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Effect of the Total Extract of Ficus Arnottiana in Rat Model of Gastric Ulcers

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A B S T R A C T
Peptic ulcer disease is a serious gastrointestinal disorder that requires well targeted therapeutic strategy. A number of drugs including proton pump inhibitors and H2 receptor antagonists are available for the treatment of peptic ulcer, but clinical evaluation of these drugs has shown incidence of relapse, side effects and drug interactions. This has been rational for the development of new anti-ulcer drugs and search for novel molecules has been extended to herbal that offer better protection and relapse. The present study is to evaluate the anti-ulcer activity by using herbal remedy *Ficus arnottiana.* The aim of the study is to evaluate the anti-ulcer activity of ethanolic extract of *Ficus arnottiana*in rats. To evaluate the anti-oxidant activity of ethanolic extract of *Ficus arnottiana*in rats.
Keywords: *Ficus arnottiana*, ulcer, H2 receptor

A R T I C L E I N F O

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Contents

1. Introduction

Peptic ulcer is one of the major gastro-intestinal disorders. Peptic ulcer is a lesion of gastric or duodenal mucosa, it occur due to an imbalance between the offensive (gastric acid secretion) and defensive (gastric mucosal integrity) factors [1]. Most injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products and certain drugs and pathological condition such as Zollinger –Ellison Syndrome, they cause the ulcers in gastric or duodenal mucosa [2]. The erosion on the stomach, it is referred to as a gastric ulcer. If it is in the duodenum (the part of the small intestine just after the stomach), it is called a duodenal ulcer. Peptic ulcer disease is a worldwide problem, affecting about 1 in 10 people.In the early 20th century peptic ulcers were thought to be caused by emotional stress and spicy foods. Peptic ulcer is more Occurs frequently in men than in women. After 45 years of age peoples have less sex differences probably because the incidence of ulcer increases in post-menopausal women. The ulcer differences between sexes are related in some way to sex hormones and that the female sex hormones protect against ulceration [3]. Duodenal ulcers are more common than gastric ulcers and usually occur in people aged fewer than 50.Gastric ulcers

are more common in people aged over 50. Duodenal ulcers are the most common ulcers found in the Western world. In 1982, Australian doctors Robin Warren and Barry Marshall first discovered a link between ulcers and H. Pylori [4].

Usually Ulcer occurs by many causative agents. But now a day's ulcer is mainly caused by five reasons.

1. Alcohol consumption
2. NSAIDs consumption
3. Smoking consumption
4. Skipped meals and poor sleep

Multiple mechanisms of protective action and anti-oxidant properties of drugs are minimizing tissue injury in humandisease. Absolute ethanol induced gastric lesions in stomach. Gastric lesion is accompanied with the formation of the free radicals (FRs) and reactive oxygen species (ROs). These radicals in particular seem to play an important role in ulcerative and erosive lesions of the gastrointestinal tract. Therefore, treatment with anti-oxidants and FR scavengers can decrease ethanol induced gastric mucosal damage [5].

Peptic ulcer disease (PUD), also known as a peptic ulcer or stomach ulcer, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus. An ulcer in the stomach is known as a gastric ulcer while that in the first part of the intestines is known as a duodenal ulcer. The most common symptoms are waking at night with upper abdominal pain or upper abdominal pain that improves with eating. The pain is often described as a burning or dull ache. Other symptoms include belching, vomiting, weight loss, or poor appetite. About a third of older people have no symptoms. Complications may include bleeding, perforation, and blockage of the stomach. Bleeding occurs in as many as 15% of people.

Common causes include the bacteria Helicobacter pylori and non-steroidal anti-inflammatory drugs (NSAIDs). Other less common causes include tobacco smoking, stress due to serious illness, Behcet disease, Zollinger-Ellison syndrome, Crohn disease and liver cirrhosis, among others. Older people are more sensitive to the ulcer causing effects of NSAIDs. The diagnosis is typically suspected due to the presenting symptoms with confirmation by either endoscopy or barium swallow. H. pylori can be diagnosed by testing the blood for antibodies, a urea breath test, testing the stool for signs of the bacteria, or a biopsy of the stomach. Other conditions that produce similar symptoms include stomach cancer, coronary heart disease, and inflammation of the stomach lining or gallbladder.

