

## Antiulcer activity of *Trichosanthes cucumerina* linn. against experimental gastro-duodenal ulcers in rats

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### SUMMARY

*Trichosanthes cucumerina* Linn. (cucurbitaceae) is widely used in Indian folk medicine for variety of disease conditions. The aim of present study was to evaluate the antiulcer activity of 50% ethanolic extract of fruits of *Trichosanthes cucumerina* Linn. (TCFE) using various experimental models of gastric and duodenal ulceration in rats. Oral administration of 50% ethanolic extract of fruits of *Trichosanthes cucumerina* Linn. was evaluated in rats against ethanol, aspirin and pylorus ligated gastric ulcers as well as cysteamine-induced duodenal ulcers. In all the models studied, the antiulcer activity of TCFE compared with that of cimetidine (100 mg/kg, p.o.), an H<sub>2</sub> receptor antagonist. TCFE showed significant antiulcer activity in ethanol-induced and aspirin-induced gastric ulcer models. In 19 h pylorus ligated rats, significant reduction in ulcer index, total acidity and pepsin activity was observed with TCFE, when compared with the control group. Mucosal defensive factors such as pH, mucin activity and gastric wall mucous content was found to be increased with TCFE. TCFE was also, afforded remarkable protection in cysteamine-induced duodenal lesions. The antiulcer activity of TCFE was comparable with that of cimetidine. Thus, TCFE possess significant antiulcer activity against both gastric and duodenal ulcers in rats. The antiulcer activity may be attributed to its cytoprotective action and inhibition of acid secretory parameters.

**Key words:** *Trichosanthes cucumerina* Linn; Gastric ulcer; Duodenal ulcer; Antiulcer activity

### INTRODUCTION

Peptic ulcer disease is a serious gastrointestinal disorder that develops on the inside lining of the stomach (a gastric ulcer) or the small intestine (a duodenal ulcer). Gastric ulcer, one of the most widespread, is believed to be due to an imbalance

between aggressive and protective factors (Alkofahi and Atta, 1999). The gastric mucosa is continuously exposed to potentially injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products (*Helicobacter pylori*) and drugs (Peskar and Maricic, 1998). These agents have been implicated in the pathogenesis of gastric ulcer via increase of gastric acid and pepsin secretion, inhibition of prostaglandin synthesis and cell proliferation growth, diminished gastric blood flow and gastric motility (Toma *et al.*, 2005). Drug

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treatment of peptic ulcers is targeted at either counteracting aggressive factors such as acid, pepsin, active oxidants, platelet activating factor, leukotrienes, endothelins, bile or exogenous factors including NSAIDs or stimulating the mucosal defences such as mucus, bicarbonate, normal blood flow, prostaglandins and nitric oxide (Borelli and Izzo, 2000). The goals of treating peptic ulcer disease are to relieve pain, heal the ulcer and prevent ulcer recurrence. Number of drugs including proton pump inhibitors, prostaglandins analogs, histamine receptor antagonists and cytoprotective agents are available for the treatment of peptic ulcer, but most of these drugs produce several adverse reactions including toxicities and may even alter biochemical mechanisms of the body upon chronic usage. Clinical evaluation of these drugs also showed development of tolerance and incidence of relapses that make their efficacy arguable (Ariyphisi *et al.*, 1986). Currently there is no cost effective treatment that meets all these goals. Hence, efforts are on to find a suitable treatment from natural product sources. Herbal medicines are generally used in such chronic disease, wherein drugs are required to be used for long periods (Dharmani and Palit, 2006).

