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EVALUATION OF GASTRIC ANTIULCER ACTIVITY OF *TRICHOSANTHES DIOICA* ROXB. LEAVES

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ABSTRACT

Trichosanthes dioica Roxb (family: Cucurbitaceae), commonly known as "Sespadula" in English and "Parwal" in Hindi and is widely grown throughout India. The leaves of this plant have also been used in traditional system of medicine for overcoming problems like constipation, fever, skin infection, wound healing and also in gastric ulcer. In the present study Aqueous extract of leaves of *Trichosanthes dioica* Roxb was evaluated for its antiulcer activity against; 1) Aspirin plus pylorus ligation model and, 2) Ethanol/HCl-induced ulcer in wistar rats. Ranitidine (100 mg/kg) was used as the standard drug. Different groups of rats (n=6 in each group) were given two doses (250 and 500 mg/kg) of *T.dioica* extract. Phytochemical analysis of the extract was also done. Phytochemical results revealed presence of tannins, saponins, triterpenoids, flavanoids. Thus only *T.dioica* extract (500 mg/kg) significantly ($p<0.001$) reduced the ulcer index in all the models used. The extract also significantly ($p<0.001$) increased the pH of gastric acid while at the same time reduced the volume of gastric juice, free and total acidities. Also it showed significant ($p<0.05$) reduction in pepsin activity. In conclusion, the present study provides preliminary data on antiulcer potential of *Trichosanthes dioica* leaves and supports the traditional use of the plant for the treatment of gastric ulcer.

INTRODUCTION: Peptic ulcer is one of the major gastrointestinal disorders, which occurs due to the imbalance between gastric aggressive and defensive factors [1]. Also, various factors contribute for the formation of gastric ulcers, such as gastric infection by *Helicobacter pylori* [2], frequent use of non-steriodal anti-inflammatory drugs (NSAIDs) [3], consumption of alcohol & nicotine etc [4]. Nowadays, research has been increased in the treatment of ulcer after the evidences of involvement of *Helicobacter pylori* and other factors in the pathogenesis of ulcer [5]. The antiulcer drugs used in the treatment of gastric ulcers like H_2-receptor antagonist [6], proton pump inhibitors reported for various side effects like, nausea, constipation, abdominal pain and diarrhea [7,8]. The disease has been also reported for high chances of recurrence and mortality. Thus there is a need for more effective and safe antiulcer agents aiming to relieve pain, heal the ulcer and delay ulcer recurrence. Herbal medicines are considered safer because of the natural ingredients with no side effects [9].

However, plant extracts are the most important sources of herbal medicine and new drug development which produce efficient results in treatment of gastric ulcers [10].

The plant *Trichosanthes dioica* Roxb belongs to family Cucurbitaceae, and commonly known as "Sespadula" in English and "parwal" in Hindi, is widely grown throughout India [11]. The various parts of the plant like leaves, tender shoots have also been used in traditional system of medicine [12, 13, 14]. The chemical constituent present in Trichosanthes dioica includes vitamin A, vitamin C, tannins and saponins [15, 16], and flavonoids, alkaloids [17]. Several pharmacological studies have been carried out in different parts of *Trichosanthes dioica* Roxb. Generally, the plant exhibited anthelminitic [18], antihyperglycaemic [19], antioxidant [17], antidiabetic [20], antipyretic [21], cholesterol-lowering [22], hepatoprotective [16] and wound healing activitiy [17].

Despite, the various claims on *Trichosanthes dioica* Roxb medicinal uses, particularly its potential to heal ulcer, no attempt has been made to our best knowledge, to scientifically confirm on this matter. Thus, the aim of the present study was to evaluate the antiulcer activity of aqueous *Trichosanthes dioica* leaves using various types of ulcerogenic models.

MATERIALS AND METHODS:

Animals: Wistar rats (160-200 gm) were procured from National Institute of Biosciences, Pune, India. The animals were maintained under standard laboratory conditions (23±20°C, 12 h light and dark cycle) with free access to water and standard pellet feed (Amrut Feed, Chakan) *ad libitum.* All the experimental procedures and protocols with animal studies were approved by the Institutional Animal Ethics Committee (protocol no. SCOP/2011-12/07), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India. Animals were naive to drug treatments and experimentation at the beginning of all studies.

Plant material: *Trichosanthes dioica* Roxb aqueous leaves extract was purchased from, Botanosys Bikaner, Rajasthan, India, along with its certificate of analysis and HPLC standardization data, and confirmatory standardization was done by thin layer chromatography.

