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Evaluation of Anti-Ulcer Activity of 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* Linn. In Experimental Rats.

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Abstract: Anti-ulcer activity of 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* L. at a dose of (100, 200 &400mg/kg b.w p.o) was investigated in Pylorus ligation, Aspirin induced mucosal damage and water immersion stress induced gastric ulcer models in Albino wistar rats (150-200gms). In all the three models, the common parameter determined was ulcer index. In acute toxicity study (423 Guideline), there was no mortality up to a dose of 2000mg/kg b.w p.o, thus considered as maximum tolerated dose. Preliminary phytochemical studies showed the presence of Alkaloids, Carbohydrates, Flavonoids, Glycosides, Tannins etc. 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* L. at a dose of 100, 200 and 400 mg/kg b.w p.o. produced significant inhibition of the gastric lesions in Pyloric ligation, Aspirin induced mucosal damage and water immersion stress induced gastric ulcer models. The extract at (100, 200 and 400 mg/kg b.w p.o.) showed significant reduction in pH, Free acidity, Total acidity of gastric acid and ulcer index as compared to control in pylorus ligation model. Results showed that the 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* L. exhibited significant and dose-dependent Anti-ulcer activity in all the ulcer models. Percentage ulcer protection of 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* L. was calculated at 100, 200 and 400mg/kg b.w.p.o. for Pylorus ligation, Aspirin induced mucosal damage and water immersion stress induced gastric ulcer models and maximum protection was found at a dose of 400mg/kg b.w.p.o with 39.9%, 43.6%, 54.7%, respectively. The ulcer protective effects of the extract were comparable with those of standard drugs. Results of our study suggest that 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* L. posses Anti-ulcer activity which may be due to the presence of flavonoids in the extract as it has astringent, anti-secretory, cytoprotective and antioxidant properties.

Keywords: *Argemone mexicana,* Anti-ulcer activity, Flavonoids, Percentage Ulcer Protection, Ulcer index.

I. INTRODUCTION

Argemone mexicana (family - Papavaraceae) known as Ghamoya is an indigenous herb found in India. It is a commonly occurring weed present in many regions of the country. It is composition of many traditional remedies. Ghamoya has occupied a pivotal position in Indian culture and folk medicine. It has been used in almost all the traditional system of medicine, such as in Ayurveda, Unani and Siddha[1]. Traditionally the plant is reported to be used as diuretic, purgative, anti-inflammatory, analgesic and believed to destroy worms, cures itching, various skin diseases and as antidote to various poisons. The seeds are purgative and sedative (Ayurveda), useful in skin diseases and leucoderma (Unani) and in homeopathy, the tincture of the whole plant is reported to be used orally for bronchitis and whooping cough. It is used to cure venereal sores, photophobia, scorpion bite, leucorrhea, dental disorders, diabetes, malarial fever, ulcers, leprosy, jaundice and dropsy (Siddha).[2] Reports on pharmacological activities are many. Some of the reported activities are Wound healing, Anti-asthamatic, Anti-stress, Hepatoprotective, Anti-HIV, Anti- diabetic, Anti- inflammatory.[3,4]

Peptic ulcer also known as "**Ulcus Pepticum",** , is a conglomerate of heterogeneous disorders, which manifests itself as a break in the lining of the gastrointestinal mucosa bathed by acid / or pepsin [5]. For over a century, peptic ulcer disease has been one of the leading causes of gastrointestinal surgery, with high morbidity and mortality rates. It effects lot of people in the world, and hence, some researchers consider this disease as "**New Plague of the Twenty-First Century".[6]**

The aim of the study was to evaluate Anti-ulcer activity of 70% Hydro-alcoholic leaf extract of *Argemone mexicana* Linn. in experimental rats.

II. MATERIALS AND METHODS

2.1 Collection and Authentication of Plant material

The leaves of *Argemone mexicana* Linn. were collected from the area of Himayat sagar and was authenticated by SMP unit of Central Research Institute of Unani Medicine, Hyderabad and voucher specimen number is 11386.

2.2 Extraction and Phytochemical Screening

The collected leaves of *Argemone mexicana* Linn. was cleaned from dust and shade dried for about 15-18 days and the shade dried leaves were crushed to get a coarse powder. The powdered leaves (500gms) was successively extracted with Ethanol and water in 7:3 ratio by soxhlation for 48hrs. Following extraction, the liquid extract were concentrated on water bath until it forms semi-solid residue. Standard methods[7,8] were used for preliminary phytochemical screening to know the nature of phytoconstituents present.

2.3 Drugs

Aspirin (200mg/kg b.w p.o), Ranitidine (50mg/kg b.w p.o), Misoprostol (100mcg/kg b.w p.o).

