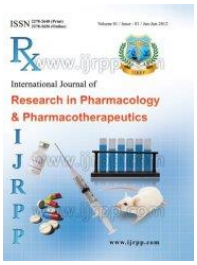
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 IJRPP |Vol.11 | Issue 2 | Apr - Jun - 2022
ISSN Online: 2278-2656 Journal Home Page: www.ijrpp.com

Research Study Open Access

Evaluation of anti-ulcer activity of methanolic extract of *psydrax dicoccos* in experimental rats

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ABSTRACT

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 *Psydrax dicoccum.* The methanolic extract of *Psydrax dicoccum* 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 methanolic extract of the *Psydrax dicoccum* having the antioxidant activity. The acute toxicity study conducted for methanolic extract of *Psydrax dicoccum* indicates that safe up to 2000mg/kg body weight. Ulcer can minimize by some life style changes like, avoid alcohol, caffeine beverages (coffee and pop), fatty foods, and highly seasoned foods. Also try to minimize stress in life. Stress may worsen ulcer symptoms.

Keywords: **Psydrax dicoccum, Anti Ulcer, Methanolic**

INTRODUCTION

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]. Peptic ulcer disease is a worldwide problem, affecting about 1 in 10 people. Duodenal ulcers are more common than gastric ulcers and usually occur in people aged fewer than 50. In 1982, Australian doctors Robin Warren and Barry Marshall first discovered a link between ulcers and H. Pylori [3,4]. Usually Ulcer occurs by many causative agents. But now a day's ulcer is mainly caused by five reasons: Alcohol consumption, NSAIDs consumption,Smoking consumption,Skipped meals and poor sleep.

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 methanol induced gastric mucosal damage [5].

NSAID-induced ulcers are symptomatic only in 1% of patients after three to six months and in 2 to 4% of patients after one year and the average age of onset of gastric ulcers is between 40 to 55 years. Endogenous prostaglandins are involved in the

regulation of mucus and bicarbonate secretion by the gastric and duodenal epithelium, mucosal blood flow, epithelial cell proliferation, epithelial restitution and mucosal immunocyte function. NSAIDs are inhibiting the prostaglandins synthesis [6]. So NSAIDs cause the ulcer in stomach. Therefore, treatment with prostaglandins analogues and anti-oxidants can decrease NSAIDs induced gastric mucosal damage. Disturbances in microcirculation, increased duodenum reflux, delayed gastric emptying and therefore can be treated with antioxidants and antiulcer agents.[7]

Stress seems to have variable effects on gastric motility, delayed gastric emptying could increase the risk of gastric ulcer, while accelerated emptying could increase the net acid load delivered to the duodenum at any given level of gastric secretion, enhancing the risk of duodenal ulcer [8]

The infectious agents, Helicobacter pylori plays a key role in the pathogenesis of acid- peptic diseases. Three of the main components of the pathogenesis of NSAID - induced gastrointestinal mucosal injury. Suppression of Cox-1 causes a profound reduction of mucosal prostaglandin synthesis which probably impairs many components of mucosal defense, the reduction of mucosal blood flow may be most important and release of endothelin - 1 is potent vasoconstriction which has been shown to induce mucosal injury.Proton pump inhibitors and H2- receptor antagonists are the most widely used drugs to treat peptic ulcer disease. They Produce some adverse reactions such as hypersensitivity, arrhythmia, impotence and haemopoietic changes, gynaecomastia, alopecia, mental confusion with is a possibility of increased rate of ulcer recurrence within one year after cessation of the treatment [9]. Thus, there is a need for more effective, less toxic and cost-effective anti-ulcer agents

Numerous medicinal plants and their formulations are used for peptic ulcer in ethno medical practices and in traditional system of medicine in India. Most of the herbal drugs speed up the natural ulcer healing process. One such anti ulcer activity possessing natural source is *boswellia serrata* as per traditional system of medicine.

Herbal Medicine is defined as branch of science in which plant based formulations are used to treat the diseases. Herbal medicine gradually lost its popularity among people and it was based on the fast therapeutic actions of synthetic drugs. Herbal medicines have no side effects, cost effective, good tolerability [10].

Therapeutic value of medicinal plants could differ depending on soil conditions, nutritional status, and climatic conditions, seasonal variations, diurnal variations and their association with other organisms[11]. Medicinal plants have always been the main sources of new drugs candidates for the treatment of gastric ulcer. The chalcone, sofalcone, kaempferol, naringin, sophoradin, cynidin, Wogonin, Apigenin these are flavonoids used for the ulcer. These flavonoids are present in medicinal plants.

