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PHARMACOLOGICAL SCREENING OF PEPGARD SYRUP BY ANTI-OXIDANT AND ANTI-ULCER ACTIVITY

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ABSTRACT

Background: Pepgard syrup is a proprietary Ayurvedic poly-herbal formulation widely used in clinical practice as Antacid for treating Heartburn, dyspepsia, Gastroesophageal reflux (GERD) and Drug-induced gastritis. There is conflicting reports regarding its anti-ulcer and ulcerogenic potential. **Aims and Objectives:** The study is with the aim of determining the gastoprotective effect of Pepgard syrup on aspirin-induced gastric ulcer in rats. **Materials and Methods:** Wistar Albino rats strains were used for the study. Aspirin was purchased from Sigma Labs, Mumbai. Anti-ulcer effect was studied in rats after inducing mucosal damage by aspirin. **Results:** It was found that **e**xtract of Pepgard syrup exhibited significant protection against aspirin-induced ulcer at dose levels of 100 mg/kg body weight. There is a dose-dependent increase in the ulcer protective action of the extract. **Conclusion**: The present study of Pepgard syrup revealed its anti-ulcer and Anti-oxidant activity.

KEYWORDS: Pepgard syrup, Anti-ulcer; Aspirin Ulcer Index, Anti-oxidant.

INTRODUCTION

Gastric ulcer is an important health problem affecting a large number of populations worldwide. In spite of extensive research, it still remains as an important cause of morbidity. It is a major target for devising newer therapeutic strategies due to its prevalence and complications. Peptic ulcer can be considered as a multifactorial disease. Factors such as increased stress, impaired mucosal resistance, genetic factors, infection with *Helicobacter pylori*, and anti-inflammatory drugs including nonsteroidal anti-inflammatory drugs (NSAID's) can damage gastric mucosa. Anti-inflammatory drugs including NSAID's are an

important proven cause for gastric ulcer, ulcer perforation, gastric, and duodenal bleeding and in ulcer death.[1] Highly selective COX-2 inhibitors were a breakthrough discovery with less incidence of gastric mucosal damage, but soon retracted many of them due to serious cardiovascular adverse events. Ulcers are lesions on the mucous membrane of the stomach or duodenum characterized by superficial loss of tissues with loss of mucosal integrity. There is a local defect with active inflammation. Peptic ulcer is considered as one of most common disease in man leading to human sufferings affecting nearly 5% of the global population. Since in majority of cases it is aggravated due to pepsin and hydrochloric acid, it is termed as peptic ulcer. Usual course of the peptic ulcer is characterized by many cycles of healing, relapses and occasional complications.[3] Imbalances between damaging and protective factors are the major contributing factor for the pathophysiology of peptic ulcer. Pepsin, acid, *H. pylori* infection, bile acids, impaired mobility, NSAID's, corticosteroids, nicotine, etc., are some of the damaging factors and protective factors include prostaglandins, mucus, epidermal growth factors, intact microcirculation, epithelial renewal, alkaline tide, nitrous oxide, phospholipids, and bicarbonate. Increased gastrin secretion and acid output with defective gastric emptying mechanism predispose to gastric ulcer. Lower postprandial pepsin secretion, raised serum PG2 and low PGI/PG2 ratios are considered as risk factors for developing a peptic ulcer.[2]

In hypo motility at antropyloric region, there is increased chance for reflex of duodenal contents into stomach which can cause chronic inflammation and ulceration. Reactive oxygen species (ROS), refluxed bile acids, cytokines such as tumour necrosis factors and exogenous agents such as *H. pylori*, NSAID's, alcohol abuse, emotional stress, and smoking can damage gastric mucosa leading to a gastric ulcer.[4] Mucous bicarbonate barrier, prostaglandins mucosal blood flow, cell renewal and migration, and antioxidants, growth factors are all act as gastro protective factors preventing the gastric mucosal injury. Gastric mucosal barrier will block the back diffusion of (H+). NSAID's can disrupt this barrier, and H+ can damage it resulting in mucosal injury.[3,4] The first line of defence is a mucus-bicarbonate layer, which serves as a physicochemical barrier to multiple molecules including hydrogen ions. Surface epithelial cells provide the next line of defence through several factors, including mucus production and epithelial cell ionic transporters that maintain intracellular pH and bicarbonate production, and intracellular tight junctions. There are certain mediators, which play an important role in cytoprotection. Epithelial cells in the surface produce bicarbonate, which diffuses up from the mucosa to accumulate beneath the mucous layer, creating a thin layer of

