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Comparitive Study Of Leaves And Roots Ethanolic Extracts Of *Acalypha Indica* On Peptic Ulcers Induced By Physical And Chemical Agents In Rodents

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ABSTRACT

Acalypha indica L (Family Euphorbiaceae) is used traditionally in Indian system of medicine for various ailments. Present study aims at the gastroprotective effect leaves and roots of Acalypha indica which were administered orally as pre-treatment for Aspirin (ASP), cold-restraint stress (CRS), pylorus ligation (PLU) and ethanol (EIU), induced ulcers. Estimation of gastric secretion parameters like volume of gastric juice, acid output, and pH value were estimated in PLU and EIU induced ulcer model. The results of the study revealed that Acalypha indica roots ethanolic extract showed dose-dependent ulcer protective effect on peptic ulcers induced by physical and chemical agents in rodents.

INTRODUCTION

Peptic ulcers appear to be produced by an imbalance between the gastro duodenal mucosal defence mechanism and damaging factors [1]. The primary defect may not reflect any abnormality in acid secretion [2]. The two most common factors that predispose to ulcer are chronic gastric infection with bacteria called Helicobacter pylori and ingestion of non-steroidal anti-inflammatory drugs (NSAID's) such as aspirin or ibuprofen [2, 3]. Ethanol is common cause of acute gastric mucosal injury in both human and animals [4]. Stress ulceration of the stomach is associated with clinical conditions like trauma, head injury, burns, shock, sepsis and neurological disorders; and is now regarded as a multifactorial phenomenon [5]. Several other factors are associated with ulcer formation, although this may have an indirect relationship. Such factors include hereditary, smoking, elevated calcium level, corticosteroids in high dose [1].

The use of natural products with therapeutic properties is as ancient as human civilization and for a long time, mineral, plant and animal products were the main resources of drugs [6]. Traditional systems are largely plant based and are the local heritage with global importance, world is endowed with a rich wealth of medicinal plants [7]. Natural products have proven to be the richest source of medicinal compounds. Although, many drugs are prepared by synthetic chemistry, most of the core structures or scaffolds for synthetic chemicals are based upon natural products. The key advantage of natural products over synthetic compounds is their greater chemical diversity.

Acalypha Linn (Family: Euphorbiaceae) A large genus of herbs and shrubs, comprising some 400 species, found throughout the

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tropics and about 9 species are found in India with medicinal importance. Acalypha indica (A indica) is commonly known as Indian acalypha; Sanskrit-Harita manjari, Kanada-Kupigida and Telugu Kuppichettu. Plant is a small annual shrub (1-2' high) occurring as a troublesome weed in gardens and roadside throughout the plains of India and found throughout the hotter parts of India, eastwards to Assam, Philippines, southwards to Singapore, Ceylon, common in fields and westwards to tropical Africa [8].

A indica has various applications in complementary and alternative medicine and used by siddha, ayuveda and Homeopathic systems. A decoction of A indica entire plant is used by hakims as a safe and speedy laxative. In cases of constipation in children, the brushied leaves introduced in the manner of a suppository, invariably give relief. The leaf of the plant, ground with common salt, quick lime or lime juice is reputed to be a parasiticide and is applied externally. It is found that a paste of the leaves with lime juice was beneficial in early cases of ringworm but had no effect in chronic case. The plant is used as expectorant as a substitute for senega and also useful remedy for bronchitis, asthma and pneumonia; also for rheumatism. The root, bruised in hot water, is employed as a cathartic, and leaves as a laxative in decoction mixed with common salt [8, 9].