Quercetin the most abundant flavonoids is reported to prevent gastric mucosal lesions produced by many ulcerogens such as indomethacin. Various biochemical mechanisms such as inhibition of the gastric proton pump, lipid peroxidation, and enhanced mucin synthesis through PG stimulation have been suggested to having its anti-ulcer property [12].

Psydrax dicoccos, synonym canthium dicoccum belongs to family rubiaceae commonly called Ceylon boxwood. Bark was used as fever, devotion of roots was used internally for treating diarrhoea. Bark powder boiled with sesame oil was used externally for rheumatic pains. The plant is used for its anti-inflammatory activity, antidiabetic and nephrotective activity. Bark contains sitoserol.quinovaic acid. Acetyl quinovaic acid and scopoletin.Leaves contain ursolic acid, quercetin, rutin 7-o, spathenol, carophyllene oxide, cedren- 13- ol.

To know the ulcer healing properties of *Psydrax dicoccos*, we therefore aimed to evaluate antiulcer activity of Psydrax dicoccos extract in rats

MATERIALS AND METHODS

Material

Drugs: Aspirin, Standard drug ranitidine.

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

Reagents: Benedict's reagent, barfoed's reagent, millon's regent, wagner's regent, Hager's regent. Mayer's regeant

Collection and Authentification of Plant Material: The whole plant of *Psydrax dicoccum* collected and authenticated.

Extraction of Plant Material: The plant is grinded in to a coarse powder with the help of suitable grinder

Hot Continuous Extraction (Soxhlet)

In this method, the finely ground crude drug is placed in a porous bag or "thimble" made of strong filter paper, which is placed in chamber E of the Soxhlet apparatus. The extracting solvent in flask A is heated, and its vapors condense in condenser D. The condensed extractant drips into the thimble containing the crude drug, and extracts it by contact. When the level of liquid in chamber E rises to the top of siphon tube C, the liquid contents of chamber E siphon into flask A. This process is continuous and is carried out until a drop of solvent from the siphon tube does not leave residue when evaporated.

Evaporation of Solvent

The filtrates (methanol extract) obtained were evaporated using Rotary evaporator in a porcelain dish. They rendered a gummy concentrate of greenish black. The extract was kept in vaccum dissecator for 7 days.

Preliminary phytochemical screening of extracts [1]

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

Test for Carbohydrates

Molisch's test: To 2-3ml of extract, few drops of α-naphthol solution in alcohol were added, shaken and concentrated sulphuric acid was added from the side of the test tube. It was observed for violet ring at the junction of two liquids.

Tests for Glycosides

Liebermann-buchard's, reaction: Mixed 2ml of extract with chloroform. added 1-2 ml of acetic anhydride and 2 drops concentrated sulphuric acid from the side of the test tube. Observed the first red then blue and finally green.

Test for Sugars

Fehling's, test: 1ml of Fehling A and 1ml of Fehling B solutions was mixed and boiled for 1 min. equal volume of test solution was added. Heated in boiling water bath for 5-10 min and observed for a yellow and then brick red precipitate.

Benedict's test: Equal volume of Benedict's regent and test solution in test tube were mixed. Heated in boiling water bath for 5min. solution may appear green yellow or red depending on amount of reducing sugar present in test solution.

Test for Amino acids

Ninhydrin tests: 3ml of test solution and 3 drops of ninhydrin were heated in boiling water bath for 10 min. observed for purple or bluish colour.

Test for proteins

Millon's, test: Mixed 3ml of test solution with 5ml of Millon's reagent, white precipitate obtained. Precipitate warmed turns brick red or precipitate dissolves given red solution.

Test for flavonoids

To small quantity of residue, added lead acetate solution observed for yellow colored precipitate. To the test solution, added few drops of ferric chloride solution observed for intense green.

Test for Alkaloids

Mayer's test: 2-3 ml of filtrate with few drops of mayer's reagent was observed for precipitate.

Hager's test: 2-3 ml of filtrate with few drops Hager's reagent was observed for yellow precipitate.

Tests for tannins and phenolic compounds

To 2-3ml of test solution added few drops of following solutions was looked for respective coloration or precipitate.

5% ferric chloride solution-Deep blue black colored, Lead acetate solution-white precipitate,*Gelatin solution- white precipitate,*Acetic acid solution, *red color solution

Animals

The animals used in the present study were adult male wistar rats (10–12 weeks old with body weight 150-200 g), obtained from the animal house. The animals were kept under (12 h light, 12 h dark cycle), with free access to standard diet and water.

