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Evaluation of the Anti-Ulcer Properties of a Controlled Release Preparation with Aqueous Extract from Verbena Hastata in Rodent Models

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Abstract

Objective: To study the anti-ulcer properties of a controlled release preparation with aqueous extract from *verbena hastate* in rodent models.

Methods: Microspheres were synthesized using a solvent evaporation technique, and their characteristics, including scanning electron microscopy images, stability, and in vitro performance, were systematically assessed and verbena hastate loaded microspheres were assessed in an in-vivo study using rats with induced gastric ulceration via ethanol/HCl. parameters examined included pH, Ulcer Index, Total acidity, and histopathological studies.

Results: The findings revealed that *Verbena hastata* harbors key active components, notably flavonoids, attributing to its prowess in combating ulcers. In addition, the study observed that microspheres containing an aqueous extract displayed the highest activity, specifically at a dosage of 200 mg/kg. This was in comparison to the standard reference, Cimetidine, which exhibited activity at a dosage of 100 mg/kg. This finding suggests a potentially enhanced or superior effect associated with the microspheres loaded with the aqueous extract in the context of the study, Additionally, the study outcomes unveiled that the administration of aqueous extract microspheres at a dosage of 200 mg/kg led to a significant reduction in ulcer incidence. This was evidenced by a notable reduction in the ulcer score when compared to the normal control group in the experimental model.

Conclusion: The results suggest that microspheres loaded with *verbena hastata* aqueous extracts demonstrated effective antiulcer activity and safety.

Keywords: Ulcer index, *verbena hastata*, Traditional drug, Controlled release formulation

Introduction

The use of the term 'traditional' in herbal medicines suggests extensive historical utilization, particularly applicable to numerous products classified as indigenous botanical therapies.In numerousless developed nations, a substantial portion of the populace depends on indigenous practitioners to fulfil their healthcare requirements. While modern medicine coexists with traditional practices, herbal medicines often retain popularity due to cultural and historical elements.

The World health organization monographs meticulously delineate the herb through various criteria, encompassing synonyms, vernacular names, and the frequently utilized plant parts. They elaborate on the herb's geographical distribution, methods for identification and characterization (involving microscopic and macroscopic examination, as well as purity test), active components (if identified), dosage form, dosing technique, therapeutic applications, and also provide insights into contra-indication and potential ADR's[1-3].

Ancient Indian medicinal flora in ulcer management

In the realm of traditional Indian medicine, where the potency of renowned medicinal plants is acknowledged for treating various ailments, there exists a scarcity of associated studies exploring the pharmacological properties of certain medicinal plants. Through systematic inquiry, this study reveals that the examined therapeutic herb possess the capability to dose-dependently prevent ulcers in rats. Additionally, the investigation delves into the acute toxicity and antiulcer activity of selected medicinal plants. The detection of significant secondary metabolite, including tannins, flavonoids, terpenoid and glycosides compounds, underscores the rich chemical profile of the substance under investigation[4-6].

Controlled release preparations

Controlled release dosage forms encompass a diverse array of prolonged-action formulations that ensure a Sustained delivery of their active constituents at a pre-established rate and for a specified duration. While the most of these formulations are tailored for oral dosing, there has been a recent introduction of similar devices for transdermal, ocular and parenteral application.

By achieving this extended duration of action, healthcare practitioners aim to optimize the effectiveness of the therapeutic intervention while simultaneously improving the overall patient experience and adherence to the prescribed treatment plan.

Mucoadhesive microspheres are recognized for their role in achieving CDD by extending the residence time at the absorption site, thus enhancing drug bioavailability. As a crucial component of novel drug delivery systems, mucoadhesive drug delivery offers numerous advantages and holds significant potential for articulating dosage forms targeting numerous chronic illnesses, therefore, the development of mucoadhesive microspheres emerges as an efficient, cost-effective and reproducible approach for effective and safe oral drug remedy. In past years, these microspheres had been crafted for buccal, oral,nasal, rectal, ocular and vaginal applications, catering to both systemic and local effects[7-10].

Plant profile

***Verbena hastata*-**Verbena hastata, commonly recognized by various names such as American vervain,simpler's joy,blue vervain and swamp verbena, is a perennial flowering plant belonging to the vervain family Verbenaceae. This plant species thrives across the continental United States and extends its growth into substantial regions of southern Canada.

