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Evaluation of anti-ulcer and analgesic activity of *Annona squamosa* leaves

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Abstract

In the present research work, medicinally important dried leaves of *Annona squamosa* were demonstrated for the identification of phytochemical compounds and Pharmacological activities. Plants were very important in medicinal field; they have similar properties as conventional drugs. Medicinal plants are safer due to their lower chances of adverse effects and better compatibility to human being. Different solvents are used to extract the biological compounds present in the leaves; among them methanol shows more biological compounds. Chemical constituents derived from plant source have a very long history in treatment of human diseases. Nearly 70% of new chemical entities reported during the past decades were from natural products. In the present study, on abdominal section histopathological observation for analgesic and antiulcer activities were reported. Analgesic activity was observed to the level of clinical importance, this activity was due to the presence of flavonoids and antiulcer activity exhibited due to mucosal defensive factor, than can be used for treatment of peptic ulcer. Further research is required to identify the active phytoconstituents present in the extract and experimentation on the healing action of drug as well as less side effects. The present investigation on mode of action may give way for establishment of new anti-ulcer and analgesic activity.

Keywords: *Annona squamosa*; Phytochemical investigation; Analgesic activity; Antiulcer activity

1. Introduction

The use of phytoconstituents to treat major ailments as drug therapy was proven to be clinically effective and less relatively toxic than the existing drugs. Plant origin drugs were gaining popularity and are being investigated for various disorders, including analgesic and peptic ulcer. In India medicinal plants have been used as therapeutic source for treating a wide variety of diseases from centuries. It is estimated by World Health Organization that, 80% of the world population must rely on traditional medicines for health care: these traditional medicines are mainly plant based. The selection of plant was made based on its availability, therapeutic value and degree of research work which is not done. According to the recent unifying concept of NSAIDS action, inflammation, fever, pain, arachidonic acid is liberated from phospholipase fraction of the cell membrane; arachidonic acid is then converted to prostaglandins via cyclo-oxygenase pathway. COX-1 is constitutively produced in stomach, kidney and blood vessels whereas COX-2 is inducible in activated leucocytes and other inflammatory cells. It is presumed that PGs sensitize blood vessels to the effects of mediators such as 5-HT, histamine and bradykinin that increase the permeability. There are various herbs that are useful and effective for pain relief many are safe for everyone, but some should be avoided. Peptic ulcer disease is a severe gastrointestinal disorder that need a well-targeted therapeutic strategy, the drugs such as H2 receptor antagonists and proton pump inhibitors are available for the treatment of peptic ulcer, but in clinical evaluation these drugs has shown incidence of relapse, side effects, and drug interaction. Local mechanism involved in mucosal hydrophobicity, rapid epithelial cell renewal and rich mucosal blood flow. The gastric mucosa synthesizes Prostaglandins known to stimulate the secretion of mucus, inhibit the secretion of gastric acid and bicarbonate. Searching for novel molecules and to develop new antiulcer molecule from herbal drugs that may give better protection and relapse

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2. Material and methods

The fresh leaves of *Annona squamosa* were collected from local area at Sathupally, Telangana. To remove debris, the leaves were washed and air dried, then crushed with mechanical grinder to get coarse powder. The powdered leave product was stored in air-tight container for extraction.

2.1. Phytochemical studies: extraction of plant material

300 gm of leave powdered was placed and extracted with ethanol for 12 hrs by Soxhlet apparatus. The marc was taken out after completion of the extraction process and was dried. The powdered marc again extracted with ethanol for 12 hours till marc became colorless. The extracted solution was concentrated by evaporation, until it becomes a syrupy greenish mass.

2.2. Preliminary phytochemical analysis

The evaporated plant extract was subjected to preliminary phytochemical investigation for the detection of various bioactive components present in leaves. The powder was used for investigation of the presence of glycosides, alkaloids, flavonoids, steroids, coumarin, tannins, carbohydrate, saponins, phenol, protein, sugar and terpenoids according to standard procedures.

2.2.1. Tests for alkaloids

- Dragendorff 's test: To 2 mL of leaf extract add 1 mL of Dragendorff"s reagent if an orange red precipitate was observed, indicates the presence of alkaloids.
- Mayer's test: To 2 mL of leaf extract add few drops of Mayer's reagent if yellowish white precipitate was observed indicates the presence of alkaloids.
- Hager's test: To 2mL of leaf extract add few drops of Hager's reagent if yellow precipitate was observed, indicates the presence of alkaloids.
- Wagner's test: To 2mL of leaf extract add few drops of Wagner's reagent if reddish brown precipitate was observed, indicates the presence of alkaloids.

