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GASTROPROTECTIVE POTENTIAL OF BIOACTIVE FRACTION FROM *LASIA SPINOSA* RHIZOME ON EXPERIMENTALLY INDUCED GASTRIC ULCERATION

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ABSTRACT: Various parts of *Lasia spinosa* (Linn.) are widely used in North East region to manage wide range of disease but so for no scientific study was done to find out its pharmacological properties which may support its use in traditional medicine. Bioactive fraction (ethyl acetate fraction, LSE) from the methanol – water (80:20) extract of Lasia spinosa rhizome was evaluated for gastroprotective and antioxidant activity. In the safety evaluation, LD50 was found to be more than 2000 mg/kg. High performance thin layer chromatography (HPTLC) finger printing of the total extract was also carried out using gallic acid as markers in an attempt to characterize the constituents responsible for the activities and also to standardize the extract. The bioactive fraction from *Lasia spinosa* rhizome (LSE; 50 and 100 mg/kg body weight) was administered orally, twice daily for 5 days for prevention from Ethanol (EtOH)-, cold-restraint stress (CRS) - and pylorus ligation (PL)-induced ulcers. Estimation of antioxidant enzymes activity was carried out in CRS-induced ulcer model. LSE showed dose-dependent ulcer protective effect in PL (48.53 – 70.13 % protection), CRS (67.74 – 86.58 % protection) and EtOH (47.28 – 74.23 % protection) induced ulcer. However, LSE reduced the ulcer index with significant decrease in LPO, SOD and increased in CAT activity in CRS induced model. The obtained data shows that ethyl acetate fraction from LSE possesses anti-ulcerogenic (a reduction of the damage in mucosa induced by free radicals) and antioxidant potential (reducing lipid peroxidation and level of SOD and preventing CAT depletion induced by CRS).

INTRODUCTION: *Lasia spinosa* (L.) Thwaites (Araceae) is a spinous perennial herb with an underground rhizome that is mostly distributed in Southeast Asia, native to Vietnam where is commonly known as "Ray gai" and used in traditional medicine as an anti-rheumatic and anti-inflammatory remedy.

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The plant usually grows surrounding the ponds, and its shoots are consumed as traditional food in many communities of Southeast Asia. However, in the folk medicine of Naga tribes of India, the porridge (pudding) of young tender leaves of *Lasia spinosa* (known locally as "jurang") is frequently used to treat intestinal worm infections [1, 2].

The plant has been reported to possess filaricidal [3], anticestodal [4], antinociceptive, anti-inflammatory and antidiarrhoeal activity [5], antimicrobial and cytotoxic [6]. In order to substantiate the claims made by local people, the current study was undertaken to evaluate the gastroprotective and *in-vivo*

antioxidant potential of ethyl acetate fraction of *Lasia spinosa* rhizome (LSE) on different experimental models of gastric lesions.

MATERIAL AND METHOD:

Preparation and fractionation of extract

The Plant was collected from Lejai area of Dibrugarh district and taxonomically identified by Dr. T. M. Hynniewta, Joint director of Botanical Survey of India, Shillong. The coarsely powdered leaves (5 kg) were exhaustively extracted with 80% methanol by maceration for 2 days at room temperature with occasional shaking. The process of extraction was repeated for four times, filtered, concentrated on rotavapour (Buchi, USA) and then freeze-dried (Freezone® 4.5, Labconco, USA) at high vacuum (133×10^{-3} mBar) and low temperature ($-40 \pm 2\ ^{\circ}C$) to get dry residue (yield - 7.10 % w/w). The residue was dissolved in water and partitioned with ether, chloroform and ethyl acetate to yield ether soluble (8.53 %, w/w), chloroform soluble (16.36%, w/w), ethyl acetate soluble (23.92 %, w/w) and an aqueous phase (51.19%, w/w) component. Total extract and all the fractions were subjected to preliminary pharmacological study by using Aspirin induced ulcer model and it was found that ethyl acetate fraction showed most promising activity.

