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PRECLINICAL EVALUATION OF HYDRO-ALCOHOLIC EXTRACT OF *LANNEA COROMANDELICA* LEAVES FOR ANTI-ULCER ACTIVITY ON ALBINO WISTAR RAT

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ABSTRACT

Due to present days heavily stressed lifestyle, the peptic ulcer has become a common disease to most of the people. The aim of this research is to evaluate a preclinical study of hydro-alcoholic extract of *Lannea coromandelica* leaves for its anti-ulcer activity on albino Wistar rat. Hydro-alcoholic extract of *Lannea coromandelica* leaves was evaluated for its anti-ulcer activity using Ulcer model by Pyloric Ligation Method, Stress-Induced Ulcer Model, and Aspirin-Induced Ulcer Model. After extraction with 16.27% yield, the extract was assayed for its anti-ulcer activity. In the pyloric ligation method, *Lannea coromandelica* leaf extract of different doses like 250mg/kg and 500mg/kg showed significant levels of protection. In the Stress-Induced Ulcer Model, the animals were made to go through continuous stress of 4 hours by water immersion technique and here *Lannea coromandelica* leaf extract of the low and high dose showed remarkable protection levels. In the Aspirin Induced Ulcer Model *Lannea coromandelica* leaf extract of the low and high dose had provided notable ulcer inhibition parameter in respect of Ranitidine which is a marketed anti-ulcer drug. The anti-microbial and anti-oxidant properties of *Lannea coromandelica* could be responsible for its anti-ulcer property.

Keywords: Hydro-alcoholic extract, anti-ulcer, Pyloric Ligation Method, Stress-Induced Ulcer Model, Aspirin-Induced Ulcer Model, Ranitidine, anti-microbial, anti-oxidant

INTRODUCTION

Ulcers are the open wound or damage in skin surface of gastrointestinal tract (stomach & duodenum) that are depicted by sloughing of dead tissue and inflammation. Acid is normally secreted by a part of digestion in the stomach but when there is an equilibrium between secretory factors (gastric acid, bile, oxidative stress, pepsin) and protective factors or acid inhibitory factors (prostaglandin, blood flow, mucus) ulcer is formed. Some factors like tobacco smoking **[1]**, NSAIDS **[2]**, Gram negative bacteria like *Helicobacter pylori* **[3]**, Crohn's disease **[4]** also stimulate ulceration.

India is a developing country and people have to struggling hard to achieve success in their life. Hence day to day lifestyle has been impaired dramatically making a shift to improper diet, fast food consumption, smoking, and stress in professional and personal life. Thus, the country sees more than 1 million ulcer cases per year.

Synthetically derived anti-ulcer drugs like proton pump inhibitors (PPI), H_2-antihistamines, Anti-cholinergics, ulcer protective drugs and anti- H. pylori drugs are available in the market but they have side effects like giddiness, nausea, headache, vomiting etc. thus making them unsuitable for daily intake.

India being a country where 80% of the population relies on herbal or natural treatment for primary health care **[5]**, herbal plants with active medicinal properties are preferred and adapted as per India's culture. In folklore there has been use of one such Indian plant for herbal treatment that is 'Indian ash tree' or *Lannea coromandelica* (L.C) which has chemical constituents like Alkaloids, Flavonoids, Glycosides, Phenols, Tannins and Triterpinoids **[6]**. It has also been extensively studied for many years by different researchers for other medicinal properties like hypotensive **[7]**, anti-inflammatory **[8]**, anti-microbial **[9]**, wound healing **[10]**, dysentery **[11]**, elephantiasis **[12]**, bruises **[13]**, sprains gum **[14]**, antioxidant activity [15], anti-diabetic activity **[16]**, vaginal trouble **[17, 18, 19]**.

In the present work we tested ethanolic extract of *Lannea coromandelica* leaves on Albino Wistar rat for ulcer treatment.

MATERIALS AND METHODS

Drugs and Chemicals: Ethanol (Loba Chemie Pvt. Ltd.), sodium hydroxide (Loba Chemie Pvt. Ltd.), hydrochloric acid (Loba Chemie Pvt. Ltd.), diethyl ether (Merck Specialities Pvt. Ltd., Mumbai.), chloroform (Merck Specialities Pvt. Ltd., Mumbai.), ranitidine (Aciloc 150 manufactured by Cadila Pharmaceuticals Ltd.), aspirin, distilled water.