alkalinity between the mucus and epithelial surface.[3] Epithelial cells also secrete mucus, which forms a gel that covers the mucosal surface and physically protects the mucosa.

Pepgard syrup is a proprietary Ayurvedic poly-herbal formulation widely used in clinical practice as Antacid for treating Heartburn, Non-ulcer dyspepsia, Gastroesophageal reflux (GERD) and Drug-induced gastritis. It contains many potential drugs, derived from plant sources; therefore, it was thought worth to undertake a pharmacological study of compound formulation in the experimental protocol to substantiate the safety claims made on it. Which considering the morbidity caused by peptic ulcer disease and dyspepsia over the world, cheap and easily available treatments with less adverse effects will always be beneficial, especially for the people in less developed and developing countries.

MATERIALS AND METHODS

Drugs and chemicals

Pepgard syrup is a proprietary Ayurvedic poly-herbal formulation of Vital Care Pvt. Ltd., Vadodara. Name of ingredients, Latin name, family, part used and quantity of the drug are given in Table 1. For the preparation of Pepgard syrup, herbal ingredients were subjected to preparation of decoction as per classical reference. Ranitidine was used as a standard drug (Kopran Pharma Ltd., Mumbai, India). All chemicals used for the study are purchased from SD-fine chemicals; India and all other reagent used were of analytical grade.

Table 1. Ingredients of Pepgard Syrup

Sr. No	Common name	Botanical name	Part used	Quantity
1	Yashtimadhu	*Glycerrhiza Glabra*	Root	500 mg.
2	Shatavari	*Asparagus racemosus*	Root	100 mg.
3	Sajikshar	*Astoneman indicum*	whole	60 mg.
4	Amla	*Emblica officinale*	Fruit	50 mg.
5	Brahmi	*Centella asiatica*	Whole plant	50 mg.
6	Trivrit	*Ipomoea turpethum*	Root	40 mg.
7	Lavanga	*Syzygium aromaticum*	flower buds	25 mg.
8	Pitpapara	*Fumaria officinalis*	Whole plant	20 mg.
9	Dhania	*Coriandrum sativum*	Fruit	20 mg.
10	Syrup Base	--	-	Q.s

Dose calculation

The dose of the test formulations was calculated by extrapolating the human dose, based on the body surface area ratio by referring to the standard table of Paget and Barnes.[5] The test drug was administered orally by oral feeding cannula.

***In vitro* antioxidant activity assay**

DPPH radical scavenging activity

The methodology described by Gulcin[6] was used with slight modifications in order to assess the DPPH free radical scavenging capacity of Extract. Product extract and standard ascorbic acid solution (0.1 ml) of different concentrations viz. 10, 20, 40, 60, 80, 100µg/ml was added to 3 ml of a 0.004% methanol solution of DPPH. An equal amount of methanol and DPPH served as control. After 30 minutes incubation in the dark, absorbance was recorded at 517 nm, and the percentage inhibition activity was calculated from [(A0-A1)/A0] ×100, where A is the absorbance of the control, and A1 is the absorbance of the extract/standard. The antioxidant activity of the extract was expressed as IC50. The IC50 value was defined as the concentration (in µg/ml) of extracts that inhibits the formation of DPPH radicals by 50%. All the tests were performed in triplicate and the graph was plotted with the average of three observations.