*Trichosanthes cucumerina* Linn. (cucurbitaceae) is a perennial climber widely distributed throughout India, Ceylon, Malaya and North Australia. It is a plant with creeping stems and tendrils. Leaves are hairy, dentate, 10 - 25 cm in length and 15 cm in diameter. Flowers are monoecious, axillary and white. Male flowers occur in long racemes with peduncles up to 30 cm in length. The female flowers are solitary. Fruits are cylindrical with waxy surface, slender and tapering 40 - 120 cm in length and 4 - 10 cm in diameter. The flesh is red and fibrous when matured. The pulp of the ripe fruits is used in sauces and is good substitute for tomato paste (Tindall, 1983). The whole plant has been used in the ayurvedic system of medicine for the treatment of hepatic and alimentary canal disorders. Fruits of *Trichosanthes cucumerina* Linn.

are used as laxative, purgative, antipyretic, alexiteric and antiulcer agent (Kirtikar and Basu, 1935). Scientific evidences regarding antidiabetic (Kirana and Srinivasan, 2008), hepatoprotective (Kumar *et al.*, 2009), anti-inflammatory (Kolte *et al.*, 1996), antifertility (Kage *et al.*, 2009), antioxidant (Adebooye, 2008), antibacterial (Hariti and Rathee, 1995), antifungal (Harit and Rathee, 1996) and antiviral (McGrath *et al.*, 1992) activities of the plant were reported. The fruits contain ascorbic acid, lycopene, phenols, flavonoids, alkaloids, tannins and saponins (Adebooye, 2008; Edeoga *et al.*, 2010).

Recently, widespread efforts have been launched to identify novel anti-ulcer drugs from natural resources. A number of cucurbitaceae plants (Yang *et al.*, 2007; Gurbuz *et al.*, 2000) have been shown to possess antiulcer activity, viz. *Cucurbita moschata* (Fruit), *Momordica charantia* (Immature fruits), *Cucumis melo* (Mature fruit), etc. A number of models are available in which to test substances can be evaluate for their antiulcer effects. Therefore, present study was undertaken to evaluate the antiulcer effect of 50% ethanolic extract of fruits of *Trichosanthes cucumerina* (TCFE) in various experimental gastric and duodenal ulcer models.

## MATERIALS AND METHODS

### Plant material and extraction

The fruits of *Trichosanthes cucumerina* were collected from Ahmedabad, India and authentication was done in the department of Pharmacognosy, L. M. College of Pharmacy, Ahmedabad and the voucher specimen LM156 was deposited in the herbarium. The fruits were completely dried in the sunlight and powdered. Fruit powder was extracted exhaustively with 50% ethanol by maceration at room temperature. The crude extract was dried at 40 °C under vacuum (Yield - 10% w/w of dried plant material). The pharmacological assays were carried out with aqueous solution of dried extract (TCFE). The doses were expressed as mg of dried extract per kg of rat.

### Drugs and chemicals

Cimetidine (Cadila, Ahmedabad) was used as reference standard. Aspirin (Cadila, Ahmedabad) and Cysteamine (Merck, Germany) were used for experimental induction of gastric and duodenal ulcers respectively.

### Animals

Wister rats (200 - 250 g) of either sex bred in Central Animal House facility of the institute were used. The animals were housed under standard conditions, maintained on a 12 h light/dark cycle and had free access to food and water up to the time of experimentation. The animals were acclimatized to the laboratory environment 1 h before the experiments. Animals were randomly distributed into groups of 10 animals each. All experiments were conducted during the light period (08.00 - 16.00 h). All the protocols were approved by the Institutional Animal Ethical Committee (IAEC) and conducted according to the guidelines of CPCSEA (Committee for the Purpose of Control and Supervision of Experiment on Animals).

### Treatment

Freshly prepared aqueous solution of dried extract of fruits of TCFE in suitable dilution was administered orally in the test animals. For the ethanol induced ulcer model, animals were divided in to five groups, each group consisting of six animals. Group 1 served as control group received distilled water (vehicle) 1 ml/kg, p.o., group 2 - 5 served as test groups received TCFE (100, 300, 500 and 800 mg/kg, p.o.) and group 6 served as positive control received cimetidine (100 mg/kg, p.o.). In aspirin induced, pylorus ligated and cysteamine induced ulcer models, animals were divided in to three groups (n = 6) viz. control, test and positive control. Control group received vehicle (1 ml/kg, p.o.), test group received TCFE (500 mg/kg, p.o.) and positive control group received cimetidine (100 mg/kg, p.o.).

