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Preclinical Investigation of a Polyherbal Formulation for Its Gastric Anti-Secretory, Anti-Ulcer by Pylorus-Ligated Model in Albino Rats

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ABSTRACT

Peptic ulcer is a condition where benign lesions of gastric or duodenal mucosa occur at a site where the mucosal epithelium is exposed to acid and pepsin, due to imbalance between offensive and defensive factors. Rumalaya-forte, the polyherbal formulation is clinically used as an anti-inflammatory and analgesic in the treatment of osteoarthritis, gout, frozen shoulder etc. As the individual constituents of Rumalaya-forte are reported to have antiulcer activity, the present study was undertaken to evaluate the antisecretory, antiulcer and free-radical scavenging properties of Rumalaya-forte in albino rats.

The gastric antiulcer activity of Rumalaya-forte was performed by using ulcerogenic models like pylorus-ligatedmodel. Rumalaya-forte was administered for 7th day and on 8th day, 30 minute prior to the induction of ulcers. The ulcer index and biochemical parameters were measured in pyloric-ligation model.

The results indicate that Rumalaya-forte decreases gastric acid secretion, pepsin activity and total protein level and increase in pH, and mucin content as compared to control in pylorus ligated models. Pretreatment with Rumalaya-forte showed significant ulcer protection against ulcer induced model as compared to control.

Key words: Antisecretory ,.Antiulcer ,Mucin, Pepsin, Rumalaya-forte

I. INTRODUCTION

Peptic ulcer is a condition where benign lesions of gastric or duodenal mucosa occur at a site where the mucosal epithelium is exposed to acid and pepsin. Gastric ulcers are caused due to imbalance between offensive and defensive factors of the gastric mucosa[1]. A number of factors such as stress, chemical agents (ethanol, tobacco etc.), bile salts, hyperosmolar NaCl, drugs (nonsteriodal anti-inflammatory agents), may lead the gastroduodenal ulcer causing damage of the mucosa by a complex biological process. The ulcer in the stomach or the duodenum seems to be an enigmatic interaction of several local changes and central nervous factors[2].

The regulation of mucosal microcirculation of gastric mucosa intimately involved in the maintenance of gastric integrity and endogenous nitric oxide (NO) has been established to have a role in this regulation. Reduced glutathione (GSH) is also important for mucosal integrity since depletion of GSH from the gastric mucosa by electrophilic compounds induces macroscopic mucosal ulceration[3].

A number of antiulcer drugs like antisecretory drugs – H_2 receptor antagonists, antimuscarinic agents, proton pump inhibitors, and mucosal protective agents– carbenoxolone sodium, sucralfate and prostaglandin analogues are available which are shown to have side effects and limitations[1].

Since herbal preparations have proved to be advantageous over the synthetic drugs, recent trends have shifted towards the use of polyherbal formulation for the treatment of peptic ulcer[1, 4] because polyherbal formulation inhibits acid secretion, formation of free radical and erosion of mucosa etc. by its individual ingredients or may be by its synergistic effects.

Rumalaya-forte is a polyherbal formulation. It contains number of medicinal herbs that have tested individually for their anti-ulcer activity. Rumalaya-forte was reported earlier for osteoarthritis, cervical and lumbar spondylosis, arthralgia, gout, frozen shoulder and sprain but not yet reported for its antiulcer activity. Therefore the present attempt has been made to investigate gastric anti-secretory, anti-ulcer and free radical scavenging properties of Rumalaya-forte. Since it can be used to treat the patient for the above

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condition and relieve the patient from side effects of NSAID which is mainly associated with gastric ulcers after chronic administration.

METHODOLOGY- PHARMACOLOGICAL SCREENING

PYLORIC LIGATED ULCER MODEL

It is a simple and reliable method for production of gastric ulceration in the rats based on ligation of the pylorus[5]. The ulceration is caused by accumulation of acidic gastric juice in the stomach and by this method several parameters can be estimated

Materials and method

Albino Wister rats of either sex weighing between 150 to 200gs were divided into three groups of 6 animals each.

Group I : Control

Group II: Ranitidine 30 mg/kg body weight, oral.