Earlier several reports on biological activities are on neutralization potential of Viper russelli russelli (Russell's viper), wound healing, post-coital antifertility activity, heamolysis, anti-ulcer, alfa amylase inhibitory activity, analgesic, anti-inflammatory, anti-bacterial, anti-malarial, anti-atherosclerotic, anti-TB, anti-diabetic, anti-anthelminthic, impetigo treatment. Phytochemicals isolated from this plant are acalyphol acetate, 2-methyl anthraquinone, β-sitosterol, tri-o-methylellagic acid, succinimide, acalyphamide (as acetate), aurantia-amide and its acetate, potassium brevifolin carboxylate, acaindinin, 1-O-galloyl-β-D-glucose, 1,2,3,6-tetra-O-β-D-glucose, corilagin, gerariin, acetonylgeranin A, euphormisin M_2, rephandusinic acid, chebulagic acid, rutin, quercetin-3 O-β-D-glucoside, flindersine, chrysin, galangin, acalyphine, triacetonamine, kaemferol, querachitol [10].

With the traditional uses of A indica in present investigation this plant's leaves and roots were undertaken for aspirin, cold restraint, pylorus ligated and ethanol induced antiulcer study.

Material and Methods

Drugs and chemicals

Organic solvents were obtained from Merck, Germany. Ranitidine, reagents and standards: acetone, hydrochloric acid, hexamethylene-tetramine, sodium nitrite, aluminium chloride, sodium hydroxide, sodium carbonate, folin-ciocalteu reagent, quercetin and gallic acid, were purchased from SRL, Sigma Aldrich.

Preparation of extract from leaves and roots and phytochemical screening

The whole plant of A indica was collected in and around Gulbarga University, Gulbarga authenticated and voucher specimen (code no. HGUG-202) has been deposited in the botany department. The collected A indica plant material was segregrated into leaves and roots seperately, shade dried, coarsely powdered and hot extraction was carried out with 80 % ethanol (24 h) successively in soxhlet apparatus resulted in their respective leaves ethanolic (LEE) and roots (REE) extracts. Phytochemical screening of secondary metabolites in LEE and REE was carried out as described by Harbone [11].

Determination of total phenolic content

The amount of total soluble phenolic content in LEE and REE of A indica was determined according to Folin-Ciocalteu method [12]. Briefly, 10 µL of extract solution from the stock solution was mixed with 100 µL of Folin-Ciocalteu reagent. After 10 min of incubation, 300 µL of 20% Na_2CO_3 solution was added and the volume was adjusted to 1 mL using distilled water. The mixture was incubated in dark for 2 h and the absorbance was measured at 765 nm using a UV-Vis spectrophotometer against blank sample. The total phenolic content was measured as gallic acid equivalents (mg GAE)/gram of dry weight (dw) and the values were presented as means of triplicate analysis.

Determination of total flavonoid content

Total flavonoid content of LEE and REE of A indica was estimated by a colorimetric method by taking 20 µL of each extract and mixed with 500 µL Milli-Q water and 30 µL of 5% $NaNO_2$ solution [13]. After 5 min of incubation at room temperature, 60 µL of 10% $AlCl_3$ solution was added. Subsequently, 350 µL of 1 M NaOH and 40 µL of Milli-Q water were added to make the final volume 1 mL. Samples were further incubated for 15 min at room temperature and the absorbance of the samples was measured at 510 nm. The total flavonoids were determined as quercetin equivalents (mg QE)/g of dw and the values were expressed as means of triplicate analysis.

Animals

Wistar strain albino rats of either sex weighing between 150-200 g were obtained from NIN-Hyderabad and were placed in PVC cages under ideal conditions (temperature 20-25 °C, humidity 70-75%) and were fed on laboratory diet. All animal experiments were conducted after clearance by institutional animal ethics (Reg. No. LCP CPCSEA 346).

Acetyl salicylic acid induced gastric ulcer

In this experiment animals were divided into seven groups with 6 animals in each, group I received Tween-80 (1%) in dH_2O, group II only aspirin (200 mg/kg), group III received ranitidine (50 mg/kg), group IV and V received dose of LEE 200 and 100 mg/kg and group VI and VII received dose of REE 200 and 100 mg/kg. Each group of animal received respective dosages test samples for five days, followed by administration of 200 mg/kg body weight expect group I. Aspirin drugs, LEE and REE

were suspended in Tween-80 (1%). On the sixth day after the last administration of the drugs and the ulcer inducing acetyl salicylic acid, the rats were killed by cervical dislocation and their stomachs were opened along the greater curvature and washed with lukewarm saline and examined under a dissecting microscope. The ulcer index was calculated for each stomach according to the method described by Parmar and Desai [14].