Preliminary phytochemical screening and HPTLC analysis:

Preliminary qualitative phytochemical screening of LSE tested for the presence of major chemical constituents. On the basis of preliminary phytochemical test HPTLC analysis was done to quantify the phenolic compounds. HPTLC analysis of LSE was performed on pre- activated (100°C) silica gel 60F254 HPTLC plates (E. Merck, Mumbai, India) along with gallic acid (SD Fine-Chem Ltd, Mumbai, India). The plates were then eluted in solvent system toluene: ethyl acetate: formic acid (7:5:1). After elution, the plates were dried and densitometrically scanned at wavelength 254 nm (WinCats software, CAMAG, Switzerland). The percentage of gallic acid in the extract was calculated by calibration using peak height ratio.

Estimation of total phenolic content (TPC):

Total phenolic compound was estimated by using Folin-Ciocalteu reagent (Sadasivam and Manikam, 1992). For the preparation of calibration curve 1ml aliquots of different concentration of gallic acid solution in methanol were mixed with 5ml Folin-ciocalteau reagent (diluted tenfold) and 4ml (75g/L) sodium carbonate. The absorption was taken after incubation period of 30 minute at 20ºC on the wavelength of 765nm. Similarly absorption of plant extract was taken. All the determination was performed in triplicate. Total content of phenolic compounds in plant methanolic extract was expressed in Gallic acid equivalent[7].

Test animals:

Sprague–Dawley rats (140–190 g) procured from CDRI, Lucknow, were maintained in a 12 h light/dark cycle at a constant temperature of 25 ^{0}C. Rats were allowed to access standard rodent feed (Dayal, India) and water. Food was withdrawn 18 h before the experiment though water was allowed *ad libitum* and allocated to different experimental groups each of six rats. All the studies were performed in accordance with the guidelines for the care and use of laboratory animals, as adopted and promulgated by the Institutional Animal Care Committee, CPCSEA, India (1589/PO/a/12/ CPCSEA).

Acute toxicity study:

A limit test for oral toxicity studies of crude extract was performed as per OECD guidelines TG 425 with 2000 mg/kg. The toxicity sign, symptoms or any other abnormities related to LSE was observed for 14 days. The study revealed that the LD50 was more than 2000 mg/kg as none of the rats shown toxic symptoms after the dose of extract for 14 days.

Antiulcer activity - Experimental procedure:

LSE in dose of 50 and 100 mg/kg and H_2 receptor blocker ranitidine (RAN) in the dose of 50 mg/kg were administered orally twice daily at 10:00 and 16:00 hrs respectively for 5 days for acute ulcer protective studies. Animals of control group received suspension of 1% carboxymethyl cellulose in distilled water (10 ml/kg) for the same administration period[8].

Pylorus ligated (PL) induced ulcers:

Drugs were administered for a period of 5 days and the rats were kept for 18 h fasting before pylorus-ligation but water was allowed *ad libitum*. At the

end of 24 h starvation, rats were anaesthetized with pentobarbitone sodium (35 mg/kg, I.P.), the abdomen was opened and pylorus ligation was done without causing any damage to its blood supply. The abdomen was then closed in two layer and rats were left in a cage with a false bottom of wide mesh wire gauze to prevent coprophagy. Water was withheld from one hour before pylorus ligation and till the end of 4 h period when the rats were sacrificed by overdosing with ether. Immediately afterwards abdomen was again opened, cardiac end of stomach was ligated and the stomach was taken out. The stomach was then cut open along the greater curvature and the mucosa was washed under slow running tap water[9]. The ulcerated area (mm^2) was measured using digital calliper. The ulcer index and the % protection are calculated by using the following formula[10, 11].

