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Antiulcer Effect of *Cinnamomum zeylanicum* Bark in Rats

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Abstract: *Cinnamomum zeylanicum* (family: Lauraceae) commonly known as cinnamon is cultivated throughout the world, mainly for its bark, a spice used as flavouring agent. The objective of the present study was to study, the effect of *C. zeylanicum* bark suspension on gastric and duodenal ulcers in rats. The two doses of *C. zeylanicum* were evaluated for ulcerogenic potential and antiulcer effects. The antiulcer study was carried out in acetic acid induced chronic gastric, pylorus ligation induced gastric, ethanol induced gastric, stress induced gastric, indomethacin induced gastric and cysteamine induced duodenal ulcers. In all these models, the common parameter determined was ulcer index. The higher dose of the cinnamon bark (100 mg kg^{-1}, p.o.) produced a significant protection in the development of the gastric ulcers in all the models whereas the low dose of the bark (10 mg kg^{-1}, p.o.) was not effective in any of the models. The effect produced by high dose of cinnamon (100 mg kg^{-1}, p.o.) was comparable to that produced by standard drugs. The *Cinnamon zeylanicum* (100 mg kg^{-1}, p.o.) produced an increase in healing of gastric ulcers and prevented the development of duodenal ulcers in rats indicating that it possess both gastric cytoprotective and antisecretory effects.

Key words: *Cinnamomum zeylanicum*, gastric ulcer, duodenal ulcer, gastric secretio, gastric cytoprotection

INTRODUCTION

Cinnamon bark is obtained from *Cinnamomum zeylanicum* and it is widely used as a flavouring agent in the preparation of food all over the world. Apart from its use as flavouring agent, it is reported to possess a wide range of pharmacological activities that includes antinociceptive (Atta and Alkofahi, 1998), antiinflammatory (Stoner and Wang, 2013), antidiabetic (Anderson *et al*., 2004; Peng *et al*., 2008), neuroprotective (Jana *et al*., 2013) and cognitive enhancing activity (Cho *et al*., 2013). It is also reported to possess antioxidant (Dugoua *et al*., 2007; Georgiev *et al*., 2013; Ayala-Zavala *et al*., 2013) and prohealing (Kamath *et al*., 2003) activities. Toxicological investigations on cinnamon revealed that it is carcinogenic (Westra *et al*., 1998) and has ability to provoke sensitivity reactions (Mihail, 1992). It is reported to increase the weight of the reproductive organs, sperm motility and sperm count (Shah *et al*., 1998) and decrease blood pressure (Preuss *et al*., 2006; El-Bassossy *et al*., 2011). The Chinese cinnamon or cassia bark, obtained from *Cinnamomum cassia* is reported to reduce the growth of *H. pylori*, the organism responsible for the development of gastric and duodenal ulcer (Martin and Ernst, 2003). Furthermore, the Chinese cinnamon possesses anti-ulcer effect in rats (Akira *et al*., 1986). Some of the chemical constituents present in the Chinese cinnamon are different from those present in the cinnamon bark (Evans, 2002) and there are no reports on the effect of administration of cinnamon bark on gastric and duodenal ulcers. The present study, investigates the effect of administration of cinnamon bark on gastric ulcer healing, gastric secretion and gastric cytoprotection in rats.

MATERIALS AND METHODS

Experimental animals: Male albino Wistar rats weighing between 200-250 g were used. Institutional Animal Ethics Committee approved the experimental protocol; animals were maintained under standard conditions in an animal house approved by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). The animals were given pellet food (Lipton India Ltd., Mumbai, India) and water *ad libitum*.

Treatments: Rats were divided into 4 groups consisting of 6 animals in each group. All the drugs were suspended in water using 0.5 sodium carboxymethyl cellulose. The animals were treated as follows:

Group 1: Vehicle (0.5 % sodium carboxy methylcellulose in water)
Group 2: Standard drug
Group 3: Cinnamon bark (10 mg kg^{-1}, p.o.)
Group 4: Cinnamon bark (100 mg kg^{-1}, p.o.)