Plant Materials: The fresh tender leaves of *Lannea coromandelica* were collected from the local area of Netaji Subhas Chandra Bose Institute of Pharmacy (NSCBIP) for research.

Extraction: The collected fresh leaves of L.C were dried under shade then grinded by hand and 100 gm of powdered leaves were placed

on the percolator with 800 ml of 70% hydroethanolic mixture for 48 hours. After which it was vacuum dried until reduced to sticky mass.

EXPERIMENT

Experimental Protocol: The anti-ulcer activity was studied using three experimental models namely 1) Ulcer model by pyloric ligation 2) Stress induced ulcer model and 3) Aspirin induced ulcer model.

Animals and Treatments: Albino wistar rat weighing between 120-200 gm used for the study were purchased from authorized animal breeder. The animals were placed in polypropylene cages (32 X 24 X 16) and housed in the departmental animal house at (25°C ± 2°C, 12:12 h light and Dark cycle) of NSCBIP (approval no: 1502/ PO/ a/11/CPCSEA). The animals were fed with rodent standard pellet diet along with water *ad libitum*. All the experimental procedure and protocols used in the study were approved by IAEC of NSCBIP college of Pharmacy, as per CPCSEA guidelines.

Animal Grouping: In all three experimental models i.e., 1) Ulcer model by pyloric ligation 2) Stress induced ulcer model and 3) Aspirin induced ulcer model, the animals were kept in fasting for 24 hrs prior to the experiments and 6 animals were studied per group. There were 4 groups each treated differently, Group 1- Untreated, Group 2 – Ranitidine 150 mg/kg P.O, Groups 3- (Low *Dose Lannea coromandelica*- L.D L.C 250 mg/kg P.O) and Group 4- (High dose *Lannea coromandelica*- H.D L.C 500 mg/kg P.O)

MODELS

Ulcer Model by Pyloric Ligation [20, 21, 22, 23]: Gateway of intestine is pylorus, the acid produced from stomach along with the food content that is chyme pass via pyloric sphincter to the intestine. It has been revealed that ligature of pylorus enables ulcer formation by stoppage of acid content drainage which is generated in the stomach. The deposition of acid pepsin leads to gastro mucosal damage by auto digestion of gastric mucosa.

Under light ether anesthesia by a small midline incision, the abdomen was opened below the xiphoid process. Pyloric portion of the stomach was slightly taken out and ligated taking proper care of the pylorus and its blood supply. Then stomach was carefully replaced and abdominal wall closure was done by interrupted sutures. All the animals were deprived of food and water during the post operative period. 30 min prior to the ligation all the animals were treated as per their group. Group 1- Untreated, Group 2- Ranitidine 150 mg/kg P.O, Groups 3- (Low Dose *Lannea coromandelica*- L.D L.C 250 mg/kg P.O) and Group 4- (High dose *Lannea coromandelica*- H.D L.C 500 mg/kg P.O)

After 4 hours, animals were sacrificed, each stomach was cut open, examined and mounted for acidity, ulcer index and percentage protection calculation.

Table 1: Results of Ulcer Model by Pyloric Ligation

Sl no	Treatment	Acidity	Ulcer incidence	Ulcer index	Ulcer inhibition (%)
1.	Control (untreated)	19.15±1.66	6/6	13.18±1.25	-
2.	Ranitidine (150mg/kg P.O)	7.06±0.52***	1/6	3.83±0.76***	70.7%
3.	L.D L.C (250mg/kg P.0)	10.85±0.71***	3/6	6.25±0.34***	52.2%
4.	H.D L.C (500mg/kg P.O)	8.51±0.83***	2/6	4.33±0.87***	66.9%

All values are mean ± SEM, n = 6. ***p < 0.001 was considered statistically significant compared with control group.

Stress Induced Ulcer Model [24, 25, 26, 27]: Stress is a condition by which body responds to any demand or threat. Any type of stress i.e., mental, psychological, physical has been revealed to aggravate the ulcer condition or even generate ulceration in victim.