Ulcer Index (UI) = 10 × Ulcerated area / Total mucosal area

$$\text{Protection (\%)} = [(UI_{Control} - UI_{Treated}) / UI_{Control}] \times 100$$

Aspirin (ASP)-induced ulcers:

Aspirin in dose of 200 mg/kg (20 mg/ml) was administered orally on the day of experiment at about 10 am with the help of an orogastric tube in the form of an aqueous water suspension and animals were sacrificed after 5 h of administration[12]. The stomach was incised along with the greater curvature and examined for ulcers as described earlier.

Cold-restraint stress (CRS)-induced ulcers:

Rats of either sex weighing 150-175g were immobilized for 2 h at 4 ^oC following the method of immobilization[13]. Briefly the animals were starved for 24 h with free access to water and 60 min after receiving the corresponding treatment they were fully stretched and strapped to a wooden plank with adhesive tape after securing each limb to the plank individually. The animals were killed after 2 h and ulcer were scored as described above.

Ethanol (EtOH)-induced ulcer:

The gastric ulcer was induced in rats by administering Ethanol (EtOH, 100%, 1ml/200 g, 1 h). EtOH were administered on the day of the experiment and the animals were scarified by cervical dislocation and stomach was incised along with greater curvature and examined for ulcers. The ulcer index was scored, based upon the product of length and width of the ulcer present in the glandular portion of the stomach (mm^2/rat) [14].

Gastric juice, pH, free acidity and total acidity determination:

The gastric juice was collected 4 h after pylorus ligation and centrifuged for 5 min at 2000 rpm. 1.00 ml of centrifuged and filtered gastric juice was taken in a conical flask. Two drops of 1% phenolphthalein indicator for total acidity and Topfer´s reagent for free acidity was added to it. It was titrated against 0.1mol/l sodium hydroxide until a permanent pink color (total acidity) or canary yellow colour (free acidity) was observed. The total/free acidity is expressed as meq./l by the following formula:-

Total/free acidity=n×0.01×36.45×1000

Where, n is the volume of NaOH consumed, 0.01 is normality of NaOH, 36.45 is molecular weight of NaOH, 1000 is the factor (to be represented in litre) [15].

Biochemical estimation:

The fundic part of the stomach of animals of CRS induced ulcer was homogenized (5%) in ice cold 0.9% saline with a Potter- Elvehjem glass homogenizer for 30 s. The homogenate was then centrifuged at 800 rpm for 10 min followed by centrifugation of the supernatant at 1200 rpm for 15 min and the obtained mitochondrial fraction was used for the following estimations.

Lipid peroxidation (LPO) product malondialdehyde (MDA) was estimated using 1, 1, 3, 3-tetraethoxypropane as the standard and is expressed as μmol/mg protein[16]. Superoxide dismutase (SOD) activity was estimated by the inhibition of nicotinamide adenine dinucleotide (reduced)-phenazine methosulphate-nitrobluetetrazolium reaction system as adapted[17] and the results have been expressed as units (U) of SOD activity/mg protein. Decomposition of H_2O_2 in presence of catalase (CAT) was followed at 240 nm[18] and results are expressed as μmole of H_2O_2 consumed/ min/ mg protein.

Statistical Evaluation:

All the data are presented as mean ± SEM and one-way analysis of variance (ANOVA) and Newman-

Keuls Multiple Comparison Test were applied for determining the statistical significance between different groups.

RESULTS:

Phytochemical analysis:

The qualitative phytochemical analysis of LSE revealed the presence of Carbohydrate, Tannins, Glycosides, Phenolic & Phytosterol. The quantitative HPTLC determination shows the presence of 0.10 % w/w of gallic acid in LSE (Figure 2A & 2B). The total phenolic content was estimated to be 75.92 ± 4.2 mg gallic acid equivalents/ g dry extract.