Scavenging of Hydrogen peroxide

A solution of hydrogen peroxide (20Mm) was prepared in phosphate buffer saline (pH 7.4), different concentrations of product extract and standard ascorbic acid solution viz. 10, 20, 40, 60, 80, 100 µg/ml in methanol (1ml) where added to hydrogen peroxide solution (2 ml). Absorbance of hydrogen peroxide at 230 nm was determined after 10 minutes against a blank solution containing phosphate buffer without hydrogen peroxide.[7] For each concentration, a separate blank sample was used for back ground subtraction. The percentage inhibition activity was calculated from [(A0-A1)/A0] x 100, where A0 is the absorbance of the control and A1 is the absorbance of extract/standard. The antioxidant activity of the extract was expressed as IC50. All the tests were performed in triplicate and the graph was plotted with the average of three observations.

Animals

Wistar albino rats weighing 150-200 g were divided into six groups each consisting of six rats was used for the experiments. The animals were obtained from the animal house attached to B.M.C.P.E.R, Modasa, Gujarat. The animals were exposed to 12 h light and 12 h dark cycle with the relative humidity of 30%–70% and the ambient temperature was 25°C ± 01°C. All animals were kept in same environmental conditions. Animals had free access to standard pellet diet and purified drinking water *ad libitium*. The experimental protocols were approved

by the Institutional Animal Ethics Committee in accordance with the guideline formulated by Committee for the Purpose of Control and Supervision on Experiments on Animals, India.

Animal Treatment protocol for Anti-ulcer activity

The experimental animals were divided into six group, six animals in each group and drug were given in following order: Thirty six albino rats were taken. They were divided into six groups of six rats each. All the rats were starved for 24h. After the fasting period, aspirin (100mg/kg, p.o.) was given. Group 1 served as the Control only receive vehicle as 2% acacia solution. Group 2 served as the Disease Control receives only aspirin (100 mg/kg, p.o.). Group 3 served as the standard as Ranitidine (100 mg/kg) + Aspirin (100 mg/kg) p.o. Group 4, 5 and 6 were treated with Pepgard Syrup at the dose level of 1,2,4 ml/kg body wt. Respectively.

Antiulcer activity

Albino rats were starved for 36 h having access to drinking water ad libitum. During this time they were housed in single cages with raised bottoms of wide wire mesh to avoid cannibalism and coprophagy. Test drug and other compounds were given orally 30 min before aspirin administration in the following manner. Aspirin dissolved in water was administered orally in a dose of 500 mg/kg body weight to all animals.[8],[9] 4 h later, the animals were sacrificed by giving heavy dose of ether. Stomach was removed and opened along the greater curvature. Mucosa was examined for total number of ulcers in each stomach and for their severity. Histopathological study was also done. Severity of each ulcer was recorded in the following manner. 0-No ulcer, 0.5-Red coloration, 1-Spot ulcer, 1.5-Hemaorrhagic streaks, 2-ulcer >3 mm < 5mm, 3-Ulcers > 5mm Histological changes limited to superficial layers of mucosa. Percentage protection=100-$u_{t/}$ u_cx100. Mean ulcer score for each animal is expressed as ulcer index. The percentage protection is calculated by using the formula. Where, u_t=Ulcer index of treated group. u_c=Ulcer index of control group

Statistical Analysis

Results are presented as Mean±SEM of six animals. Statistical differences between the means of the various groups were evaluated using one-way analysis of variance (ANOVA) followed by Dunnett test using graph pad prism software. The significance difference if any among the groups at $p \leq 0.05$ was considered statistically significant.

RESULTS AND OBSERVATION

Antioxidant Activity of 'Pepgard Syrup'

Antioxidant activity of Pepgard syrup was carried out using DPPH and Hydrogen peroxide model comparing with ascorbic acid as standard antioxidant. Results are given in Table. 2 And graphical presentation is given in Fig. i & ii.

