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Antiulcer activity of ethanolic bark extract of *Dalbergia sissoo* on experimental ulcer models

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ABSTRACT

Gastric ulcer is one of the major health problem in the world. There is great demand of alternative herbal remedies for the treatment of ulcer as they have better cultural acceptability, minimal side effects, and better compatibility with the human body.*D. Sissoo* has been traditionally used for various ailments including gastric problem. Our study aimed to evaluate the antiulcer activity of crude ethanolic bark extract of *Dalbergia sissoo*(EBED) using pylorus ligation and Indomethacin induced ulcer model in Wistar albino rats.Antiulcer activity was evaluated by using four groups as; control (tween 80 1% v/v solution, 5 ml/kg), standard (Ranitidine 80 mg/kg), 250 mg/kg and 500 mg/kg of bark extract given orally (p.o.). Various parameters like mean ulcer index, percentage protection, volume of gastric juice, gastric P^H, protein, carbohydrate, pepsin, free and total acidity and ratio of total carbohydrates and proteins (TC:TP) were determined. Our study revealed the significant decrease ($p<0.01$) in mean ulcer index in EBED treated group in both the models compared to control. Furthermore, our study showed the significant decrease ($p<0.01$ and $p<0.001$) in the offensive factors like free and total acidity, pepsin content and protein content whereas significant increase in the defensive factors like total carbohydrate content($p<0.01$) and TC:TP as compared to control in dose dependent manner. We concluded that EBEDpossess more potent antiulcer activity than leaf extract in our previous study in reducing the development of gastric ulcer as well as increasing the healing of the gastric ulcer in dose dependent manner.

Keywords: *Dalbergia sissoo*, Peptic ulcer, Pylorus ligation, Indomethcin induced ulcer

INTRODUCTION

Peptic ulcer disease (PUD) is a chronic inflammatory condition involving a group of disorders characterized by ulceration in regions of the upper gastrointestinal (GI) tract where parietal cells secrete pepsin and hydrochloric acid[1]. It encompasses both gastric and duodenal ulcers and has been a major threat to the world's population over past two centuries, with a high morbidity and substantial mortality[2]. Peptic ulcer and gastritis have been associated with multi-pathogenic factors and could be due disturbances in natural balance between aggressive (acid and pepsin) and maintenance of mucosal integrity through the endogenous defense mechanism e.g. mucus, bicarbonates, mucosal blood supply, Prostaglandins (PGs) etc. [3]. Various treatment

regimens have been established since 25-30 years for the effective management of the disease with the greater understanding of the pathogenesis including; antacids, proton pump inhibitors, anticholinergic and H_2-antagonists. These medicines exhibit several adverse reactions; gynecomastia, hematopoietic changes, acute interstitial nephritis [4],thrombocytopenia [5], anaphylaxis reactions [6], nephrotoxicity and hepatotoxicity[7]. Moreover, PUD remains a vital clinical problem with widespread use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) [5]. Numerous studies have demonstrated that herbal medicines can effectively treat gastric ulcer in humans and various animal models *via* divergent mechanisms[8]. Thus, there is greater interest in search of herbal drugs as they have better cultural acceptability, minimal side effects, better compatibility with the human body and are also inexpensive in nature [9]. Encouraging findings on previous studies on antiulcer activity; *Ocimumsanactum*[10], *Emblica officinalis*[11], *Asparagus recemosus*[12], *Bidenspilosa*[13], *Bauhinia purpurea*[14] etc. have further attracted the attention of herbal medicines in PUD.Indomethacin initiates lipid peroxidation mediated by Reaction Oxygen Species (ROS) [15]which might eventually lead to oxidative stress diminishing various cellular functions with pathological conditions [16]. The association of oxidative stress and gastric ulcer is well recognized [17]. *Dalbergia sissoo* (Family: Fabaceae) is a deciduous tree with a light crown and an often crooked trunk originating in the foothills of the Himalaya up to 1500m in Pakistan, Nepal, India and Bangladesh [18]. It has been extensively used in Ayurveda and other systems of medicine for its clinical effects; aphrodisiac, abortifacient, expectorant, anithelminthic, antipyretic and also in the treatment of various digestive and skin diseases[19, 20]. Various *in vivo* antioxidant[19];analgesic [20];anti-spermatogenic[22]; anti-nociceptive[23] ;anti-diabetic[24]; anthelmintic[25] and antidiarrheal[26] have been reported. Most investigations have been performed on the leaves, whereas significant differences in the chemical composition of the root and the leaves have been reported [27]. We previously reported the antiulcer activity of leaf extract of D. sissoo[21]. The major objective of present study is to evaluate the antiulcer effect of EBED in pyloric ligation and Indomethacin induced ulcer models which has not been undertaken yet to the best of our knowledge.