Induction of gastric ulcer is a major adverse effect caused by NSAIDs. Therefore, they have been used widely to establish animal models of gastric ulcer. A single dose of oral indomethacin can induce gastric ulcer-like damage in rats, which reaches a maximum 3 d after administration. Oral administration of *Myristicamalabarica* extract once daily for 3 d induced a >60% reduction in macroscopic damage score. Similarly, oral *Piper betel* extract at a dose of 2 mg/kg per day for 7 d significantly reduced ulcer index in a rat model of indomethacin-induced gastric ulcer. Its efficacy was comparable to misoprostol, a conventional anti-ulcer drug. Mehrabani et al have reported that oral *Teucriumpolium* extract lowered ulcer index in 24 h and induces a > 90% reduction in ulcer index. Likewise, oral administration of *Phyllanthusemblica* fruit extract for 7 d induced 79.39% inhibition of ulcer index. Moreover, oral beeswax extract for 5 d induced significant acceleration of ulcer healing in a rat model. These results suggest that herbal medicines could be useful in treating NSAID-induced gastric ulcer.

2. Materials and Methods

Materials used

Drugs: Aspirin, Standard drug ranitidine.

Plant material: *Ficusarnottiana L*. were purchased from local markets in wargal. It was identified and authentificated by Professor Dr. Md. Mustafa, Department of botany, Kakatiya university, Wargal, AP.

chemicals: 0.01N NaOH, phenolphthalein indicator, Topfer's reagent, 80% ethanol, Formalin, gum acacia, Anaesthetic ether obtained from Zeal chemicals, wargal.

Reagents:

Benedict's reagent, barfoed's reagent, million's regent, wager's regent, Hager's regent. Mayer's regent.

Animals:

Healthy wistaralbino rats weighing between 200-250g were used for the study. The animals were procured from Sainath agencies, laboratory animals, Hyderabad and the animals were kept in polypropylene cages (6 in each cage) and animals were acclimatized to our lab environment for about a week prior to the study, so that they could adapt to the new environment. Animal house were maintained under standard hygienic conditions, at 25 ± 2^0C, humidity (60 ± 10 %) with 12 hrs day and night cycle, with food and water *ad libitum*. The experiments were carried out prior approval from Institutional Animal Ethical Committee (IAEC).

Extract preparation:

The root pieces were shade-dried and made into a coarse powder which was passed through a 40-mesh sieve to get a uniform particle size and then used for extraction. A weighed quantity (500 g) of the powder was then subjected to continuous hot extraction in Soxhlet apparatus with and ethanol and the residual marc was collected. The extract was filtered through a cotton plug, followed by whatman filter paper (no.1). The extract was evaporated under reduced pressure using a rotovac evaporator at a low temperature (40-60°C) until all the solvent had been removed to give an extract sample [95].

Preliminary phytochemical screening of extracts:

Qualitative chemical tests were conducted for ethanolic extracts to identify the various phytoconstituents by employing standard screening tests.

Acute Toxicity Studies:

The acute toxicity was determined on female albino rats by fixed dose method of OECD Guide line no 420 given by CPCSEA. Groups of 6 rats were administered test drug by oral route at a dose of 2000, 300mg/kg (6 animals in each dose) and mortality was observed after 24 hr. The safe dose was found to be mg/kg body weight. For this study two doses were selected [96].

Methodology

Aspirin induced ulcer model: The albino rats were randomly divided into four groups of six animals each. Animals were fasted for 24 h before experiment but with free access to water.

Table.1. Experimental design ofAspirin induced ulcer model.

Groups	Treatment
I	control (250mg/kg aspirin)
II	Ranitidine (20mg/kg)
III	***Ficusarnottiana***250 mg/kg
IV	***Ficusarnottiana***400mg/kg

Experimental procedure: First group treated with Aspirin in a dose of 250 mg/kg was administered orally on the day of experiment at about 10 AM with the help of an oral feeding tube in the form of an aqueous water suspension. 2^{nd}, 3^{rd}, 4^{th} groups of animals were treated with ranitidine, low and high doses of beet root extracts respectively one hour before aspirin administration. One hour after drug treatment of 2^{nd}, 3rd, 4^{th} groups of animals were treated with 250mg/kg aspirin by p.o, to induce ulcers. The animals were sacrificed after 4hr of aspirin administration. The stomach was opened and calculates the ulcer index and percentage inhibition of ulcer [98].

Estimated parameters:

Estimation of gastric volume, pH:

The gastric content that was transferred into centrifuge tubes was used for estimation of gastric volume, pH. The tubes were centrifuged at 1000 rpm for 10 min and the gastric volume was directly read from the graduation on the tubes. The supernatant was then collected and pH was determined by using a digital pH meter [100].

Determination of total acidity

An aliquot of 1ml gastric juice diluted with 1ml of distilled water was taken into a 50 ml conical flask and two drops of phenolphthalein indicator was added to it and titrated with 0.01N NaOH until a permanent pink colour was observed. The volume of 0.01N NaOH consumed was noted [100].