Group III: Rumalaya-forte 161.5mg/kg body weight[6].

The animals were fasted in individual fasting cages for 24 h. Care being taken to avoid coprophagy. Control vehicle, Rumalaya-Forte and standard drug Ranitidine were administered by oral route. The test animals were treated with for 7th day and on 8thday in 24 hr fasted rats the pyloric ligation was carried out 30 min after the drug administration in each group of animals. Under light ether anesthesia, the abdomen was opened and the pylorus was ligated. The abdomen was then sutured. After 4hrof pyloric ligation, the animals were sacrificed with excess of anesthetic ether, and the stomach was isolated. Gastric juice was collected and then centrifuged. The supernatant was used for measuring the volume of gastric juice, pH, total acidity, pepsin activity and total protein content. Ulcer index was determined by opening the glandular portion of the stomach along the greater curvature, and the severity of hemorrhagic erosions in the acid secreting mucosa was assessed on a scale of 0 to 3[7].

Mean ulcer score for each animal is expressed as ulcer index. The percentage protection was calculated using the formula –

Percentage of ulcer protection = 100 – Ut/Uc x 100

Where, Ut = ulcer index of the treated group

Uc = ulcer index of the control group

REAGENTS FOR BIOCHEMICAL ESTIMATION OF FREE AND TOTAL ACIDITY, TOTAL PROTEIN, MUCIN AND PEPSIN IN GASTRIC JUICE

REAGENTS FOR ESTIMAION OF FREE AND TOTAL ACIDITY

Freshly prepared 0.01 N Oxalic acid solution, 0.01 N sodium hydroxide, Topfer's reagent, 1% phenolphthalein, 50% absolute ethanol.

REAGENTS FOR ESTIMATION OF TOTAL PROTEIN

Sodium carbonate ,0.1 N sodium hydroxide solution, aqueous copper sulphate , Phenol reagent (Folin and Ciocalteu's reagent), Bovine albumin as standard.

REAGENTS FOR ESTIMATION OF MUCIN

Alcian blue 8GX,Sucrose solution (0.25M) ,Sodium acetate (0.05M) , Magnesium chloride (0.5 M) , Diethyl ether ,Dilute hydrochloric acid.

REAGENTS FOR ESTIMATION OF PEPSIN

Trichloro acetic acid (TCA) ,Sodium hydroxide , Hydrochloric acid(pH 2.1) , Phenol reagent (FolinCiocalteu's reagent) , Standard Phenol solution ,1% bovine albumin with hydrochloric acid at pH 2.1 was used.

METHODS FOR BIOCHEMICAL ESTIMATIOM OF FREE AND TOTAL ACIDITY, TOTAL PROTEIN, MUCIN AND PEPSIN IN GASTRIC JUICE

COLLECTION OF GASTRIC JUICE

Gastric juice was collected from pylorus ligated rats. The gastric thus collected was centrifuged and the volume of gastric juice as well as pH of gastric juice was noted. The gastric was subjected to biochemical estimations as follows:

DETERMINATION OF FREE AND TOTAL ACIDITY[7]

One ml of gastric juice was pipetted into a 100ml conical flask, added 2 or 3 drops of Topfer's reagent and titrated with 0.01N Sodium hydroxide until all traces of red colour disappears and the colour of the solution was yellowish orange. The volume of alkali added was noted. This volume corresponds to free acidity. Then 2 or3 drops of phenolphthalein solution were added and titration was continued until a definite red tinge appears. Again the total volume of alkali added was noted. The volume corresponds to total acidity. Acidity was calculated by using the following formula:

$$\text{Acidity} = \frac{\text{Vol of NaOH} \times \text{N of NaOH} \times 100}{0.1} \text{ meq/L/100g}$$

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Statistical significance was determined by using ANOVA followed by Dunnet's't' test.

