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Preliminary Phytochemical and Pharmacological Studies on the *Clerodendrum indicum* (L) Kuntze

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ABSTRACT

The objective of the present study was to evaluate the antiulcer activity of *Clerodendrum indicum* methanolic extract against aspirin induced ulcers. The leaves were extracted with methanol and chloroform as solvents using Soxhlet extraction method and aqueous extract by maceration method. The extract was evaluated against aspirin induced ulcer models. Further, extract was evaluated for gastric autopsy of animals infected with Helicobacter pylori bacteria. Morphology of stomach was also studied after treatment with plant extract.

The drug has been found to be very effective in inhibiting gastric ulceration. This is evident from reduction in ulcer index parameters. Besides, significant reduction in acid secretory parameters such as total acidity, total acid output and volume of gastric secretion were also observed. Morphological studies showed less conspicuous petechial marks and hemorrhages in stomach tissues after treatment with test drugs. Histopathological study revealed that *C. indicum* extract reduced stomach damages and eradicated H. pylori infections. **Conclusion:** It can be concluded from the study that C. indicum possess antiulcer activities.

Keywords: Helicobacter pylori, Naproxen, Ethanol, Histamine, Ulcer index, Ulcer area

INTRODUCTION

Peptic ulcer is one of the most prevalent diseases around the world affecting four million people each year. Peptic ulcer is the term which refers to acid peptic injury of the digestive tract, and it results in mucosal break reaching the submucosa [1]. The disease involves an imbalance between offensive and defensive factors such as pepsin, acid and Helicobacter pylori; and bicarbonates, prostaglandins, mucin, nitric oxide and growth factors, respectively [2, 3]. It has been also found that there is a chronic remitting course of peptic ulcer disease with imperfect correlation between symptoms and the presence of an ulcer. Helicobacter pylori infection is a very common cause of primary peptic ulcers. It is associated with 70% of gastric ulcers and 95% of duodenal ulcers [4, 5]. Other risk factors responsible to produce peptic ulcer disease are alcohol consumption, cocaine, tobacco and amphetamine use, chronic administration of nonsteroidal anti-inflammatory drugs (NSAIDs), fasting, Zollinger–Ellison syndrome and cancer treatment with angiogenesis inhibitors [5, 6].

Peptic ulcer treatment involves using a number of chemically produced drugs with aim to reduce the rate line the stomach and upper portion of the small intestine or to eliminate H. pylori infestation. The existing drugs cause several adverse effects; conversely, indigenous herbal drugs are devoid of side effects which might better treat peptic ulcers. Medicinal plants possess numerous active phytoconstituents that are responsible for several biological activities [7, 8]. The herbal drugs are less toxic than synthetic drugs; however, the toxicity evaluation is required to determine the safety profile of herbal drug. In this concern, the drugs of natural origin can be used for the management of gastric ulcers as a better alternative to synthetic drugs [9].

In our study we have selected the plant Clerodendrum indicum (L) Kuntze belonging to the family Verbenaceae. This is a deciduous shrub widely distributed in the Western Ghats of India. [10] As per the traditional claims, the roots of this plant are a potential source of medicine for ailments such as allergic disease, body soreness, respiratory illness, infectious disease, dropsy, eye diseases, fever, inflammation, malaria, opthalmia, rheumatism, snakebite, tuberculosis, ulcers, and wounds. [11, 12, 13] Studies reported various chemical constituents from the plant, like stigmasterol, bis(2-ethylhexyl) phthalate, hispulidin, serratumin A, acteoside, martynoside, serratumoside-A,myricoside, ursolic acid, spinasterol, spinasteryl-β-D-glucopyranoside etc., in various parts of plant

including the stem, root, and aerial part. [14, 15, 16] Based on the tradition use of C. indicum in ulcer healing treatments, the protocol of the present study was designed to evaluate its effect against peptic ulcer.

MATERIALS AND METHODS

Collection of plant material: Clerodendrum indicum L. were collected from the botanical garden of local region of Gwalior, Madhya Pradesh.