Chemical constituents

Through the examination of physicochemical and spectroscopic data, the compounds were determined and recognized ashastatoside, verbenalin,verbascoside, martynosideleucosceptoside A,apigenin 7-O-β-D-glucuronide methyl ether, lophirone B, luteroin lophirone C, luxenchalcone, ursolic acid, oleanolic acid, and (22R)-stigmast-5-ene-3β,4β,7α,22-tetrol[11].

Therapeutic application

Blue vervain, or Verbena hastata, is a herb used traditionally for its potential therapeutic benefits. While it's known for stress relief, anti-inflammatory properties, and antioxidant activity, scientific research is limited. It has been used for digestive and respiratory support, menstrual discomfort, and immune system boosting. However, caution and consultation with a healthcare professional are advised due to the lack of extensive scientific evidence[12-15].

Collection and authentication of plant materials

Extraction

The process initiated with the pulverization of the stems of *Verbena hastata*, resulting in a powder. Subsequently, 200 grams of this powdered material were meticulously dissolved in 500 millilitres of distilled water within a 1000 milliliter beaker. The concoction underwent a 15-minute boiling process, followed by a 24-hour maceration period. The resultant mixture was then meticulously filtered using a suction pump, with the concentrated filtrate diligently collected. The collected filtrate underwent a drying process, ultimately yielding a dried filtrate that was employed in the subsequent formulation steps. This systematic procedure ensured the extraction and concentration of essential components from the Verbena hastata stems for use in the formulation process[11]**.**

Preparation development (Mucoadhesive microspheres)

Method

A precisely measured quantity of polymers, including sodium CMC, Carbopol and HPMC was liquified in 50 ml of acetone to produce a uniform and consistent polymer solution**.** Subsequently, the *Verbena hastata* extract was introduced into the homogeneous polymer solution, where it was evenly dispersed and meticulously blended to ensure thorough integration, During this stage, the drug-containing phase was gradually introduced at 150 °C in liquid paraffin, which included 1% of span 80, with moving at 1000 rpm to create an emulsion. Following this, the emulsion was allowed to reach room temperature, and stirring persisted to facilitate the evaporation of acetone. Smooth, discrete microspheres were generated, collected through decantation, washed with the petroleum ether, and subsequently stowed in desiccators[16].

Assessment of mucoadhesive microspheres

Microsphere stability was evaluated under the following condition

1. Normal RT condition (RT (25C±2 °C)

2. Stressed condition (40±5 °C)

3. Humid condition (7±5 °C)

4. Fridge-freezer (5 C-8 °C).

This research investigation spanned a duration of 30 days, during which the content of the drug encapsulated within the microspheres was meticulously determined (table 1).

Surface electron microscopy

SEM was conducted to investigate and analyze the size and shape characteristics of the microspheres.The examination of the structure of the microspheres was conducted utilizing SEM. This analytical technique allowed for a detailed and comprehensive study of the microspheres' physical structure and surface characteristics. In this particular method, microscopes are affixed directly to the sample using both-sided adhesive tape and subsequently layered with a thin layer of gold. A modest quantity of microsphere is evenly distributed onto the gold-coated stub. Following this preparation, the sample stub is positioned within the scanning electron microscope (SEM). Subsequently, a scanning electron photograph is captured, providing a detailed and magnified view of the microspheres' surface characteristics (fig. 1).

In vitro dissolution study

The mucoadhesive microspheres, representing an equal of 100 mg, were accurately weighed and subjected to examination using the USP dissolution apparatus Type II, also known as the Rolex Tablet Dissolution Test Apparatus. This investigation was conducted in 900 mililitre of 0.1N (Normal) HCl dissolution media with a pH of 1.2, maintaining a rotational speed of 100 rpm at a temperature of 37 °C. Samples of 1 ml were taken at defined intervals over 12 hours. Fresh medium was promptly replaced to maintain sink conditions. Analysis was done spectrophotometrically at 279 nm, and the cumulative drug release percentage was calculated using a standard calibration curve[17, 18](fig. 2)

Pharmacological screening

Experimental animals

Animal experiments were conducted following approval from the institutional Animal Ethics Committee, registered under the Committee for the Control and Supervision of Experiments on Animals (CCSEA) (SIPS/IAEC/2023/05). Wistar rats weighing 150–200 g were chosen, housed in polyacrylic cages under standard laboratory conditions (25±2 °C), and provided with a standard dried pellet diet and water ad libitum. Rats were acclimatized for 7 days before experiments, which occurred in a noise-free room between 08:00 and 15:00 h. Each experiment involved a distinct group of rats (n=6).