Table 2: Antioxidant Activity of 'Pepgard Syrup'

No.	Antioxidant Model	IC_{50} value Alcohol extract	IC_{50} value Ascorbic acid
1	DPPH Method	83.857	42.5
2	Hydrogen peroxide method	86.842	57.827

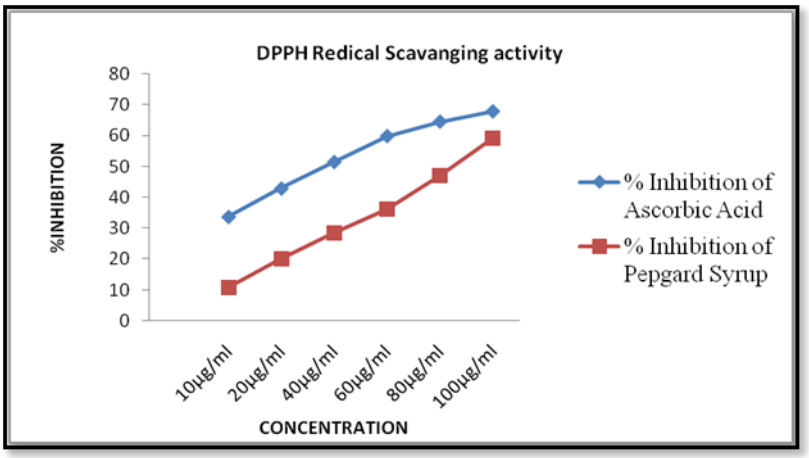


Fig. i

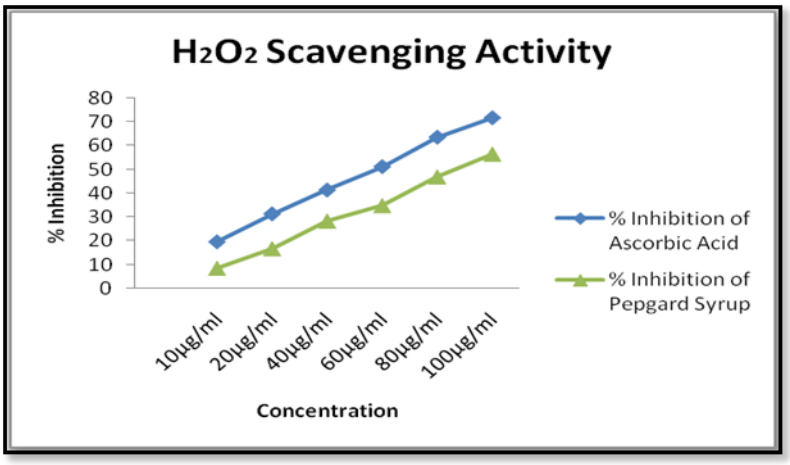


Fig. ii

There was a significant reduction in the concentration of DPPH and H_2O_2 radicals due to the scavenging ability by increasing the dose of alcohol extract of Pepgard syrup and Ascorbic acid, as a reference standard. Maximum inhibition of DPPH and H_2O_2 radicals scavenging

ability with 100µg/ml of alcoholic extract of Pepgard syrup and Ascorbic acid was exhibited 59.259% and 67.836% in DPPH assay and 56.39% and 71.78% in H_2O_2 assay respectively. The IC_{50} values were 42.5µg/ml and 83.857µg/ml in DPPH radical scavenging assay and 57.827 µg/ml and 86.842µg/ml H_2O_2 radical scavenging assay for Ascorbic acid and alcohol extract of Pepgard syrup respectively.

Anti-ulcer activity of Pepgard syrup by Aspirin induced ulcers model.

Normal animal had shown 0.333 ulcer index, aspirin induced; disease control had elevated ulcer index 4.0, standard (ranitidine) reduced ulcer index to 0.416±0.250. Pepgard syrup also inhibited ulcer in a dose of 1ml showing ulcer index 2.75±0.822, 2 ml ulcer index 21.58±0.343 and 4 ml ulcer index 2 0.833±0.519. Result indicated that Pepgard syrup exhibited antiulcer activity in a dose dependent manner. The photographs of open stomach of each group are given in Fig. No.iii, Histopathological microphotographs are given in Fig. No. iv and the results are summarized in Table No.3 with graphically presentation in Fig. No.v