Cold stress induced gastric ulcers

Adult albino rats of either sex weighing between 150-200 g were divided into eight groups of six animals each. The group I received the vehicle Tween-80 (1%, 1 ml) p. o., which served as control. Group II received diazepam at a dose of 1 mg/kg body weight. Group III received ranitidine at a dose of 50 mg/kg body weight. . Group IV and group V received the LEE at a dose of 200 mg/kg and 100 mg/kg body weight respectively. Group VI and group VII received the REE at a dose of 200 mg/kg and 100 mg/kg body weight respectively. Group VIII received diazepam 1 mg/kg b.w. as a standard. The extract doses were administered orally. Animals were deprived of food for 48 hours before the experiments. The water was allowed ad libitum to animals. The water was removed 1 hour before restraint and exposed to a temperature of 4C for 2 hours. Two hours after stress, the stomach of the animals was opened along the greater curvature and the severity of gastric ulcer was assessed in terms of mean ulcer index [15].

Pylorus ligated gastric ulcer model

The animals were divided into seven groups of 6 animals each. Animals were deprived of food for 48 hours but had free access to water. The animals were divided into six groups of six animals each. Group I and II received the vehicle Tween-80 (1%, 1ml) which served as the control. Group III received ranitidine at a dose of 50 mg/kg body weight, which served as standard for comparison. Group IV and group V received the LEE at a dose of 200 mg/kg and 100 mg/kg body weight respectively. Group VI and group VII received the REE at a dose of 200 mg/kg and 100 mg/kg body weight respectively. All the drugs were administered orally, at 30 minutes after the drug administration, the abdomen was incised and the pylorus was ligated by means of a technique of Shay et al [16], under ether anesthesia except for group I. 4 hours after pylorus ligation, the animals were sacrificed and the gastric content was collected and centrifuged at 5000 rpm for 10 minutes. The supernatant was collected and the volume of the gastric juice was expressed as ml/100 g of body weight. In order to determine the acidity, the supernatant was titrated with NaOH (0.01 N) using Topfer's reagent and phenolphthalein as indicators for free and total acid [17].

Ethanol induced gastric lesions

The animals were divided into seven groups of 6 animals each and were deprived of food for 48 hours but had free access to water. Group I received the vehicle Tween-80 (1%, 1ml) that served as the control. Group II received ranitidine at a dose of 50 mg/kg body weight, which served as standard for comparison. Group III and IV received LEE at a dose of 200 mg/kg and 100 mg/kg body weight respectively. Group V and VI received the ethanol extract of REE at a dose of 200 mg/kg and 100 mg/kg body weight respectively. Lesions were induced 1 hour after drug treatment by oral administration of 1 ml of 40% ethanol and after one hour animals under light ether anesthesia [18], the abdomen was immediately opened, and the stomach was ligated at the pylorus end. 4 hours after pylorus ligation, the animals were sacrificed and the content was drained and centrifuged at 5000 rpm for 10 minutes. Aliquots of supernatant were used for determination of free and total acidity by titrating with 0.01 N NaOH using Topfer's reagent and phenolphthalein as indicators [17]. Dissolved mucosubstances were estimated by scraping the gastric mucosa using a spatula. The hexose, fucose [18], hexoseamine [19] and sialic acid [20] levels were estimated. Stomach was opened along the greater curvature and the total area of lesion was measured [18].

Statistical analysis

The results of the spectrophotometric analysis were expressed as Mean ± S.D upon three independent analyses. All values have been expressed as mean S.D. Statistical significance was determined by using ANOVA followed by Dunnet test.