Extraction of leaves powder: The extract were shade dried and reduced to coarse powder in a mechanical grinder and passed through sieve No. 40. The powdered material obtained was then subjected to successive extraction in batches using methanol and chloroform, solvents in a Soxhlet extractor. The different extracts obtained were evaporated in rotary evaporator to get a semisolid mass. The extracts thus obtained were subjected to phytochemical analysis. Aqueous extraction of drug was done by maceration Process. For this practical aqueous solution (water) was used for extraction of *Clerodendrum indicum*. The plant powder{10 gm) was kept in a flask and 50 ml of water. It was shaken for 4-5 days and then solvent infused extract was formed which was used for chemical tests. [17]

Preliminary phytochemical analysis: The extracts of plants were subjected to qualitative analysis for the various phytoconstituents like alkaloids, carbohydrates, glycosides, phytosterols, saponins, tannins, proteins, amino acids and flavonoids. [18, 19]

Thin Layer Chromatography (TLC): Clerodendrum indicum L. TLC was performed with a mixture of Ethyl acetate: chloroform: methanol (7:2:1) for aqueous, Hexane: ethyl acetate: formic acid (6:3.5:0.5) for chloroform and Hexane; Toluene: ethyl acetate: few drops of formic acid (7:2:1: few drops) methanol extract a solvent method (mobile phase) using precoated silica gel G plate (stationary phase). For detection, Iodine chamber was used. The Rf value was calculated for a separate location. The thin layer chromatography was conducted and extreme strain" was observed. Activation of pre-coated silica gel 60 TLC plates by injection at 110-120 °C during furnace usage for 30 minutes proceeding to sample spotting. The sample was applied on 60 TLC capillary silica gel precoated plates. The Rf value of the fraction constituent variable was detected. [20]

Antioxidant Content

A-Estimation of Total Phenolic Content: As normal, phenolics have been calculated using gallic acid. A solution of 100µg / ml of gallic acid stock has been prepared. A 0.5ml aliquot was pipette out of the above stock into a volumetric flask of 25ml. 10ml of distilled water and 1.5ml of reagent Folin ciocalteus were added. After 10 min 4 ml, 20 per cent of sodium carbonate was added and up to 25 ml of volume is made using distilled water. A stock solution of 1mg / ml in ethanolic extract in methanol has been prepared. 0.5ml of extract was taken from the above stock in 25ml volumetric flask. 10ml of distilled water and 1.5ml of reagent Folin ciocalteus were added. After 10 min 4 ml, 20 per cent of sodium carbonate was added and up to 25 ml of volume is made using distilled water. At 455nm the absorption of both the check and the normal solution was taken after 30min. [21]

B-Estimation of Total Flavonoid Content: As standard, flavonoids were determined using rutin. A rutin solution of 100 µg / ml stock was packed. A 0.5ml aliquot had been pipette out of the stock above. Methanol aluminum chloride, a few drops of distilled water and 4ml of methanol have been added. A stock solution of 1mg / ml was prepared in ethanolic extract methanol. Add 0.5ml 2% ethanol aluminum chloride, few drops of distilled water and 4ml of methanol from the above stock. After 20min both normal and test solution absorbance was taken at 455 nm. [22]

Pharmacological In-Vivo Studies

Animals: Male albino Wistar rats weighing between 200-225 gm were used. The experiment protocol was approved by the Institutional Animal Ethics Committee (IAEC). The Animals were housed and maintained in animal house of the institute, Animals were kept in cages while maintaining a temperature 26+2°C with 12 hours : 12 hours dark and light cycles. They were fed standard diet and water ad libitum given. Animals that were subjected for administration of standard drugs used and selected extracts, were fasted for 18 hours before administration of drugs to the experimental animals. All animals were maintained under standard conditions in an animal house approved by Committee for the Purpose of Control, and Supervision on Experiments on Animals (CPCSEA). [23, 24]

Acute Toxicity Study: The acute oral toxicity study was performed according to the OECD guidelines (Organization for Economic Co-operation and Development) (Office of prevention, pesticide and toxic substance) Up and Down procedure. The different extracts were suspended using 0.5% sodium carboxy methylcellulose and were administered orally. The concentration was adjusted in such a way that it did not exceed 1ml/kg b/w of the animal. [24, 25]

Experimental Models: For single dose study the animals was divided in following groups

- **Group-I:** Normal control treated group; Received 1 ml saline to all the animals for 7 days.