MATERIALS AND METHODS

Animals and chemicals

Wistar albino rats weighing between 180-220 g of either sex were used in the experiment. Animals were maintained under standard conditions in an animal house approved by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Standard drugs; Ranitidine and Indomethacin were obtained from Time Pharmaceutical Pvt. Ltd., Nawalparasi, Nepal and all other chemical reagents used were of analytical grade. The study protocol was approved by Institutional Animal Ethical committee and was carried out in Mallige College of Pharmacy, Bangalore, India.

Plant material and preparation of extract

The barks of *D. sissoo* were collected from FRLHT (Foundation for Revitalization of Local Health Traditions) garden, Bengaluru and verified by senior botanist Dr. K Ravikumar, FRLHT. A voucher specimen (Herbarium number: MCP/DPCL/2012-13/305/36) of the plant was preserved in Mallige College of Pharmacy, Bangalore, India. The barks of *D. sissoo* were chopped into small pieces and dried under shade at room temperature for 25 days, powdered using a mechanical grinder and passed through the sieve (coarse 10). Thus obtained powder was subjected to petroleum ether decantation for about 4 hours (78±2°C) in Soxhlet apparatus and the marc obtained was air dried followed by extraction with 90% ethanol (48 hours at 78±2°C). Finally, thus obtained extract was concentrated to dryness using rotary evaporator to obtain black to dark brownish mass which was then stored in an air tight container under refrigeration for further studies. The percentage yield of EBED was found to be 20%.

Phytochemical screening

EBED was subjected to qualitative phytochemical screening using standard color

reactions as described in standard procedures [22, 23].

Acute toxicity (ld50)

EBED having the same chemical constituents was found to be safe up to 5000 mg/kg body weight (p.o.) while tested in mice [24], hence 1/20th and 1/10th of no lethal dose were taken as effective dose (i.e; 250 mg/kg,& 500 mg/kg B.W, p.o.) for the EBED in evaluation of anti-ulcer potential in rats.

Pylorus ligation induced ulcer model in rats [25-27]

Healthy wistar albino rats of either sex weighing between 180-220 g were divided into four group containing six rats each. First group, the control group received vehicle (tween 80; 1% solution, 5 ml/kg, p.o.); second group, the standard drug treated group received Ranitidine (80 mg/kg, p.o.); third and fourth group received 250 mg/kg and 500 mg/kg, p.o. EBED respectively for 14 days. The animals were fasted for 36 hours with water *ad. Libitum* prior to the experiment and care was taken to avoid coprophagy and cannibalism by placing them individually in the cages. After fasting, different doses of test substances were administered orally with no water given during and after experimentation. Half an hour after drug administration animals were anesthetized under light ether anesthesia and the pylorus portion of the stomach was slightly lifted out and ligated, avoiding traction to the pylorus and damage to its blood supply. Stomach was placed back carefully and the abdominal wall was closed with sutures. The animals were deprived of food and water during the postoperative period and they were sacrificed six hours after pylorus ligation by over dose of ether anesthesia. The stomachs were isolated and the content was collected in different test tubes and centrifuged at 3000 rpm. Finally, supernatant was collected and the parameters like p^{H}, volume of the gastric juice, estimation of free acidity, total acidity, pepsin content, total proteins and total carbohydrates were measured according to the standard procedures [28-31]. The stomachs were then incised along the greater curvature and then washed with normal saline, pinned on the flat surface to observe for lesions/ulcers in the glandular portion of the stomach. The numbers of ulcers per stomach were noted and severities of the ulcers were scored microscopically with the help of hand lens (10X) and then ulcer index and percentage protection were calculated.