### Acute toxicity test

Different doses (100 - 5000 mg/kg) of TCFE were administered orally to five groups of mice (6 in each). Mortality within 24 h was recorded (Irwin, 1962). The LD<sub>50</sub> was estimated from the graph of probit against log-dose of the extract.

### Ethanol- induced gastric ulcer model

1 ml of 80% ethanol was administered orally to 36 h fasted rats (Robert *et al.*, 1979). In treatment group, drugs were administered orally 1 h before the administration of ethanol. After 2 h of ethanol administration, animals were sacrificed; stomachs were removed, opened along the greater curvature, and examined for lesions. Lesion severity was determined by measuring ulcer index (Ganguly and Bhatnagar, 1973).

### Aspirin-induced gastric ulcer model

Aspirin was suspended in 1% CMC in water and administered orally at the dose of 500 mg/kg to 36 h fasted rats (Hemmati *et al.*, 1973). In treatment group, drugs were administered orally one hour before the administration of aspirin. The rats were sacrificed 6 h after aspirin administration, the stomachs removed and opened along the greater curvature to determine ulcer index of glandular mucosa (Ganguly and Bhatnagar, 1973).

### Pylorus ligation-induced gastric ulcer model

Rats (36 h fasted) were anesthetized with light ether anesthesia. A portion of the abdomen was opened by a small incision below the xiphoid process. Pyloric portion of the stomach was slightly lifted out avoiding traction to the pylorus or damage to its blood supply. The stomach was replaced carefully and interrupted sutures closed the abdominal wall. The drugs were administered orally and animals were sacrificed at the end of 19 h after pylorus ligation. The stomachs were removed and opened along the greater curvature. The glandular portion of stomach was observed for measurement of ulcer index (Shay *et al.*, 1973).

The contents were drained into tubes, centrifuged and subjected to analysis for various biochemical parameters. The volume and pH of gastric juice were measured. Total acidity (Hawk *et al.*, 1954), Total acid output (Goel *et al.*, 1985), pepsin activity (Debnath *et al.*, 1974), total carbohydrate (Nair *et al.*, 1974) and protein content (Lowry *et al.*, 1951) were estimated. Finally, the total carbohydrate to protein (TC/PR) ratio i.e mucin activity was derived. Gastric wall mucus content (GWMC) was measured from glandular portion of stomach (Corne and Motrissier, 1974) and was expressed as mg of alcian blue per g of wet glandular tissue (Kulkarni and Goel, 1996).

#### Cysteamine-induced duodenal ulcer model

Cysteamine hydrochloride was administered in two doses of 400 mg/kg in 10% aqueous solution at an interval of 4 h to rats (Szabo, 1978). Treatments were given one hour before the first dose of cysteamine. Parameters studied in this model were percentage mortality, total lesion area, score of intensity and ulcer index. Ulcer index was calculated as the sum of arithmetic mean of the intensity in a group and the ratio of the positive/total multiplied by 2.

#### Statistical analysis

The results were expressed as mean  $\pm$  SEM. The significance of difference between mean values for various treatments was tested using student 't' test. One way ANOVA followed by Tukey's multiple range test was used whenever applicable to access statistical significance of differences between groups. A 'p' value less than 0.05 was considered as statistically significant.

## RESULTS

#### Acute toxicity test

Oral administration of TCFE did not show any toxic symptoms up to 5 g/kg dose in mice.

**Table 1.** Effect of TCFE against ethanol induced gastric ulcer model in rats

Treatment	Dose (mg/kg, p.o.)	Ulcer Index
Control	-	2.19 $\pm$ 0.36
TCFE <sup>a</sup>	100	1.83 $\pm$ 0.18
	300	0.88 $\pm$ 0.10*
	500	0.80 $\pm$ 0.12*
	800	0.21 $\pm$ 0.04*
Cimetidine <sup>b</sup>	100	1.17 $\pm$ 0.08*

n = 6. Expressed as mean  $\pm$  SEM. <sup>a</sup>Anova: F (4,39) = 12.19 (UI), followed by Tukey's multiple range test; <sup>b</sup>Student's t test, \*P < 0.05 when compared with control group.