GASTRIC MUCOSAL DEFENCIVE STUDY

Estimation of total protein[8]

The dissolved proteins in gastric juice was estimated in the alcoholic precipitate obtained by adding 90% alcohol with gastric juice in 9:1 ratio respectively. Then 0.1ml of alcoholic precipitate of gastric juice was dissolved in 1ml of 0.1N NaOH and from this 0.05 ml was taken in another test tube, to this 4 ml of alkaline mixture was added and kept for 10 min. then 0.4ml of phenol reagent was added and again 10 min was allowed for colour development. Reading was taken against blank prepared with distilled water at 610 nanometer in Hitachi 15-20 spectrophotometer. The protein content was calculated from the standard curve prepared with bovine albumin and has been expressed in terms of mcg/ml of gastric juice.

Statistical analysis carried out by using ANOVA followed by Dunnet's't' test.

Estimation of mucin[9]

After the collection of gastric juice, the glandular portions excised and opened down the lesser curvature. The everted stomachs were soaked for 2h in0.1 % alcian blue 8GX dissolved in 0.16M sucrose buffered with 0.05M sodium acetate adjusted to a pH with HCl. Uncomplexed dye was removed by 2 successive washes of 15 and 45 min in 0.25M sucrose solution. Dye complex with mucus was diluted by immersion in 10ml aliquots of 0.5M magnesium chloride for 2hr. The resulting blue solutions were shaken briefly with equal volume of diethyl ether and optical density of the aqueous phase was measured at 605 nm in Hitachi 15-20 spectrophotometer. The mucin content of the sample was determined from the standard curve of mucin has been expressed in mcg/g of wet gland tissue.

Estimation of pepsin[10]

From each determination place 4 tubes (1) and (2) containing 5 ml of substrate, (3) and (4) containing 10 ml of TCA in the water bath at 37 °C. The gastric juice was mixed with equal volume of HCl at pH 2.1, warmed to 37 °C added 1 ml of mixture to each of tubes 1 and 4. Incubated for 15 min at the end of which time mix tube 1 with tube 3. Allowed to stand both for about 4 min. 1+3 gives test and 2+4 gives blank. Filtered, 25 to 30 min after the beginning of the filtration, 2 ml of filtrate was pipetted into 10ml of NaOH. Mixed by gentle rotation, then 1 ml of phenol reagent was added and again mixed by gentle rotation. After 30 min the intensity of the color was measured at 680 nm in Hitachi 15-20 spectrophotometer. The difference between test and blank gives the measures of peptic activity. As standard, mixed 2 ml of freshly prepared phenol solution containing 50mcg/ml with 10 ml NaOH and 1 ml of phenol reagent was added and was measured at 680 nm after 5 to 10 min.

II. RESULTS

Results of pyloric ligation ulcer model

When compared with Ranitidine, Rumalaya-forte showed less effect on pylorus ligated ulcer model. Rumalaya- forte showed less antacid and anti-secretory activity than that of Ranitidine. There is significant increase in mucin content (553.1±84.31) in Rumalaya-forte treated group when compared with control (287.3±28.75) and Ranitidine (533.6±26.31). Rumalaya-forte treated group showed significant reduction in protein (247.5±24.10) as compared to control (459.3±26.11) and pepsin content (52.20±2.383) as compared to control (84.68±3.083) .

Table 1. Ulcer index of Control rats,Ranitidine treated rats,7 days treatedRumalaya-forte rats (4 hrs. pylorus ligation) and Rumalaya-forte Versus Ranitidine (ANOVA) of pyloric ligation

Sl. No.	Body weight					Ulcer index			% Ulcer protection
	C	**R**	**R-F**	**C**	**R**	**R-F**	**C**	**R**	**R-F**

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1 2 3 4 5 6	150 175 150 150 190 160	190 180 180 175 150 150	150 180 180 200 190 150	15.5 11.5 12 13.5 10.5 12.5	2.5 3 4 2 0.5 3	3.5 5 4.5 5.5 3.5 4	0%	80.13%	65.59%
Mean ± SE				12.58 ± 0.7120	2.50 ± 0.4830	4.333 ± 0.3333			
F, df value				101.7,(2/17)					
P value				<0.001					