2.4 Experimental Animals

The experimental protocol was approved by Institutional Animal Ethics Committee, Central Animal House (Registration No.9769/2011/CPCSEA), SICRA Labs Pvt. Ltd., Hyderabad, India. Female Albino Wistar rats (150-250g) were used for Acute Toxicity study and male wistar rats weighing between 150-250 g were used for evaluating antiulcer activity. The animals were maintained under standard laboratory conditions, 12-hr light/ dark cycle under controlled temperature. All animals were acclimatized to laboratory environment for at least one week and they were given standard pellet diet and water ad libitum before the commencement of experiment.

2.5 Acute Toxicity Study (OECD Guideline 423)

Animals were fasted prior to dosing, food but not water was withheld overnight. Following the period of fasting, the animals were weighed and test substance was administered. After the substance had been administered, food was withheld for further 3-4 hours. As a dose was administered in fractions over a period, it was necessary to provide the animals with food and water depending on the length of the period.[9,10] Three animals were used for each step. The dose level of the extract to be used as the starting dose was selected from one of the four fixed dose levels 500, 1000, 1500 and 2000mg/kg body weight.[11] The starting dose level selected was such that which was most likely to produce mortality in some of the dosed animals. After administration of the test sample, the animals were observed continuously for first four hours for behavioral changes and for 48 hours for mortality, if any.

2.6 Evaluation of Anti-Ulcer Activity of 70% Hydro-Ethanolic Leaf Extract Of *Argemone mexicana* Linn.

2.6.1. Pylorus ligation model

30 male Wistar albino rats (150-250gm) were divided into five groups, six animals in each. The animals were fasted for 48hrs before the operative procedure, however, they were given free access to water. To prevent cannibalism and coprophagy, the animals were housed singly in cages with raised bottom of wide wire meshes. Group 1 was considered as Control and received normal saline. Group 2 (standard) received standard drug Ranitidine (50mg/kg b.w p.o) in normal saline while groups 3, 4 and 5 (Test) were given 70% hydro-ethanolic leaf extract *Argemone mexicana* in doses 100, 200 and 400 mg/kg b.w. p.o. in normal saline, respectively. Group 2,3,4,5 and 6 were then anesthetized using ether anesthesia. A one inch midline abdominal incision was made below the xiphoid process. The pylorus was carefully lifted out with minimal handling and traction and ligated without damaging its blood supply. The stomach was replaced and the abdominal wall closed with sutures.[12]

After 17-19 hours of pylorus ligation, the animals were sacrificed and the stomach was dissected out. The content of stomach was drained into graduated centrifuge tube and the volumes of gastric content, pH of gastric acid was determined. After this, the stomach was opened along the greater curvature pinned on the cork plate and inner surface was observed for ulcers microscopically with the help of hand lens (10x) and scoring was done.[13]

The ulcer index as in equation(1) was calculated and the ulcer severity[14] was graded as mention below.

Scoring of ulcers was made as follows:

Normal coloured stomach	:	0
Red colouration	:	0.5
Spot ulcer	:	1
Hemorrhagic streaks	:	1.5
Ulcers ≥ 3 but ≤ 5	:	2
Ulcers >5	:	3

The ulcer index (UI) was calculated as follows:

$UI = (UN+US+UP)X10^{-1}$ (1)

UN= Average of number of ulcers/animal

US= Average of severity of scores

UP= Percentage of animals with ulcer {(Total ulcers in a group/Total number of animals in group)X100}

Ulcer index and acidity of the gastric content of the treated animals were compared with control.
The percentage protection was determined by equation (2):

$$\% \text{ Protection} = \frac{(\text{Ulcer index})_{\text{control}} - (\text{Ulcer index})_{\text{test}}}{(\text{Ulcer index})_{\text{control}}} \times 100 \quad (2)$$

Estimation of Gastric volume, PH, Free Acidity and Total Acidity:

The gastric content was centrifuged at 1000 rpm for 10 minutes and the volume was noted, then 1ml of the supernatant liquid was pipetted out and diluted to 10ml with distilled water. The pH of this solution was noted. By titrating the solution against 0.1 N Sodium Hydroxide using Topfer's reagent as indicator (Dimethyl-amino-azo-benzene with phenolphthalein), titration was carried out to the end point when the solution turned to orange colour. The volume of NaOH was noted which corresponds to the free acidity.