**Table 2.** Effect of TCFE against aspirin induced gastric ulcer model in rats

Treatment	Dose (mg/kg, p.o.)	Ulcer Index
Control	-	1.23 $\pm$ 0.08
TCFE	500	0.38 $\pm$ 0.06*
Cimetidine <sup>b</sup>	100	0.48 $\pm$ 0.04*

n = 6. Expressed as mean  $\pm$  SEM. Anova: F(2,17) = 56.73 (UI), followed by Tukey's multiple range test, \*P < 0.05 when compared with the control group.

#### Ethano induced gastric ulcer model

The results are summarized in Table 1. TCFE showed significant dose dependent reduction in ulcer index at 300, 500 and 800 mg/kg, when compared with the control group ( $p < 0.05$ ). Similarly, positive control group treated with cimetidine also produced significant reduction in ulcer index as compared with control group.

#### Aspirin induced gastric ulcer model

As shown in Table 2, TCFE treatment (500 mg/kg, p.o.) showed significant reduction in ulcer index when compared with the control group ( $p < 0.05$ ). Positive control, cimetidine treated animals also showed significant reduction in ulcer index as compared to control animals ( $p < 0.05$ ).

#### Pylorus ligation induced gastric ulcer model

As shown in Table 3, TCFE (500 mg/kg, p.o.) and cimetidine (100 mg/kg, p.o.) treatments showed

**Table 3.** Effect of TCFE on ulcer index and acid secretory parameters in pylorus ligated gastric ulcers in rats

Parameters	Control	TCFE (500 mg/kg) (p.o.)	Cimetidine (100 mg/kg) (p.o.)
Ulcer index	0.66 ± 0.11	0.21 ± 0.05*	0.14 ± 0.05*
Vol. of gastric content (ml/100g)	3.67 ± 0.24	4.69 ± 0.48	4.15 ± 0.13
pH	2.20 ± 0.19	5.38 ± 0.32*	5.20 ± 0.07*
Total acidity (mEq/L)	14.77 ± 0.94	8.79 ± 0.56*	9.83 ± 0.20*
Total acid output (mEq/100 g)	54.04 ± 4.70	42.31 ± 5.93	40.22 ± 0.88
Pepsin activity (µg/ml)	750 ± 41.03	320.0 ± 42.10*	310.0 ± 31.97*

n = 6. Expressed as mean ± SEM. ANOVA: F(2, 17) = 20.17 (UI); 2.15 (Vol); 54.52 (pH); 20.62 (TA); 2.39 (TAO); 36.22 (Pep), followed by Tukey's multiple range test, \*P < 0.05 when compared with control group.

significant reduction in ulcer index ( $p < 0.05$ ) as compared to control animals. None of the treatment groups showed any marked change in volume of gastric acid secretion parameter. There was significant rise in gastric pH by TCFE (500 mg/kg, p.o.) and cimetidine (100 mg/kg, p.o.) as compared to control group (Table 3). The treatment groups, TCFE (500 mg/kg, p.o.) and cimetidine (100 mg/kg, p.o.) showed significant reduction in total acidity when compared with the control group (Table 3). Total acid output remained unaltered in all the treatment groups. Along with total acidity, pepsin activity was significantly reduced by TCFE (500 mg/kg, p.o.) and cimetidine treatment (100 mg/kg, p.o.) (Table 3). Significant rise in total carbohydrate

content was observed in treatment groups (TCFE and cimetidine) as compared with the control group (Table 4). At the same time, protein content was significantly reduced in both the treatment groups (Table 4). Based on the results of total carbohydrate and protein content, mucin activity was determined in terms of TC/PR ratio increased significantly as compared to control. Gastric wall mucous content was increased significantly in TCFE treated group as compared to control (Table 4).