Gastric ulceration induced by Ethanol/HCl in rats (Chronic)

Following Mizui and Dotuchi's method (1983) with modifications, rats weighing 150-200 g underwent a 24-hour fasting period. The experimental protocol involved administering a 1.5 ml mixture of ethanol/HCl (70% ethanol and 5% HCl) on the first day, half of this dose on the second day, and the remaining half on the third day. Verbena hastata microspheres, freshly prepared at a dose of 100 mg/kg orally, were administered from day 1 to 10. The vehicle control group received only the vehicle (1% CMC), and a third group received cimetidine at 100 mg/kg orally as a positive control[19, 20].

Feed withdrawal occurred 24 hours before the last drug dose. One hour post the final dose, rats were incubated with a 1.5 ml ethanol/HCl mixture (70% ethanol and 5% HCl), and sacrifice followed after 4 hours. Stomachs were examined for ulcer score protection percentage using a predetermined scale[21].

Acute toxicity study

Following OECD guideline 423, acute oral toxicity studies were performed on healthy rats using the fixed-dose method. Verbena hastata microspheres were orally administered to six groups of rats (n=6) at doses of 50, 100, 200, 500, 1000, and 2000 mg/kg/day over four days. Close monitoring for mortality and behavioral changes was conducted to evaluate the potential antiulcer effect.[22].

Acute toxicity studies revealed the safety of verbena hastata plant extract up to a dose of 2000 mg/kg, indicating no mortality or toxicity upon oral administration. No adverse effects, such as diarrhea, convulsion, salivation, tremors, lethargy, sleep, or coma, were observed. Animals showed no signs of aggression, weakness, food refusal, weight loss, or unusual behavior during handling. Following OECD guidelines, safe doses of 200 mg/kg (1/10th of the safe dose) and 100 mg/kg (half of 200 mg/kg) were chosen for the comparative study[23].

Groups

The animals were housed in an environment adhering to standard conditions of temperature and humidity, and they underwent an acclimatization period lasting three days to ensure their adaptation to the experimental setting. Subsequently, the animals were categorized into five groups, each consisting of six individuals (n=6)

Group 1, as vehicle-treated, received normal saline solution;

Group 2, as negative control, received1.5 ml of ethanol/HCl mixture (70% ethanol and 5%HCl);

Groups 3, positive control, received cimetidine at 100 mg/kg p. o.

Groups 4, received microsphere *verbena hastate* freshly prepared (100 mg/kg p. o.) respectively.

Groups 5, received microsphere *verbena hastata* freshly prepared (200 mg/kg p. o.) respectively

Chemicals

In this investigation, Cimetidine from Mankind, India, played the role of the benchmark drug for comparison with the experimental groups. All other chemicals and materials employed in the study adhered to rigorous standards of quality.

Statistical analysis

The findings were eloquently expressed as the mean ± standard error of the mean (SEM). A meticulous statistical scrutiny ensued, employing the one-way analysis of variance (ANOVA).

Histopathological studies

Histopathological exploration involved rinsing excised stomachs in saline and preserving them in 10% formaldehyde. Sections, stained with hematoxylin and eosin, provided insight into histopathological changes. Rats, induced with ulcers via Ethanol/HCl, were treated with Verbena hastata microspheres (100 mg/kg and 200 mg/kg p.o.) before Ethanol/HCl administration. Following outlined procedures, rats were sacrificed, and stomach sections unveiled histological appearances: Vehicle control (A), Negative control (B), Positive control (C), Cimetidine–pretreated (D), and microsphere-pretreated (100 mg/kg p.o. (E) and 200 mg/kg p.o.). Magnified at 10X, these images capture the intricate histological details[24, 25].