Titration was continued further till the solution regained pink colour and the total volume of NaOH was noted which corresponds to the total acidity[14].
Acidity is calculated by equation (3):

$$\text{Acidity} = \frac{\text{Volume of NaOH} \times \text{Normality of NaOH} \times 100}{0.1} \text{ mEg/L/100gms} \quad (3)$$

2.6.2 NSAIDs (Aspirin) Induced Mucosal Damage In Rats:

30 Male Albino rats 150-200gms were divided in to 5 groups with 6 in each. The animals were fasted for 24 hours. Group 1 (Control) received normal saline, Group 2 was treated with standard drug Misoprostol (100mcg/kg b.w.) in normal saline p.o and groups 3, 4 and 5 was treated with 70% Hydro- Ethanolic leaf extract of *Argemone mexicana* in a dose of 100mg/kg b.w p.o, 200mg/kg b.w p.o and 400mg/kg b.w p.o. respectively in normal saline. After 30 minutes, gastric ulcer was induced by administrating Aspirin (200mg/kg b.w p.o) in normal saline to all groups. After 4 hours, the rats were sacrificed using anesthetic ether and their stomachs was dissected out and they were opened along greater curvature for the determination of gastric lesions. Ulcer index was calculated noting the number of ulcers per animal and severity was scored by observing the ulcers microscopically with the help of hand lens (10x)[14].
Scoring of ulcer was made as follows:

Normal coloured stomach	:	0
Red colouration	:	0.5
Spot ulcer	:	1
Hemorrhagic streaks	:	1.5
Ulcers ≥ 3 but ≤ 5	:	2
Ulcers >5	:	3

The ulcer index (UI) will be calculated by equation (1) and percentage protection by equation(2).

2.6.3 Water Immersion Stress Induced Ulcer in Rats

30 Male Albino rats 150-200gm were divided in to 5 groups with 6 in each. Stress induced ulcers was induced by placing the rats in glass cylinder (height 45cm, diameter 35cm) containing water up to 35cm maintained at 35°c for 3 hrs for forced swimming. Animals were fasted for 24 hours prior to the experiment. Group 1 was considered as Control group and received normal saline. Group 2 received standard drug Ranitidine (50mg/kg b.w p.o) in normal saline and group 3, 4 and 5 were treated with 70% Hydro- Ethanolic extract of leaf *Argemone mexicana* in a dose of 100mg/kg b.w p.o, 200mg/kg b.w p.o and 400mg/kg b.w p.o respectively in normal saline. After the drug treatment, all animals of the groups were placed in water individually and allowed to swim for 3 hours. Then the animals were dissected and stomach was removed. Stomach was opened along the greater curvature, ulcer index and % protection was calculated by equation (1) & (2) respectively.[14]

2.7 Statistical Analysis:

The data was represented as Mean ± SEM. The data of anti-ulcer activity of 70% Hydro- Ethanolic leaf extract of *Argemone mexicana* was analysed by one way ANOVA followed by Dunnett's *t*-test and the whole analysis was carried out using Graph Pad Prism 6.0 version ©1992-2004. 'P' value were considered significant when *P<0.05, **P<0.01, *** P<0.001 when the test and reference were compared with the control group.

III. RESULTS

3.1 Extraction & phytochemical analysis:

The %yield of 70%Hydro-ethanolic leaf extract of *Argemone mexicana* for 500gms was found to be 27.2%.

Preliminary phytochemical analysis of 70%Hydro-ethanolic leaf extracts of *Argemone mexicana* Linn. showed the presence of Alkaloids, Carbohydrates, Flavonoids, Glycosides, Tannins, Triterpenoids, Phenols, Saponins and Steroids.

3.2 Acute Toxicity Study:

Acute toxicity study for 70%Hydro-ethanolic leaf extracts of *Argemone mexicana* Linn. was carried out in female wistar rats. It was observed that there was no gross evidence of any abnormalities up to 4 hrs and no mortality was observed in animals up to the end of 48 hours at the maximum tested dose level of 2000mg/kg b.w. in rats. This was considered as Maximum Tolerated Dose (MTD) and thus, $1/5^{th}$, $1/10^{th}$ and $1/20^{th}$ dose of 2000mg/kg b.w i.e., 100mg/kg b.w., 200mg/kg b.w. and 400mg/kg b.w was selected for the experimental studies.

