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Original Article

EVALUATION OF ANTIULCER ACTIVITY OF MUCOADHESIVE MICROGRANULES CONTAINING RANITIDINE HYDROCHLORIDE IN EXPERIMENTAL RATS

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ABSTRACT

Objective: Ranitidine hydrochloride is a competitive inhibitor of histamine H2-receptors, the drug of choice in the treatme f ulcer. The drug has a short biological half-life of approximately 2–3 h, thus a sustained release dosage form of ranitidine HCl is desirable. The aim of this study was to formulate and *in vitro* evaluate micro granules of ranitidine HCl using 8% aloe vera powder due to cytoprotective effects.

Methods: Micro granules were prepared by wet granulation method using aloe vera powder as bio-adhesive polymer. The animals were albino male Wistar rats, divided into 4 groups. One group as a control group, the second group as placebo, third groups received ranitidine without aloe vera, and fourth groups as the treated group received ranitidine micro granules. The damage of ulceration was induced with absolute ethanol, dosing at 1 ml/200 g animal body weight. The microscopic observation was done at the first and third day after treatment.

Results: At the first day, the reference and treated group showed the lower ulcer number score mean and ulcer diameter score mean than placebo group. The ulcer index and curative value of reference group were better than treated group, 51.3% and 29.7% respectively. But, at the third day, ulcer index and curative value of treated group possessed better result than reference group, confirming that aloe vera acts as mucoadhesive polymer and gives the release of drug in a sustained manner.

Conclusion: Aloe vera powder (*Aloe vera* (L.) Webb) can be used to formulate micro granules for the prolonged delivery of ranitidine HCl. The micro granules containing in ranitidine dose of 0,04 mg/kg body weight reduce the ulceration induced by absolute ethanol

Keywords: Aloe vera powder, Microgranules, Ranitidine HCl, Ulceration, Macroscopic view

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INTRODUCTION

Ranitidine hydrochloride is a competitive in itor of histamine H2-receptors, drug of choice in the treatment of duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome (ZES), gastroesophageal reflux disease (GERD), and erosive esophagitis [1]. The recommended adult oral dosage of ranitidine is mg twice daily or 300 mg once daily. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 h but not up to 10 h. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine HCl is desirable [2].

There are a number of approaches that can be used to prolong gastric retention time, one of them is polymeric bioadhesive systems. Studied by Maru and Singh [3], aloe vera gel can act as natural polymer bioadhesive in many biomedical applications, including drug delivery systems because of their polysaccharide contents. This substance be found in the parenchymal tissues of Aloe vera [4]. Therefore, the objective of this study is to examine the influence of 8% of aloe vera powder applied as mucoadhesive agent containing in ranitidine micro granules.

MATERIALS AND METHODS

The materials

The materials used were Aloe vera (*Aloe vera* (L.) Webb) powder, aqua destilata, FDC green, ethanol 96% (technical grade), sodium chloride (technical grade), ranitidine hydrochloride (pharmaceutical grade), polyvinylpyrrolidone K-30 (pharmaceutical grade), lactose (pharmaceutical grade), carbopol 934 P (pharmaceutical grade), acid hydrochloride (analytical grade), formaldehyde (analytical grade), ethanol absolute (analytical grade).

The instruments

The instruments used were an oven (Binder), tray, mixer, ceramic mortar, sieve no. 60 mesh, drying apparatus, pH meter (Hanna instrument), moisture content (G-Won Hitect Co. LDT, RRC), stopwatch, spectrophotometer UV-Vis mini 1240 (Shimadzu), dissolution apparatus type I basket (Veego VDA 6-DR), freeze dryer, water restraint, oral injection spuit, glass apparatus, surgical apparatus, anal l scales, and digital camera.

Preparation of Aloe vera powder

Aloe vera (Aloe vera (L.) Webb) which has been identified were washed, then cutted, and peeled. The aloe vera was heated by water (at a temperature of 70 °C for 10 min) to g*et al.* oe vera gel. The gel was filtered and blended into aloe vera pulp, then dried using freeze dryer (at a temperature of 0 °C and pressure of 4.58 torr) by adding dextrin 15%. Next, the obtained dried powder was sieved through the sieve no 60 mesh. The characteristics were tight, white-brownish, odourless, tasteless, and loose powder [5]. From 6.6872 kg aloe vera pulp was obtained 436 grammes of aloe vera powder. Therefore the yield was 6.52%.