RESULTS

Determination of phyto-constituents

The % yield of LEE and REE from plant material leaves and roots respectively found to be 10 and 5 %. Phytochemical screening was carried out of LEE and REE observed the presence of steroids, flavonoids, phenolics, terpenoids, glycosides. The results of total phenolic content in LEE and REE were evaluated by using Folin-Ciocalteu method possessed an abundance of amounting to 23.88±0.29 and 14.66±1.44 mg GAE/g d.w. respectively. The flavonoid contents of LEE and REE in terms of quercetin equivalents were between 19.77±0.32 and 5.32±1.04 respectively. All results are shown in Table 1.

Acetyl salicylic acid induced gastric lesions

From Table-2 it is evident that standard ranitidine at dose of 50 mg/kg weight exhibited good activity, effective in reducing the ulcer index by 70.25 %. The LEE at a dose of 200 mg/kg body weight was better than at dose of 100 mg/kg body weight but showed poor activity compared to standard ranitidine. But the REE at a dose 200 mg/kg b.w. showed 55.61 % protection and only 40.98 % at 100 mg/kg b.w. The REE found to protect more than leaves but less than standard ranitidine at 200 mg/kg b.w.

Stress induced gastric ulcer

The results of the experiments are tabulated (Table -2). Diazepam at dose of 1 mg/kg and ranitidine at a dose of 50 mg/kg b.w. signfiicantly reduced the ulcer index caused due to cold restraint with 74.06 and 70.25 % protection. The results of % protection of REE (58.14 % protection) was better than LEE (41.31 % protection) at a dose of 200 mg/kg b.w. and 100 mg/kg b.w. both extracts were ineffective.

Table-1: Yield, phytochemical tests, flavonoid and phenolic content and Total antioxidant and DPPH screening of leaves and roots extract of Acalypha indica Linn.

S no.	Part of Plant	Yield %	Phytochemical screening							Quantitative estimation	
			Steroids	Alkaloids	Terpenoids	Flavonoids	Phenolics	Glycosides	Saponins	Flavonoids[a]	Phenolics[b]
1	Leaves	10	+ve	-ve	+ve	+ve	+ve	+ve	-ve	19.77±0.32	23.88±0.29
2	Roots	5	+ve	-ve	+ve	+ve	+ve	+ve	-ve	5.32±1.04	14.66±1.44

+ve represents presence and -ve represents absence of secondary metabolites. a: Gallic acid; b: Quercetin; equivalents mg/g dw plant material respectively. Each value is expressed as a mean ± standard deviation (n = 3).

Pylorus ligated gastric lesions

In pylorus ligated induced gastric lesions standard ranitidine has shown (Table-2) anti-secretory action at a dose of 50 mg/kg b.w. by improving pH, reducing acidity, reduced gastric volume and reduced mean ulcer score. The mean ulcer score was found with percentage of ulcer protection/inhibition by 67.24 %. The REE at 200 mg/kg b.w. with 66.62 % protection was comparable with standard ranitidine and reduced with 100 mg/kg b.w. The REE at 200 mg/kg shows antisecretory action comparable to standard in present study (table 3).The LEE at 200 and 100 mg/kg b.w. found to be ineffective.

Ethanol induced gastric lesions

Percentage protection of standard ranitidine found to be 68.19 % at dose of 50 mg/kg b.w, the REE at 200 mg/kg b.w. with 64.55 % was comparable to standard (Table-2) and also found pH improving, reduction in acidity and reduced gastric volume (Table-3). The biochemical estimations of the gastric mucosa were carried out in control, ranitidine, and extracts treated groups of A indica (Table-4) that were comparable to standard. The results of REE at 100 mg/kg was good with 59.82 % protection but not much in pH, gastric volume, acidity and biochemical parameters. LEE found to be ineffective to protect the ulcer induced by 40 % ethanol. Results are tabulated (Table-2, -3 & -4).

Table 2: Ulcer protective effect of leaves and roots ethanolic extract of Acalypha indica L. in aspirin, cold restraint, ethanol and pylorus ligated induced gastric lesions model.