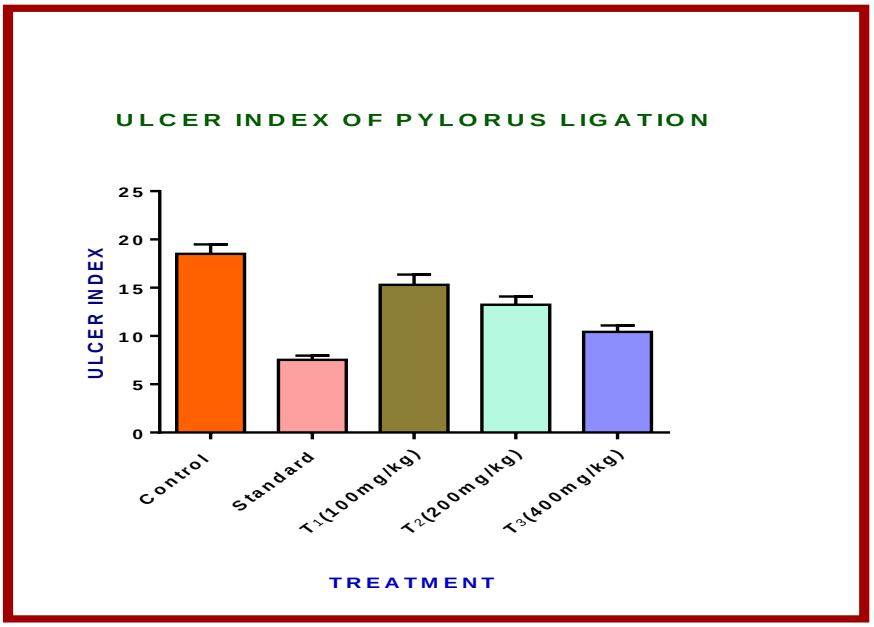
3.3 Evaluation of Anti-Ulcer Activity of 70% Hydro-Ethanolic Leaf Extract Of *Argemone mexicana* Linn.

3.3.1 Pylorus ligation model:

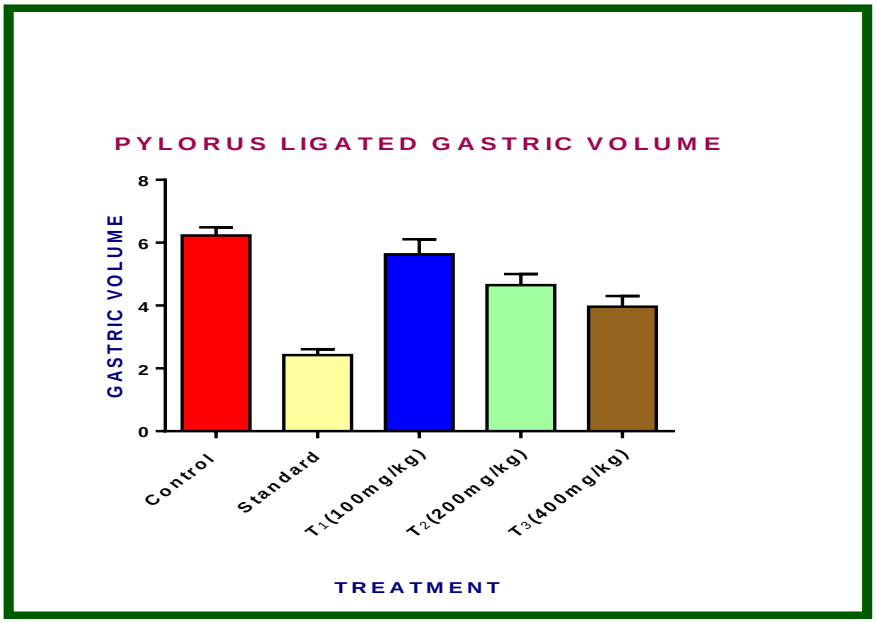
The 70%Hydro-ethanolic leaf extract of *Argemone mexicana* Linn. in the doses of 100, 200 and 400 mg/kg b.w. produced a reduction in the ulcer index, gastric volume, free acidity, total acidity and raised gastric pH significantly in comparison with control group. The Ranitidine treated group produced significant reduction in gastric ulcer and total acid output as compared to control group. The results of the present study indicate that 70%Hydro-ethanolic leaf extract of *Argemone mexicana* Linn. dose dependently reduced the total volume of gastric juice, free and total acidity of gastric secretion and has activity against gastric ulcers in rats. The control animals had ulcers and haemorrhagic streaks, whereas in animals administered with the 70%Hydro-ethanolic leaf extracts of *Argemone mexicana* Linn. there was significant reduction in ulcer index ($P < 0.001$). The results have been tabulated in Table 1 and represented in graph 1(a), 1(b), 1(c), 1(d), 1(e).

Table 1:Effect of 70% Hydro-Ethanolic Leaf Extract of *Argemone mexicana* Linn. in Pylorus Ligated Ulcer Model in Rats