Formulation of micro granules containing with ranitidine HCl

Micro granules were prepared in a ceramic mortar by the modified wet granulation technique. Ranitidine HCl, 8% aloe vera powder, Carbopol 934P, PVP K-30, FDC green, and lactose were weighted, then blended and mixed thoroughly. Next, the proper amount of 5% PVP K-30 in ethanol (and FDC green) was gradually added to moisten the pow The wet granules were sieved no 30 and 40 mesh, then dried (at a temperature of 35 °C for 25 min). The micro granules were compressed to get the tablet form. Both placebo and Ranitidine without aloe vera was used to compare the antiulcer activity test (fig. 1).

A B C

Fig. 1: Tablet (A) Placebo; (B) Ranitidine without aloe vera; (C) Ranitidine micro granules

Experimental animals

Inbred albino strains of Wistar rats of male sex weighing 250-300 g procured from the animal house of Yayasan Pharmasi, College of Pharmacy were used for the study. The animals were maintained in transparent cave sized of 50 cm (D) x 30 cm (W) x 30 cm (H) (1500 cm^2) at a temperature of 28±1 °C and standard 12 h: 12 hour day/night rhythm. Prior to the experiment, the animals were acclimatised to the laboratory conditions. The experimental protocol was based on ARRP Guideline 20: Guidelines for the Housing of Rats in Scientific Institutions.

The animals were divided into four groups, each consisting of five rats. One group represented the control group receiving distilled water orally. The second group has a role as a positive group which given placebo tablet. Third groups as the reference group receiving ranitidine without aloe vera, and fourth groups as the treated group received micro granules containing with ranitidine HCl. The gastric ulcers were induced in rats (second, third, and four group) by administrating absolute ethanol (90%) (1 ml/200 g animal body weight.) [6].

All the groups of the animal were kept for overnight fasting fed only with the tap water during 6 h. This treatment was based on 1-2 h of ranitidine HCl elimination half time. After 6 h of administration, the animals were sacrificed by cervical dislocation.

The animals were dissected and the stomach was taken out. This specimen was soaked with 10 ml 0,5% formaldehyde during 10 min, then cut off and washed by normal saline. The stomach was opened along the greater curvature and the mucosa was exposing for evaluation [7].

RESULTS AND DISCUSSION

The *in vivo* antiulcer activity of the ranitidine micro granules were investigated using ethanol-induced ulcer (1 ml/200 g animal body weight). Ethanol has contributed to an ulcer with some mechanism. Kaur *et al.* [8] examined that ethanol can increase the neutrophil at gastric mucosa, activate the pathway of mitogen-activated protein kinase (MAPK), and improve the reactive oxygen species generation.

The absolute ethanol can damage the gastric mucosa directing into neutrophil infiltration (fig. 2.). This bio-molecule is the main source of inflammatory mediator and released the reactive oxygen species, like superoxide, hydrogen peroxide, and myeloperoxidase. ROS has cytotoxic effects because they lead the damage of gastric mucosa [9, 10]. Therefore, the abnormality of blood microcirculation happened and the body circulation was stopped, causing the tissue necrosis [11].

The reactive oxygen species deactivated the proton pump of $H^+K^+ATPase$, which lead to the release of acid gastric. Increasing of gastric acid can be booster by H-2 (Histamine-2). The intracellular mitogen-activated protein kinase (MAPK) causing the activation of NF-kb, modulate the molecules which have a role in the immune and inflammation system, such as IL-1β, IL-2, IL-6, IL-8, IL-12, iNOS and COX-2 [12].

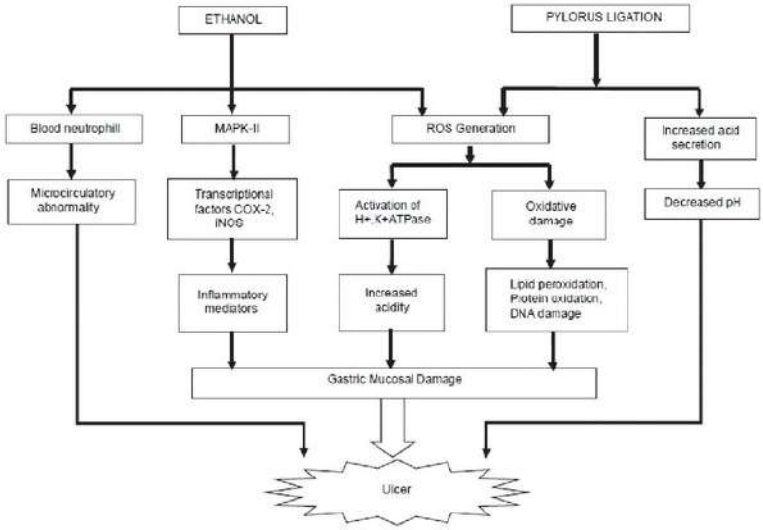


Fig. 2: The ulceration mechanism [8]