Antiulcer study:

Effects of LSE at doses of 50 and 100mg/kg twice a day for 5 days prevented the acute gastric ulcers in a dose dependant manner in PL (48.53 – 70.13 % protection), CRS (67.74 – 86.58 % protection) and EtOH (47.28 – 74.23 % protection) induced ulcer. The range of percentage protection of RAN was 70.13 – 86.58 % in various gastric ulcer models **(Table 1).**

TABLE 1. GASTROPROTECTIVE ACTIVITY OF *LASIA SPINOSA* RHIZOME EXTRACT ON ETHANOL, COLDRESISTANT STRESS AND PYLORUS LIGATED INDUCED ULCERS

Treatment (mg/kg)	PL induced ulcer		EtOH induced ulcer		CRS induced ulcer	
	Ulcer index mm^2/ rat	protection %	Ulcer index mm^2/ rat	protection %	Ulcer index mm^2/ rat	protection %
Ulcer control	23.5 ± 3.1	-	22.8 ± 3.0	-	18.0 ± 2.1	-
LSE 50	12.1 ± 2.1[a]	48.53	12.0 ± 1.3[a]	47.28	6.7 ± 0.7[a]	67.74
LSE 100	6.9 ± 1.8[b]	70.38	6.8 ± 1.8[b]	73.49	2.0 ± o.7[a]	88.91
RAN 50	7.0 ± 1.7[b]	70.13	5.6 ± 1.6[b]	74.23	2.4 ± 0.4[a]	86.58

Mean ± S.E.M. for six rats. [a]p< 0.01, [b]p< 0.001 compared to respective control group

In the gastric secretion studies, compared with control, the rat treated with LSE at the dose of 100 mg/kg significantly showed a tendency to decrease gastric juice, free acidity and total acidity when compared with control group **(Table 2).** The LSE was found to be safe up to 2000 mg/kg with no sign of mortality or change in behavioural pattern. This results suggests that the plant extract is not toxic and to be safe.

Gastric secretion measurements of pylorus-ligated rats showed that LSE significantly decreased the gastric content, total, free acidity and increased pH at doses of 50 mg/kg and 100 mg/kg. RAN (50 mg/kg), the reference compound used also showed significant reduction of all these secretory parameters **(Table 2).**

TABLE 2. VOLUME OF GASTRIC JUICE, PH, FREE ACIDITY AND TOTAL ACIDITY IN PL INDUCED GASTRIC ULCER

Treatment (mg/kg)	Gastric content (ml)	pH	Total Acidity (mmol/h)	Free Acidity (mmol/h)
Ulcer control	2.070±0.08	2.90±0.21	4181.20±111.30	3108.72±221.13
LSE 50	1.870±0.04[a]	3.13±0.12	3836.02±92.36[a]	2632.02±83.84[a]
LSE 100	1.640±0.03[b]	5.58±0.18[b]	1818.27±137.21[b]	1512.86±89.40[b]
RAN 50	1.620±0.07[b]	6.12±0.24[b]	1640.80±48.83[b]	1484.38±168.93[b]

Mean ± S.E.M. for six rats. [a]p< 0.05, [b]p< 0.001 compared to respective control group

Antioxidant study:

With pretreatment of LSE 50 and 100 mg/kg doses, the LPO and SOD levels dropped significantly (p< 0.001), CAT values showed gradual but not significant increase at 100 mg/kg dose levels. RAN at the dose of 50 mg/kg reduced the LPO, SOD and further increased CAT value respectively **(Figure 1)**.

DISCUSSION: HPTLC analysis showed the presence of phenolic compound in LSE. The presence of high percentage of the gallic acid in the extract justifies the potent antioxidant activity exhibited. Antioxidants play a major role in repairing the gastric damage. Gallic acid scavenges free radicals, block •OH-mediated oxidative damage and play important role in the prevention and therapy of diseases.

