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Evaluation of In-vivo antiulcer activity of Microspheres containing *Adina cordifolia* extract

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Abstract

The administration of Adina cordifolia extract significantly reduced ulcer formation and promoted healing in the treated animal models compared to controls. A notable decrease in ulcer area and depth was observed, accompanied by a reduction in oxidative stress markers and inflammatory responses. The extract demonstrated a protective effect on gastric mucosa, suggesting its potential as a therapeutic agent for ulcer management. Adina cordifolia extract exhibits promising antilucer activity in vivo, indicating its potential for further development as a natural treatment option for ulcer-related conditions. Further studies, including clinical trials, are recommended to confirm its efficacy and safety in human subjects.

Introduction:

The objective of the current study was to develop a gastroretentive formulation of aselected herb. Gastroretentive drug delivery system (GRDDS) helps the formulation to keep for a longer time in the stomach environment for better healing of gastric diseases. Moreover, the floating system keeps the formulation in floating state on gastric fluid for longer duration and thus, enhance sits retention in stomach. The prolonged residence in the stomach is needed for the sustained action of drugs required for better healing of some ailments like ulcers.

Material and method:

Collection and Authentication of selected plant material

Before the study began, a botanist authenticated and identified the leaves of the chosen plant by collecting them from a reputable source. For future use, a sample was retained at the department as a specimen.

Preparation of extract of Adina cordifolia leaf

Adina cordifolia leaf extract was made using the technique given by Yang Zo et al., 2013 with small modifications. The collected leaves were cleaned by washing thoroughly three times with water followed by temperature -controlled shade drying. Ina grinder, the dried leaves were reduced in size, sieved (40 mesh) and then kept in an airtight glass jar. Leaf powder was pretreated with petroleum ether to remove the pigments and fatty compounds. The de fatted powder (50g) of dried leaves was extracted with ethanol using Soxhlet apparatus. Afterwards, ethanol was evaporated to dryness of the extract (Ou-Yanget al., 2013).

Formulation of the gastro protective formulation (floating microspheres) of *Adina cordifolia* was developed by using the following method:

By dissolving various amounts of chitosan in 10 mL of 5 percent aqueous acetic acid, high

molecular weight chitosan solution was prepared. The weigh edamoun to f extract (500mg) was dispersed in 10 mL ethanol to prepare extract solution. This prepared ethanol extract solution was dispersed in the aforementioned polymer mixture solution (20mL), it took roughly 5 minutes to emulsify gently into 100 mL of light liquid paraffin with variable surfactant concentrations and stirring speeds. To this w/o emulsion , Glutaraldehyde (GA) was added as across linking agent at different amounts, and for two hours the mixture was stirred. The vacuum-filtered produced microspheres were next washed with petroleum ether and water to get rid of the unreacted GA and liquid paraffin as well as the adherent surfactants. As a result, solid microspheres were produced by drying at 50 °C for 24 hours and stored in a desiccator (Patashnik *et al.*, 1997; You *et al.*, 2005).

Various trial batches were prepared to select the concentration of excipients like Chitosan(Polymer), Span 80 (Emulsifying agent), Glutaraldehyde (Cross-linkingagent) and formulation parameters like stirring speed

Sr.no.	Formulationcode	Extract(mg)	Chitosan(%)	GA(mL)	Span 80(%w/w)	Liquidparaffin(mL)	RPM
1.	F1	500	0.5	1	1	100	**700**
2.	F2	500	1	1	1	100	**700**
3.	F3	500	1.5	1	1	100	**700**
4.	F4	500	2	1	1	100	**700**
5.	F5	500	2.5	1	1	100	**700**
6.	F6	500	1.5	1	0.1	100	**700**
7.	F7	500	1.5	1	0.5	100	**700**
8.	F8	500	1.5	1	1	100	**700**
9.	F9	500	1.5	1	1.5	100	**700**
10.	F10	500	1.5	2	1	100	**700**
11.	F11	500	1.5	5	1	100	**700**
12.	F12	500	1.5	7	1	100	**700**
13.	F13	500	1.5	2	1	100	**400**
14.	F14	500	1.5	2	1	100	**800**
15.	F15	500	1.5	2	1	100	**1200**
16.	**F16**	**500**	**1.5**	**2**	**1**	**100**	**1600**

In-vivo study

Evaluation of Anti-ulcer potential

In experimental rats, the prepared *Optimized formulation*'s ability to prevent stomach ulcers was assessed. The Maharshi Dayanand University institutional animal ethics committee authorized the study protocol for using animals.