Chemicals: Cinnamon was procured from local market. The sample was identified by Regional Research Institute, Bangalore, India. A voucher specimen is preserved in the regional research institute for future reference.

Experimental models

Ulcerogenic potential: The method described by Takeuchi *et al.* (1998) was followed. The animals were divided into 4 groups as mentioned earlier and treated for 4 days. Aspirin (22 mg kg^{-1}, p.o.) was used as standard ulcerogenic agent. On the 5th day, the animals were fasted for 24 h and were given the cinnamon bark or aspirin. After 6 h of drug administration, the animals were sacrificed under ether anaesthesia for determination of ulcer scores. Stomachs were cut along the greater curvature and the ulcers were given scores based on their intensity as follows:

0 = No ulcer
0.5 = Red colouration
1.0 = Spot ulcers
1.5 = Haemorrhagic streaks
2.0 = Ulcers ≥3 but ≤5
3 = Ulcer >5

Acetic acid induced ulcer: The method described by Asad *et al.* (2001) was followed. Gastric ulcers were induced by applying glacial acetic acid (0.05 mL) onto the anterior serosal surface of the stomach using a mould of 6 mm diameter. The animals were treated once daily for 10 days as mentioned earlier, after induction of ulcer. Ranitidine (50 mg kg^{-1}, p.o.) was used as standard antiulcer agent. Rats were sacrificed on the 10th day, stomachs were removed for determination of ulcer index, ulcer score and histopathological examinations. The ulcer index was calculated using the formula (Ganguly, 1969):

$$\text{Ulcer index} = 10/X$$

Where, X = Total mucosal area/Total ulcerated area. The ulcers were given scores based on their intensity as follows:

0 = No ulcer
1 = Superficial mucosal erosion
2 = Deep ulcer or transmural necrosis
3 = Perforated or penetrated ulcer

The stomach samples were subsequently processed for histological examination. The 4 indices namely regenerated glandular epithelial width; regenerated surface epithelium width, capillary density and collagen content were selected to reflect the rate and quality of ulcer healing (Asad *et al.*, 2001).

Regenerated lining epithelial width: Regenerated lining epithelial width was defined, as the average distance from the origin of regenerated lining epithelium to the surface of the ulcer.

Capillary density with the granulation tissues of the ulcers: The capillary density was determined using eyepiece reticule (X 100 magnification) on the H&E stained sections in the ulcer centre, each field was 140×140 μm at least 4 fields were examined on each section. Capillary density within the granulation tissue of the ulcers was expressed as the average capillary numbers in the field.

Collagen content within the scar tissue of the ulcer: Collagen content in scar tissues displayed blue colour in sections stained by Masson's stain and were determined by point count using one square eyepiece reticule (X 100 magnification). Collagen content was expressed as:

$$\text{Volume} = \frac{\text{Total number of points falling on the tissue}}{\text{Total number of points in the reticule}}$$

Regenerated glandular epithelium: Total length of the epithelium found in the secretory gland.

Pylorus ligation induced ulcers: The pyloric ligation was done under ether anaesthesia on rats fasted for 36 h. The drugs were administered intraduodenally immediately after pylorus ligation. Ranitidine (50 mg kg^{-1}, p.o.) was used as standard gastric antisecretory agent. Animals were sacrificed 6 h later. The stomach was isolated for determination of ulcer index using the formula mentioned earlier. The gastric juice accumulated in the stomach was centrifuged and the free and total acidity (Hawk *et al.*, 1947), mucin (Corne *et al.*, 1974), pepsin content (Debnath *et al.*, 1974) and total proteins (Lowry *et al.*, 1951) were estimated (Kulkarni, 1999).

Ethanol induced ulcers: The rats were fasted for 36 h before administration of ethanol (1 mL/200 g, p.o.). Standard drug (misoprostol 100 μg kg^{-1}, p.o..) or bark suspension at lower dose (10 mg kg^{-1}, p.o.) and higher dose at (100 mg kg^{-1}, p.o.) were administered 1 h before ethanol administration. After 1 h animals were sacrificed, stomachs were isolated and ulcer index was determined (Brzozowski *et al.*, 1998).