Indomethacin induced gastric ulcer model [25, 32, 33]

All the groups for standard and treatment were allocated similar to that of pylorus ligation model and received the respective test substances as described above for the 14 days. On the 14th day, gastric ulcer was induced with indomethacin (40 mg/kg, p.o.) after fasting the entire group for 24 hours. The animals were then given overdose of ether anesthesia and sacrificed 4 hours after the treatment with ulcerogenic agent, the stomachs were removed and then incised along the greater curvature and then washed with normal saline, pinned on the flat surface to observe for lesions/ulcers in the glandular portion of the stomach. The number of ulcer was noted and area measured severity of the ulcers scored microscopically with the help of hand lens (10X) and ulcer index and percentage protection calculated.

Scoring for ulcers and calculation of ulcer index

Based on their intensity of ulceration as observed from the hand lens, the scores were given as: 0(normal stomach), 1(superficial ulcer), 2(deep ulcers), and 3(perforation).

The ulcer index was determined using the formula:

$$Ulcer\ Index\ = U_N + U_S + U_P \times\ 10^{-1}$$

Where, U_N = Average of number of scores per animal

U_S = Average of severity score &

U_P = Percentage of animals with ulcers

Calculation of percentage protection

The percentage protection was calculated by using the formula:

$$Percentage\ protection = \frac{U_c - U_t}{U_c} \times 100$$

Where, U_t = Ulcer index of treated group & U_c = Ulcer index of control group.

Statistical analysis

Results are expressed as Mean ± SEM and analyzed by Graph Pad Prism (Version 6.00). Test for significance was done by one way ANOVA followed by Dunnett's comparison tests where $p<$

0.05 and $p< 0.01$ wereregarded as significant and $p< 0.001$ as very significant as compared to standard used.

RESULTS AND DISCUSSION

Results for phytochemical screening

Results for preliminary phytochemical screening of EBED revealed the presence of alkaloids, saponins, flavonoids, phenols, tannins, terpenoids, and glycosides while amino acids being absent.

Results for indomethacin induced gastric ulcer model

Oral administration of EBED in 250 and 500 mg/kg showed significant reduction (*p<0.01*) in the ulcer index values as compared to the control group in a dose dependent manner (500 mg/kg showing more reduction on the ulcer index than 250 mg/kg dose). Similarly, the percentage protection of the EBED in doses 250 mg/kg and 500 mg/kg was found to be 46.4% and 55.01% where standard drug ranitidine (80 mg/kg) showed the protection of 78.92% **(Table 1).**

Table 1: Effect of EBED *on* ulcer index and percentage protection in Indomethacin induced gastric ulcer model in rats.

Groups	Ulcer Index	% Protection
Control	21.12 ± 2.01	-
RAN	4.45 ± 0.51***	78.92
250 BE	10.23 ± 0.03**	51.56
500 BE	8.32 ± 0.05**	60.6

N = 6 animals in each group. Values are expressed as Mean ± SEM. *$P<0.05$ **$P<0.01$and***$p<0.001$as compared to control. RAN: group treated with Ranitidine (80 mg/kg), 250 BE: group treated with 250 mg/kg EBED, 500 BE: group treated with 500 mg/kg EBED.