#### Cysteamine induced duodenal ulcer model

Results of cysteamine-induced duodenal ulcer model are shown in Table 5. TCFE (500 mg/kg, p.o.) treatment showed significant reduction in the

**Table 4.** Effect of TCFE on mucoprotective parameters in pylorus ligated gastric ulcers in rats

Parameters	Control	TCFE (500 mg/kg, p.o.)	Cimetidine (100 mg/kg, p.o.)
Total carbohydrate(µg/ml)	496.67 ± 46.69	1192.2 ± 76.77*	880.5 ± 54.45*
Protein content(µg/ml)	294.7 ± 67.04	77.67 ± 5.82*	46.17 ± 1.14*
TC : PR ratio	2.18 ± 0.41	15.62 ± 0.79*	19.08 ± 1.12*
GWMC	57.63 ± 7.90	84.79 ± 2.72*	74.21 ± 7.99

n = 6. Expressed as mean ± SEM. Anova: F(2,17) = 28.11 (TC); 10.10 (PR); 98.15 (TC:PR); 3.60 (GWMC), followed by Tukey's multiple range test, \*P < 0.05 when compared with control group.

**Table 5.** Effect of TCFE on cysteamine induced duodenal ulcers in rats

Treatment	Ulcer incidence No %	Mortality No. %	Ulcer score	Total lesion area (mm <sup>2</sup> )	Ulcer index
Control	8/8 100	3/8 37.5	2.50 ± 0.28	88.38 ± 3.87	4.5
TCFE (500 mg/kg, p.o.)	8/8 100	1/8 12.5	1.44 ± 0.21	37.95 ± 2.72*	3.44
Cimetidine (100mg/kg, p.o.)	8/8 100	0/8 0.0	0.90 ± 0.12*	41.2 ± 3.04*	2.9

n = 6. Expressed as mean ± SEM. Anova : F(2,23) = 68.74 (Lesion area); 11.50(ulcer score); followed by Tukey's multiple range test. \*P < 0.05, when compared with control group.

total lesion area when compared with control group. Similarly, positive control animals treated with cimetidine (100 mg/kg, p.o.) also provide significant protection against cysteamine-induced duodenal lesions as compared to control animals.

## DISCUSSION

Present study investigated antiulcer activity of 50% ethanolic extract of fruits of *Trichosanthes cucumerina* in various experimental gastroduodenal ulcer models. Assessment of acute toxicity is the first step in the toxicological investigation of an unknown substance. *Trichosanthes cucumerina* is a safe drug as observed from the results of acute toxicity test. 50% ethanolic extract of fruits of *Trichosanthes cucumerina* showed significant antiulcer effect against ethanol and aspirin induced gastric ulcers. Ethanol is a commonly used ulcerogenic agent and when given by gavage to rats, it produces severe gastric hemorrhagic lesions. The mechanism of ethanol induced gastric lesions is varied, including the depletion of gastric mucus content, damaged mucosal blood flow and mucosal cell injury. Ethanol administration may evoke gastric secretion through a more direct action on the stomach, involving the release of gastrin, histamine (Glass *et al.*, 1979) and endogenous endothelin (ET - 1) from vascular endothelial cells in the fundic mucosa (Ogawa and Yabana, 1993). Also, certain prostaglandins are capable of protecting rats against gastric mucosal lesions caused by necrotizing agents like ethanol and strong acid (Robert, 1979). Oxygen free radicals are implicated in the pathogenesis of ethanol-induced gastric mucosal injury (Szelehji and Brune, 1988; Hiraishi *et al.*, 1999) apart from other mechanisms such as mucosal leukotriene release (Peskar *et al.*, 1986), submucosal venular constriction (Oates and Hakkineu, 1988). Ethanol-induced gastric injury is associated with the significant production of free radicals leading to increased lipid peroxidation which causes damage to cell and cell membranes (Fridovich, 1978). Accumulation of activated