Group No.	Treatment	Mean ulcer index ± S.D (% protection)			
		ASP	CRU	PLU	EIU
II	Control	2.05± 0.18	35.83± 4.16	3.54± 0.16	5.50± 0.18
III	Std	0.61** ± 0.04 (70.25)	10.00**± 3.65 (72.1)	1.16**± 0.10 (67.24)	1.75**± 0.07 (68.19)
IV	LEE200	1.25 ± 0.09 (39.3)	21.03± 5.68 (41.31)	2.66± 0.16 (24.86)	4.15± 0.16 (24.55)
V	LEE100	1.75± 0.24 (14.64)	26.66± 6.79 (25.6)	3.08± 0.28 (13)	4.91± 0.29 (10.73)
VI	REE200	0.91± 0.18 (55.61)	15.00*± 1.82 (58.14)	1.18**± 0.21 (66.62)	1.95**± 0.30 (64.55)
VII	REE100	1.21± 0.05 (40.98)	22.16± 2.07 (38.16)	1.75*± 0.45 (50.57)	2.21*± 0.11 (59.82)
VIII	Diazepam	-	9.16**± .651 (74.06)	-	-

ASP : Aspirin induced ulcer model; CRU : cold restraint ulcer model; PLU : pylorus ligated model; EIU : Ethanol induced ulcer model. STD : standard for reference drug ranitidine 50 mg/kg b.w.; LEE200 and LEE100 leaves ethanolic extract of A indica at 200 and 100 mg/kg b.w. ; REE200 and REE100 roots ethanolic extract of A indica at 200 and 100 mg/kg b.w.; Significance levels at ** P < 0.01, compared with control values.