Phytochemical screening: Preliminary phytochemical screening of *T.dioica* extract was performed for the presence of alkaloids, tannins, saponins, tannins, carbohydrates, triterpenoids, flavonoids and steroids [23, 24].

Drugs and chemicals: Aspirin and Ranitidine both were obtained from Jain Pharma, Bhosari, Pune, India. All other chemicals used in the study were of analytical grade obtained from local supplier in Pune, India.

Acute toxicity studies: The acute toxicity study of *T. dioica* aqueous extract was performed in a single dose administration of 5000 mg/kg (p.o.) [25]. Rats were fasted for 24h before the administration of *T. dioica* extract. The control group was given CMC 1ml/kg. The toxicity signs and symptoms or any mortality were observed at 0, 30, 60, 120, 180 and 240 min after *T. dioica* extract administration. The animals were observed continuously once a day for next 14 days. The number of rats that survived was recorded at the end of the toxicity study period.

Aspirin plus pylorus ligation-induced ulcer: The experiment was carried out according to the method of Goel et al (1985) with certain modifications [26]. Aspirin (200 mg/kg) was administered orally in non-fasted rats once daily for five days. *T. dioica* extract (250 and 500 mg/kg), CMC (1ml/kg) as control or ranitidine (100 mg/kg) as positive control were administered 30 min before each aspirin treatment. On sixth day immediately after aspirin treatment pylorus-ligation was performed on 36 h fasted rats. The animals were sacrificed with an over dose of ether after 4 h of pylorus ligation. The stomach was removed and the content was drained in glass tube. The volume of gastric juice was measured and centrifuged at 2000 rpm for 15 min. The supernatant obtained was used for determination of free acidity, total acidity [27], pH and pepsin activity [28]. The inner surface of stomach was examined for ulcers. Ulcer score and ulcer index was determined according to method of Vogel and Vogel (1997) [29].

Ethanol/HCl-induced chronic ulcer: Ulceration was induced according to the method of Mizui and Dotuchi (1938) with slight modifications [30]. 1.5 ml of ethanol/HCl mixture (70% ethanol and 5% HCl) were given on the first day, half its dose in same volume on second day and additional half of the second dose in same volume on third day.

T. dioica extract (250 and 500mg/kg), CMC (1ml/kg) and ranitidine (100mg/kg) were administered orally prior to ethanol/HCl treatment. The drug administration was done from day 1 to 10. Feed was withdrawn 24 h before the last dose of drug. 60 min after last dose ethanol/HCl mixture (70% ethanol and 5% HCl) at 1.5ml dose was given orally. After 4 h the animals were sacrificed, stomach of each animal was cut along the greater curvature and the surface was observed for ulcer. The ulcer score and ulcer index were determined (Vogel and Vogel, 1997) [29].

Histopathological evaluation: The stomach samples from Aspirin plus pylorus ligation and Ethanol/HCl induced ulcer groups were preserved in 10% formalin solution and sent for histopathological analysis to Dr. Deshpande laboratories, Pune, India.

Statistical analysis: The results were expressed as mean ± standard deviation of mean (SD). Analysis of variance (ANOVA) was performed to compare and analyse the data followed by post hoc test. Results were considered significant when $P \leq 0.001$ and $P \leq 0.05$.

RESULTS:

Phytochemical screening: The phytochemical screening of *T. dioica* extract showed the presence of alkaloids, triterpenoids, flavonoids, tannins and saponins.

Acute toxicity: The rats treated with *T. dioica* extract 5000mg/kg orally showed no signs of mortality.

Aspirin plus pylorus ligation-induced ulcer: Using this model of ulcer induction, the gastric secretory parameters were measured which showed that *T. dioica* extract (500 mg/kg) significantly decreased the gastric content, pH, free acidity, total acidity and pepsin activity (**Table 1**). Also there was significant reduction in ulcer score and ulcer index of *T. dioica* extract at dose of 500 mg/kg (**Table 2**).

Ethanol/HCl-induced chronic ulceration: In ethanol/HCl mixture-induced ulceration, pretreatment with *T. dioica* extract at a dose of 500 mg/kg showed significant reduction in ulcer score and ulcer index (Fig.1 A, B). While Ranitidine (100 mg/kg) standard also showed significant decrease in the above parameters.

Histopathological evaluation: Aspirin plus pylorus ligation and ethanol/HCl induced ulceration caused lesions including hemorrhagic erosion, oedema and leucocytes infiltration of gastric mucosal layer. Pretreatment with *T. dioica* extract at dose of 500 mg/kg and Ranitidine 100 mg/kg showed significant protection against all the observed damages in gastric mucosa.