Acute toxicity studies

Objective of performing Acute Toxicity Studies

The aim of performing acute toxicity studies is for establishing the therapeutic Index (TI) of a particular drug and to ensure the safety in vivo. Acute toxicity study is generally carried out for the determination of LD50 value in experimental animals.

Requirements

Animal: wistar rats, 150-200gm, Drugs/extracts: Ranitidine/extracts of *Psydrax diccocum*

Procedure

The overnight fasted rats were weighed and selected. The extracts were dosed in a stepwise procedure, with the initial dose being selected as the dose expected to produce some signs of toxicity and were observed for a period of two weeks. The Wistar rats of single sex, weighing between 150 to 200 g were selected and divided in to 5 groups each consisting of 5 animals. They were maintained under at 12 hr light/dark and allowed free access to water .The animals were subjected for acute toxicity study using each extract at a dose of 2000 mg/kg orally in 5 groups and observed at regular intervals of 1, 2, 4, 8, 12 and 24 hours for skin changes, morbidity, aggressiveness, increase oral secretion, sensitivity to the sound and pain as well as respiratory movements and mortality.

Method of Induction and Experimental Animal Protocol

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 of Aspirin induced ulcer model.

Groups	Treatment
I	control (250mg/kg aspirin)
II	Ranitidine (20mg/kg)
III	**MEPD** 200mg/kg
IV	**MEPD** 400mg/kg

Experimental procedure

First group treated with Aspirin in a dose of 250 mg/kg was administered orally on the day of experiment with the help of an oral feeding tube in the form of an aqueous water suspension. 2nd, 3rd, 4th 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 2nd, 3rd, 4th 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.

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.

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.

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 colour was 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.

$$\text{Acidity} = \frac{\text{Volume of NaOH x Normality x 100}}{0.1} \text{ mEq/1it/100gm}$$

Determination of Ulcer Index (UI)

The ulcerative index was calculated by severity of gastric mucosal lesions and graded as follows; 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% methanol buffer formalin and processed though graded methanol, 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 microscope. The different histopathological indices screened were: congestion, hemorrhage, edema, necrosis, inflammatory and dysplastic changes, erosions and ulcerations

Statistical analysis

The values are expressed as mean value ± standard deviation (SD). The data were evaluated by using the SPSS (version 12.0) and one-way ANOVA, followed by Bonferroni t-test. Statistical significance was considered when value of $P < 0.05$.

RESULTS & DISCUSSION

Table 2: Phytochemical Analysis

Phytoconstituents	Present or Absent
Carbohydrates	Absent
Glycosides	Present
Fats	Absent
Gums & mucilages	Absent
Proteins & amino acids	Present
Saponins	Present

Pharmacological studies

Acute toxicity studies

The methanolic extract of *Psydrax dicoccum* was subjected for the acute toxicity study to determine the therapeutic dose using Wistar rats. Acute oral toxicity study was performed as per OECD guidelines. Acute toxicity study carried out on MEPD up to the dose of 2000 mg/kg demonstrated that the extract did not show any sign of toxicity and mortality. Hence 200 and 400 mg/kg dose of the extract selected for evaluation of anti-ulcer activity.

Effect of methanolic extract of Psydrax dicoccum in Aspirin induced gastric ulcer

In aspirin induced gastric ulcer model, the ulcer index of control group is 13.083±0.4282. The animals treated with methanolic extract of *Psydrax dicoccum* at 400 mg/kg dose showed significant (*P<0.01*) reduction in the number of ulcer and ulcer index is 10.516±0.42816. Ranitidine at 20mg/kg showed significant (*P<0.01*) reduction in the number of ulcer and ulcer index is 10.562±0.4216. Extract at 200mg/kg shows the protection against the aspirin induced gastric ulcer, ulcer index 10.35±0.5627. Administration of *Psydrax dicoccos* 1 h before the induction of gastric lesions by aspirin showed significant activity, and inhibited the ulcer index .The methanolic extract of *Psydrax dicoccum* was found to possess remarkable ulcer-

protective properties at 200 mg/kg and 400 mg/kg when compare to toxic control group.

Table 3: Effect of methanolic extract of *Psydrax dicoccos on* ulcer index and %ulcer protection in aspirin induced gastric ulcer.

