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Protective effect of *Tinospora cordifolia* on experimentally induced gastric ulcers in rats

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Abstract

Objectives: To study the possible antiulcer effects of alcoholic extract of *Tinospora cordifolia* in different animal models of ulcers. Methods and materials : The alcoholic extract of the whole plant was prepared and tested for antiulcer activity at the dose of 400 mg/Kg PO in pyloric ligation, ibuprofen and cold restraint induced gastric ulcer models. The effect of the extract was compared with famotidine (3.6mg Kg PO). Besides, the effect was also compared with misoprostal (7.2 μg/kg PO) in case of ibuprofen induced ulcer model. The antiulcer effects of the drugs were assessed on the parameters such as number, size and index of ulcers and the volume, acidity, and pH of gastric juice. Result: The extract of *Tinospora cordifolia*, famotidine and misoprostol significantly ($p<0.05$) reduced ulcer index in the models employed. While the antiulcer effect of the extract was comparable to that of the standard drugs in ibuprofen and stress induced ulcer models, its effect was significantly ($p<0.05$) lesser than that of famotidine in pyloric ligation method. Conclusion: *Tinospora cordifolia* possesses gastric ulcer protective principles.

Key Words: *Tinospora cordifolia*, gastric ulcer, famotidine, antiulcer.

1. Introduction

Peptic ulcer is one of the common gastrointestinal diseases and has become almost a hallmark of the so-called civilized life. Its incidence has been estimated to be 10% of the general population [1]. In the pathogenesis of this group of ulcerative disorders of the upper gastrointestinal tract what appears to have in common is the participation of acid and pepsin. Last two decades have witnessed introduction of a number of new drugs varied from H_2 blockers to proton pump inhibitors for the treatment of duodenal and gastric ulcers. None of these drugs are free from toxicities and are able to contain ulcers completely. Efforts have also been made to find suitable alternative remedies from plant and animal origins for the treatment of peptic ulcers. *Tinospora*

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cordifolia, a genus of deciduous woody climbers, could be one amongst them.

The plant is distributed in the tropics of Asia, Africa and Australia. It is widely used against a number of disorders in the Indian subcontinent. It is known as Guducci or Amrita in Sanskrit and Gulancha in Hindi.

In the Ayurvedic literature this plant is reported to have been used against peptic ulcers and other disorders such as rheumatism, jaundice etc [2]. In the preliminary investigations *T.cordifolia* is proved to be an antiulcerogenic [3].

Besides, it is also reported to have antioxidant property in the *in vivo* oxidative stress studies [4]. Currently a number of studies have implicated the role of oxidative stress in the pathogenesis of peptic ulcers [5,6].

On the other hand drugs possessing antioxidant property have been observed to mitigate the ulcers [7]. Thus, the antioxidant property of *T.cordifolia* could be expected to play a promising role in containing peptic ulcers. In view of these the present study has been undertaken to evaluate in detail the antiulcer effect of the alcoholic extract of *T.cordifolia* in three different peptic ulcer models.

2. Materials and methods

2.1 Plant material

Dried plant material was procured from a local Ayurvedic shop. The plant was authenticated by Professor Manohar Pai, Department of Botany, Bhandarkar's College Kundapur.

2.2 Preparation of extract

A coarsely powdered, air-dried, plant material (1.0 Kg) was exhaustively extracted with 95% ethyl alcohol by reflex condensation (at 60-80°C) method. The extract was concentrated under reduced pressure till it attained a syrupy consistency. Later the syrupy mass was evaporated in air to dryness (Yield 35 g). The extract was stored in refrigerator.

2.3 Animals

Studies were conducted in male Wistar rats of 180-200 g weight. The animals were locally bred and maintained under standard laboratory conditions. They had free access to water and food (Hindusthan Lever rat feed pellets) *ad libitum.* However, rats were fasted for 24 h and water was withdrawn 1 h before administration of drugs. The experimental protocol was approved by the institutional animal ethical committee.