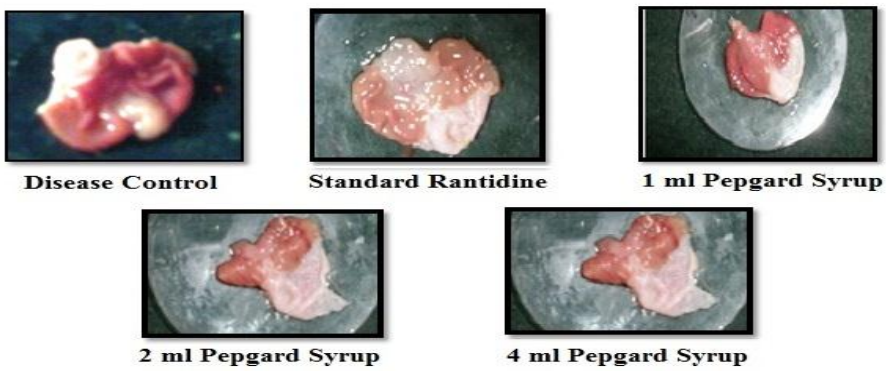
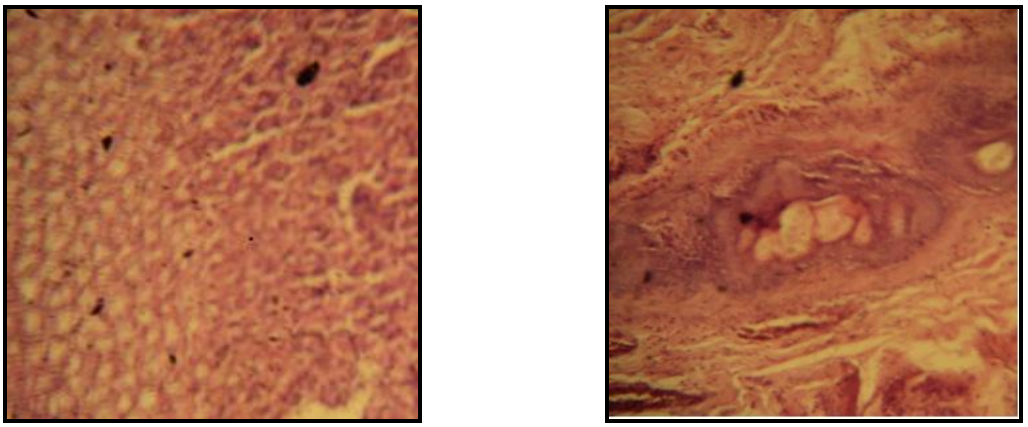
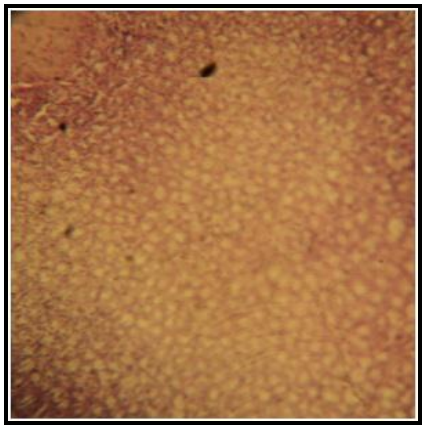


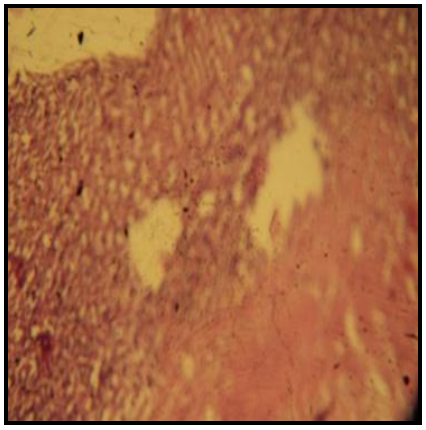
Fig.iii. Macroscopical view of Aspirin induced gastric ulceration in Rats.