Discussion

Herbal remedies have gained popularity as alternatives to clinical therapy, experiencing a surge in demand. The use of controlled release formulations has also risen, as they contribute to better therapeutic effects. Mucoadhesive microspheres are recognized for achieving controlled drug delivery, extending the formulation's residence time at the absorption site, thereby enhancing drug bioavailability. This approach, forming part of novel drug delivery systems, holds significant potential for formulating dosage forms targeting various chronic diseases. Controlled release formulations of herbal drugs not only optimize drug utilization but also offer improved therapeutic effects without notable side effects.

While antiulcer agents play a crucial role in managing ulcers by controlling gastric secretions, their effectiveness is often accompanied by prominent side effects. Recognizing the imperative to seek more efficacious agents with fewer side effects, the focus of research has shifted towards controlled release formulations of herbal drugs. Herbs, known for housing various bioactive compounds, have demonstrated significant antiulcer activity, making them a promising avenue for exploration and development in the quest for improved therapeutic options.

The literature survey unveiled the presence of antiulcer activity in Verbena Hastata. Given the high value of Verbena Hastata in the Ayurvedic system of medicine for various disorders, it was deemed worthwhile to assess its antiulcerogenic potential using diverse models.

Verbena hastata is known for its diverse therapeutic properties, including anti-bacterial, antisecretory, wound healing, antioxidant, sore throat healing, gingivitis and antidiabetic activities, along with anti-inflammatory, antipyretic, antidiarrheal, antimicrobial, anti-inflammation, and antisecretory attributes. The primary focus of this study is to formulate a controlled release system for ulcer management, incorporating these herbal properties.

Controlled release preparations offer controlled and continuous drug release at the site of action, enhancing therapeutic effects. Limited research has been conducted on herbal controlled release formulations for peptic ulcer treatment. Among various controlled release dosage forms, microspheres serve as crucial particulate carriers, efficiently delivering drugs to targeted sites.

Mucoadhesive microspheres, recognized for extending drug residence time and enhancing bioavailability, play a crucial role in achieving controlled drug delivery. This innovative drug delivery system holds potential for crafting dosage forms tailored to address diverse chronic diseases. Leveraging these carriers for targeted drug delivery offers benefits like superior storage stability and straightforward large-scale production. Microsphere formulations assure stability, targeting, and sustained release of encapsulated molecules, amplifying the therapeutic impact of natural herbal drugs. This study endeavours to pioneer a novel particulate-based strategy for selectively delivering a drug, enabling controlled release of herbal constituents.

Pharmacological profiling

Acute oral toxicity studies

Healthy rats underwent acute oral toxicity studies using the fixed-dose method. Verbena hastata microspheres were orally given at doses ranging from 50 to 2000 mg/kg/day for four days across five groups of rats (n=6). Throughout the study, close monitoring revealed no signs of mortality or behavioral changes in any of the animals.

Ethanol-induced peptic ulcer

Mucoadhesive microspheres, incorporating Verbena hastata aqueous extracts at 200 mg/kg, exhibited a notable decrease in Ulcer index, gastric volume, free acidity, total acidity, and elevated gastric pH compared to the control group. Cimetidine, the reference drug, demonstrated a significant reduction in gastric ulcer and total acid output. The study highlighted active constituents, such as flavonoids in Verbena hastata microspheres, contributing to their antiulcer activity. Maximum antiulcer efficacy was observed with aqueous extract microspheres at 200 mg/kg, akin to standard cimetidine (100 mg/kg).

In the Ethanol-induced models, Verbena hastata microspheres demonstrated antiulcer potency. Results indicated a substantial reduction in ulcer incidence at 200 mg/kg compared to the control, evidenced by a decrease in the ulcer score in the model.

Conclusion

Gastric ulcers stem from a delicate equilibrium between aggressive factors and the preservation of mucosal integrity. Peptic ulcers can arise from excessive gastric acid or diminished mucosal protection. Ethanol-induced ulcers result from the corrosive interaction between ethanol and acid, causing mucous membrane injury.

In response, Verbena hastata extract-loaded microspheres showcased a protective shield against ethanol-induced ulcerations, demonstrating potential benefits. These microspheres displayed antisecretory activity, reducing gastric volume and acidity. Importantly, aqueous extract microspheres exhibited no ulcerogenic potential, reinforcing their safety.