2.4 Drug treatment

The extract of the plant was administered in the dose of 400mg/Kg; which was around 1/10th of the oral safe dose that was established in mice during the preliminary acute toxicity studies carried out in our lab. The standard anti-ulcer drugs and their doses used in the study were famotidine (3.6 mg/Kg) for pyloric ligation & stress induced models and misoprostol (7.2 μg/kg) & famotidine (3.6 mg/kg) for ibuprofen induced peptic ulcer model.

These doses were so arrived by computing the human doses to rat. The extracts and the drugs were suspended in 1% sodium corboxy methyl cellulose to administer them orally in the volume of 2.5 ml/Kg.

Ten groups of animals each group containing 8 rats were used. While three groups of animals each were used for Pyloric ligation and Stress ulcer models, four groups of animals were used for ibuprofen induced ulcer model.

2.5 Ulcer Induction

2.5.1 Pylorus-ligation method

One hr after either the vehicle or drug administration the pylorus of rats was ligated under light ether anaesthesia as described by

Shay *et al* (8). Nineteen hrs later the rats were killed and their stomachs were dissected out after ligating the cadiac end. Each stomach was cut open along the inner curvature and the contents were collected. The mucosa was then washed and the extent of ulceration was scored as per the method of Rao *et al* [9].

The gastric juice collected from each stomach was centrifuged and its volume and pH were measured. Free and total acidity were estimated titrimetrically with 0.01 N NaOH using Toepfer's reagent and phenolphthalein as indicators [10]. Acidity of the gastric juice was expressed as mEq/L/hr/100 g body weight.

2.5.2 Stress-induced ulcers

Animals starved for 24 h were immobilized in stress cages and forced to remain in cold room at a temperature of 4-6°C for 3 h [11] . The rats were then killed and the ulceration was scored. Vehicle or drugs were administered 30 minutes before immobilization.

2.5.3 Ibuprofen-induced ulcers

Ibuprofen in the dose of 300 mg/kg was administered orally at 15 h intervals to fasted rats to produce gastric ulcers [12]. The animals were killed 6 h after the second dose of ibuprofen and the ulcers were scored. Vehicle or the test drugs were administered 1 h before each dose of ibuprofen administration.

2.6 Statistical analysis

Results were expressed as Mean±SE. The data was analyzed by one way ANOVA followed by Scheffe's post-hoc test.

3. Results

The severity of gastric ulceration in all three models was assessed based on the means of ulcer number, ulcer size and ulcer index (a product of number and size). All there models produced moderate to severe ulcers in control group of animals; in that the maximum was by stress induced method. Both, famotidine and the extract of *T.cordifolia* significantly ($p<0.05$) reduced the ulcer number, size and index as compared to control group in all the three ulcer models.

These parameters were also significantly ($p<0.05$) reduced by misoprostol (another standard drug) in ibuprofen induced ulcer

Table 1.
Effect of ethanolic extract of *T.cordifolia* on peptic ulcers in experimentally induced ulcers.

Ulcer induction method.	**Ulcers**	**Groups**			
		Control	**Famotidine (3.6 mg/kg)**	***T.cordifolia* (400 mg/kg)**	**Misoprostol (7.2 mg/kg)**
Pyloric ligation	Number	7.75 ± 0.43	0.67± 0.43[a,b]	2.75 ± 0.37a	-
	Size (mm)	18.3 ± 0.62	1.0 ± 0.44[a,b]	4.00 ± 0.93[a]	-
	Index	138 ± 9.6	0.93 ± 0.8[a,b]	11.8 ± 3.0[a]	-
Stress	Number	24 ± 0.82	1.7 ± 0.62[a]	2.67 ± 0.33[a]	-
	Size (mm)	47 ± 2.58	0.33 ± 0.33[a]	3.83 ± 0.91[a]	-
	Index	1172 ± 116	0.34 ± 0.32[a]	11.5 ± 3.72[a]	-
Ibuprofen	Number	11.0 ± 0.82	0.17 ± 0.17[a]	0.16 ± 0.22[a]	0.12 ± 0.001[a]
	Size (mm)	31.8 ± 3.5	0.50 ± 0.32[a]	0.5 ± 0.34[a]	0.11 ± 0.010[a]
	Index	363 ± 62.6	0.09 ± 0.33[a]	0.11 ± 0.34[a]	0.02 ± 0.003[a]

a = $p < 0.05$ *vs* control; b = $p < 0.05$ *vs T.cordifolia* ; n = 8 ; Values are in Mean ± SEM.