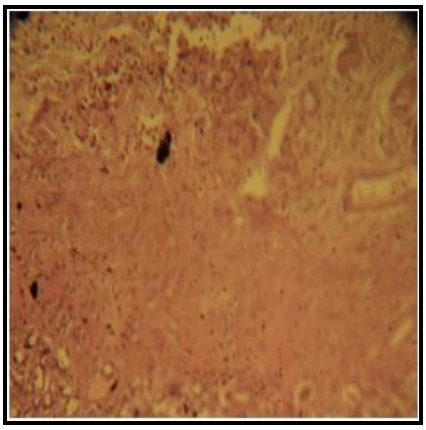
1) Normal control **2) Disease control**



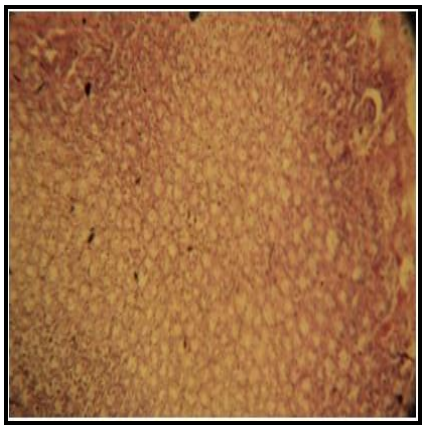
3) Standard Ranitidine



5) 1 ml Pepgard syrup



4) 2 ml Pepgard syrup



6) 4 ml Pepgard syrup

Fig.iv Histopathological microphotograph of Rat Stomach in different group.

Table 3. Mean ulcer index

Groups	Body Wt. (gm)	ULCER INDEX					Total score	Mean ulcer Index±SEM	% Protection
		0	0.5	1	1.5	2			
Normal	170	0.5	-	-	-	-	0.5	0.333 ±0.110	-
	180	0.5	-	-	-	-	0.5		
	200	-	-	-	-	-	-		
	190	0.5	-	-	-	-	0.5		
	185	-	-	-	-	-	-		
	175	0.5	-	-	-	-	0.5		
Disease Control (100mg/kg Aspirin)	155	0.5	1.0	1.5	2.0	-	5.0	4.0±0.4701	-
	180	0.5	1.0	1.5	-	-	3.0		
	175	0.5	1.0	1.5	2.0	-	5.0		
	155	0.5	1.0	1.5	-	-	3.0		
	160	0.5	1.0	1.5	-	-	3.0		
	175	0.5	1.0	1.5	2.0	-	5.0		
Std. Ranitidine (100mg/kg)	170	-	-	-	-	-	0	0.416±0.250***	89
	165	0.5	-	-	-	-	0.5		
	175	-	-	-	-	-	0		
	155	0.5	1.0	-	-	-	1.5		

	180 170	- 0.5	- -	- -	- -	- -	0 0.5		
1 ml pepgard syrup	150 160 155 170 165 175	0.5 0.5 0.5 0.5 0.5 0.5	1.0 1.0 1.0 1.0 1.0 -	1.5 - 1.5 - 1.5 -	- - 2.0 - 2.0 -	- - - - - -	3.0 1.5 5.0 1.5 5.0 0.5	2.75±0.822	31.5
2ml pepgard syrup	175 150 185 165 160 160	0.5 0.5 0.5 0.5 0.5 0.5	1.0 1.0 - 1.0 1.0 1.0	1.5 - - - - -	- - - - - -	- - - - - -	3.0 1.5 0.5 1.5 1.5 1.5	1.58±0.343**	60.5
4 ml pepgard syrup	160 175 165 180 155 160	0.5 - 0.5 - 0.5 -	1.0 - - - 1.0 -	- - - - 1.5 -	- - - - - -	- - - - - -	1.5 0 0.5 0 3.0 0	0.833±0.519***	79.18

Values are the Mean±SEM of six rats/treatment.

Significance *P <0.05, **P<0.001 and *** P<0.001 vs. Disease Control. Statistically Analysed by one-way analysis of variance (ANOVA) followed by Dennett's multiple comparison test.