- **Group-II:** Disease control; Received aspirin (200mg/kg) according to body weight of animals for continuous 7 days.

- **Group-III:** Reference Standard Drug (RSD); Received ranitidine (20mg/kg) followed 30 min later by aspirin (200 mg/kg) according to body weight for continuous 7 days.

- **Group-IV:** 250 mg/kg Methanolic extract of *C. indicum* leaves: Received MECI at 250 mg/kg after 30 min administration of aspirin (200mg/kg) for continuous 7 days.

- **Group-V:** (500 mg/kg Methanolic extract of *C. indicum* leaves: Received MECI at 500 mg/kg after 30 min administration of aspirin (200mg/kg) for continuous 7 days.

On 8th day animals were sacrificed by cervical dislocation and stomach were collected for further investigation about degree of ulcer. [26]

Evaluation Of Anti-Ulcer Activity

Measurement of gastric lesions: The stomach was turned along with higher straight and put on a stable or clear mirror centenar for measurement after the development of gastric ulcers. The ulcers were viewed using a magnifying glass and tracing on clear paper, which was then placed on a graph sheet and the ulcer diameters measured. Scanning electron microscope (SEM) was used to undertake a microscopical inspection. Takagi and Okabe devised the following scores/ratings to evaluate the ulcer -index and the seriousness of stomach lesions:0 show not any such lesion, 1 represent mucosal inflammation and small patch, 2 write down one to five minor scraps (up to1-2.1 mm), 3 stand for<5 minor lesions or one or more medium lesions (3-4 mm), 2–4 intermediate lesions, or a single large lesion (greater than 4 mm), Ulcers with perforations (number 5) The equations below are used to figure out the ulcer index, % preventive ratio & % curative ratio. [27]

Total gastric secretion score/number of ulcerated animals = ulcer index (UI)

(U-I of ulcer-genic treated groups/ Ulcer index of ulcer-genic treated) - (U-I of drug treated/ UI of ulcer-genic treated) = % protective ratio

Calculation of free acidity and total acidity: A clean vial was filled with 0.1 milliliters of gastric juice and 0.9 milliliters of distilled water. Then, Topfer's reagent was used as an active indicator to titrate this produced combination till the colour turned canary yellow. Then, two drops of phenolphthalein were added, and the colour was adjusted through titration until it turned persistent pink. [28]

Evaluation Of Oxidative Stress Marker: Up to (0.4 gm to 0.8 gm) of stomach tissues were placed into a 0.1 M phosphate buffer (pH 7.4), homogenized with the use of a homogenizer, and centrifuged at 4000 for 10 min. For oxidative assays like MDA and GSH, the supernatants were collected and employed. [29]

Statistical Analysis: The statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Dunnet comparison test. For comparing nonparametric ulcer scores, ANOVA followed by non-parametric Dunn posttest was used. The values are expressed as mean ±SEM and $p<0.05$ was considered significant. [30]

Results And Discussion

Extraction Of Plant Leaves: Extraction of plant Clerodendrum indicum leaves in different solvent were extracted the active constituents. The percentage yield and colour of extract were mentioned in Table 1.

Table 1: Extraction of Clerodendrum indicum leaves in different solvents.

Solvent(s)	Raw Material	Extract (gm)	Color
Aqueous	10g	0.24g	Dark brown color
Methanol	50g	3.98g	Light brown color
Chloroform	50g	3.11g	Slightly green

Preliminary Phytochemical Investigation: Obtained dry extract of leaves was subjected to the process of phytochemical screening for the identification and availability of active constituents. Qualitative chemical analysis of various extracts of Clerodendrum indicum leaves.