***C=Control, R=Ranitidine, R-F= Rumalaya-forte**

PYLORIC LIGATION MODEL

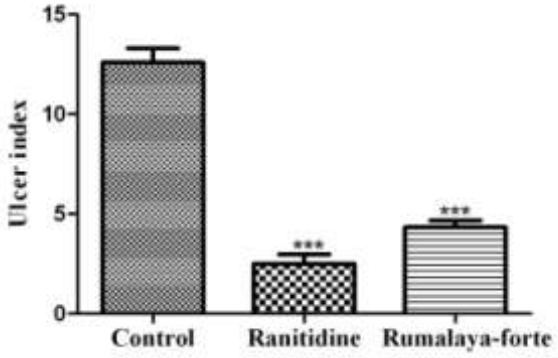

Fig.1.All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

% ULCER PROCTECTION

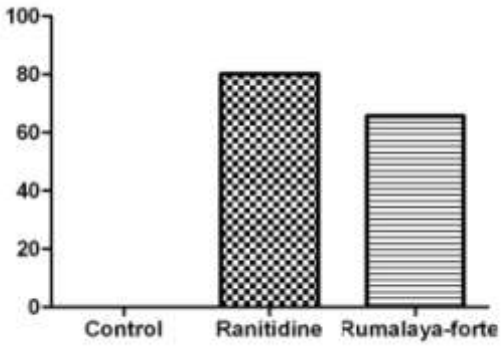

Fig.2

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Antacid activity

Table 2. (Acid volume, pH, free acidity, total acidity of Control rats, Ranitidine treated and Rumalaya-forte treated rats) and Antacid activity of Rumalaya-forte when compared with Ranitidine

Sl. No.	Body weight			Vol. of gastric juice in ml/100g body weight			pH			Free acidity meq/l/100g			Total acidity meq/l/100g		
	C	R	R-F	C	R	R-F	C	R	R-F	C	R	R-F	C	R	R-F
1	150	190	150	4.05	1.75	2.3	2.5	4.1	4.0	39	20	26	86	47	55
2	175	180	180	4.10	1.95	2.5	2.3	4.2	3.6	45	18	24	87	45	52
3	150	180	180	3.80	2.10	2.4	2.1	4.5	3.5	41	17	29	91	48	58
4	150	175	200	3.50	2.00	2.3	2.5	4.2	3.4	43	18	23	94	43	56
5	190	150	190	3.40	1.85	2.5	2.2	4.1	3.7	38	19	28	88	41	53
6	160	150	150	3.65	2.00	2.4	2.5	4.3	3.8	44	22	30	92	39	57
Mean ± SE				3.767± 0.1078	1.942 ±0.05 06	2.400 ±0.03 65	2.350 ±0.07 18	4.23 3±0 .061 1	3.66 7±0 .088 1	41.6 7±1 .145	19.0 0±0 .730 3	26.6 7±1 .145	89.6 7±1 .282	43.8 3±1 .424	55.1 7±0 .945 8
F, Df				174.3, 2/17			167.5, 2/17			126.4, 2/17			374.4, 2/17		
P				<0.0001			<0.0001			<0.0001			<0.0001		