Cold restraint stress induced ulcers: The bark suspension at lower dose (10 mg kg^{-1}, p.o.) and higher dose (100 mg kg^{-1}, p.o.) or ranitidine (50 mg kg^{-1}, p.o.) were administered 30 min prior to subjection of stress. The

animals were placed in a restraint cage and the cage was placed at a temperature of 2°C for 2.5 h. The animals were sacrificed and ulcer index was determined (Parmar and Desai, 1993).

Indomethacin induced gastric ulcers: The animals were fasted for 36 h and the gastric ulcers were induced by the administration of indomethacin (20 mg kg^{-1}, p.o.). The bark suspension at both the lower (10 mg kg^{-1} p.o.) and higher dose (100 mg kg^{-1}, p.o.) and the standard drug, misoprostol (100 μg kg^{-1}, p.o.) were given 1 h prior to the administration of indomethacin. After 4 h, the animals are sacrificed and ulcer index was determined (Parmar and Desai, 1993).

Cysteamine induced duodenal ulcers: Duodenal ulcers were induced by administering cysteamine hydrochloride (400 mg kg^{-1}, p.o.) twice at a interval of 4 h. The bark suspension at lower dose (10 mg kg^{-1}, p.o.) and higher dose (100 mg kg^{-1}, p.o.) or ranitidine (50 mg kg^{-1}, p.o.) were administered 30 min prior to each dose of cysteamine hydrochloride. After 24 h, all the animals were sacrificed and the duodena were excised carefully and cut opened along the antimesentric side. The duodenal ulcer area, score and index were determined (Parmar and Desai, 1993). The ulcers were given scores based on their intensity as follows:

0 = No ulcer
1 = Superficial mucosal erosion
2 = Deep ulcer or transmural necrosis
3 = Perforated or penetrated ulcer

The ulcer index was calculated using the equation:

$$\text{U.I.} = \text{Arithmetic mean of intensity in a group} + \frac{\text{Number of ulcer positive animals}}{\text{Total number of animals}} \times 2$$

Statistical analysis: Values are expressed as mean±SEM. Statistical significance was assessed using one-way Analysis of Variance (ANOVA) followed by Tukey test. For ulcer score, one-way ANOVA followed by non-parametric Dunn's test was used.

RESULTS

Ulcerogenic potential: Administration of both doses of cinnamon bark suspension for 5 days to normal animals did not produce any gastric damage. Aspirin, a known ulcerogenic agent produced severe gastric damage characterized by bleeding and an increase in the ulcer score (2.16±0.30).

Effect on ulcer healing in acetic acid induced chronic gastric ulcers: *C. zeylanicum* bark suspension (100 mg kg^{-1}, p.o.) showed significant reduction in ulcer score ($p<0.01$), ulcer index ($p<0.001$) and regenerated surface epithelium width ($p<0.001$) when compared to control. There was no significant difference between the cinnamon (100 mg kg^{-1}, p.o.) and ranitidine (50 mg kg^{-1}, p.o.) treated group in the earlier mentioned parameters indicating the effect produced by cinnamon is comparable to that produced by ranitidine. The collagen content in the ulcerated tissue was significantly increased by all the treatments ($p<0.001$). The lower dose of the cinnamon (10 mg kg^{-1}, p.o.) was less effective, as it produced significantly less increase in the regenerated surface epithelium ($p<0.05$) compared to ranitidine (50 mg kg^{-1}, p.o.) and higher dose of cinnamon (100 mg kg^{-1}, p.o.) and significantly less effect on regeneration of glandular epithelium compared to ranitidine ($p<0.05$). Ranitidine (50 mg kg^{-1}, p.o.) produced significant effect in all the parameters except capillary density in the scar tissue (Table 1).