TABLE 1: EFFECT OF *T. DIOICA* EXTRACT ON GASTRIC CONTENT, pH, FREE ACIDITY, TOTAL ACIDITY AND PEPSIN ACTIVITY IN ASPIRIN PLUS PYLORUS LIGATION-INDUCED ULCER IN RATS

Treatment	Dose (kg^{-1})	Gastric content (ml)	pH of gastric content	Free acidity (meq./l)	Total acidity (meq./l)	Pepsin activity (µg/ml)
Control	1 ml	2.733±0.1282	1.800±0.09309	2066±121.5	2855±112.0	3.072±0.03240
Ranitidine	100 mg	1.017±0.08333[a]	4.300±0.1528[a]	607.5±121.5[a]	1397±112.0[a]	1.845±0.3024[b]
T.dioica	250 mg	2.067±0.1116	2.233±0.1585	1580±153.7	2066±121.5[a]	3.137±0.1008
T.dioica	500 mg	1.317±0.1352[a]	3.300±0.1461[a]	972.0±121.5[a]	1762±112.0[a]	2.173±0.1863[c]

Values are represented as mean ± SD. Statistical analysis was done by one-way ANOVA followed by post hoc test. [a] $P < 0.001$ as compared to control; [b] $P < 0.01$ as compared to control; [c] $P < 0.05$ as compared to control

TABLE 2: EFFECT OF *T. DIOICA* EXTRACT ON GASTRIC ULCER IN ASPIRIN PLUS PYLORUS LIGATION-INDUCED ULCER IN RATS

Treatment	Dose (kg^{-1})	Ulcer score	Ulcer index
Control	1 ml	2.667±0.2108	16.83±0.4014
Ranitidine	100 mg	0.5000±0.2236[a]	6.000±0.4472[a]
T.dioica	250 mg	1.500±0.2236[c]	15.17±0.4014
T.dioica	500 mg	0.6667±0.3333[a]	7.500±0.6191[a]

Values are represented as mean ± SD. Statistical analysis was done by one-way ANOVA followed by post hoc test. [a] $P < 0.001$ as compared to control. [c] $P < 0.05$ as compared to control.

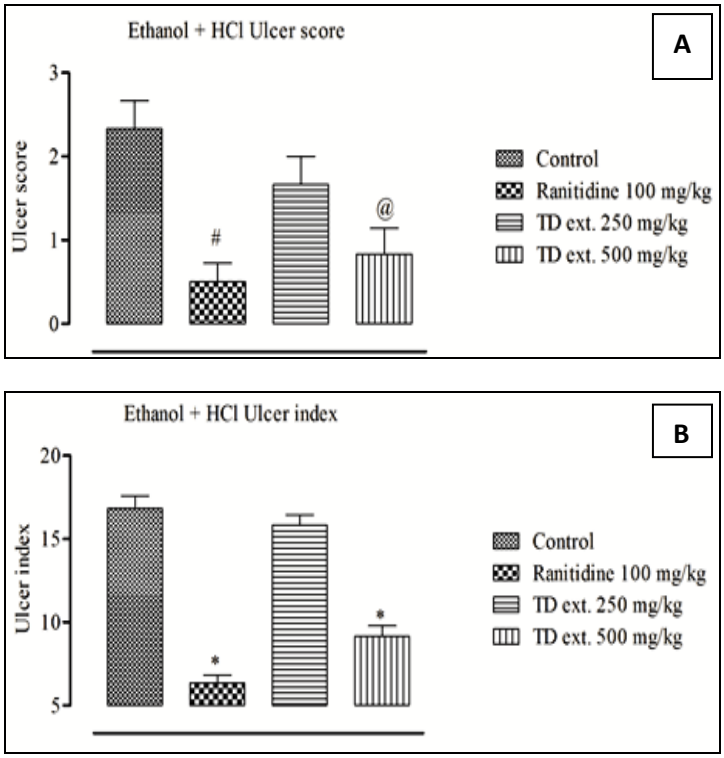

FIG.1. EFFECT OF *T.DIOICA* EXTRACT AT 250 MG/KG AND 500MG/KG, RANITIDINE 100MG/KG STANDARD ON ETHANOL/HCl (70% ETHANOL AND 5% HCl) INDUCED CHRONIC ULCERS IN RATS. (A) Ulcer score; (B) Ulcer index. Statistical analysis was done by one-way ANOVA followed by post hoc test. (n=6) in each group. $^{@}P < 0.05$, $^{\#}P < 0.01$ and $*P < 0.001$ were considered significant as compared to control.