Experimental protocol

Wistar rats, which weigh 200–250 g on average, served as the study's experimental subjects. Throughout the studies, animals were kept in typical cages with unrestricted use of food and drink. Five groups of six rats each were created for the experiment, which may last up to seven days. For seven days, the animals in the first group (the

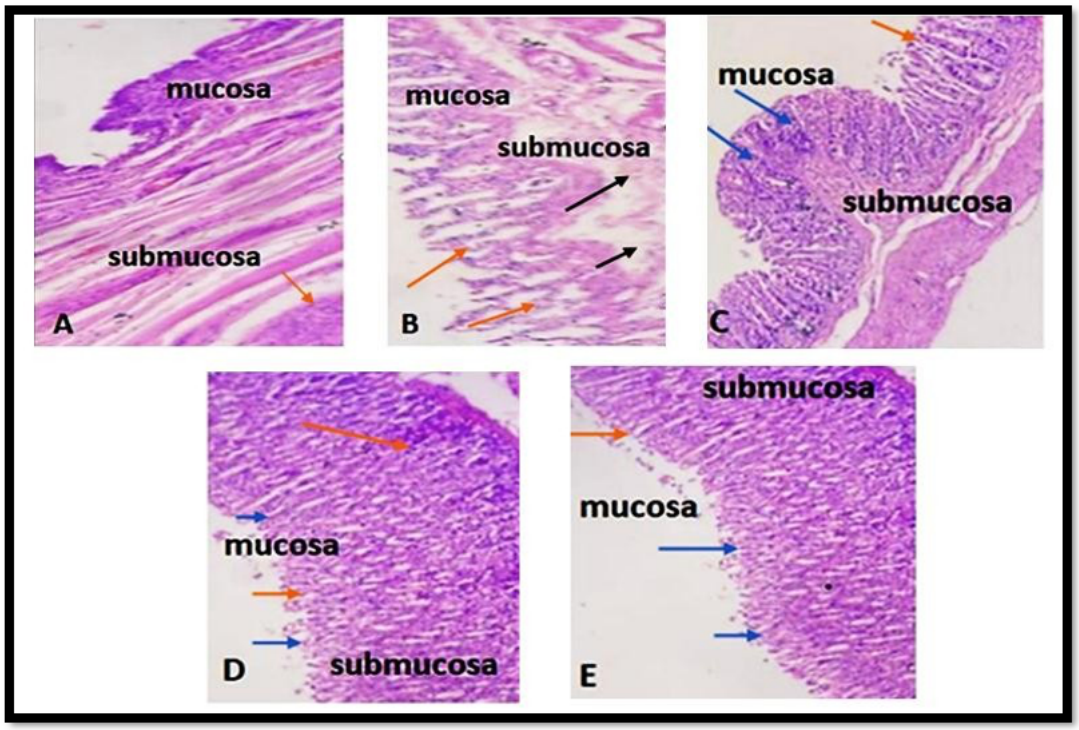
control) were given normal saline, while alcohol (5 mL/kg, the negative control) and omeprazole (20 mg/kg, the positive control), respectively, were given to the second and third groups. The fourth and fifth groups, referred to as the test groups, received 500mg/kg doses of EEAC and *Optimized formulation* solution, respectively (Almasaudi *et al.*, 2016; Raish *et al.*, 2021). Rats from the test groups, including the positive control group, received100% ethanol (5 mL/kg b.w.) on the final day to cause stomach ulcers (Huang *et al.*,2014). After two hours, the animals were put to sleep by cervical dislocation while being given intra peritoneal injections of sterile saline with ketamine (80-100 mg/kg) and "xylazine" (10-12.5 mg/kg). Their stomachs were then removed. Haematoxylin and eosin dye was used to stain the stomach wall specimen in order to prepare the sections for microscopic examinations (Raish*etal.*,2018). The volume, pH, and overall acidity of the stomach fluid, as well as the gastric ulcer index (GUI), were also calculated using the following methods:

Gastric Ulcer Index (GUI)

With the use of the Guth et al.(1979) approach, the stomach clumps were split open along the front surface, was hed with cold normal saline, placed flat on cardboard after being dried between sheets off ilterpaper, in order to inspect any macroscopic lesions (Guthetal.,1979). Each gastro intestinal cavity was carefully inspected, & the degree of the ulcers was determined, scoring 0' in the case of no lesions (normal stomach) 0.5, hyperaemia (red colour) 1, haemorrhagic patches 2,1–5 little ulcers 3, numerous small and large ulcers 4, numerous small and large ulcers 6, stomach full of perforated ulcers (Hauleetal., 2012; Kunchandy et al., 1985). Also, the following equation was used to calculate the protection index(PI):

$$PI = \frac{\text{UI(Ulcerated)} - \text{UI (pretreated)}}{\text{UI(Ulcerated)}}$$

Gastric volume and pH determination The stomach's contents were pouredin to tubes, then centrifuged them for 10 minutesat1000 rpm to calculate the gastric volume. In addition, the pH of the substance was assessed when distilled water and gastric juice (1 mL each) were combined (Raishetal., 2018). Determination of total acidity To aliquoted stomach fluid (1mL), 1mL of distilled water was added and two drops of the phenolphthalein indicator, NaOH(0.01N) was also added intitrationsuntila persistent pink colour was seen inthe prepared solution (Raishetal., 2018).The following formula was used to translate the acidity in to mEq/L: Total Acidity=Volume of NaOH×N×100 N=Normality Statistical analysis The statistical significance of the observed "data" was evaluated using Graph Pad Prism9 software (CA, United States). One-way analysis of variance (ANOVA) was used to analyse the data, and then Dunnett' stest. Results with probability (p-value) less than 0.05 were regarded as significant, and all data are shown as mean ± standard deviation(S.D.) Results and discussion: Further, the histopathology of stomach sections from the animals of different groups indicated that ethanol causes the gastric lesions, acute degeneration, necrosis, and hemorrhages, as well as considerable worsening of the gastric mucosa (Figure 5.38 A-B). Also, the stomach wall demonstrated significant inflammatory cell infiltration and submucosal swelling. Besides the oxidative stress, ethanol also induces the expression of various pro-inflammatory media to rslike TNF-αandIL-1andIL-6 which is responsible for the damage of gastric mucosa and sub-mucosa. Treatment with Omeprazole, ACE and Optimized formulation significantly reduce the gastrulas ions and alters Thean atomy of the stomach mucos Ain comparison to the negative control group. Micrographs of stomach tissue of Optimized formulation treated animals also justified the better absorption of extracts as the architecture of sub-mucosacells was significantly improved as compared to ACE treated rats (Figure 5.38 C-E). Further literature revealed that Adina cordifolia extract, along with the scavenging of free radicals, also reported to reduce these rumlevelso fTNF-α,IL-1βandIL-4 in experimental animals which just ified the protection of gastric mucosa fromde teriorating effects of ethanol. Moreover, the protection of gastric sub-mucosa with Optimized formulation hint that the enhanced residence time of floating microsphere in gastric fluid could be responsible for the better activity of prepared formulation



Group	GastricUlcer index± SD	ProtectionI ndex±SD	pH	Gastricvolume (mL)	TotalAcidityi n mEq/L
GP1 (Normal)	0.00±0.00	99.98±0.00	2.45±0.12	1.52±0.16	303 ± 16.76
GP2(ETH ulcerated)	5.68±0.05	0.01±0.23	1.38±0.09	3.25±0.11	371 ± 12.42
GP3 (OME+ETH)	1.47±0.04	80.5±0.12	2.77±0.21	0.78±0.77	215 ± 18.68
GP4 (*ACE*+ETH)	1.83±0.06	75.48±0.12	2.08±0.08	1.60±0.09	241 ± 10.43
GP5 (*Optimized formulation*+E TH)	2.38±0.09	72.0±0.18	2.62±0.13	1.63±0.05	244 ± 11.60

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