2.2.2. Tests for flavonoids

Shinod's test: To 2 mL of plant extract add ten drops of dilute hydrochloric acid and a piece of magnesium if a deep pink colour was observed indicates the presence of flavonoids.

2.2.3. Test for phenolic compounds and tannins

Ferric chloride test: To 1 mL of leaf extract add 2 mL of 5% ferric chloride solution if dark blue colour was observed that indicates the presence of phenolic compounds and tannins.

2.2.4. Tests for proteins

Biuret test: To 1 mL of leaf extract add 2 drops of 3% copper sulphate and few drops of 10% sodium hydroxide, if violet or red colour was observed indicates the presence of proteins.

2.2.5. Test for carbohydrates

Benedict's test. To 5 mL of Benedict's reagent add few drops of leaf extract, then heat it for five minutes, if dark red precipitate was observed indicates the presence of carbohydrates.

2.2.6. Tests for glycosides

Keller Killiani test: To 2 mL of leaf extract add 0.5 mL of glacial acetic acid and 2-3 drops of ferric chloride mix it, add 1 mL of concentrated H_2SO_4 on the walls of the test tube. If deep blue colour was observed at the junction of two solutions indicates the presence of cardiac glycosides.

2.2.7. Tests for saponins

To 5 mL of leaf extract add few drops of Na_2CO_3 solution in a test tube. After vigorous shaking, keep it as side for five minutes, ff foam was observed indicates the presence of saponins.

2.2.8. Test for steroids

Salkowski test: The leaf extract was treated with chloroform and concentrated H_2SO_4, if red colour observed, indicates the presence of steroids.

2.3. Evaluation of anti-ulcer activity

2.3.1. Animal study

Male albino-Wistar rats were used in the present evaluation, average weight of each rat is 150-200g.

Housing and feeding condition

All the rats were placed at room temperature (25 to 30° C) in the animal house. As per the internationally accepted ethical guidelines for the care of laboratory animals, all the animals were housed and treated. All rats were fed with standard food and were acclimatized to standard laboratory conditions of temperature (25 to 30°c) and maintained an 12:12 hrs light, dark cycle prior to the experiments.

Extract: Ethanolic extract of *Annona squamosa* leaves.

Standard drug used

- Omeprazole (20mg/kg)
- Acetic acid (1%v/v)
- Pentazocine (30mg/kg)

Omeprazole and the *Annona squamosa* extract were placed in 0.5% CMC.

2.3.2. Anti-ulcer activity

The anti-ulcer activity of the ethanolic leaf extract of *Annona squamosa* was performed by different models in experimental Wistar rats.

2.4. Experimental procedures

2.4.1. Aspirin induced ulcer

Male albino-Wistar rats were separated into four groups, in each group six animals and were fasted for 24 hrs prior to the experiment in perforated steel cages to avoid coprophagy.

- Group I - control.
- Group II - received 50mg/kg, p.o ethanolic extract of leaves.
- Group III - received 100mg/kg, p.o ethanolic extract of leaves.
- Group IV - received 20mg/kg, p.o Omeprazole as standard.

One hour after the drug administration, the animals were treated with aspirin 200mg/kg by p.o, to induce ulcers. One group is kept as control without any treatment. After 4 hrs, the animals were sacrificed, and stomach was opened and percentage inhibition of ulcer was recorded.

2.4.2. Pylorus ligation model

The animals were divided into four groups, in each group six animals are placed

- Group I - received 1% CMC (1.0ml/kg p.o) as vehicle control
- Group II - received 20mg/kg, p.o *Omeprazole* as standard drug
- Group III - received 50mg/kg, p.o ethanolic extract of leaves.
- Group IV - received 100mg/kg, p.o ethanolic extract of leaves.

All the animals in the group were fasted for 36 h after the respective assigned treatment and were anaesthetized with ether. A small midline incision was done below the xiphoid process by opening the abdomen and pylorus portion of stomach was lifted out and ligated. To avoid traction to the blood supply precautions were taken, the stomach was sutured with interrupted sutures. To recover and stabilize in individual cages, animals were allowed and were deprived

of water during post-operative period. The animals were sacrificed by an excess dose of ether four hours after the pyloric ligation. The stomach was removed carefully, and the gastric contents were collected, and the gastric juice was centrifuged at 1000 rpm and gastric volume was noted. Free and total acidities of the supernatant were determined by titrating with 0.1 N NaOH and expressed as mEq/ L /100 g. The stomach was open along with the greater curvature and pinned onto a soft board for evaluation of the gastric ulcers and to calculate ulcer index.

2.5. Evaluation of analgesic activity

2.5.1. Analgesic activity

The ethanolic extract of Annona squamosa were used for determination of analgesic activity by Acetic acid induced writhing method

2.5.2. Experimental procedure

The analgesic activity was determined on mice, fasted for 12 hrs prior to the experiment, the animals were separated into four groups, in each group four mice are used.