Groups (n=5)	Treatment	UI	% ulcer protection
I	Control	13.083±0.4282	0.00
II	Standard	10.562±0.4216**	24.74
III	***Psydrax dicoccos*** 200 mg/kg	10.35±0.5627ns	7.613
IV	***Psydrax dicoccos*** 400mg/kg	10.516±0.42816**	24.16

*Values express as mean ± SEM; n=6 in each group, statistical comparisons as follows: significant at P<0.01** compared to control group, P>0.05 ns-non significant*

Volume of gastric content

Gastric content volume high (3.21±0.121) in control group. Gastric content volume siginificantly decreases in methanolic extract of *Psydrax dicoccum* at 200 (2.179±0.213) and 400mg/kg (2.183±0.195) doses. Gastric content volume in standard group (2.185±0.195).

Table 4: Effect of methanolic extract of *Psydrax dicoccos* on gastric content volume

Groups	Treatment	Volume of gastric content
I	Control	3.21±0.121
II	Standard	2.185±0.195**
III	***Psydrax dicoccos*** 200 mg/kg	2.179±0.213**
IV	***Psydrax dicoccos*** 400mg/kg	2.183±0.195**

*Values express as mean ± SEM; n=6 in each group, statistical comparisons as follows: significant at P<0.01** compared to control group*

Table 5: Effect of methanolic extract of *Psydrax dicoccos* on gastric juice PH

Groups	Treatment	PH
I	Control	3.831±0.118
II	Standard	3.891±0.138**
III	***Psydrax dicoccos*** 200 mg/kg	3.758±0.192**
IV	***Psydrax dicoccos*** 400mg/kg	3.868±0.185**

*Values express as mean ± SEM; n=6 in each group, statistical comparisons as follows: significant at P<0.01** compared to control group.*

Table 6.: Effect of methanolic extract of *Psydrax dicoccos* on total acidity

Groups	Treatment	Total acidity(mEq/lit)
II	Control	56.4±1.482
III	Standard	55.6±1.216
IV	***Psydrax dicoccos*** 200 mg/kg	53.2±1.324
V	***Psydrax dicoccos*** 400mg/kg	54.4±0.233

Values express as mean ± SEM; n=6 in each group, statistical comparisons as follows: significant at P<0.01** compared to toxic control group.

Free acidity (mEq/lit)

In pylorus ligation induced gastric ulcer model the free acidity high (28.3±2.171) in control group. Free acidity significantly decreases in methanolic extract of *Psydrax dicoccus* at 200 (20.2±0.447) and 400mg/kg (21.76±0.288) doses. Free acidity significantly decreases in standard group (24.4±0.180) compared toxic control group.

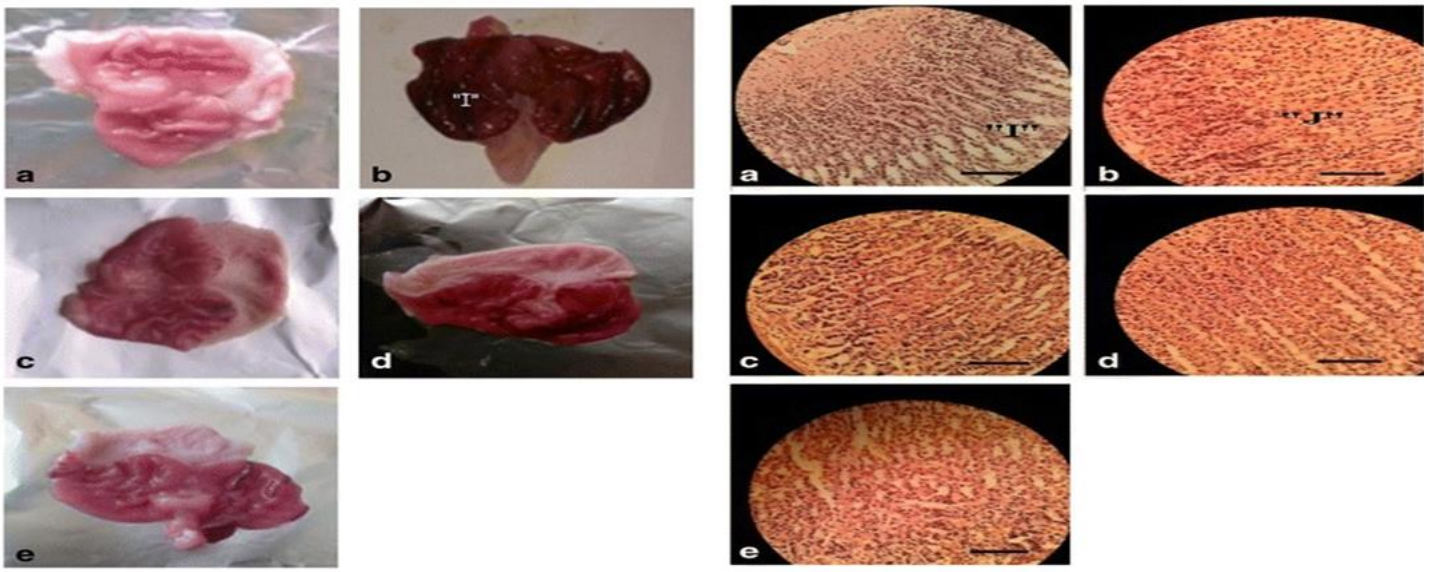
Table 7: Effect of methanolic extract of *Psydrax dicoccos on* free acidity