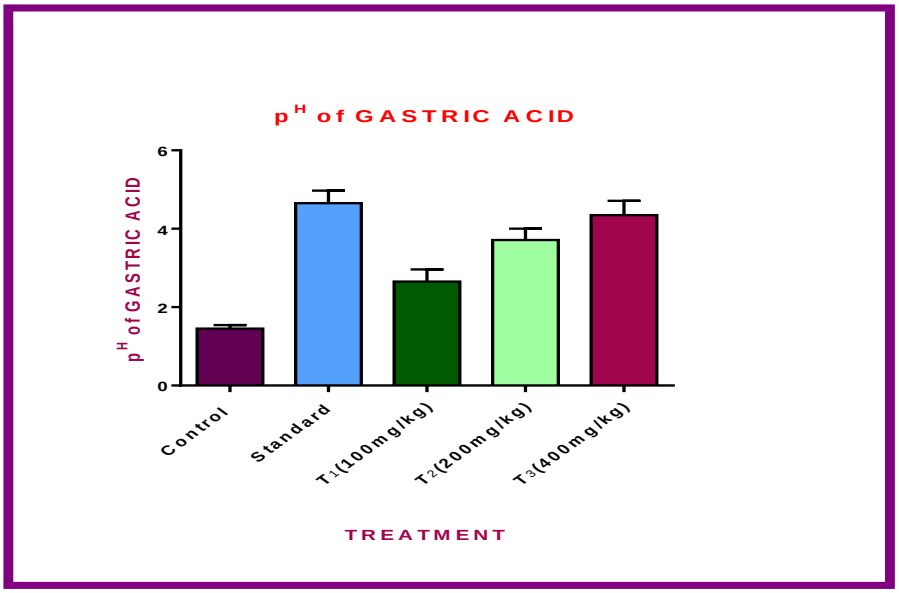
Treatment	Dose	Ulcer index [Mean ± SEM]	% Protection	Volume of gastric acid (ml) [Mean ± SEM]	PH [Mean ± SEM]	Free Acidity [Mean ± SEM]	Total Acidity [Mean ± SEM]
Control	(5ml/kg b.w) p.o	18.50±0.98	-	**6.23**±0.26	1.45±0.09	86.26±3.34	118.43±4.22
Ranitidine	(50mg/kg b.w) p.o	7.54±0.43***	59%	2.42±0.19***	4.65±0.32***	46.43±1.49***	34.50±2.18***
Argemone Mexicana(T1)	(100mg/kg)b.w p.o	15.31±1.05	17%	5.63±0.48	2.65±0.31	74.23±2.27	96.67±6.29
Argemone Mexicana(T2)	(200mg/kg)b.w p.o	13.23±0.87*	28%	4.65±0.35*	3.71±0.29*	63.17±2.23*	87.33±7.06*
Argemone Mexicana(T3)	(400mg/kg)b.w p.o	10.42±0.68**	43.6%	3.96±0.34**	4.35±0.36**	54.21±1.96**	65.52±3.48**



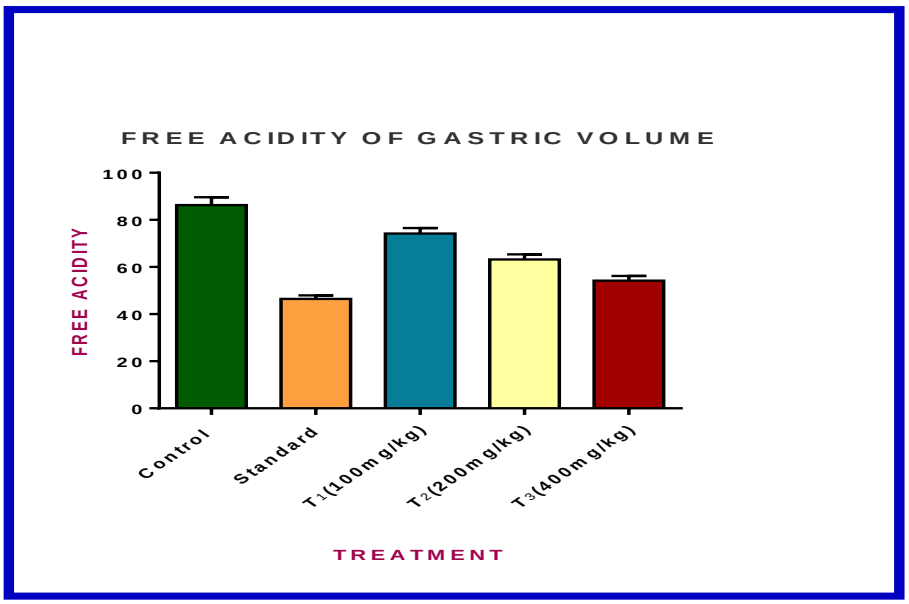
Graph 1(a): Effect of 70% hydro-ethanolic leaf extract of *Argemone mexicana* linn. on ulcer index in pylorus ligated ulcer model in rats