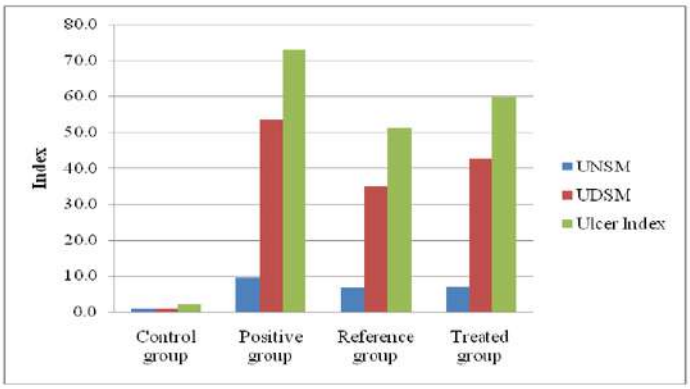


Fig. 3: The comparison of UNSM, UDSM, and Ulcer index of all groups (at the first-day treatment)
Note: UNSM: Ulcer number score mean, UDSM: Ulcer diameter score mean

Table 1: The observation of ulcer damage at the first-day treatment

	Ulcer parameters			Ulcer index	Curative value (%)
	UNSM	UDSM	AP (%)		
Control group	1.0±0.0#	1.0±0.0#	0	2.0	0
Placebo group	9.5±3.5*	53.5±2.0*	100	73.0	0
Reference group	6.5±0.0*#	34.8±2.9*#	100	51.3	29.7
Treated group	8.8±3.2*	45.8±5.0*	100	64.7	18.3

Note: UNSM: Ulcer number score mean, UDSM: Ulcer diameter score mean, AP: Animal percentage, *Significantly different from control group (**P<0.05), #Significantly different from placebo group (**P<0.05)

Fig. 3: and table 1: showed that both ulcer numbers score mean and ulcer diameter score mean in control group has significant different than others. This result proved that induction method using absolute ethanol 1 ml/200 g can stimulate the ulceration. The reference group has the lowest ulcer number score mean, and ulcer diameter score means which correspond to ulcer index and curative value, 51.3% and 29.7% respectively. On the other side, the treated group showed 64,7% and 18,3% for ulcer index and curative value, but there is no significant effect than the placebo group. It can be concluded both reference and the treated group were able to decrease the ulcer damage at the first-day treatment. The best curative value was obtained in the reference group (fig. 4.).

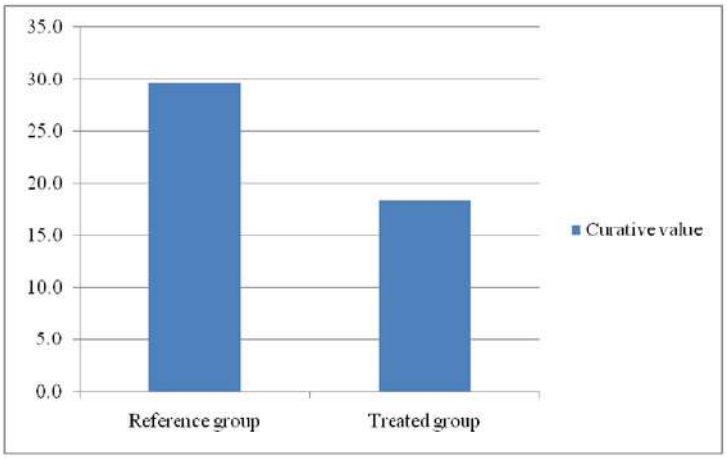


Fig. 4: The curative value of reference and treated group (at the first-day treatment)

The result of prolongation until three days was described on fig. 5. and table 2. The same result happened due to the recovery of ulceration. Ulcer index both reference and the treated group have less percentage which related to the increase of curative value than first-day treatment. The treated group showed better curative value than the reference group (fig. 6.). The macroscopic view appeared in fig. 7, confirming that the stomach perforation did not seen in the reference and treated group.