Groups	Treatment	Free acidity(mEq/lit)
II	Control	28.3±2.171
III	Standard	24.4±0.180
IV	***Psydrax dicoccos*** 200 mg/kg	20.2±0.447
V	***Psydrax dicoccos*** 400mg/kg	21.76±0.288

*Values express as mean ± SEM; n=6 in each group, statistical comparisons as follows: significant at P<0.01** compared to toxic control group*

Histopathological evaluation

Gross appearance of the gastric mucosa. a Normal control: no mucosal damage was observed, b Aspirin control: marked ulcers along with hemorrhagic streaks and mucosal damage were observed, c 20 mg/kg ranitidine, mild injuries were observed in the gastric mucosa as compared to the methanol control group, d 200 mg/kg methanolic extract of Psydrax dicoccum : moderately reduced gastric mucosal damage and ulcers were observed, e 400 mg/kg methanolic extract o*f Psydrax dicoccum:* significantly reduced gastric mucosal damage and ulcers were observed, "I" indicates gastric mucosal damage and hemorrhagic streaks



a Normal control: no mucosal damage was observed, b Aspirin control: marked ulcers along with hemorrhagic streaks and mucosal damage were observed, c 20 mg/kg ranitidine, mild injuries were observed in the gastric mucosa as compared to the methanol control group, d 200 mg/kg methanolic extract of *Psydrax dicoccum* : moderately reduced gastric mucosal damage and ulcers were observed, e 400 mg/kg methanolic extract of Psydrax dicoccum: significantly reduced gastric mucosal damage and ulcers were observed, "I" indicates gastric mucosal damage and hemorrhagic streaks, "J" indicates degeneration of gastric mucosa and infiltration of inflammatory cells frequently observed in the specimen from the stomach, "K" indicates almost complete regeneration of gastric mucosa. Aspirin causes mucosal damage by decreasing cytoprotective prostaglandin levels through inhibition of PG synthesis and also results in back diffusion of H+ ions into the gastric mucosa and inhibits the release of mucus. In this model methanolic extract of *Psydrax dicoccos* was produced its ulcer protective effect by counteracting the inhibition of PG synthesis and enhancing the mucus release. *Psydrax dicoccos* extract was significantly reducing the ulcer index compare to control group.

DISCUSSION

Ulcer is a major disease of gastrointestinal system which affect 10% world population with different aetiologies. This concerned has led to an increased demand of natural products and treatment of ulcer with medicines of plant origin show safer than synthetic drugs.

Literature shows that aspirin is one of the chemical agent and used for induction of ulcer. Aspirin causes gastrointestinal injury, chronic usage of aspirin causes upper gastrointestinal bleeding and formation of ulcer.In our study the significant increase in ulcer index was observed in aspirin induced ulcer model and rats with ulcer formation administered orally with methanolic extract of *Psydrax dicoccos* (200mg & 400mg) and standard drug rantidine, reduced ulcer properties were observed. Hence proven that Psydrax dicoccos was supported by literature.

According to experimental study marked increase in ulcer index were observed in untreated ulcer rats. The rats with ulcer formation showed the marked reduction in ulcer index when compared with untreated ulcer rats and this shows the beneficial effect of plant extract. The present study reveals the formation of gastric content, gastric juice and total acidity. This is in support of present finding which showed extract of *Psydrax dicoccos* found to be effective against aspirin induced ulcer model.Histopathological studies of aspirin control marked ulcer shows the haemorrhagic streaks and mucosal damage. With the help of extract, significantly reduced gastric mucosal damage and ulcers were observed. Stastical analysis of observation suggest that methanolic extract of *Psydrax dicoccos* have antiulcer property.

CONCLUSION

In conclusion, the methanolic extract of *Psydrax dicoccos* at the doses of 200mg & 400 mg clearly demonstrated antiulcer activity in experimental model of rats.

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