The acute toxicity study confirmed the safety of aqueous extracts up to 2000 mg/kg. Aqueous extract microspheres at 200 mg/kg significantly curtailed ulcer incidence in Ethanol-induced Models, accompanied by reduced ulcer scores. Animals treated with these extracts also experienced diminished gastric volume and acidity. Rich in flavonoids and tannins, Verbena hastata extracts exhibited antiulcer activity, confirmed through phytochemical studies. Statistical analyses, including one-way ANOVA and post-tests, supported the conclusion that these microspheres held promising antiulcer activity.

List of Declarations-

a. Availability of data and material- The data used to support the findings of this study are included within the article.

b. Competing interests- The authors declare that the manuscript work was conducted in the absence of any commercial relationship that could be construed as a potential conflict of interest.

c. Funding- None

d. Authors contribution- Each author has contributed equally

e. Acknowledgements- Not applicable

Observation and results

A. Characterization of microspheres Stability Study

Table 1. Stability studies of Sample in Environmental condition

S. No.	Storage Condition	Time (Days)	Physical Stability (Visual Observation)		
			COLOR	STATE	ODOUR
1	NC	Initial	NCC	NCC	NCC
2	NC	One week (7th day)	NCC	NCC	NCC
3	NC	Two week (14th day)	NCC	NCC	NCC
4	NC	Three weeks (21st day)	NCC	NCC	NCC

5	NC	Four weeks (28th day)	NCC	NCC	NCC
6	SC	SC Initial	NCC	NCC	NCC
7	SC	One week (7th day)	NCC	NCC	NCC
8	SC	Two week (14th day)	NCC	NCC	NCC
9	SC	Three weeks (21st day)	NCC	NCC	NCC
10	SC	Four weeks (28th day)	NCC	NCC	NCC

NC- Normal condition (e.g. room temperature 25C ± 2 C), SC- Stress condition (40± 5 C, %RH- 70± 5), NCC- No change.