Determination of free acidity

Instead of phenolphthalein indicator, the Topfer's reagent was used. Aliquot of gastric juice was titrated with 0.01N NaOH until canary yellow colourwas observed. The volume of 0.01N NaOH consumed was noted. The free acidity was calculated by the same formula for the determination of total acidity [100].

Determination of Ulcer Index (UI) The ulcerative index was calculated by severity of gastric mucosal lesions and graded as follows; [100]

0=no ulcer

1=superficial ulcer

2=deep ulcer

3=perforation

$UI=UN+US+UP \times 10^{-1}$

UN=average of number of ulcers per animal

US=average of severity score

UP=Percentage of animals with ulcers

% gastro protection was calculated according to;

% gastro protection = (UIC-UIT)/UIC*100

Where, UIC-ulcer index of control.

UIT-ulcer index of test

Histopathological evaluation

The gastric tissue was fixed in 10% ethanol buffer formalin and processed though graded ethanol, xylene and impregnated with paraffin wax; sections were made by microtome. After staining with haemotoxylin and eosin stain (Culling, 1974), the sections were examined under a research microscope by a person who was not aware of experimental protocols. The different histopathological indices screened were: congestion, hemorrhage, edema, necrosis, inflammatory and dysplastic changes, erosions and ulcerations [101].

In-vitro Antioxidant activity

DPPH free radical-scavenging activity:

The methanolic solution of DPPH (0.1 mM, 1 ml) was incubated with 3 ml of different concentrations of the FA extract ranging from 10-100 µg/ml. Incubation was carried out at room temperature (25^0C) for 30 min. For each concentration, the assay was run in triplicate. At the end of the incubation period, the optical density of each sample was determined at 517 *nm*. Ascorbic acid solution was used as a standard. EC_{50} values (concentration required to scavenge 50% of the free radicals) for both ascorbic acid and the root extract were determined. The radical scavenging activity of the tested sample was expressed as an inhibition percentage (IP) [102].

DPPH Scavenged (%) = $(A_{DPPH} - A_{test} / A_{DPPH}) \times 100$

Where,

A_{DPPH} is the absorbance of the 0.1 mM of DPPH solution and

A_{test} is the absorbance in the presence of the extract or ascorbic acid.

IC_{50} value was determined from the graph obtained using standard ascorbic acid by using the "y = mx + c" formula from the slope of the graph.

Statistical analysis

The statistical data was expressed as mean ± S. E.M .Statistical analysis was carried out by using one-way analysis of variance (ANOVA) followed by Dunnett's Multiple Comparison test. Differences between the data were considered significant at $P<0.05$ [102].

3. Results and Discussion

Table:2. Phytochemical Analysis.

Phytoconstituents	Present or Absent
Carbohydrates	Present
Glycosides	Present
Fats	Present
Gums &mucilages	Absent

Proteins & amino acids	Present
Saponins	Present
Tannins & Phenolic compounds	Present
Phytosterols	Absent
Flavonoids	Present
Alkaloids	Absent

Pharmacological studies:

Acute toxicity studies

The ethanolic extract of *Ficusarnottiana*was subjected for the acute toxicity study to determine the therapeutic dose using albino rats in controlled environment. Acute oral toxicity study was performed as per OECD-423 guidelines. Acute toxicity study carried out on EEFA up to the dose of 2000 mg/kg demonstrated that the extract did not show any sign of toxicity and mortality. Hence 250 and 400 mg/kg dose of the extract selected for evaluation of anti-ulcer activity.

Effect of ethanolic extract of *Ficusarnottiana* in Aspirin induced gastric ulcer: In aspirin induced gastric ulcer model, the ulcer index of control group is 11.083±0.4282. The animals treated with ethanolic extract of *Ficusarnottiana* at 400 mg/kg dose showed significant (*P<0.01*) reduction in the number of ulcer and ulcer index is 8.516±0.42816. Ranitidine at 20mg/kg showed significant (*P<0.01*) reduction in the number of ulcer and ulcer index is 8.516±0.42816. Extract at 250mg/kg shows the protection against the aspirin induced gastric ulcer, ulcer index 10.35±0.5627. Administration of beet root 1 h before the induction of gastric lesions by aspirin showed significant activity, and inhibited the ulcer index in dose dependent manner. The ethanolic extract of *Ficusarnottiana* was found to possess remarkable ulcer-protective properties at 250 mg/kg and 400 mg/kg when compare to toxic control group.