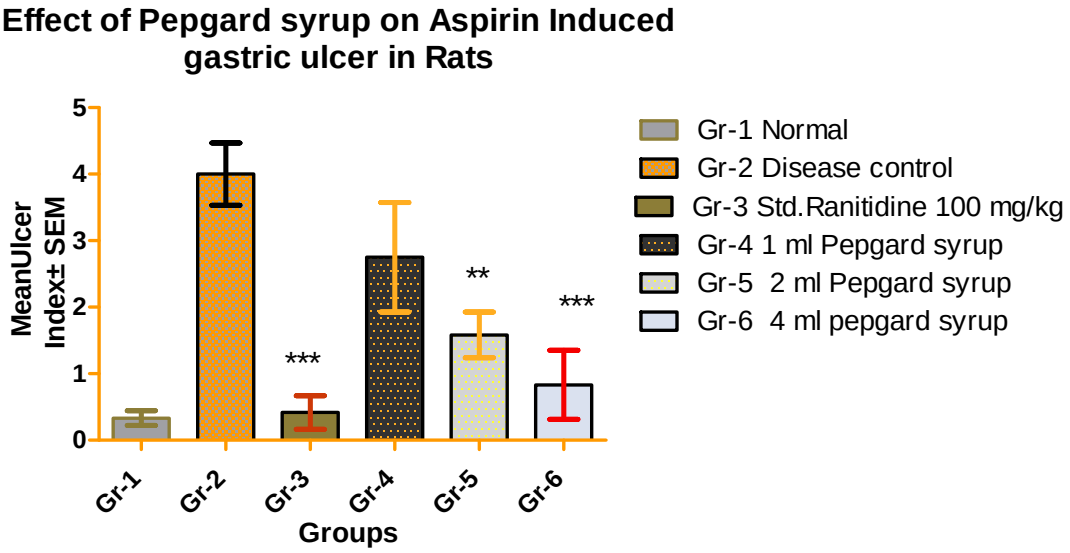


Fig.v Effect of Pepgard Syrup on Aspirin Induced Gastric Ulcer in rats

HISTOPATHOLOGICAL STUDIES

Histopathological microphotograph of rat stomach in normal, Disease control group, ranitidine treated, 1 ml pepgard syrup, 2 ml pepgard syrup and 4 ml Pepgard syrup are given in Fig.v. respectively.

1) Normal control: Histopathological microphotograph revealed that No congestion, no necrosis only gastric lesion .supercritical mucosal layer and muscularis mucosa unaffected.

2) Disease control (100 mg/kg Aspirin): that necrosis and a granulocytosic area were observed and gastric lesions were predominant over vast surface area, perforations with complete mucosal destruction.

3) Standard Ranitidine (100mg/kg Ranitidine): that no congestion, no necrosis and gastric lesions in Ranitidine treated Group. Superficial mucosal layer and muscularis mucosa were remain unaffected

4) 1 ml Pepgard syrup: moderate congestion and muscularis mucosa.

5) 2 ml Pepgard syrup: no congestion, no necrosis, very less ulcer site.

6) 4 ml Pepgard syrup: there were histological changes limited to the superficial layers with no congestion and no necrosis in 4 ml Pepgard syrup treated group.

DISCUSSION

Although in most of the cases the etiology of ulcer is unknown, it is generally accepted that ulcer results from an imbalance between aggressive factors and the maintenance of the mucosal integrity through the endogenous defence mechanism. To regain the balance, different therapeutic agents including herbal preparations are used to inhibit the gastric acid secretion or to boost the mucosal defence mechanism by increasing mucus production.

Different studies give highlights to various causes for the development of peptic ulcer. Ulcers caused by aspirin could be due to their direct effect or release of noxious substances including free radicals.[11] Antioxidants play a major role in repairing the gastric damage. Total antioxidant activity, metal chelation, radical scavenging (DPPH) effects and reducing power as well as activities destructive to active oxygen species such as the superoxide anion radical, hydroxyl radical, and hydrogen peroxide are widely used for this purpose.[10] Hydrogen peroxide (H_2O_2) is a strong oxidizer. To prevent that, our cells also contain antioxidant enzymes known as peroxiredoxins that degrade H_2O_2 molecules. In the present antioxidant study Pepgard Syrup exhibited potent antioxidant activity.