Table 2: Preliminary Phytochemical Investigation of different extracts

S. No.	Phytoconstituents	Successive extraction		
		Aqueous	Chloroform	Methanol
1.	Carbohydrate	-	-	+
2.	Protein	-	-	+
3.	Tannins	+	-	+
4.	Flavonoids	+	+	+
5.	Alkaloids	-	++	++
6.	Glycosides	-	-	+
7.	Terpenoids	+	-	+
8.	Saponins	-	-	-
9.	Amino acid	-	-	+

Present- (+) Absent- (-)

Thin Layer Chromatography: Using silica gel G, the TLC plates were prepared and left for air drying. Hot air drying in a hot air oven at (80-100 °C) for 1 hr. allowed these plates. Extracts from petroleum ether and ethanol solvents was spotted on the TLC plates. The plates were dried and produced for fast screening into suitable solvents. The plates were run in the solvent system below and were dried at room temperature (25 °C). Iodine chamber and UV chamber used to detect TLC plate.

Table 3: TLC of extracts (Rf value)

Extract	Solvent System	No. of Spots	Rf value
Aqueous Extract	Ethyl acetate: chloroform: methanol (7:2:1)	5	0.11 0.15 0.19 0.34 0.52
Chloroform Extract	Hexane: ethyl acetate: formic acid (6:3.5:0.5)	6	0.01 0.06 0.10 0.21 0.52 0.67
Methanol	Hexane; Toluene: ethyl acetate: few drops of formic acid (7:2:1: few drops)	6	0.01 0.21 0.32 0.46 0.55 0.66

The best solvent system for TLC of extract were Ethyl acetate: chloroform: methanol (7:2:1) for aqueous extract, Hexane: ethyl acetate: formic acid (6:3.5:0.5) for chloroform and Hexane; Toluene: ethyl acetate: few drops of formic acid (7:2:1: few drops) for methanolic extract TLC of Clerodendrum indicum shows the presence of 5, 6 and 6 compounds respectively with different R_f values in Different colour using the iodine chamber detecting reagent which suggests that the presence of 5-6 compounds in the extracts.

Antioxidant Content: The total phenolic contents of ethanol and water extracts of sample were examined using the diluted Folin-Ciocalteu Reagent (FCR). Gallic acid standard curve is required to evaluate the total phenol content of the selected sample. Because gallic acid is 3, 4, 5- trihydroxy benzoic acid and it is a kind of total phenol. Gallic acid standard curve is shown in Figure 4. The total flavonoid content of aqueous, chloroform and methanol extract of the selected samples is shown in Table 4. Total flavonoid content in the aqueous, chloroform and methanol extract of *Clerodendrum indicum* was found to be 5.32, 5.11 and 6.11 µg QE/100g of the extract respectively. This indicates that methanol extract of *C. Indicum* has the highest total flavonoid content when compare to the other two extract.

Table 4: Total Phenolics & Flavonoids content of extracts

Plant extracts	Total phenolics (mg gallic acid equivalent/g)*	Total flavonoid (mg rutin equivalent/g)*
Aqueous extract	3.78	5.32
Chloroform	3.99	5.11
Methanol	4.32	6.11

Pharmacological Activity

Acute Toxicity Study: In this study, after being given a dose of C. indicum extract 300 mg/kg and 2000 mg/kg the weight of animals was increased. 0 days of the weight of animals no change in a weight of all animals. Again, noticed that there no toxic effect and behavioral change in all animals group. No toxicity signs were observed in the animals throughout the 14 days study period of dose 300 mg/kg and 2000 mg/kg. Therefore, the extract may be safe at these doses and the oral LD_{50} is considered smaller than 2000 mg/kg in rats.