Effect in pylorus ligation induced gastric ulcers: The high dose of *C. zeylanicum* bark (100 mg kg^{-1}, p.o.) suspension and ranitidine produced a significant reduction in ulcer index ($p<0.05$), free acidity ($p<0.001$) and total acidity ($p<0.001$) when compared to control. They also produced a significant decrease in the pepsin content ($p<0.01$), total proteins ($p<0.001$). An increase in the mucin content was also observed after treatment with high dose of cinnamon (100 mg kg^{-1}, p.o.) suspension and ranitidine. There was no significant difference between cinnamon (100 mg kg^{-1}, p.o.) and ranitidine in any of the parameters. The low dose of bark suspension (10 mg kg^{-1}, p.o.) did not show any significant effect in pylorus ligated

Table 1: Effect on regenerated glandular and surface epithelium width, capillary density and volume of collagen content in acetic acid induced chronic gastric ulcers

Treatments	Regenerated glandular epithelium width (μm)	Capillary density (No) in 19600 μm^2	Vol. of collagen content	Regenerated surface epithelium (μm)	Ulcer score	Ulcer index
Vehicle (1 mL kg^{-1}, p.o.)	97.02±8.112	5.13±0.625	0.090±0.010	96.00±7.23	2.83±0.166	0.46±0.087
Ranitidine (50 mg kg^{-1}, p.o.)	149.40±7.424***	6.38±0.239	0.197±0.004***	144.56±3.44***	0.17±0.168***	0.16±0.034**
Cinnamon (10 mg kg^{-1}, p.o.)	108.58±6.373^{++}	4.50±0.645	0.170±0.004***	112.08±8.28$^{*\#}$	1.34±0.210	0.24±0.032*
Cinnamon (100 mg kg^{-1}, p.o.)	120.85±8.314	5.87±0.718	0.205±0.015***	142.32±7.06***	0.34±0.210**	0.12±0.015***

All values are mean±SEM, n = 6; $^{*,**,***}p<0.05$, 0.01 and 0.001 when compared to control group; $^{+,++}p<0.05$ and 0.01 when compared to ranitidine; $^{\#}p<0.05$ when compared to cinnamon (100 mg kg^{-1}, p.o.)

Table 2: Effect on free acidity, total acidity, ulcer index, mucin content, pepsin content and total proteins in pylorus ligated rats

Treatments	Free acidity (mEq L^{-1})	Total acidity (mEq L^{-1})	Ulcer index	Mucin content (µg g^{-1})	Pepsin content (µg 6 h^{-1})	Total proteins (mg mL^{-1})
Vehicle (1 mL kg^{-1}, p.o.)	6.66±0.49	11.50±0.84	0.22±0.05	0.13±0.01	0.23±0.02	14.17±0.78
Ranitidine (50 mg kg^{-1}, p.o.)	3.83±0.30***	5.83±0.30***	0.08±0.06*	0.91±0.09***	0.07±0.01**	7.51±0.53***
Cinnamon (10 mg kg^{-1}, p.o.)	7.50±0.42+++	13.00±0.68+++	0.10±0.03	0.32±0.09++	0.21±0.05++###	8.34±0.41***
Cinnamon (100 mg kg^{-1}, p.o.)	3.66±0.33***	4.16±0.70***	0.02±0.01*	0.70±0.16**	0.07±0.01**	7.33±0.12***

All values are mean±SEM, n = 6; *, **, ***p<0.05, 0.01 and 0.001 when compared to control group; ++, +++p<0.01 and 0.001 when compared to ranitidine; ###p<0.01 when compared to cinnamon (100 mg kg^{-1}, p.o.)