In this model ulcer was induced by immersing the rats in water for 4 hours. 30 min prior to immersion all the rats were treated as per their groups. Group 1- Untreated, Group 2- Ranitidine 150 mg/kg P.O, Groups 3- (Low Dose *Lannea coromandelica*- L.D L.C 250 mg/kg P.O) and Group 4- (High dose *Lannea coromandelica*- H.D L.C 500 mg/kg P.O). After 4 hours, animals were sacrificed. Each stomach was cut open, examined and mounted for acidity, ulcer index and percentage protection calculation.'

Table 2: Results of Stress Induced Ulcer Model

Sl no	Treatment	Acidity	Ulcer incidence	Ulcer index	Ulcer inhibition (%)
1.	Control (untreated)	15.34±1.21	6/6	12.83±0.87	-
2.	Ranitidine (150mg/kg P.O)	3.40±0.46***	1/6	1.916±0.16***	85.06%
3.	L.D L.C (250mg/kg P.0)	6.51±0.58***	2/6	4.66±0.33***	63.63%
4.	H.D L.C (500mg/kg P.O)	5.23±0.66***	1/6	2.41±0.25***	81.16%

All values are mean ± SEM, n = 6. ***p < 0.001 was considered statistically significant compared with control group

Aspirin Induced Ulcer Model [28, 29, 30, 31]: Aspirin is an acetyl salicylic acid derivative of NSAID. It is a non-selective COX-2 inhibitor and also used as an analgesic. Due to non-selectivity of COX pathway, it produces ulceration in patients as a side effect. Blockage of COX-1 pathway leads to inhibition of prostaglandin synthesis thus leading to damage of mucosal layer in stomach. This mechanism was used here in this model for ulcer induction.

All the animals were deprived of food and water for 24 hours before the experiment in their respective cages. Then the following treatments were done: Group 1- Untreated, Group 2- Ranitidine 150 mg/kg P.O, Groups 3- (Low Dose *Lannea coromandelica*- L.D L.C 250 mg/kg P.O) and Group 4- (High dose

Lannea coromandelica- H.D L.C 500 mg/kg P.O). After 45 min aspirin (200 mg/kg) was administered orally to induce gastric ulcer. After 4 hours, animals were sacrificed. Each stomach was cut open, examined and mounted for acidity, ulcer index and percentage protection calculation.

Table 3: Results of Aspirin Induced Ulcer Model

Sl no	Treatment	Acidity	Ulcer incidence	Ulcer index	Ulcer inhibition (%)
1.	Control (untreated)	17.33±0.98	6/6	13.82±1.14	-
2.	Ranitidine (150mg/kg P.O)	6.20±0.46***	1/6	1.91±0.26***	85.30%
3.	L.D L.C (250mg/kg P.0)	10.75±0.94***	2/6	4.33±0.33***	66.60%
4.	H.D L.C (500mg/kg P.O)	8.93±0.78***	1/6	2.416±0.71***	81.40%

All values are mean ± SEM, n = 6. ***p < 0.001 was considered statistically significant compared with control group

Acidity [21]: Stomach was dissected out from sacrificed rats and contents were collected into clean test tubes. The total volume of gastric content was measured. Gastric content was centrifugated at 1000 rpm for 10 min. Supernatant liquid about 1 ml was pipetted out and dilution was performed to 10 ml with distilled water. Thereafter solution was titrated against 0.01N NaOH using phenolphthalein as an indicator. The volume of NaOH required, was noted and acidity was calculated using the following formula:

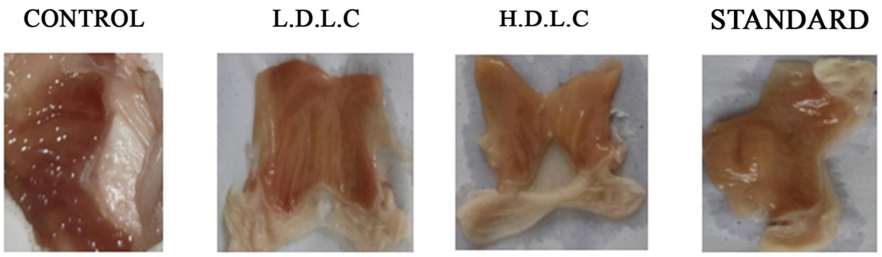
Acidity= [(Volume of NaOH × normality × 100) / 0.1] mEq/L