Antiulcer Activity: The antiulcer activity of C. indicum extract in aspirin induced gastric ulcer model is illustrated in Table 5. The anti-ulcer activity of C. indicum extract in aspirin induced gastric ulcer model is evident from its significant reduction in gastric volume, free acidity, total acidity and ulcer index. Because the plants extract treated animals significantly inhibited the formation of aspirin induced gastric ulcer in the stomach and also decreased both acid concentration and gastric volume. The increase in the gastric volume of the untreated Aspirin+PL group is undoubtedly due to increased production of HCL as it is evident from the total acidity of the gastric juice. At the same time methanolic extract of C. indicum (250 mg/Kg) and methanolic extract of C. indicum (500mg/Kg) treated groups did not produce any significant changes in the biochemical parameters and they preserved the normal architecture of the stomach mucosa by significantly reducing the gastric volume and ulcer index as compared to PL control animals. This further establishes the fact that the extracts have ulcer protective in nature.

Table 5: Effect of *C. indicum* leaves extract on free acidity and total acidity in aspirin induced gastric ulcers in rats

S. No.	Groups	Free Acidity	Total Acidity
1.	Group-I	86.34±1.238	89.56±1.521
2.	Group-II	92.45±2.856	110.33 ± 2.856
3.	Group-III	22.00 ±1.528 a***	28.00±2.528a***
4.	Group-IV	51.23 ±2.856b***	53.00 ±2.528b***
5.	Group-V	42.32±1.887c***	46.03± 1.887c***

Values are expressed as mean ±SD (n=6). Group I: Normal Control, Group II: Negative Control, Group III: Standard, Group IV: Low dose, Group V: High dose. a Compared with group 2 and group 3; b Compared with group 3 and group4; c Compared with group 3 and group 5; ** *p<0.001 (One-way ANOVA followed by Fisher's test).

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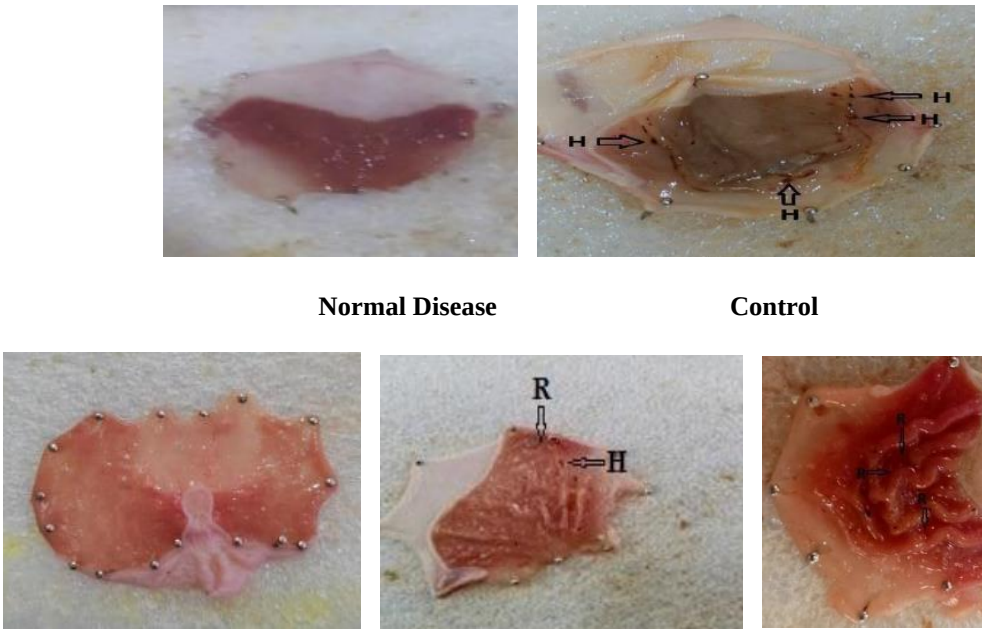
Table 6: Effect of C. indicum leaves extract on gastric volume and ulcer index in aspirin induced gastric ulcers in rats

S. No.	Groups	Gastric volume	Ulcer index
1.	Group-I	0.78±0.002	0
2.	Group-II	5.580±1.45	14.06±0.569
3.	Group-III	1.640±0.213a***	1.95±2.154
4.	Group-IV	3.800±2.515b***	6.79±0.365
5.	Group-V	2.510±0.254c***	5.68±1.854

Values are expressed as mean ±SD (n=6). Group I: Normal Control, Group II: Negative Control, Group III: Standard, Group IV: Low dose, Group V: High dose. a Compared with group 2 and group 3; b Compared with group3 and group4; c Compared with group 3 and group 5; ** *p<0.001 (One-way ANOVA followed by Fisher's test).