Table 3: Effect on ulcer index in indomethacin, ethanol and stress induced gastric ulcers

Treatments	Indomethacin induced gastric ulcers	Ethanol induced gastric ulcers	Stress induced gastric ulcers	Cysteamine induced duodenal ulcers		
				Ulcer area	Ulcer score	Ulcer index
Vehicle (1 mL kg^{-1}, p.o.)	0.233±0.039	0.673±0.156	0.152±0.048	28.83±3.628	2.66±0.210	6.80
Misoprostol (100 µg kg^{-1}, p.o.)	0.000±0.000***	0.024±0.011**	0.000±0.000*	0.16±1.167***	0.33±0.210**	0.36
Ranitidine (50 mg kg^{-1}, p.o.)						
Cinnamon (10 mg kg^{-1}, p.o.)	0.153±0.041++#	0.875±0.173+++###	0.075±0.037	9.50±1.455***+#	1.83±0.307	3.58
Cinnamon (100 mg kg^{-1}, p.o.)	0.028±0.009***	0.210±0.092*	0.004±0.003*	00.00±0.000***	0.16±0.167**	2.00

All values are mean±SEM, n = 6; *, **, ***p<0.05, 0.01 and 0.001 when compared to control group +, ++, +++p<0.05, 0.01 and 0.001 when compared to misoprostol; #, ##p<-0.05 and 0.01 when compared to cinnamon (100 mg kg^{-1}, p.o.)

rats, except that it produced a significant decrease in the total proteins content ($p<0.001$) when compared to control. Furthermore, there was significant difference in free acidity ($p<0.001$), total acidity, pepsin content ($p<0.01$) and mucin content ($p<0.01$) in cinnamon (10 mg kg^{-1}, p.o.) treated group compared to high dose of cinnamon (100 mg kg^{-1}, p.o.) and ranitidine (Table 2).

Effect on indomethacin induced, ethanol induced and stress induced gastric ulcers: The indomethacin induced gastric ulcers were significantly reduced by high dose of *C. zeylanicum* bark suspension (100 mg kg^{-1}, p.o.) and misoprostol ($p<0.001$). A similar effect was observed in ethanol induced gastric ulcers and stress induced gastric ulcers wherein the high dose of *C. zeylanicum* suspension ($p<0.05$) and standard drugs; ranitidine ($p<0.05$) or misoprostol ($p<0.01$) showed significant reduction in ulcer index. The effect produced by cinnamon (100 mg kg^{-1}, p.o.) and standard drugs; ranitidine or misoprostol were similar, as no significant difference between these groups. However, the lower dose of cinnamon (10 mg kg^{-1}, p.o.) was not effective in any of these models and there was significant difference between cinnamon (10 mg kg^{-1}, p.o.) and high dose of cinnamon (100 mg kg^{-1}, p.o.) or standard drugs in indomethacin induced and ethanol induced gastric ulcers (Table 3).

Effect on cysteamine induced duodenal ulcers: The high dose of cinnamon (100 mg kg^{-1}, p.o.) and ranitidine produced a significant reduction in the ulcer area ($p<0.001$) and score ($p<0.01$) when compared to control. The lower dose of cinnamon (10 mg kg^{-1}, p.o.) was effective only in reducing ulcer area significantly ($p<0.001$) compared to control, however the effect was significantly less compared to high dose of cinnamon ($p<0.05$) and ranitidine ($p<0.05$) (Table 3).

DISCUSSION

The present study dealt with the effect of *C. zeylanicum* bark suspension on gastric and duodenal ulcers using different models to evaluate the effect on ulcer healing, gastric secretion and gastric cytoprotection. As mentioned earlier, the Chinese cinnamon is reported to possess anti-ulcer effect in rats (Akira *et al*., 1986). Some of the chemical constituents present in the Chinese cinnamon are different from those present in the cinnamon bark (Evans, 2002) and there are no reports on the effect of administration of cinnamon bark on gastric and duodenal ulcers. The present study was evaluated using 2 different doses of cinnamon of 10 and 100 mg kg^{-1} orally. These doses were selected because cinnamon or its extract are used in different concentrations as food additives. Moreover, earlier reports on the pharmacological effects have used doses ranging from as low as 2.5 mg kg^{-1} orally to 250 mg kg^{-1}.