Ulcer Score [21]: Based on ulcer sore severity, the sore was given score as**;** 0- Normal coloured stomach**,** O.5- Red colouration**,** 1- Spot ulcers**,** 2- Ulcers equal to 3 or more but less than equal to 5, 3- Ulcers greater than 5. From the ulcer scores, mean ulcer score of each animal was calculated.

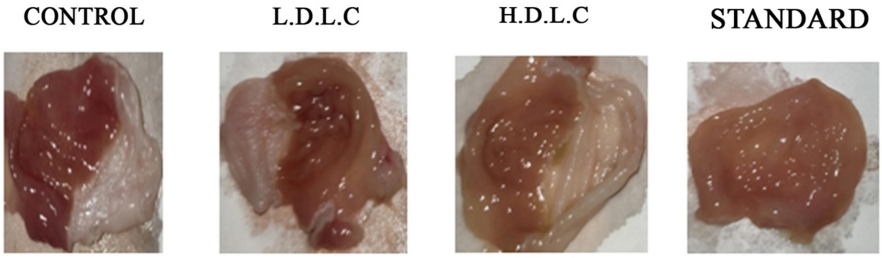
Ulcer index calculation = [average number of ulcers + average ulcer severity score+ (percentage of ulcer incidence X 10^{-1})]

Ulcer inhibition % is achieved by = (C-T/C) × 100. Where, C = ulcer index in control group, T = ulcer index in treated groups.

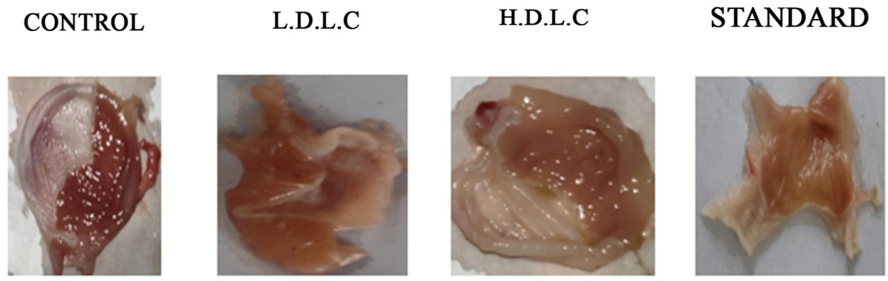
Statistical Analysis: The data are expressed as Mean ± SEM, n= 6, $p<0.001$ while compared with untreated control. The significance among the groups was assessed using (ANOVA) i.e., one way analysis of variance which was further re-assessed using Dunnet's post-parametric comparison test between the data of control and treated groups.



Ulcer formation in pyloric ligation model



Ulcer formation in stress induced ulcer model



Ulcer formation by aspirin induced model

Figure 1: Ulcer formation by pyloric ligation, stress induced and aspirin induced models

RESULTS AND DISCUSSION

Extraction: Net yield upon extraction of *Lannea coromandelica* leaves from percolation and vacuum dryer was 16.27%.

Ulcer Model by Pyloric Ligation: Gastro intestinal tract is composed of different important organs starting from buccal cavity to anus. Stomach is a "J-shaped" structure having three important parts namely fundus, body and pylorus. Oesophagus enters with the fundus of stomach by a sphincter that is cardiac sphincter. At the pylorus the duodenum (first part of small intestine) gets start and this entry is controlled by pyloric sphincter. While the sphincter is ceased mechanically, the acid secreted in the stomach gets accumulated thereby causing ulcer production. In the untreated control group where the animals were not given any treatment, all animals were affected with many lesions in stomach. Pre-treatment with Ranitidine had given major protection against ulcer production in rats. L.C

leaf extract of different doses 250 mg/kg and 500 mg/kg had shown different levels of protection. It was evident that both Ranitidine and L.C caused significant decrease in two different parameters i.e., ulcer index and total acidity while compared with untreated control. In the present study, Ranitidine, L.C.L.D, and L.C.H.D showed 70.7%, 52.2%, 66.9% of ulcer inhibition respectively as compared to untreated control.