***C=Control, R=Ranitidine, R-F= Rumalaya-forte**

VOLUME OF GASTRIC ACID

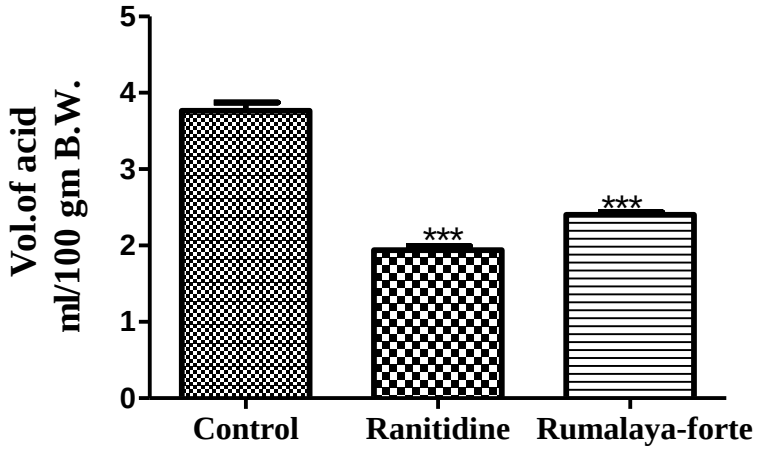

Fig.3. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

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pH OF GASTRIC JUICE

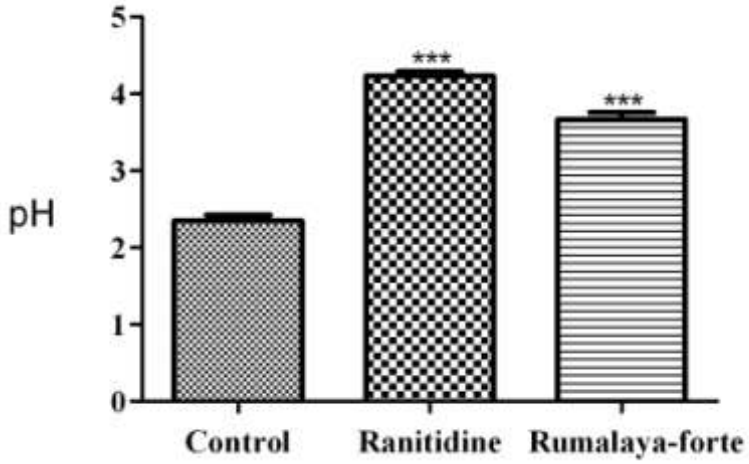

Fig.4. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

FREE ACIDITY

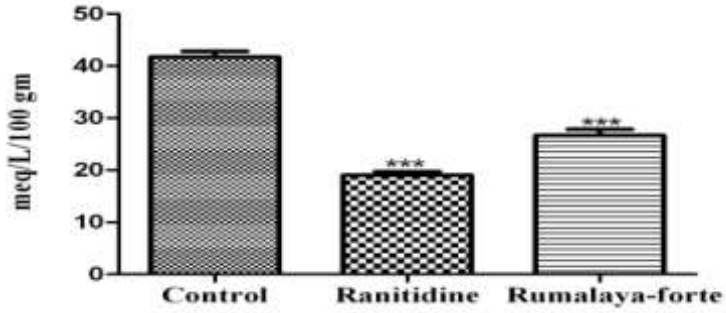

Fig.5. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

TOTAL ACIDITY

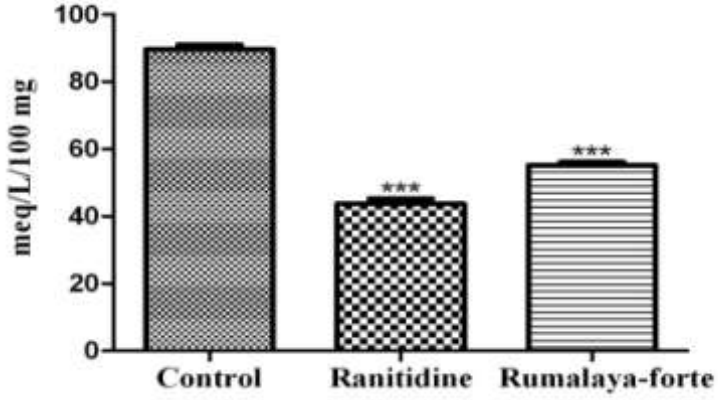

Fig.6. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

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Table 3. Estimation of mucin, protein and pepsin activity of Control/Ranitidine treated/ Rumalay-forte treated and Comparative study of mucin, protein and pepsin activity of Rumalaya-forte treated with Ranitidine treated.