The bark suspension increased the healing of gastric ulcers induced by acetic acid. The pathophysiology and healing of acetic acid induced ulcer in rats resembles to that of human peptic ulcer disease (Kulkarni, 1999). The ulcerated tissues were also subjected to histopathological examination to determine the effect of cinnamon bark suspension on formation of collagen, regeneration of glandular epithelium and capillary density, all of which are essential process for the healing of ulcers. The increase in regenerated surface epithelial width and volume of collagen content confirmed the ulcer healing effect of cinnamon bark.

Pylorus ligation induced ulcer was used to study the effect of extracts on gastric acid and gastric mucus secretion (Debnath *et al*., 1974). The ligation of the pyloric end of the stomach causes accumulation of gastric acid in

the stomach that induces ulcers. The cinnamon bark suspension and ranitidine significantly decreased the free and total acidity and also increased the mucus content when compared to control. This suggests that *C. zeylanicum* bark suspension has both antisecretory effect and gastric cytoprotective effects.

Ethanol induced gastric ulcer was employed to study the cytoprotective effect of the bark. The gastric lesion formation in this model is due to stasis in gastric blood flow that contributes to the development of the hemorrhage and necrotic aspects of tissue injury. Alcohol rapidly penetrates the gastric mucosa causing plasma membrane damage leading to increased membrane permeability to sodium and water. There is also a massive intracellular accumulation of calcium. All these events lead to cell death and exfoliation in the surface epithelium (Brzozowski *et al*., 1998). The *C. zeylanicum* bark suspension was effective in this model indicating that it possesses gastric cytoprotective effect.

Indomethacin is known to produce mucosal erosions and ulcers. The gastric mucus production is stimulated by prostaglandins and deficiency of prostaglandins is primarily responsible for ulceration seen after indomethacin administration (Parmar and Desai, 1993). Like in the ethanol induced gastric lcers, the *C. zeylanicum* bark suspension was effective in reducing ulcer index. This model confirmed the cytoprotective effect of the bark suspension. This cytoprotective property of the cinnamon may be attributed to the antioxidant property of cinnamon (Dugoua *et al*., 2007).

Stress induces ulcers due to histamine release that enhances acid secretion and reduces mucus production (Parmar and Desai, 1993). There is also an increase in gastric motility that increases folds in the stomach making it susceptible for damage by gastric acid. The *C. zeylanicum* bark suspension and ranitidine were effective in reducing the ulcers. This reduction may be due to local effect on gastric motility or secretion. It might also be due to central effects of cinnamon constituents, as many antistress agents acting through central nervous system are reported to reduce development of stress induced ulcers.

Cysteamine induced duodenal ulcer in rat is the widely used model of peptic ulcer disease. Agents having cytoprotective and antisecretory effect are effective in this model. Cysteamine hydrochloride inhibits secretion of mucus secretion in the proximal duodenum and also stimulates gastric acid secretion rate. It also induces a delay in gastric emptying and stimulates gastrin secretion (Parmar and Desai, 1993). The *C. zeylanicum* bark suspension was effective in reducing the ulcer area.

C. zeylanicum bark contains; cinnamaldehyde, eugenol, trans cinnamic acid, hydroxyl cinnamaldehyde, O-methoxy cinnamaldehyde, cinnamyl alcohol, a-terpineol, limonene and oligomeric procyanidins (Evans, 2002). Cinnamaldehyde has been reported to reduce development of stress and serotonin induced ulcers in mice and to reduce stomach and intestinal motility (MHP, 2007). Furthermore, eugenol is reported to have preventive effect on PAF and ethanol-induced gastric mucosal damage (Capasso *et al*., 2000). The antiulcer activity found may be due to eugenol and cinnamaldehyde. Other components of the cinnamon bark could, also be responsible for antiulcer effect and further studies have to be carried out to determine effect of individual components before concluding the constituent(s) responsible for the antiulcer effect.

CONCLUSION

The cinnamon bark increased healing of gastric ulcers in rats. It also showed gastric antisecretory and gastric cytoprotective effect. The results of the present study suggest that consumption of *C. zeylanicum* bark may be beneficial in healing of ulcers in patients suffering from peptic ulcer disease.

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