partly, for the antisecretory and antiulcer activities of the tested suspension. The observation on acute toxicity test revealed that the cinnamon suspension is well tolerated and neither caused any deleterious effects nor lethality in the animals.

Conclusively, the findings of the present study clearly indicated both antisecretory and antiulcerogenic properties of the cinnamon aqueous suspension. The exact antiulcerogenic mechanism(s) remains unknown. However, the suspension contains substances that might enhance endogenous prostaglandins, mucus synthesis, and possess antioxidative properties. The antisecretory mechanism cannot be dismissed.

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REFERENCES