- Group I – be given acetic acid 1%w/v.
- Group II - be given extract 50mg/kg.
- Group III - be given extract 100mg/kg.
- Group IV - Standard 30mg/kg.

This activity was performed by acetic acid induced writhing method. The ethanolic extract was prepared as dose 50 and 100 mg/kg body weight, an acetic acid (1%w/v) is suspended in 1% suspension of carboxy methyl cellulose. An aliquot of 0.25 ml of these suspensions were injected intraperitoneally into each animal. The animal reacts were observed as characteristic stretching behavior, a series of constrictions occur that travel along the abdominal wall, sometimes accompanied by turning movements of the body and extension of the hind limbs. A group of four animals were used as test group in prior to acetic acid administration, test drugs are given orally. The mice are kept individually into glass chambers and number of writhes is noted for 10 min in each animal. A writhe is identified for scoring by stretch the abdomen at least one hind limb with simultaneous stretching.

$$\text{Formula for computing percent inhibition is } = \frac{\text{Average writhes in control group} - \text{writhes in test group } \times 100}{\text{Writhes in the control group}}$$

The period with the greatest percent of inhibition is considered the peak time % decrease in activity= 100-(test / standard × 100)

3. Results and Discussion

The present research shows that the ethanolic extract of *Annona squamosa* leaves having analgesic activity and gastro-protective action against *aspirin* induced ulcer model, pylorus ligation mode, *aspirin* induced ulcer model and acetic acid induced writhing model.

3.1. Phytochemical analysis

Qualitative chemical tests of leaf extracts of *Annona squamosa*:

The Phytochemical investigation of the leave extract of *Annona squamosa* showed the presence of carbohydrates, glycosides, alkaloids, Phyto steroids, flavonoids, Protein and amino acids, saponins, tannins and phenolic compounds. The various phytochemical compounds present in the leaf extract of *Annona squamosa* shown in the table 01. In previous works reported that these compounds will be able to stimulate mucus, bicarbonate and prostaglandin secretion, and counteract with the deteriorating effects of reactive oxidants in gastrointestinal lumen. Tannins are shown that outermost layer of the mucosa and render it less permeable and more resistant to chemical and mechanical injuries. Tannins that inhibit ulcer development due to their protein precipitating and vasoconstriction effects. Their astringent activity may help precipitation of micro proteins on the ulcer site, so formation of an impervious layer over the line that hinders gut secretions and protects the underlying mucosa from toxins and other irritants.

Table 1 Qualitative chemical tests of leaf extracts of *Annona squamosa*

Phytochemicals	Pet. ether	Ethanol	Chloroform	Acetone
Carbohydrates	+	+	-	+
Glycosides	+	+	+	+
Alkaloids	+	+	-	+
Phyto steroids	-	+	+	-
Flavonoids	+	+	-	-
Protein & amino acids	-	+	-	-
Saponin	-	+	+	-
Phenols & tannins	-	-	-	+

3.2. Anti-ulcer screening

3.2.1. Aspirin induced ulcer model

Table 2 Effect of *Annona squamosa* Leaf on *Aspirin* induced ulcers

Groups	Ulcer Index	% Protection
GroupI - Control	19.76±0.10	--
Group II – Standard (*Omeprazole*)	3.28±0.06	76.4 %
Group III – *Annona squamosal* Extract 100mg	5.97±0.08	62.43%
Group IV – *Annona squamosal* Extract 50mg	8.14±0.08	51.22 %

Data were analysed by one-way ANOVA followed by Dunnett's test.

3.2.2. Histopathology Examination

The Histopathology Examination reports demonstrate a prominent damage, loss of mucus and chief cells as well as marked infiltration of the leucocytes to the stomach surface of the rats in group-I treated only with aspirin. In Group-II, the standard group showed no damage to the gastric mucosa. The histopathological sections of group- III, treated with ethanolic extract of *A. squamosa* shown a reduction in the ulcer focus and a hyperplastic gastric mucosa with regenerating mucosal epithelium. The section of IV- group rats shown mucosal erosion and ulceration to the stomach surface illustrating a less protection to the mucosa and the gastric epithelium.

3.2.3. Ulcer index (UI)

Oral administration of ethanolic extract of *Annona squamosa* at doses of 50 and 100mg/kg exhibited dose dependent inhibition percentage of 51.22 and 62.43 respectively compared to the ulcer control, proving the anti-ulcer activity. The standard drug *omeprazole* (20mg/kg) shown 76.4 percentage protection when compared with ulcer control. *Aspirin* is a cyclooxygenase inhibitor which suppresses gastroduodenal bicarbonate secretion, reduces endogenous prostaglandin biosynthesis and disrupts the mucosal barrier as well as mucosal blood flow in animals.