Sl. No.	Body weight			Mucin content (mcg/g of wet gland)			Protein content (mcg/ml)			Pepsin activity (µmol/ml)		
	C	R	R-F	C	R	R-F	C	Ran	C	C	R	R-F
1	150	190	150	301.88	438.27	847.22	417.00	228.22	173.36	81.34	39.52	57.23
2	175	180	180	199.65	496.45	574.07	561.04	209.28	290.61	76.16	41.63	48.49
3	150	180	180	275.23	601.22	200.00	450.17	169.14	337.09	86.62	48.36	44.23
4	150	175	200	231.74	591.64	591.36	510.12	201.57	223.45	77.85	45.84	59.13
5	190	150	190	314.43	502.94	544.74	425.49	175.63	209.37	90.72	50.14	55.21
6	160	150	150	401.04	571.27	561.48	392.17	221.92	251.23	95.38	56.73	48.93
Mean ± SE				287.3± 28.75	533.6±26 .31	553.1±8 4.31	459.3±2 6.11	201.92± 9.842	247.5±24. 10	84.68± 3.083	47.04±2 .533	52.20±2. 383
F, df				7.634,(2/17)			41.84,(2/17)			57.83,(2/17)		
P value				<0.005			<0.0001			<0.0001		

***C=Control, R=Ranitidine, R-F= Rumalaya-forte**

MUCIN CONTENT

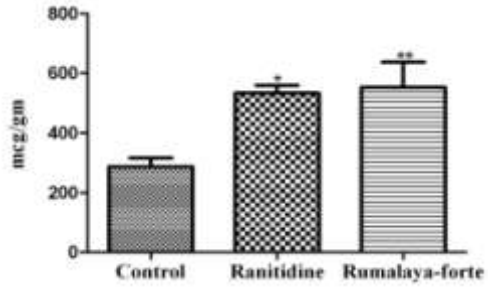

Fig.7. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

TOTAL PROTEIN

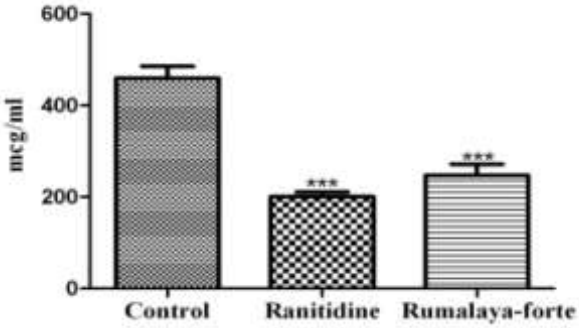

Fig.8. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**

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PEPSIN ACTIVITY

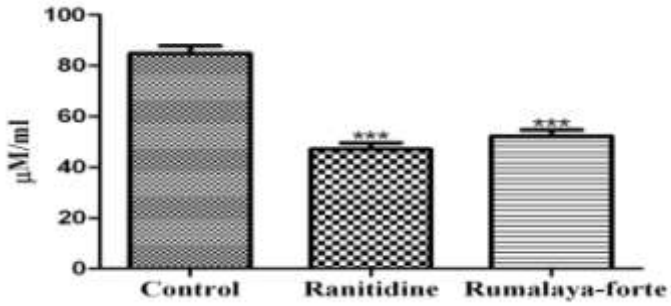
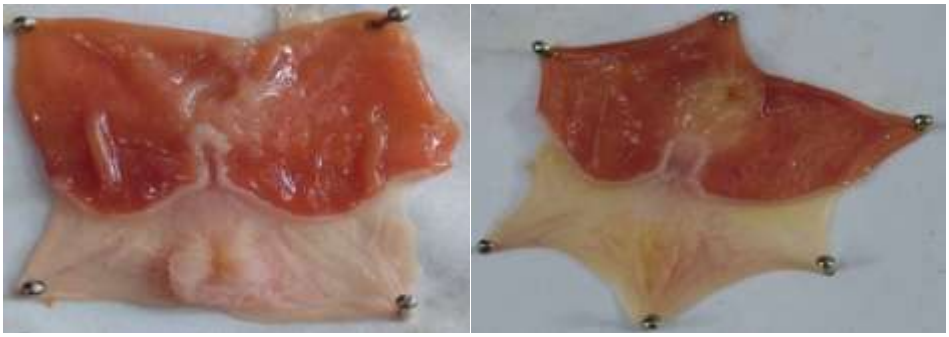
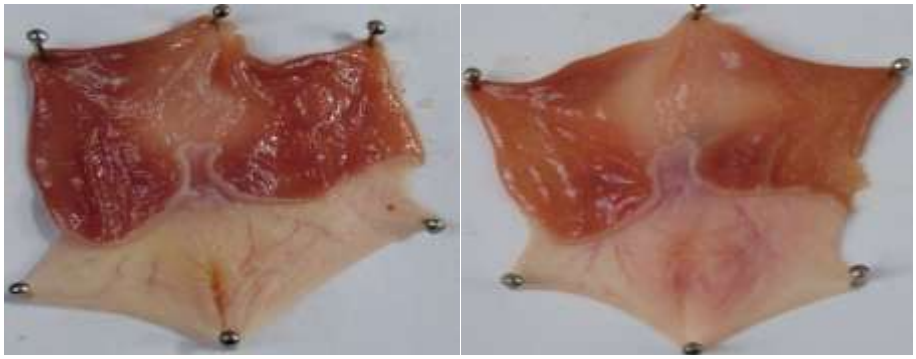