Microscopic Examination: In Aspirin treated group, more than 10 hemorrhage spot and deep perforation and it is easily seen in figure 1. In ranitidine treated group, overall redness was there on the surface but there was no hemorrhage spot and it is easily seen in figure 1. In MECI (250mg/kg) treated group there was redness on the surface of tissue and 1-2 small patches and it is easily seen in figure 1. In MECI (500mg/kg) treated group there was no patches and no hemorrhage spot, slight redness was there but almost enact tissue and it is easily seen in figure 1. In N-saline treated group, no redness, no hemorrhage spot, no patches a complete entact skin was there and it is easily seen in figure 1.



Normal Disease **Control**

Standard **250 mg/kg** **500 mg/kg**

Figure 1: Microscopic Examination

Oxidative Stress Marker: The oxidative stress marker were depicted that the basal activity of GSH were reduced by induced group (Aspirin control) while the animals of test group (MECI at 250mg/kg and MECI at 500 mg/kg) were restored GSH level at dose – dependent manner and also same goes to standard group. While finding also proved that significant oxidative changes with an enhance of lipid peroxidation as increment of MDA level in induced group (Aspirin control group) which indicate that tissue damage due to ulceration or necrosis but when it comes to test group (MECI) it was reduced according to dose dependent manner and same goes with standard group which received ranitidine (20 mg/kg).

Table 7: Computed the value of oxidative stress marker

S. No.	Groups	GSH (nM/mg protein)	MDA (nM/mg protein)
1.	Group-I	259± 2.016	57.00± 1080
2.	Group-II	98.75± 8.985	78.00± 1.581
3.	Group-III	249.8± 2.136	60.00± 1.291
4.	Group-IV	115.0± 4.564	67.25± 0.8539
5.	Group-V	248.5± 2.255	61.25±0.7259

Biochemical Parameter

Serum amylase: Group which received aspirin means induced group had higher serum amylase level which is 1400 u/i. Group which received ranitidine along with aspirin had lower serum level as compare to induced group which is 530 u/i. Group which were control which received only saline had the value of serum amylase approximately equivalent to standard which is 553 u/i. Group which were test which received MECI 500 mg/kg (methanolic extract of *C. indicum* leaves) had lowest serum amylase value which is 251 u/i. So from the above result it is clearly seen that ulcer induced group had elevated level of serum amylase as compare to standard, control and test so elevation of serum amylase level is an indication of ulcer which is confirmed by histopathology and oxidative stress results, but we can say that MECI (methanolic extract of *C. indicum* leaves) is possess inhibitory property for amylase as the amylase level of test group is very low as compare to control and standard.

CONCLUSION

Gastric acid secretion in oxyntic glands is started by the release of histamine through cells like entrochromaffin, while gastrin is released by G cells. Therefore, methanolic extract received animals showed anti-histaminic impacts and inhibit H_2 receptor in the stomach, and result indicate that MECI is very effective on peptic ulcer because of high acidity in the stomach. The administration of MECI at 500 mg/kg resulted in protective effects from the stomach mucosa, whereas minor numbers of inflammatory cells and surface ulcers were seen at 250 mg/kg, demonstrating that MECI had gastroprotective. This study concluded that the methanolic extract of C. indica leaves possess anti-ulcer activity against aspirin-induced gastric ulcer as it played significant role in normalized hematological indication and histopathological changes in the stomach of albino Wistar rats. Antioxidant constituents of this plant might support in anti-ulcer activity. So now opening the possibility of this plant uses as alternative therapy to gastric ulcer.

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