Scanning electron microscopy

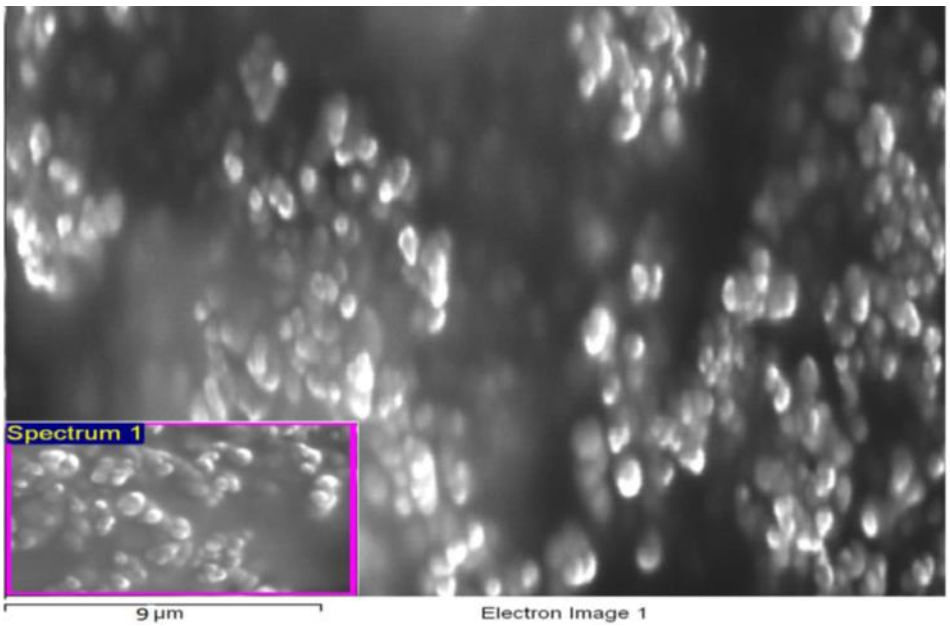


Fig 1. Scanning electron microscopy formulation of microsphere

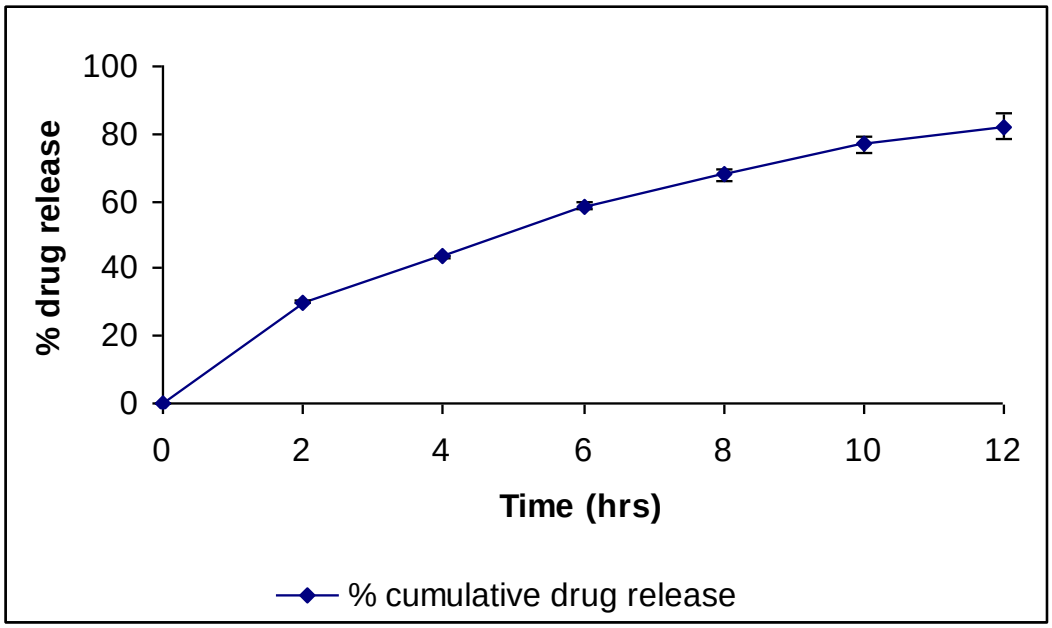


Fig 2. In vitro drug release profile of microspheres formulation

B. Pharmacological screening

(B) Ulcerogenic effect (Ulcer Index):

Table 2. Anti-ulcerogenic effect of microsphere *verbena hastata* against Ethanol/HCl induced ulcerogenic agents in rats

Treatment	Dose	Ulcer index
Control	0.9 %	0.31
Negative Control	1.5 ml (1.5 ml of ethanol/HCl)	19.73****
Positive Control	100 mg/kg p.o.(cimetidine)	5.48
Microsphere *verbena hastata*	100 mg/kg p.o.	6.3^{aaaa}
Microsphere *verbena hastata*	200 mg/kg p.o.	5.22^{bbbb}

Table 2. Values are expressed as mean ± S.E.M. (n = 6), ****p < 0.0001 "*" versus Control; ^{aaaa}p < 0.0001, ^{bbbb}p < 0.0001; "a" "b" versus Negative control

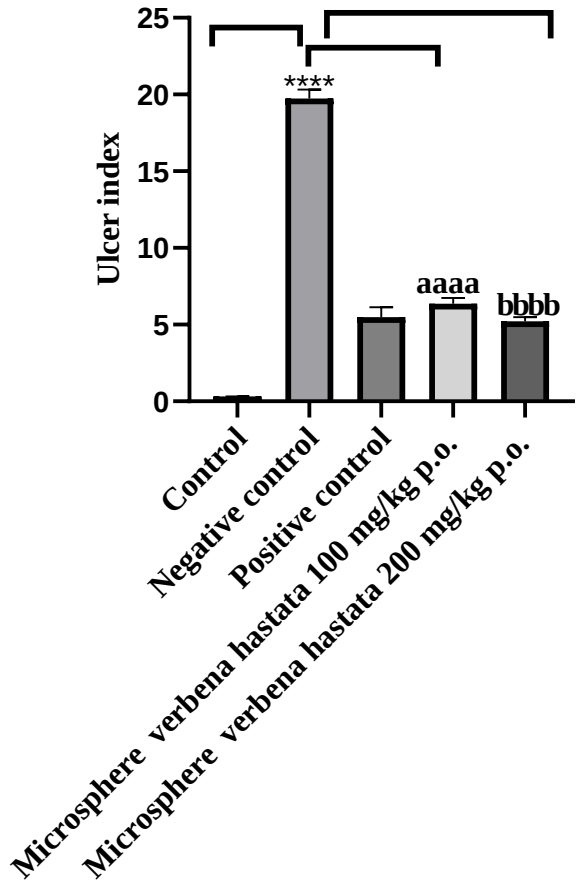


Fig 3. Values are expressed as mean ± S.E.M. (n = 6), ****p < 0.0001 "*" versus Control; ^{aaaa}p < 0.0001, ^{bbbb}p < 0.0001; "a" "b" versus Negative control