Fig.9. All values are expressed as Mean ± S.E.M.
***p<0.05, **p<0.01, ***p<0.001, when compared to control.**



Normal **Control**



Ranitidine **Rumalaya-forte**

Fig 10. Photographs of rat stomach in pyloric ligation induced ulcer models

III. DISCUSSION

PYLORIC LIGATION INDUCED ULCER MODEL[29][30][31][32][33][34][35][36]

The results in pyloric ligation model showed significant reduction in basal gastric secretion and inhibition of ulcers by Rumalaya-forte. This suggest that the antiulcer activity of Rumalaya-forte on gastric mucosa may be due to the reduction of gastric secretion through one or more of the possible mechanisms.Moreover, gastric acid is an important factor for the genesis of ulceration in pyloric ligation ulcer in rats. Gastric acid secretion is regulated by many factors including anxiety, vagal activity, cholinergic, histaminergic and gastrinergic neurotransmissions, the activities of various post-synaptic receptors and the proton pump. It is therefore, difficult to elucidate the relationship between the mechanisms of inhibition of gastric acid by Rumalaya-forte. In Shay-ligated rats, gastric juice is accumulated in the stomach which contains mainly HCl and pepsin which are the most important factors for degeneration of gastric mucosa and formation of ulcers. In this experiment we observed that

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Rumalaya-forte has reduced the volume of acid as well as increase the gastric pH. The reduced severity of ulcers in this model could be due to its effect in reducing volume and acidity of gastric secretion. Suppressants of gastric acid secretion are known to increase the healing of both human and experimental gastric ulcers[81].

The current data clearly demonstrated that Rumalaya-forte inhibited the aggressive factor, gastric acid secretion. The anti-ulcerogenic effect of the Rumalaya-forte may be related to its antisecretory action since acid is a major factor in the development of peptic ulcer. However, certain anti-ulcer drugs increase the amount of gastric mucus secretion in gastric mucosa[82, 83].This mucus consists of mucin-type glycoproteins, which can be detected by amounts of alcian blue binding.Rumalaya-forte increased the alcian blue binding to mucosa. The increase in bound alcian blue suggested protective effect of orally administered Rumalaya-forte. This may be via the formation of protecting complexes between Rumalaya-forte and mucus, which can act as a barrier against several agents, introduced to the stomach.The possible mechanism of gastric mucosal protection by orally administered Rumalaya-forte may be partly due to reinforcement of resistance of the mucosal barrier by a protective coating or may have increased the formation of mucoproteins. In addition, its antisecretory activity and direct cytoprotective action cannot be excluded.

Rumalaya-forte has shown increased pH and decreased total acidity of gastric fluid. The antiulcer effect was also supported by the decreases in the aggressive factors like pepsin and an increase in defensive factors like mucin. The decrease in the protein content of gastric juice by Rumalaya –forte suggests the decrease of leakage of plasma proteins into gastric juice. This further suggests the increase in glycoprotein content of the gastric mucosa and that acts as a coating as well as protective barrier on the mucosa.

IV. CONCLUSION

The results in pyloric ligation model showed significant decrease in ulcer index, acid volume, pepsin, total and free acidity and increase in pH and mucin content so Rumalaya-forte is used as an anti-ulcer agent.

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