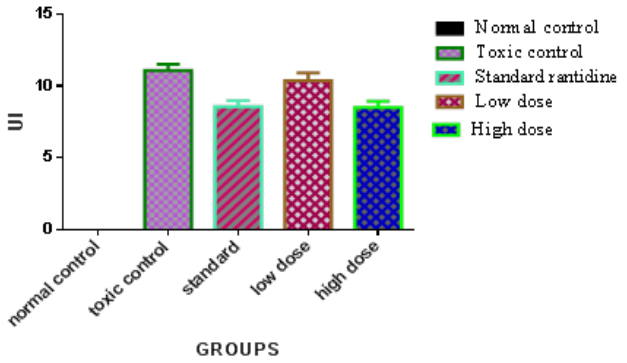

Figure 1. Effect of ethanolic extract of *Ficusarnottiana* on ulcer index in aspirin induced gastric ulcer

a. Volume of gastric content:

In pylorus ligation induced gastric ulcer model the gastric content volume high (3.2±0.1291) in control group. Gastric content volume siginificantly decreases in ethanolic extract of *Ficusarnottiana* at 250 (2.433±0.233) and 400mg/kg (2.15±0.1945) doses. Gastric content volume siginificantly decreases in standard group (1.983±0.113) compared control group.

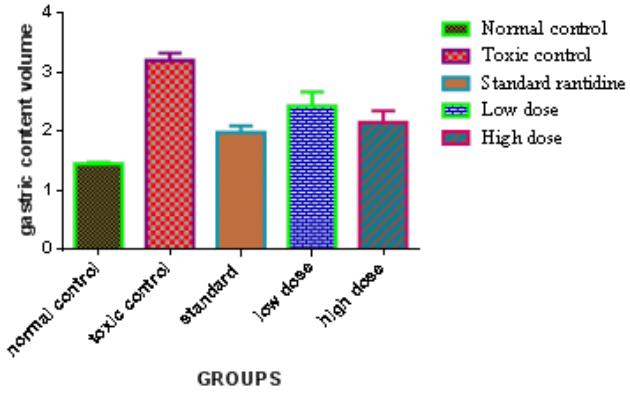

Figure 2. Effect of ethanolic extract of *Ficusarnottiana* on gastric content

b. Volume of Gastric juice:

In pylorus ligation induced gastric ulcer model the Gastric juicevolume high (2.133±0.1022) in control group. Gastric juicevolume significantly decreases in ethanolic extract of *Ficusarnottiana* at 250 (1.4±0.2817) and 400mg/kg (1.183±0.1327) doses. Gastric juicevolume significantly decreases in standard group (1.4±0.2817) compared control group.

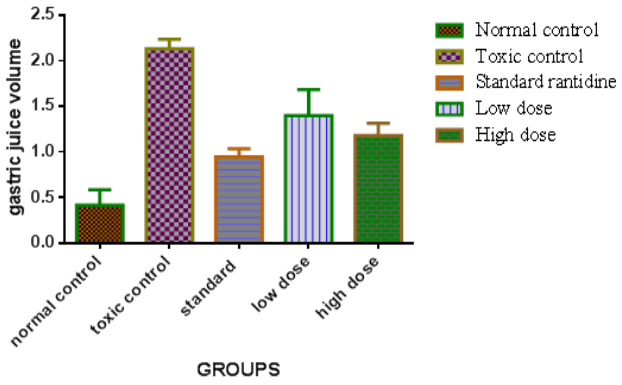

Figure 3. Effect of ethanolic extract of *Ficusarnottiana* on gastric juice

c. PH:

In pylorus ligation induced gastric ulcer model the Gastric juice PH low (1.865±o.1018) in control group. Gastric juice **P**H significantly increases in ethanolic extract of *Ficusarnottiana* at 250 (2.8±0.1932) and 400mg/kg (3.46±0.1936) doses. Gastric juicePH siginificantly increases in standard group (4±0.1238) compared control group.

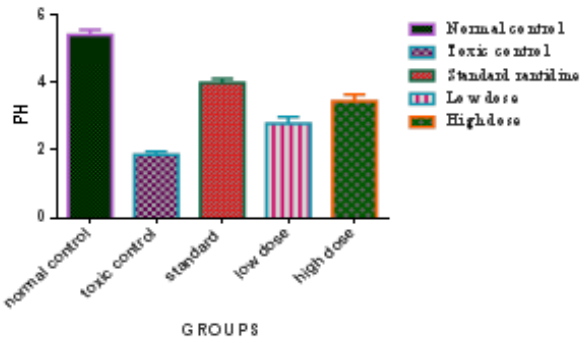

Figure 4. Effect of ethanolic extract of *Ficusarnottiana* on gastric juice PH

d. Total acidity (mEq/lit):

In pylorus ligation induced gastric ulcer model the total acidity high (705±1.478) in control group. Total acidity significantly decreases in ethanolic extract of *Ficusarnottiana* at 250 (162.5±1.315) and 400mg/kg (52.8±0.2358) doses. Total acidity significantly decreases in standard group (44.6±0.2186) compared toxic control group.