Table 2.
Effect of ethanolic extract of *T.cordifolia* on gastric acid secretion in pyloric ligation method

Drugs	Dose (mg/kg)	Volume of gastric juice (mL/100 g body weight)	pH	Free acidity (mEq/L/hr/ 100 g body weight)	Total acidity (mEq/L/hr/ 100 g body weight)
Control	-	12.27 ± 0.55	1.81 ± 0.057	1.61 ± 0.59	3.64 ± 0.64
Famotidine	3.6	4.08 ± 0.32[a,b]	2.82 ± 0.06[a,b]	0.46±0 .07[a,b]	1.88 ± 0.07[a]
T.cordifolia	400	7.8 ± 0.51[a]	2.21 ± 0.14[a]	0.87 ± 0.08[a]	2.03 ± 0.11[a]

a = $p < 0.05$ *vs* control; b = $p < 0.05$ *vs T.cordifolia*.; n = 8; Values are in Mean ± SEM

model. The antiulcer effect of *T.cordifolia* was comparable with that of the standard drugs in ibuprofen and stress induced ulcer methods. However, its effect was significantly ($p<0.05$) lesser than that of famotidine in pyloric ligation method (Table 1).

Famotidine and *T.cordifolia* extract significantly ($p<0.05$) reduced the pH, volume, free acidity and total acidity of gastric juice. However, the antisecretory influence of the extract was significantly ($p<0.05$) inferior to that of the standard drug (Table 2).

4. Discussion

The present study was undertaken to see if the ethanolic extract of *T.cordifolia* could show antiulcer effect in three different models of peptic ulcers. The extract showed comparable antiulcer effects to the standard drugs in stress and ibuprofen induced ulcers, while its antiulcer effects were inferior to famotidine in case of pyloric ligation method.

An increase in the acid secretion, a decrease in the gastric mucosal protection and an induction of oxidative stress in gastric mucosa are the important factors that are implicated in the pathogenesis of peptic ulcers. It is an established fact that acid secretion and its stasis induce ulcers in pyloric ligation method. The antisecretory effect of *T.cordifolia* was not in accordance with that of famotidine (H_2 blocker) and therefore its antiulcer effects too.

However, in other two models its antiulcer effects were similar to that of the standard drugs. This implies that *T.cordifolia* might possess other antiulcer mechanism as well. NSAIDs are known to cause gastric ulceration by inhibiting the synthesis of PGE_2 (a prostaglandin that protects the gastric mucosa). *T.cordifolia* extract exhibited antiulcer actions against ibuprofen induced gastric ulcers. These effects of the extract were on-a-par-with misoprostol (a prostaglandin derivative commonly used to reverse the NSAID induced ulcers).

This, therefore, suggests that *T.cordifolia* may have cytoprotective action on GI mucosa. Stress induces activation of sympathetic and parasympathetic systems leading to generation of ischaemia by reducing the blood flow to gastric mucosa. The gastric mucosal damage caused by local ischaemia would generate oxidative stress to lead to ulcers. Beside, stress is also reported to decrease prostaglandin synthesis through oxidative stress [13].

In the present study *T.cordifolia* extract was found to reduce the stress induced ulcers. This gives an impression that *T.cordifolia* could have reduced the oxidative stress (besides other

mechanism) to contain peptic ulcers. The reports that antioxidants reduce stress-induced ulcers [7] and *T.cordifolia* possess antioxidant effect [5] strengthen our argument. However, the exact mechanism needs to be explored.

In a nutshell, *T.cordifolia* has got antiulcer activity. It being cheap, less toxic, widely used and easily available, might play as an adjunct to the existing drugs in the pharmacotherapy of peptic ulcers.

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