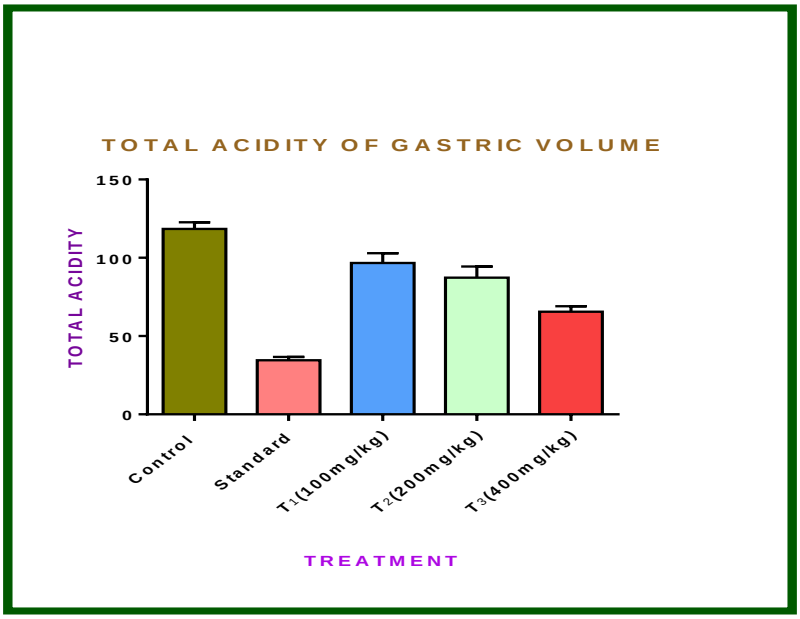
Graph 1(b): Effect of 70% hydro-ethanolic leaf extract of *Argemone mexicana* linn. on volume of gastric acid in pylorus ligated ulcer model in rats



Graph 1(c): Effect of 70% hydro-ethanolic extract leaf of *Argemone mexicana* linn. on pH of gastric acid in pylorus ligated ulcer model in rats



Graph 1(d): Effect of 70% hydro-ethanolic leaf extract of *Argemone mexicana* linn. on free acidity in pylorus ligated ulcer model in rats



Graph 1(e): Effect of 70% hydro-ethanolic leaf extract of *Argemone mexicana* linn. on total acidity in pylorus ligated ulcer model in rats

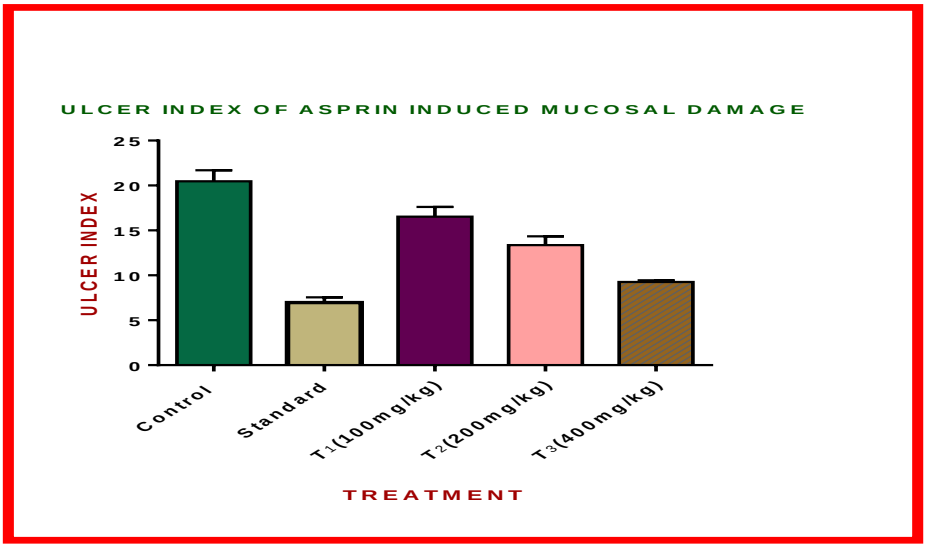
3.3.2 NSAIDs (Aspirin) Induced Gastric Ulcers in Rats:

Effect of 70% Hydro-Ethanolic Leaves Extract of *Argemone mexicana* on ulcer index in Aspirin Induced ulcer models in rats:

Ulcer index decreased significantly (***P<0.001) in Misoprostol treated group up to 6.97±0.59, compared to control group in which the value was 20.46±1.24 and the percentage protection was 66%. In groups treated with 70% Hydro-Ethanolic leaves extract of *Argemone mexicana* L., the values of ulcer index significantly reduced to 16.53±1.09, 13.36±0.98 and 9.26±0.18 at doses 100, 200 and 400 mg/kg b.w., respectively when compared to control group. The results were significant (**P<0.01) at a dose of 400 mg/kg b.w when compared to control group and the % protection was 54.7% as compare to 66% in Misoprostol treated group. The results have been tabulated in Table 2 and represented by graph 2.