Results for pylorus ligation ulcer model

Oral administration of EBED in 250 and 500 mg/kg showed significant reduction in the parameters like ulcer index (*p<0.01* for BE 250 and BE 500*)*, volume of gastric juices (*p<0.01* for BE 250 and *p<0.05* for BE 500), free and total acidity (*p<0.001* for BE 500), total protein contents (*p<0.001* for BE 250 and BE 500), total pepsin content (*p<0.001* for BE 250 and BE 500) whereas significant increament in the parameters like p^H of gastric juice (*p<0.05* for BE 250and *p<0.01*for BE 500), total carbohydrates content (*p<0.01* for BE 250 and *p<0.001*for BE 500) and TC:TP ratio in dose dependent manner. Similarly, the percentage protection against the ulcer induced was also increased in dose dependent manner; 500 mg/kg showing high protection than 250 mg/kg dose where the percentage protection of the standard ranitidine (80 mg/kg) was found to be 70.25% which was highest among all the groups (**Table 2**). The results from both experimental models indicates that the EBED has potential antiulcer activity as compared to the standard Ranitidine.

Table 2: Effect of EBED on different parameters in Pylorus ligation induced ulcer model in rats.

Parameters	Control	RAN	250 BE	500 BE
Ulcer Index	16.15 ± 1.01	4.8 ± 0.77**	8.17± 1.32**	6.73±1.00**
Percentage Protection	-	70.27	49.41	58.32
VOLUME OF GASTRIC JUICE (Ml)	9.4 ± 0.87	2.1 ± 0.34**	4.3 ± 0.59**	3.6 ± 0.75*
P^H Of Gastric Juice	2.5 ± 0.22	5.4 ± 0.23***	3.9 ± 0.22*	4.6 ± 0.14**
FREE ACIDITY (Meq/L)	34.5 ± 2.08	5.8 ± 0.64***	14.2± 0.91**	8.8±0.67***
TOTAL ACIDITY (Meq/L)	75.8 ± 3.37	19.6 ± 1.89**	34.5± 2.55**	29.4 ± 1.67*
Total Pepsin (µg/ml tyrosine)	245.57 ± 3.93	142.63±2.48***	202.03±0.67***	180.74±1.37***

Total Proteins (µg/ml)	405.29 ± 6.31	298.77 ±5.14***	354.68±3.62***	345.72±4.06***
Total Carbohydrates(µg/ml)	474.81 ± 6.00	665.27±4.73***	525.34 ± 2.70**	591.15±6.47***
Tc:Tp Ratio	1.17	2.22	1.48	1.71

N = 6 animals in each group. Values are expressed asMean ± SEM. **P<0.05, **P<0.01* and ****P<0.001* as Compared to control.