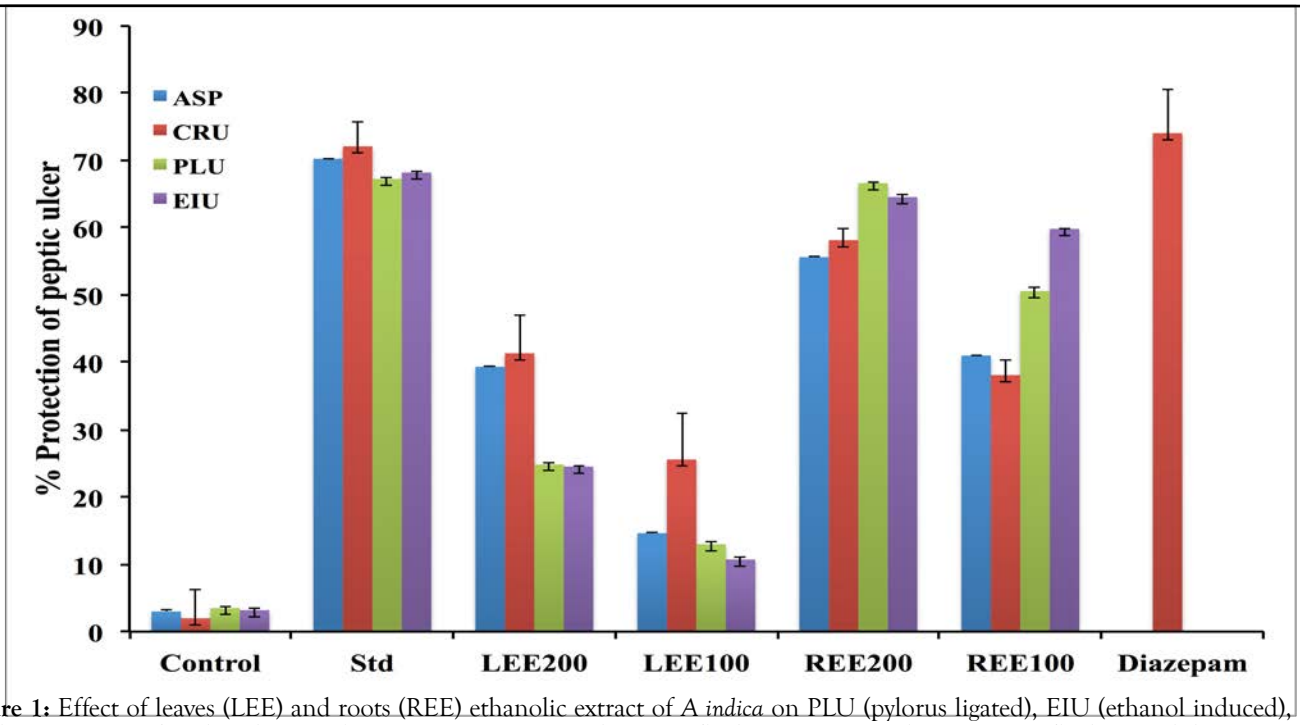

Figure 1: Effect of leaves (LEE) and roots (REE) ethanolic extract of *A indica* on PLU (pylorus ligated), EIU (ethanol induced), CRU (cold restraint stress) induced gastric lesions in rats at 200 and 100 mg/kg b.w. STD ranitidine at 50 mg/kg b.w. and diazepam 1 mg/kg b.w. Y axis : % protection of peptic ulcer ; X axis : control, standard, LEE, REE samples against ASP, PLU, EIU, CRU models of inducing peptic ulcers.

Discussion

Plant products have antiulcer potential and the reports are well documented in literature, but with limited clinical data are known to support their application as gastro-protective agents. These botanical products have high efficacy and low toxicity are on demand for therapeutic application [22]. The Flavonoids and phenolics are secondary metabolites of plants that are biological importance and reported for their antiulcer properties [23]. In the present study the leaves show more concentration of flavonoids and phenolics content over roots ethanolic extract, but the roots ethanolic extract found to be more effective. The roots ethanolic extract at 200 mg/kg dose was effective in protecting peptic ulcer induced by aspirin, cold stress, pylorus ligation and ethanol induced models. It is well known that aspirin is a non steroidal inflammatory drug (NSAIDs) that on long term use cause gastritis as side effect as these damage mucosal lining with increase in acid secretion and back diffusion of H^+ ions by intereference in PG synthesis involved in to reduction of inflammation [24]. The gastroprotective effect of the roots ethanolic extract may be due to its ability to inhibit the synthesis of prostaglandins/leukotrienes effectively over the

Table 3: Antisecretory and ulcer protective effect of leaves and roots extract of A indica L. in pylorus ligated rats and ethanol induced ulcer models.

Treatment	Pylorus ligated model			Ethanol induced model		
	Gastric content (ml)	pH	Acidity Total m E_g	Gastric content (ml)	pH	Total Acidity m Eq
Control	3.15± 0.27	2.40±0.03	69.66±0.61	4.23±0.44	2.72± 0.76	66.83± 3.13
Ranitidine	1.56**± 0.24	4.75**± 0.09	46.83± 0.93	5.233±0.85	4.79**± 0.51	46.25**± 2.09
LEE200	2.60± 0.30	3.97± 0.25	64.85±2.18	4.34± 0.49	2.95± 1.48	65.40± 3.72
LEE100	3.83± 0.47	2.74± 0.24	66.90±2.60	5.50± 0.42	2.10± 0.23	66.66± 2.35
REE200	2.15± 0.42	4.5*± 0.04	42.58± 0.58	4.96±0.133	4.06*± 0.21	53.33*± 2.12
REE100	3.06± 0.32	3.00± 0.30	64.31±3.02	5.68±0.27	3.15± 0.43	62.35± 4.3

Significance levels at **P < 0.01, *P < 0.05compared with control values.

Table 4: Biochemical parameters of ulcer protective effect of leaves and roots ethanolic extract of A indica L. on ethanol induced gastric ulcers.