Table 3. pH and Total acidity

Treatment	Dose	pH	Total acidity (mEq/L/100g)
Control (Nacl)	0.9 %	3.2	0.00
Negative Control	1.5 ml (ethanol/HCl)	2.2	99****
Positive Control	100 mg/kg p.o. (cimetidine)	6.3****	73

Microsphere *verbena hastata*	100 mg/kg p.o.	4.3^{aaaa}	80^{aaaa}
Microsphere *verbena hastata*	200 mg/kg p.o.	3.8^{bb}	77.8^{bbbb}

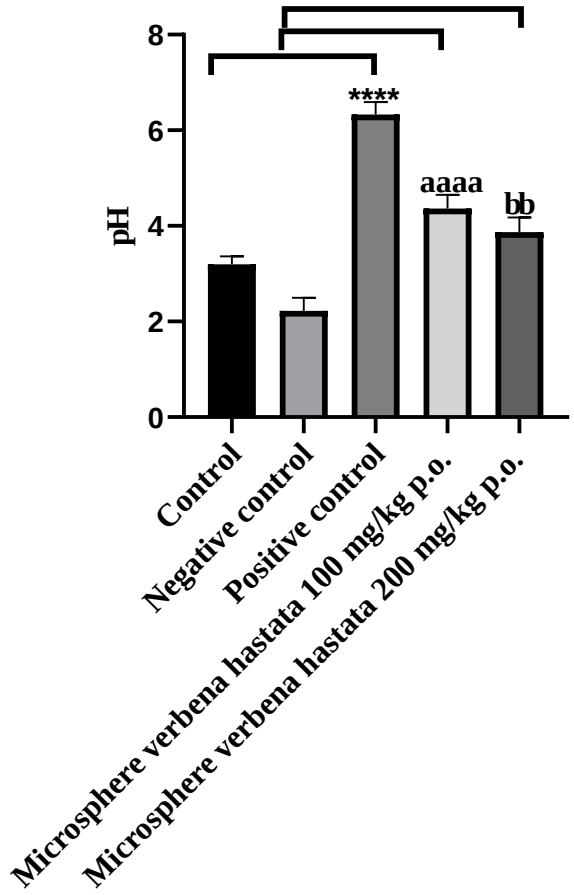


Fig 4. Values are expressed as mean ± S.E.M. (n = 6), ****$p < 0.0001$ "*" versus Control; $^{aaaa}p < 0.0001$, $^{bb}p < 0.01$; "a" "b" versus Negative control