neutrophils in the gastric mucosa may be a source for free radicals (Tepperman and Soper, 1990). The ethanol-induced gastric mucosal damage was shown to be associated with the significant reduction in the non-protein sulphhydryl concentration in cultured rat gastric mucosa cells (Szabo *et al.*, 1981). Results of the present study showed that TCFE (300, 500 and 800 mg/kg, p.o.) prevented gastric tissue damage against ethanol-induced stress. Thus, the protection afforded by TCFE in ethanol model can be correlated to decrease in vascular permeability and thereby preventing damage to the capillary endothelium and release of arachidonate metabolites. Furthermore, antioxidant activity (Adebooye, 2008) of *Trichosanthes cucumerina* was also reported. Antioxidative properties may at least partially be one of the possible mechanisms by which TCFE ameliorated the ethanol induced gastric lesions.

Prostaglandins have long been known to be mucoprotective and ulcer healing agents. Prostaglandins protect gastrointestinal mucosa by forming a cytoprotective layer and increasing the secretion of bicarbonate ions that neutralise the gastric acidity. All therapeutically useful NSAIDs including aspirin act by inhibiting the synthesis of prostaglandins (Tamblyn *et al.*, 1997). Conventional NSAIDs cause non-selective inhibition of cyclooxygenase, which leads to reduction in bicarbonate secretion and reduced mucous production (Raskin, 1999). Coupled with it is vasoconstriction that occurs due to NSAIDs, which causes hypoxia and consequent formation of ulcer. Aspirin has been recorded to cause mucosal damage by several factors such as inhibiting prostaglandin synthesis, enhancing acid secretion, increasing back diffusion of H<sup>+</sup> ions, decreasing mucin secretion and breaking of mucosal barrier (Goel and Bhattacharya, 1991).

Thus, the antiulcer activity of the fruits of *Trichosanthes cucumerina* in aspirin induced ulcers can be related to its cytoprotective action.

Pylorus ligated induced ulcers are thought to be caused due to increased presence of acid and

pepsin in the stomach. Gastric hypersecretion plays an important role in production of experimental ulcers by pylorus ligation (Kitagawa *et al.*, 1978). Increased biosynthesis of nucleic acids and increased metabolism of carbohydrates and thereby exhaustion of carbohydrates and other compensatory mechanisms could also be responsible for ulceration due to pylorus ligation (Mozsik *et al.*, 1969). The essential criteria, which determine the status of mucosal defense barrier against the offensive assault of acid-pepsin is the quality and quantity of gastric mucus secretion (Sanyal *et al.*, 1983). Increased mucus secretion by the gastric mucosal cells can prevent gastric ulceration by several mechanisms including lessening stomach wall friction during peristalsis and acting as an effective barrier to the back diffusion of hydrogen ions. The TC/PR ratio has been accepted as a reliable index of mucosal resistance (Sanyal *et al.*, 1983). TCFE pretreatment have shown significant reduction in protein levels with corresponding increase in carbohydrate level leading to marked rise in mucin activity. It is evident from the biochemical parameters that TCFE has antiulcer effect in pylorus ligation model. The mechanism of their antiulcer activity can be related to the acid neutralizing property, reduction in acid-pepsin secretion and strengthening of mucosal barrier.

Cysteamine-induced ulcers are considered to be due to continuous hypersecretion of gastric acid (Takeuchi *et al.*, 1987). The pathogenesis of cysteamine-induced duodenal ulcers includes enhanced gastric acid secretion (Takeuchi *et al.*, 1987), increased duodenal motility (Tanaka *et al.*, 1989), delayed gastric emptying (Briden *et al.*, 1985) and decreased duodenal bicarbonate secretion in response to acid (Briden *et al.*, 1985). It is suggested from our results that test drug and cimetidine possess significant antiduodenalulcer activity. The mechanism of this activity can be related to inhibitory effect of acid and pepsin activity.

In conclusion, the results obtained in the present study suggest that 50% ethanolic extract of fruits of

*Trichosanthes cucumerina* has antiulcer activity, which lend pharmacological justification to the use of the plant extract by traditional medicine practitioners in the treatment of alimentary canal disorders. The antiulcer activity of this extract may be attributed to its cytoprotective action and inhibition of acid secretory parameters.

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