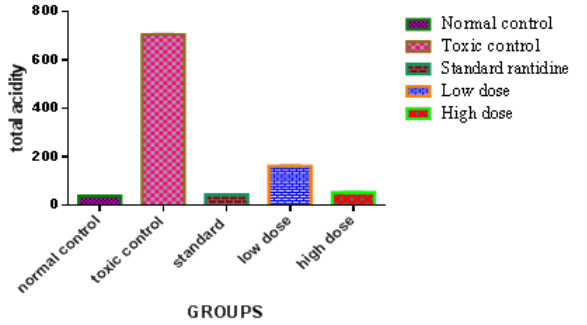

Figure 5. Effect of ethanolic extract of *Ficusarnottiana* on total acidity

e. Free acidity (mEq/lit):

In pylorus ligation induced gastric ulcer model the free acidity high (283±2.171) in control group. Free acidity significantly decreases in ethanolic extract of *Ficusarnottiana* at 250 (66.3±0.4447) and 400mg/kg (21.76±0.2088) doses. Free acidity significantly decreases in standard group (24±0.1880) compared toxic control group**.**

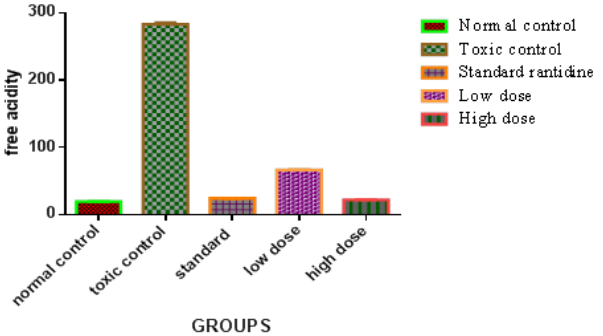

Figure 6. Effect of ethanolic extract of *Ficusarnottiana* on free acidity

In-Vitro Anti-oxidant activity:

DPPH free radical scavenging activity: DPPH is a relatively stable free radical which when encounters proton donors' such as antioxidants, the radicals get quenched and absorbance gets reduced. Results indicated definite scavenging activity of the extract towards DPPH radicals when compared with standard ascorbic acid. IC_{50} value for standard Ascorbic acid was found to be 43.137µg/ml., whereas the IC_{50}value for ethanolic extract of *Ficusarnottiana* was found to be 41.024 µg/ml.

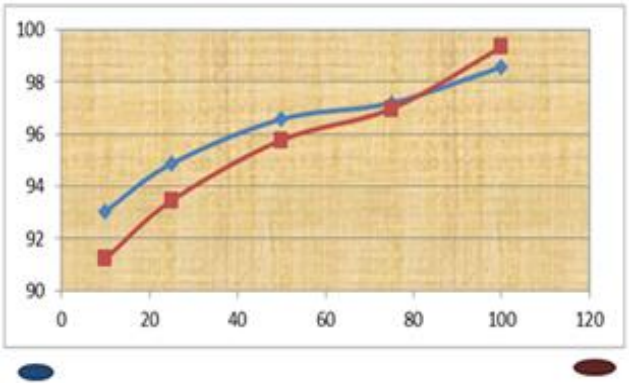

Figure.7. anti-oxidant activity of beet root& ascorbic acid

4. Conclusion

In conclusion, the ethanolic extract of *Ficusarnottiana* treated groups shows a significant effect when compared to control group animals which indicating that the plant having the anti-ulcer activity. And also the results showed that the ethanolic extract of the *Ficusarnottiana* having the antioxidant activity. The acute toxicity study conducted for ethanolic extract of *Ficusarnottiana* indicates that safe up to 2000mg/kg body weight. Ulcer can minimize by some life style changes like, avoid eating at least two hours before bed time and whatever foods might cause discomfort, such as alcohol, caffeine beverages (coffee and pop), fatty foods, and highly seasoned foods. It is important to try to stop smoking, since smoking has been linked to ulcer formation, reduced healing, and ulcer recurrences. Also try to minimize stress in life. Stress may worsen ulcer symptoms.

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