DISCUSSION

A recent epidemiological survey in India demonstrated 7.8% of study population have PUD with greater incidence of gastric ulcer than duodenal ulcer over the past two decades[34]also it is one of the most common diseases in Nepal[35].Phytotherapy are inspiring source of new bioactive molecules gaining greater interest in pharmaceutical industry for gastric ulcer associated with the use of allopathic drugs[36]. Clinical and experimental studies have explained that herbal medicines are effective for gastric ulcer and the cost of herbal medicine for gastric ulcer is only about one-sixth of that of western medicine [37]. Interestingly, positive test for phytochemicals; flavonoids, terpenioids phenolic compounds, provided us preliminary idea about antioxidant activity. These phyotchemicals interact with other molecules, such as proteins and polysaccharides to form an impervious microlayer on the ulcer site by precipitating the microproteins, thereby protecting underlying tissues from toxins and other irritants[38, 39] . Terpenoids and saponins have shown to possess anti-inflammatory and antiulcer property[40, 41], polyphenols stimulate the antioxidative defense enzyme activities [42], flavonoids are cytoprotective[43, 44], tannins prevent ulcer development due to their protein precipitating and vasoconstricting effects[45]. These all secondary metabolites were positive in our study. Imbalance between free radical formation and scavenging capacity results in oxidative stress which further deregulates cellular functions leading to different pathological conditions including ulcer[16] .Ulcer index values in both the screening models were significantly *(p<0.01)* reduced which may be due to presence of flavonoids and phenolic compounds having excellent antioxidant property, in agreement with previous report [45, 46] . The reduction of ulcer index as well as percentage of protection was found much better with EBED in both the experimental models as compared with leaf extract in our previous study [21]. It may be due to variation of secondary metabolites in leaf and bark extract. Low pH value has been linked to pathogenesis of ulcer in experimental models[47]. Dose dependent effect noticed for increase in pH and total acidity in groups treated with EBED in our study demonstrated gastroprotective environment. The significant decrease in ulcer index and gastric volume in EBED treated experimental groups may be attributed to either free radicals formation or stimulation of cytoprotective prostaglandin synthesis [34]. PGE_2 and PGI_2 stimulate the secretion of mucus bicarbonate and hydrophobic surfactants like phospholipids secretion in gastric epithelial cells[48]. Thus, the possible involvement of EBED on enhancing mucosal resistance could have offered gastro protection. In pylorus-ligated rats the gastric acid secretion is an important factor for generation of ulceration. Significant reduction in gastric secretion and ulcers formation by EBED after pylorus ligation suggested the cytoprotective mechanism in gastric mucosa may involve direct reduction of gastric secretion. The increase in total carbohydrate : protein (TC:TP) ratio is the direct reflection of mucin activity, which is indicated by the enhanced level of individual mucopolysaccharides like hexose, hexosamine, fucose and sialic acid[49]. Decrease in protein content in the gastric juice also signifies decrease in leakage from the mucosal cells indicating mucosal resistantce. The wide distribution of adherent mucus content in the gastrointestinal tract plays a pivotal role in cytoprotection and repair of the gastric mucosa [31].Our results showed that EBED causes an increase in total TC: TP ratio suggesting a significant increase in the glycoprotein content from mucosal cells of the

gastric mucosa. Here, the decrease in protein content of gastric juice in an indication of the decrease in leakage of plasma proteins into gastric juice[50]. Thus, with these findings we can predict the mechanism of action of EBED may be due to the coating property leading to protective activity on gastric mucosa. In the present study, increase in P^H, decrease in free and total acidity, decrease in volume of gastric juice and pepsin concentration were evidenced in ulcerated animals treated with EBED, which is highly desirable for gastro protection and antiulcer effect. Ulcerated rats showed an alteration in the peptic activity which is in accordance with the previous report [50].Our results supported in two main approaches for treating peptic ulcer; reducing the production of gastric acid and re-enforcing gastric mucosal protection [51, 52]. The modification in pepsin concentration after the treatment with EBED depicts the efficacy of the extracts on gastric secretions and it can be assumed due to the direct action on the acid producing cells. NSAIDS such as Indomethacin have been reported to induce gastric ulceration by down regulation of the biosynthesis of cytoprotective prostaglandins; PGE_2 and PGI_2 by inhibition of the cyclooxygenase pathway of arachadonic acid metabolism[53, 54], which decreases mucus content, surface-active phospholipid bicarbonate secretion, and mucosal proliferation[55]. The possible protective effect of the EBED in indomethacin-induced ulcers may be due to increased mucus secretion. The cytoprotective efficacy of EBED may be due to the free radical scavenging activity or increase in mucus secretion, , supported by a recent study concluding the prevention of ulcer through scavenging of free radicals[56]. The offensive factors were reduced and defensive factors were much increased in present study than by the leaf extract in our previous report suggesting that EBED has more potent antiulcer activity. The phytochemical differences in leaf and bark extract of *D. sissoo* would be an interesting area for further research.

CONCLUSION

In conclusion, EBED is more potent antiulcer agent than leaf extract in our previous study in reducing the development of gastric ulcer and also increasing the healing of the gastric ulcer in dose dependent manner in both the experimental ulcer induced models. The antiulcer effect of EBED may be due to any of the probable mechanisms viz. reduction in gastric acid secretion, antioxidant action, mucoprotection or gastric cytoprotection attributed by the presence of various secondary metabolites.

Competing interests

The author(s) declare that they have no competing interests.

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