Aspirin can cause ulcers by interfering with the stomach's ability to protect itself from gastric acids. While stomach acids are vital to the digestive process, they can cause damage if the protective barriers of the stomach are compromised. Normally, the stomach has three protections against gastric acid 1) Mucus produced by foveolar cells that line the stomach. 2) Bicarbonate produced by foveolar cells which helps neutralize stomach acid. 3) Blood circulation that aids in the repair and renewal of cells in the stomach's mucosal layer.

Disruption of prostanoid synthesis is another contributing factor for aspirin-induced ulcers. It appears that the development of gastric mucosal damage by aspirin, and possibly other ulcerogenic NSAIDs, involves hypersecretion of tissue-destructive free radicals which may come from (a) enhanced conversion of hydroperoxy to hydroxy fatty acids in the lipooxygenase pathway, (b) accelerated xanthine-oxidase activity in the mucosa, and (c) possibly from the drugs themselves. The inhibition of gastric mucosal prostaglandin production occurs rapidly following oral administration of ulcerogenic drugs. This is correlated with the rapid absorption of these drugs through the mucosa. Inhibition of prostglandin coincides with the earlier stages of injury to the cell membranes of the mucosa with the concomitant loss of the permeability characteristics of the mucus and electron microscopic evidence of damage to mucosal, parietal, and endothelial cells. The later changes also reflect rapid ischemia which appears to develop in the mucosa during aspirin injury.[12] NSAID's such as aspirin and indomethacin are known to induce gastric ulceration. The reason being attributed principally to inhibition of biosynthesis of cytoprotective prostaglandins such as prostaglandin E and prostacyclin by inhibition of cyclooxygenase pathway of arachidonic acid metabolism, resulting in overproduction of leukotrienes and other products of 5-lipoxygenase pathway.[13] Role of cytoprotection in preventing ulcer generation is clearly shown.[14] Different studies show role of ROS, for the genesis of gastric ulcer.[15] A small part of oxygen used is converted to ROS, i.e., the superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (•OH). They are highly toxic to cells and can cause oxidative damage. Ischemia-reoxygenation-induced gastric mucosal injury shows role of ROS in pathogenesis of gastric ulcer.[16] *H. pylori* is an important causative agent leading to chronic Type B gastritis, peptic ulcer, adenocarcinoma, and mucosa associated lymphoid tissue lymphoma affecting stomach.[17] Various studies show the role of ROS in NSAID's and *H. pylori* [18] induced gastric mucosal injury. These ROS decreases the level of endogenous antioxidants such as α tocopherol, glutathione and ascorbate, and augment oxidative mucosal damage. Ulcers induced by aspirin could be due to

their direct effect or release of noxious substances including free radicals.[19] A specific •OH scavenger, dimethyl sulfoxide found to inhibit gastric ulceration produced by ischemia, stress,[20] showing the role of •OH in causing mucosal ulceration. Antioxidant potential of melatonin was found to be the reason for its anti-ulcer property by scavenging ROS.

The present study revealed that Mean ulcer Index and histopathology study revealed that Pepgard syrup had shown Anti ulcer activity in a dose dependent manner. The Pepgard Syrup shows a significant inhibitor of gastric mucosal lesions caused by aspirin in rats thereby confirming its anti-ulcerogenic activity. The cytoprotective effect could be partially due to the presence of phyto-constituents like saponin, flavonoid, tannin alkaloid, glycoside, Carbohydrates and triterpenoid content in Pepgard syrup and its reactive oxygen species scavenging property. The antioxidant mechanism of Pepgard syrup against gastric mucosal lesions was supported by its *in vitro* antioxidant potency as evidenced by its high DPPH and H_2O_2 value.

CONCLUSION

The present study with Pepgard syrup revealed that it has significant anti-oxidant and anti-ulcer activity. Pepgard syrup was found to possess anti-oxidant and anti-ulcer activity properties in in-vivo and in-vitro models, and these findings suggest that the significant gastroprotective activity could be mediated by its antioxidant activity. Therefore, Pepgard syrup is relatively safe for peptic ulcers and related disorders in human for long period.

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