Group No.	Treatment	Protein (µg/g)	Total Hexose (µg/g)	Hexoseamine (µg/g)	Fucose (µg/g)	Sialic acid (µg/g)
I	Control	451.67± 14.53	324.67± 7.60	142.25± 2.81	69.5± 3.19	34.33± 2.56
II	STD	322.5**± 7.04	438.17** ± 13.97	152.17± 8.38	90.00** ± 3.6	61.00**± 3.67
V	LEE200	416.67±33.33	351.67± 3.47	145.33± 10.28	70.66± 4.17	38.33± 2.78
VI	LEE100	441.67±41.66	324.17± 7.46	140.67± 7.51	72.50± 3.09	34.167± 4.16
VII	REE200	331.67**±43.6	425.83**± 5.97	145.17**± 9.16	87.16**± 4.07	60.83**± 5.23
VIII	REE100	438.33±29.68	310.83± 19.68	144.00± 10.95	69.167± 3.27	26.66± 4.21

Significance levels at **P < 0.01, compared with control values.

leaves ethanolic extract. Stress plays an important role in aetiopathology of gastroduodenal ulceration by a number of factors like increase in gastric motility, vagal over activity, mast cell granulation and decreased gastric mucosal blood flow and PG synthesis [25]. Stress leaves a lasting imprint on cognitive behaviour and is believed to be important in causation of hyperacidity and ulceration. Diazepam when injected both peripherally and central, attenuate several stress responses like gastric ulcerogenesis and plasma corticosterone [26]. The roots extract was also effective to gastric ulcerogenesis due to cold restraint stress induced ulcer model. Pyloric ligation induced ulcers are thought to be due to auto digestion of mucosa by gastric juice leading to break down of mucosal barrier [27]. The pylorus ligation model is helpful in determination of the antisecretory property with the changes in gastric volume, its pH, acidity and other are studied. The ligation of pylorus end of stomach causes accumulation of gastric acid in the stomach that increases stomach wall friction, ruptures mucosal layer, cells disintegrate, and gastric ulcers form [28]. The roots ethanolic extract at 200 mg/kg b.w. treated animals significantly inhibited the formation of ulcers in the pylorus ligated rats and also decreased both the concentration and increased the pH, it is suggested that REE suppress gastric damage induced by aggressive factors. Ethanol induced damages are induced by distrubance of mucosal microcirculation, ischemia and appearance of free radicals, degranulation of mast cells, inhibition of prostaglandin and decrease in mucus production [29]. Ethanol is noxious peptic ulcer inducing agent in experimental animals to screen drugs for cytoprotective activity that may be by decreasing lipid peroxidation, hydroxyl radical and super oxide anion production in gastric mucosa may be due to induce prostaglandin production, that in turn stimulates mucus and bicarbonate synthesis [30]. The roots ethanolic extract of A indica significantly protected effectively gastric mucosa against various insults may be by increasing gastric mucin content and increased the pH and decreased the free and total acidity in rats, which in turn reduces the activity of pepsin and prevent mucolysis suggesting its potent gastroprotective effect. The roots ethanol extract could overcome all the aggressive factors and increase mucin secretion; increase protein signifies decrease in leakage from the mucosal cells indicating increased mucosal resistance.

The roots ethanolic extract of *A indica* significantly effective in protecting gastric mucosa against all the ulcerogenic models of the study. This in turn protects the stomach from all the above mentioned challenges. Medical treatment of peptic ulcer is dependent on correcting the imbalance between the offensive and defensive factors. The test extracts acts on both the parameters of equation which govern the treatment of peptic ulcer and thus can be useful clinically. However, further studies are needed to assess its safety profile before it is put into use clinically.

Conclusion

Gastric mucosal damages induced in different experimental ulcer models have different mechanisms. In the present investigation of anti-ulcer study of leaves and roots ethanolic extracts, roots ethanolic extract at 200 mg/kg b.w. could significantly reduce ulceration in 4 models under study. This antiulcer potential may be due to the mixture phytoconstituents distribution at 200 mg/kg b.w. concentration in roots with synergitic effect.

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Authors Column

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