Pylorus ligation-induced ulcers are due to auto-digestion of the gastric mucosa and break down of the gastric mucosal barrier[19]. It utilizes neither exogenous ulcerogens nor induced by exogenous

interfering factors. Ulcers are believed to develop because there is an excess of acid and pepsin for a given degree of mucosal defense. Synthetic NSAIDs like aspirin causes mucosal damage by interfering with prostaglandin synthesis, enhance acid secretion, increase back diffusion of H^+ ions, and breaking up of the mucosal barrier [20, 21]. Stress plays an important role in etiopathology of gastro-duodenal ulceration. Stress-induced ulcers are probably medicated by histamine release with enhancement in acid secretion, reduction in mucous production[8].

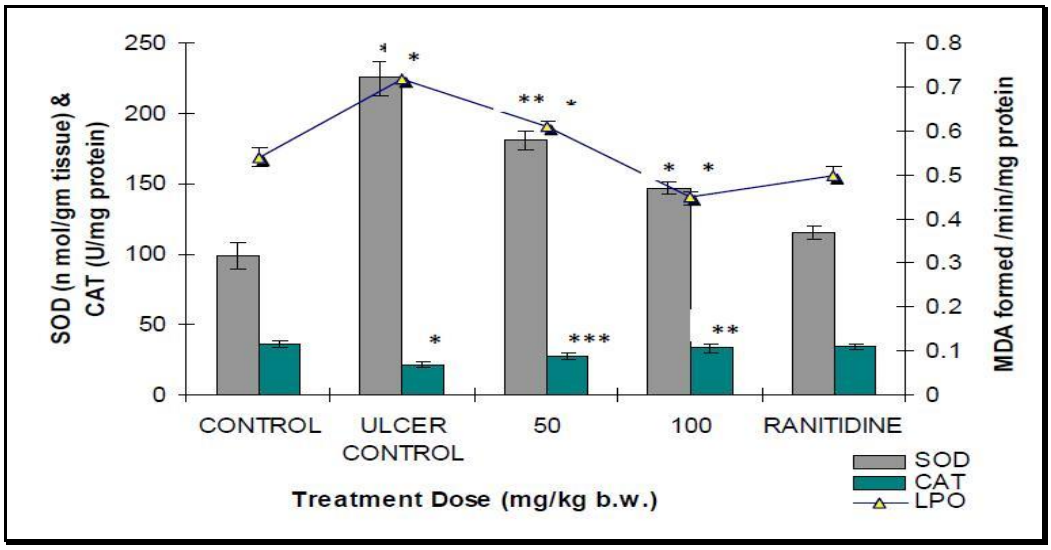

FIG.1. EFFECT OF ETHYL AETATE FRACTION OF *LASIA SPINOSA* RHIZOME ON LIPID PEROXIDATION (LPO), SUPEROXIDE DISMUTASE (SOD), AND CATALASE (CAT) IN COLD-RESTRAINT STRESS –INDUCED GASTRIC ULCERS.

Values are mean ± SEM for 6 rats.
* P < 0.001 compared to respective control group,
** P < 0.01 compared to respective control group.
***P < 0.05 compared to respective control group

HPTLC analysis:

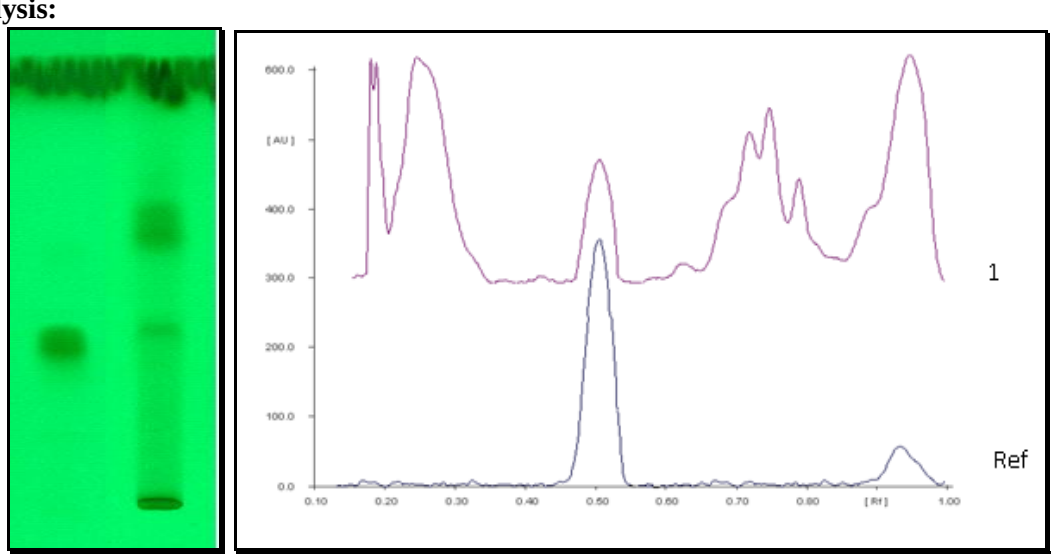

FIGURE: 2A **FIGURE: 2B**

FIGURE 2A:
TLC profile of test solution of ethyl acetate fraction from the rhizome of *Lasia spinosa* extract (LSE) under UV lights at 254 nm.
Ref: Gallic acid standard; 1: LSE

FIGURE 2B:
HPTLC densitometric scan of ethyl acetate fraction from the rhizome of *Lasia spinosa* extract (LSE) under UV lights at 254 nm.
Ref: Gallic acid standard; 1: LSE

Increase in gastric motility, vagal over activity, mast cell degranulation[22] decreased gastric mucosal blood flow[23] and decreased prostaglandin syntheses are involved in genesis of stress induced ulcers[8]. The incidence of ethanol-induced ulcers is predominant in the glandular part of stomach was reported to stimulate the formation of leukotriene C_4 (LTC_4), mast cell secretary products and reactive oxygen[24]. According to our results, LSE has a potent gastroprotective action, since it was effective against PL and CRS-induced gastric lesions. In addition, gastroprotective effect of LSE at higher dose (100 mg/kg) was comparable to ranitidine against lesions induced by ethanol. This data suggests that the LSE has an important cytoprotective action against the direct necrosing action of ethanol.

Generally Stress causes both sympathetic (causes direct arteriolar vasoconstriction) and parasympathetic (induces an increased motility and muscular contraction) stimulation of stomach leading to local hypoxia and near or actual "ischemia". The ischemic condition caused an increase in the level of H_2O_2 (by the action of SOD), which, in conjugation with O_2 generates $OH^{\bullet}$ via the methyl catalyzed Haber-Weiss reaction[25]. Hydroxyl radicals thus generated oxidizes important cellular constituents such as structural and functional proteins, membrane lipids and depletes glutathione. Lipid peroxidation causes loss of membrane fluidity, impaired ion transport and membrane integrity and finally loss of cellular functions.

Stress also causes inactivation of prostaglandin synthetase leading to decreased biosynthesis of prostaglandin-the master molecule for gastroprotection against all forms of insults to the mucosa. Stress-induced ulcers also involve damage by reactive oxygen species (ROS) apart from acid and pepsin related factors. Superoxide ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\bullet}$) are important ROS causing tissue damage. The experimental data stated that the CRS aggravates the ulcer severity along with increase in, lipid peroxidation and SOD as compared to normal rats. SOD converts the reactive $O_2^{-\bullet}$ to H_2O_2, which if not scavenged by CAT can by itself causes lipid peroxidation by generation of $OH^{\bullet}$. Hence decrease in CAT levels has led to increase in accumulation of these ROS and thus, has caused increased lipid peroxidation and tissue damage[26]. LSE was found to decrease free radical-mediated lipid peroxidation and alteration in circulating enzymatic antioxidants, CAT and SOD, indicate the involvement of these enzymes in ulcer. The antisecretory properties of LSE were confirmed because it significantly decreased the gastric content, total and free acidity.

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