Stress Induced Ulcer Model: Gastric ulcer is an imbalance between the aggressive and defensive factors. The basolateral membrane of parietal cell has four important receptors namely muscarinic (M_1), histaminic (H_2), gastrin (G) and prostaglandin (P), among them M_1, H_2 and G are responsible for positive movement of parietal cell, may enhance acid secretion in stomach. Prostaglandin produces inhibitory signal on proton pump, reduces the acid secretion. On the other hand, it enhances the mucus production which produces a protective layer in stomach. Ulcer may get worsen in presence of various factors and most importantly due to stress. Stress causes various alterations in neurotransmitter hence causing overproduction of acid in stomach.

In the present study stress induced ulcer model has been selected to find whether the drug is able to reduce the stress related ulcer. Animals were made to go through a continuous stress of 4 hours by water immersion technique. The controlled group showed ulcer index of 12.83 whereas Ranitidine, L.D.L.C and H.D.L.C showed 1.916, 4.66, and 2.41 ulcer index respectively. In the other parameter like total acidity, L.CL.D and H.D.L.C showed significant decrease in total acidity that resembles with standard Ranitidine. Also, L.C in the two different doses of 250 mg/kg and 500 mg/kg showed promising anti-ulcer activity in all parameters in dose dependent manner.

Aspirin Induced Ulcer Model: Near about 3000 types of diseases are continuously making threat to us. To overcome the situation, we have to take different types of medicines while most of them having various levels of side effects. N.S.A.I.D.S produces ulcer as a common side effect. Aspirin is a salicylic acid derivative which acts on arachidonic acid pathway by blocking both COX 1 and COX 2. Due to blockage of COX 1, prostaglandin secretion gets inhibited followed by depletion of mucous and bicarbonate ion thereby causing ulceration in presence of excess gastric acid.

In this model the controlled group showed total acidity 17.33. At the same time Ranitidine, L.D.L.C and H.D.L.C showed total acidity 6.20, 10.75 and 8.93 respectively. Whereas in ulcer inhibition parameter L.D.LC along with H.D.L.C showed significant level of protection as compared to untreated control groups. Also, ulcer index of L.D.L.C and H.D.L.C were much lower than control groups and closer to standard group that was treated with Ranitidine.

CONCLUSION

In the present study, the hydroalcoholic leaf extract of L.C was evaluated for its anti-ulcer activity on rats. The observation substantiates the folklore use of L.C for the treatment of ulcer. The leaves of L.C were collected, washed and percolated with 70% ethanol and the obtained yield was 16.27%. The extract was given orally at two different doses of 250 mg/kg and 500 mg/kg body weight. The three models involved are namely 1) ulcer model by pyloric ligation, 2) stress induced ulcer and 3) aspirin induced ulcer to evaluate the anti-ulcer potential of L.C extracts in different conditions.

Any drug that reduces the microbial load in any type of wound is definite to increase the chance of recovery from ulcer. Lipid per-oxidation is a process for several types of wounds and ulcer. Drug that is capable of inhibiting lipid per-oxidation is believed to increase the healing potential by increasing the blood circulation, preventing the cell damage and promoting DNA synthesis. It is believed that the anti-ulcer property of L.C may be due to its anti-microbial and anti-oxidant property. Further study in this subject will definitely raise the hope of getting an easily available and affordable drug in the field of anti-ulcer treatment.

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ABBREVIATION

NSAIDS: Nonsteroidal anti-inflammatory drugs, **L.C:** *Lannea coromandelica*, **NSCBIP:** Netaji Subhas Chandra Bose Institute of Pharmacy, **IAEC:** Institutional animal ethics committee (India), **CPCSEA:** The committee for the purpose of control and supervision of experiments on animals, **P.O:** Per oral, **L.D L.C:** Low dose *Lannea coromandelica*, **H.D L.C:** High dose *Lannea coromandelica*, **COX:** Cyclooxygenase, **ANOVA:** Analysis of variance, **DNA:** Deoxyribonucleic acid.

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