Table 2:Effect of 70% Hydro-Ethanolic Leaf Extract of *Argemone mexicana* Linn. on Ulcer Index In Aspirin Induced Gastric Ulcers In Rats

Treatment	Dose	Ulcer index [Mean ± SEM]	% Protection
Control	(5ml/kg b.w) p.o	20.46±1.24	-
Misoprostol	(100µg/kg b.w) p.o	6.97±0.59***	66%
Argemone Mexicana(T1)	(100mg/kg)b.w p.o	16.53±1.09	19%
Argemone Mexicana(T2)	(200mg/kg)b.w p.o	13.36±0.98*	34.7%
Argemone Mexicana(T3)	(400mg/kg)b.w p.o	9.26±0.18**	54.7%



Graph 2: Effect of 70% hydro-ethanolic leaf extract of *Argemone mexicana* linn. on ulcer index in aspirin induced gastric ulcers in rats

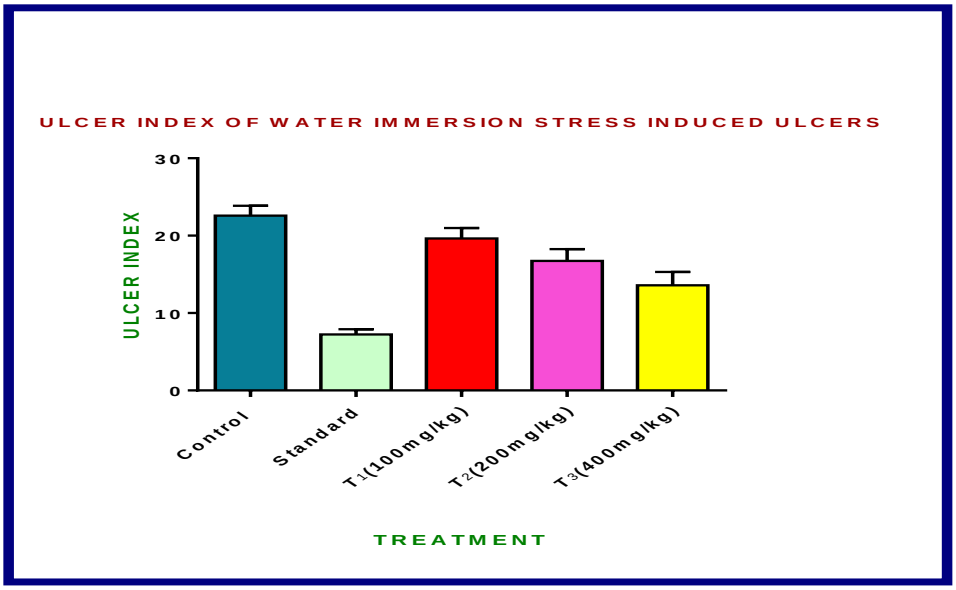
3.3.3 Water Immersion Stress Induced Ulcer in Rats

Effect of 70% Hydro-Ethanolic Leaves Extract of *Argemone mexicana* Linn. On ulcer index in Water Immersion Stress Induced Ulcer in Rats:

Ulcer index in Ranitidine treated group decreased significantly (***P<0.001) up to 7.23±0.68, compared to control group in which the values was 22.58±1.28 and the percentage protection was 68.6%. In groups treated with 70% Hydro-Ethanolic leaves extract of *Argemone mexicana* L., the values of ulcer index significantly reduced to 19.63±1.36 16.73±1.52 and 13.58±1.73 at dose of 100, 200 and 400 mg/ kg. b.w., respectively when compared to control group. The results were significant (**P<0.01) at a dose of 400 mg/kg b.w when compared to control group and the % protection was 39.9%. The results have been tabulated in table 3 and represented by graph 3.

Table 3: Effect of 70% Hydro-Ethanolic Leaf Extract of *Argemone mexicana* Linn. on Ulcer Index In Water Immersion Induced Stress Ulcers In Rats

Treatment	Dose	Ulcer index [Mean ± SEM]	% Protection
Control	(5ml/kg b.w) p.o	22.58±1.28	-
Ranitidine	(50mg/kg b.w) p.o	7.23±0.68***	68.6%
Argemone Mexicana(T1)	(100mg/kg)b.w p.o	19.63±1.36	13%
Argemone Mexicana(T2)	(200mg/kg)b.w p.o	16.73±1.52*	35%
Argemone Mexicana(T3)	(400mg/kg)b.w p.o	13.58±1.73**	39.9%



Graph 3: Effect of 70% hydro-ethanolic leaf extract of *Argemone mexicana* linn. on ulcer index in water immersion induced stress ulcers in rats

IV. DISCUSSION

The Anti-ulcer activity of 70% Hydro-Ethanolic leaves extract of *Argemone mexicana* L. was evaluated by pylorus ligation, Aspirin induced mucosal damage and water immersion stress induced ulcer models which operates by distinct mechanism of ulcerogenesis.