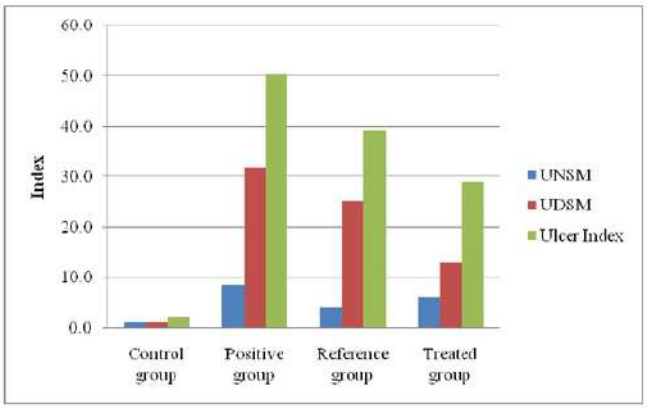


Fig. 5: The comparison of UNSM, UDSM, and Ulcer index of all groups (at the third-day treatment)
Note: UNSM: Ulcer number score mean, UDSM: Ulcer diameter score mean

Table 2: The observation of ulcer damage at the third-day treatment

	Ulcer parameters			Ulcer index	Curative value (%)
	UNSM	UDSM	AP (%)		
Control group	1.0±0.0#	1.0±0.0#	0	2.0	0
Placebo group	8.5±4.2*	31.8±0.7*	100	50.3	0
Reference group	4.0±0.0*#	25.3±2.5*#	100	39.3	21.9
Treated group	6.8±4.9*	20.8±1.9*#	100	37.7	25.2

Note, UNSM: Ulcer number score mean, UDSM: Ulcer diameter score mean, AP: Animal percentage, *Significantly different from control group (**P<0.05), #Significantly different from placebo group (**P<0.05)

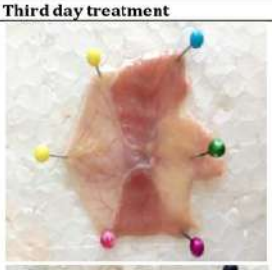
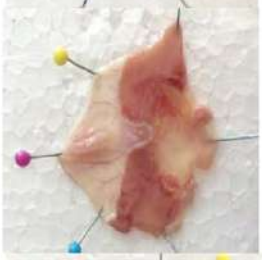
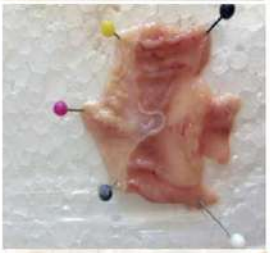
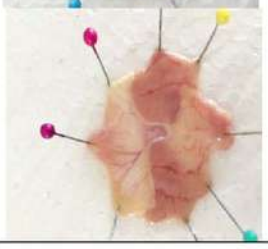
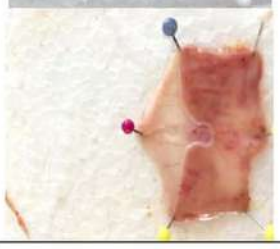
	First-day treatment	Third day treatment
Control group		
Placebo group		
Reference group		

Fig. 7: Macroscopic view of antiulcer activity test

During the course of the study, the incidence and severity of alcohol-induced ulcerations can be reduced by ranitidine micro granules. Administration of Aloe vera as bioadhesive polymer enhances mucous resistance and results in decreased of ulcer index and ulcerated surface [13]. According to Hiruma-Lima *et al.* [14], gastric mucus is a viscous, elastic, adherent and transparent gel formed by water and glycoproteins covering the entire gastrointestinal mucosa. These authors reported that the protective properties of the mucus barrier depends not only on its gel-like structure but are also related to the amount or thickness of the layer covering the mucosal surface. Mucus protects the gastric mucosa against irritants, such as ethanol, HCl and acetyl acid. The cytoprotective action of A. vera may be due to its active ingredients like tannins, saponins and flavonoids [15, 16]. The antagonist H-2 receptor, ranitidine is having a mechanism of action on the development of acute ulcers by inhibiting the secretion of gastric acid. Thus, the formulation of ranitidine in aloe vera micro granules has successfully possessed cytoprotective effects and acid reducing effects.

CONCLUSION

Aloe vera powder (*Aloe vera* (L.) Webb) can be used to formulate micro-granules for the prolonged delivery of ranitidine HCl. The micro-granules containing in ranitidine dose of 0,04 mg/kg body weight reduce the ulceration induced by absolute ethanol. Therefore, the results were suggestive of anti-ulcerogenic activity of ranitidine micro granules. However, the cellular mechanisms for these actions remain to be established.

CONFLICT OF INTERESTS

Declared none

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