3.3. Pylorus ligation induced ulcers

Data were analysed by one-way ANOVA followed by Dunnett's test.

The ethanol extract of leaf exhibited a dose dependent inhibition percentage of 27.44 and 41.09 at doses of 50 & 100mg/kg dose respectively. The standard drug *Omeprazole* shown an inhibition percentage of 61.13. The extraction and standard drug compared with ulcer control. The results are shown in table 4.

Table 3 Effect of *Annona squamosa* on pylorus ligation induced ulcers

Groups	Ulcer Index	% Protection
Group I - Control	15.68±0.10	--
GroupII – Standard (*Omeprazole*)	5.85±0.10	61.13 %
Group III – *Annona squamosal* Extract 100mg	8.76±0.10	41.09%
Group IV – *Annona squamosal* Extract 50mg	10.45±0.10	27.44 %

Table 4 Effect of *Annona squamosa* on gastric secretions, free acidity and total acidity on pylorus ligation model

Group	Gastric Volume	pH	Free Acidity	Total Acidity
Control	5.23 ± 0.10	1.45 ± 0.08	68.64 ± 1.12	71.64 ± 1.34
Std (*Omeprazole*)	1.56 ± 0.05	4.55 ± 0.07	27.65 ± 0.96	37.37 ± 0.81
Extract 100mg	2.76 ± 0.08	3.76 ± 0.08	45.83 ± 0.45	55.87 ± 1.45
Extract 50mg	3.83 ± 0.04	2.65 ± 0.09	55.39 ± 0.85	64.98 ± 1.25

Data was analysed by one-way ANOVA followed by Dunnett's test.

3.3.1. Histopathology examination

The histopathological observation of stomach of the rats shown a best picture of the gastric lesions and the damage occurred to the mucosa. Significant acute ulceration was noted in group-I which was Pylorus ligation. The pylorus ligation induced extensive macroscopic mucosal damage which can be known by the injury to the epithelia of the mucosa, elongated haemorrhagic lesions were noted running perpendicular to the axis of the stomach.

3.4. Analgesic activity

3.4.1. Acetic acid induced writhing method

Table 5 Effect of *Annona squamosa* Leaf on Acetic acid induced ulcers

S. No	Groups	Number of writhing's	% decrease in activity
1	Control (acetic acid)	46.02±4.11	-
2	*A. squamosa* extract 50mg/kg	16.95±1.56	79.86%
3	*A. squamosa* extract 100mg/kg	8.76±0.58	87.37%
4	Standard (*pentazocine*) 20mg/kg	5.34±0.57	89.87%

Data were analysed by one-way ANOVA followed by Dennett's test.

The ethanolic extraction of leaves produced significant analgesic activity in dose dependent manner and a significant effect was observed at a dose of 100 mg/kg. The result of the data reflects the intensity of analgesic activity at peripheral area, which is compared with standard drug (*pentazocine*). Drugs, which are centrally both peripheral and central, such as *pentazocine*, only inhibit the late phase. A few alkaloids have been reported to produce analgesic activity. The pharmacological studies of extract showed that, extract possessed analgesic activity to varying extent. It showed that alkaloids present in this extract may be responsible for the pharmacological action. The extract was tested at two different doses (50 and 100mg/kg) to know if they were dose dependent. First the control group of animals were tested with the acetic acid, and then observed the number of writhes produced by the animal. The extract exhibited a percentage inhibition of 79.86 and 87.37 at doses of 50 and 100 mg/kg respectively. These shows that ethanolic extract

of *Annona squamosa* shows high significantly decrease in the writhing response induced by acetic acid when compared with control group.

4. Conclusion

In the present work medicinally important active ingredients of dried leaves of *Annona squamosa* were studied with special emphasis on natural conditioning. Primary phytochemical and Pharmacological conditioning were studied and reported. Histopathological observation for antiulcer exertion was done on abdominal section. Antiulcer and analgesic conditioning were studied. It was set up that antiulcer exertion displayed was due to mucosal protective factor. Hence it can be used for operation of peptic ulcer. Analgesic exertion was displayed to the position of clinical significance. It was set up that the exertion was due to the presence of flavonoids. Chemical substances deduced from factory have got a veritably long history in treatment of mortal conditions. Nearly 50 of new chemical realities introduced during the once two decades were from natural products. farther exploration is needed to insulate the active phytoconstituents present in the excerpt and trial on the mending action of medicine on habitual ulcer as well as on the possible side goods. The disquisition on mode of action may pave way for establishment of new anti-ulcer remedy authority.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Our institution has ethical approval with registration number: 1769/PO/Re/S/ 14/CPCSEA.

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