DISCUSSION: Peptic ulcer is considered as one of the modern age epidemic which has been affecting approximately 10% of world population [31]. Previously reported that peptic ulcer is an imbalance between acid and pepsin along with the weakness and damage of the gastric mucosal barrier [32], which is commonly associated with excess generation of exogenous and endogenous reactive oxygen species and free radicals. In the acute toxicity study, the *T. dioica* extract, at the dose of 5000 mg/kg, exhibited no signs of toxicity. According to toxicologists throughout the world, any test substance that is not lethal on acute administration at a concentration of 5000 mg/kg body weight is essentially nontoxic [33]. Based on the toxicity study, the current doses regime (250 and 500 mg/kg) was chosen for the antiulcer study.

The phytochemical tests of the *T. dioica* extract showed the presence of various phytoconstituents like tannins, saponins, flavonoids and triterpenoids. Thus it can be suggested that presence of saponins and flavonoids may be responsible for *T. dioica* antiulcer activity [34, 35].

In acute study, for evaluation of anti-ulcer activity in rats Aspirin plus pylorus ligation model [26] was used and ulcer score was observed. From observed ulcer score, ulcer index was calculated. As ulcer formation leads to increase in secretion of gastric content, so the gastric volume in aspirin plus pylorus ligated rats were measured. Also pH, free acidity, total acidity and pepsin activity were calculated from observed readings. In vehicle treated group aspirin plus pylorus ligation increased the acid secretion, which in turn caused increase in gastric volume, low pH, increased free acidity, total acidity and pepsin activity resulted in higher ulcer score and ulcer index. The extract of *T. dioica* at dose of 500 mg/kg reduced the ulcer score and ulcer index with significant decrease in gastric volume, free acidity, total acidity and pepsin activity.

For chronic study, Ethanol/HCl model [30] was used for development of chronic ulcer in rats. Ulcer score and ulcer index were determined for evaluation of antiulcer activity of *T. dioica* extract. Ethanol/HCl is reported for gastric ulcer formation [36], and also widely used to induce experimental gastric ulcer in animals [37]. Ethanol/HCl increases superoxide anion, hydroxyl radical production and lipid peroxidation in the gastric mucosa, and together with other reactive metabolites react with most of the cell components [38]. These lead to changes in the cells structures and functions or contributing to other mechanisms that ultimately help enhanced oxidative damage. Earlier studies revealed that Ethanol/HCl induces gastric mucosal injury by causing extensive damage to mucosal capillaries resulting in increased vascular permeability, oedema formation and epithelial lifting [39, 40, 41].

The Ethanol/HCl induced ulcer model was used to screen drugs for possible cytoprotective activity [42] and the ability of *T. dioica* extract at dose of 500 mg/kg to reduce Ethanol/HCl induced gastric ulcer partly suggested the involvement of local and nonspecific mechanism called cytoprotection. Cytoprotection may occur due to the capacity of some compounds to induce prostaglandin production, which in turn stimulates mucus and bicarbonate synthesis [43]. According to Rachchh and Jain (2008) [44], other than free radicals, ulcers induced by chemicals like Ethanol/HCl are due to several contributing factors including effects on mucosal blood flow, platelet thrombi, damage to capillary endothelium, and release

of arachidonate metabolites, and platelet activating factor (PAF). Thus, the protection afforded by *T.dioica* extract at dose of 500 mg/kg in Ethanol/HCl model can be linked to decrease in vascular permeability and, in so doing, preventing damage to the capillary endothelium. The ability of *T. dioica* extract (500 mg/kg) to reduce Ethanol/HCl-induced gastric ulcer is further suggested to be attributed to its previously reported anti-inflammatory [45] and antioxidant effects [17]. Administration of antioxidants, on the other hand, has been demonstrated to inhibit Ethanol/HCl induced gastric injury in rat [46, 47].

Thus, it can be speculated that the *T. dioica* extract at a dose of 500 mg/kg antiulcer activity could be ascribed to its anti-inflammatory activity [45], as well as antioxidant activity [17].

Results of this study provided preliminary data for the first time that the leaves of *T. dioica* may possess significant antiulcer activity. In acute study, observed reduction in ulcer score and gastric secretion may be attributed to its antisecretory activity. In chronic study, reduction in ulcer score may be due to its antiulcer and partly cytoprotective activity. These observed effects of *T. dioica* may be linked with its antioxidant and anti-inflammatory effect due to the presence of bioactive compounds like flavonoids, saponins and tannins in it.

Thus the present study confirms the use of *Trichosanthes dioica* Roxb leaves in the traditional management of peptic ulcer disease. Hence, further studies are required to confirm the exact mechanism underlining the ulcer healing and ulcer protecting property of the *T. dioica* extract and to identify the chemical constituents responsible for it.

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