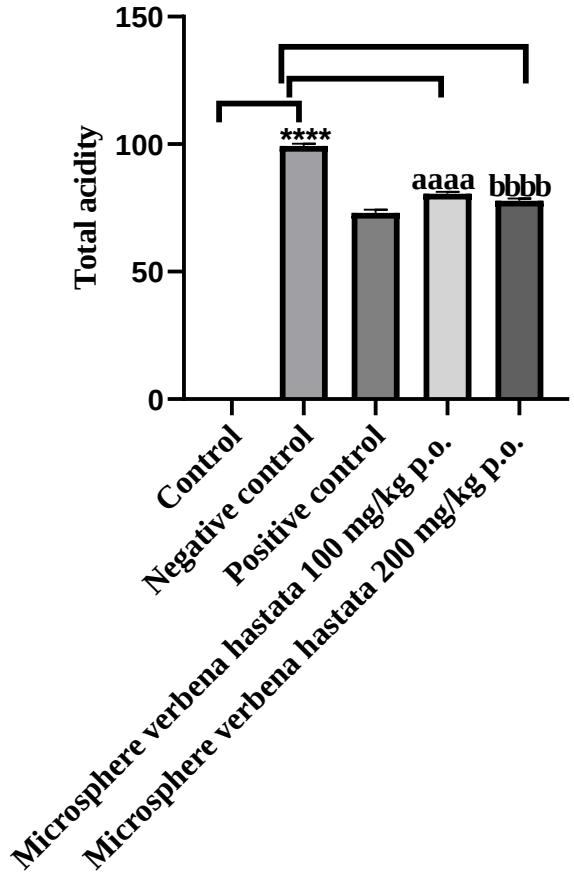
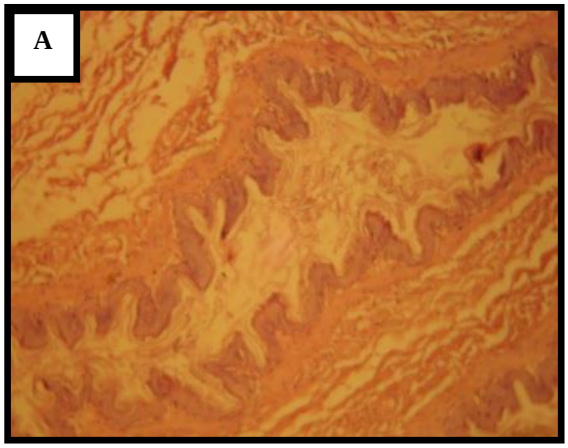
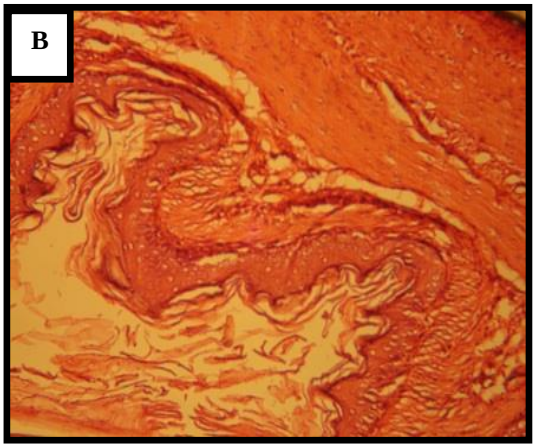
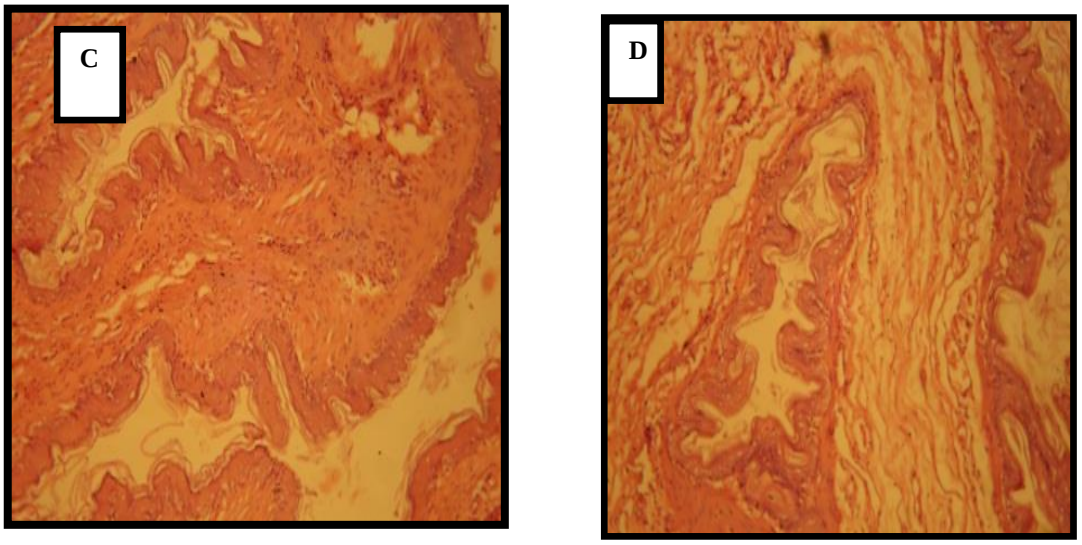


Fig 5. Values are expressed as mean ± S.E.M. (n = 6), ****p < 0.0001 "*" versus Control; ^{aaaa}p < 0.0001, ^{bbbb}p < 0.0001; "a" "b" versus Negative control





A. Control **B. Negative Control**



C. Positive Control (200mg/kg p.o.)

D. Microsphere of Verbena Hastata

Fig 6. Histology of rat gastric tissue after ulcer induction by Ethanol/HCL and protection by microsphere *Verbena hastata*

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