It is well known fact that gastric secretions are under vagal control. Vagal over activity appears to contribute to any stress ulcer formation. Various causes are responsible for the development of ulcers due to pylorus ligation model, such as increased metabolism of carbohydrates, increased synthesis of nucleic acids and also exhaustion of carbohydrates and other complementary mechanisms[15].

In the present study, upon pylorus ligation, there was a decrease in the volume of gastric acid after the administration of 70% Hydro-Ethanolic leaf extract of *Argemone mexicana* Linn. (100mg/kg b.w., 200mg/kg b.w. and 400mg/kg b.w.) when compared with that of control group. The decrease in the gastric acid was found to be dose-dependent.

In addition, the extract showed a significant increase in the $_{P}$H of the gastric acid at a dose of 400mg/kg b.w when compared to control group, in addition to this, there was also reduction observed in its free acidity, total acidity and ulcer index and maximum protection was obseerved after the treatment with the extract at a dose of 400mg/kg b.w, and an inference may be drawn that the extract may be having an Anti-ulcer activity.

In NSAIDs induced gastric ulcer model, the ulcers were induced in rats by the administration of Aspirin (200mg/kg b.w, p.o). There will be elimination of the prostaglandins from the stomachs, which may cause ulceration, as it is known that the prostaglandins have the major role in the gastric mucosa production. Hence, the elimination of prostaglandins reduces the protective mucosa secretion and increases acid secretion, thereby leading to ulceration[16].

In the present study, in gastric ulcer model induced by Aspirin (200mg/kg b.w p.o) in rats the values of ulcer index were reduced in the treated group (9.26±0.18) and there was a significant reduction in the ulcer index (**P<0.01) as compared with the control group (20.46±1.24), and the reduction in ulcer index was found to be dose-dependent.

The ulcers can also be induced by subjecting the animals to the stress; viz., water immersion stress induced ulcer model. The mechanism of inducing ulcer in this model can be explained as during stress, gastrointestinal peristalsis becomes disturbed and the gastrointestinal lining may become abraded, buckled or even broken. Once this happens, the gastric acid can erode the wall behind the lining. During stress there can be an increase in gastric acidity and this may ulcerate even a normal, intact mucinoid lining[17].

In the present study, the results in the water immersion stress induced ulcer model were significant and the ulcer index was seen to be reduced upon increasing the dose of (400mg/kg b.w. p.o.) in treated group (13.58± 1.73) and there was a significant reduction in ulcer index (**p<0.01) as compared to the control group (22.58±1.28).

Thus, the results obtained in the present investigation is suggestive that 70% Hydro- ethanolic leaf extract of *Argemone mexicana* Linn. is having anti-ulcer activity in rats which may be due to presence of flavonoids which has astringent property. It was mentioned that flavonoids have been reported to act in the gastrointestinal tract, having antispasmodic, anti-secretary, anti-diarrheal, antiulcer, and antioxidant properties. Flavonoids are among

the cytoprotective materials for which anti-ulcerogenic efficacy has been extensively confirmed. They protect the gastric mucosa against a variety of ulcerogenic agents via several mechanisms of action, mainly free-radical scavenging and antioxidant properties, increased mucus production, antisecretory action, and inhibition of the *Helicobacter pylori* growth. Tannins prevent ulcer development due to their protein precipitating and vasoconstricting effects. Their astringent action can help to precipitate microproteins on the ulcer site, thereby, forming an impervious layer over the lining, which hinders gastric ulcer in rats, as evidenced by the gut secretions, and protects the underlying mucosa from reduction in the ulcer scores[6].

Further qualitative studies are required for the phytochemistry which is responsible for the specific observed effects.

V. CONCLUSION

The effect of anti-ulcer activity of 70% Hydro- Ethanolic leaf extract of *Argemone mexicana* Linn. seems to be effective and significant at a dose of 400mg/kg b.w. The presence of flavonoids which have astringent property could be responsible for the anti-ulcer activity, and is more likely to be involved in the reaction with the proteins of the layer tissues and thereby showing the activity.

Having confirmed the anti-ulcer activity of leaves of *Argemone mexicana* Linn. on GIT, it deserves further studies to identify which exact chemical constituent of the 70% Hydro-Ethanolic leaf extract mediated the specific observed effects and investigate their mechanism, as also the isolation and characterization of active principles responsible for anti-ulcer activity.

Inspite of number of medicinal plants that have been shown to be effective against ulcer diseases in traditional medicine, the treatment of peptic ulcers is still a big challenge and development of new drugs is a necessity.

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