RATS EXPOSED TO OSYRIS QUADRIPARTITA DECNE LEAVES SHOWED BOTH ANTI-ULCER AND ANTIOXIDANT ACTION

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Abstract:

The leaves of Osyris quadripartita Decne) have historically been used in folk medicine to treat dermatitis and snake bites because of its astringent properties. Experimental research has revealed that the methanolic extract of Osyris quadripartita Decne which is high in tannin, possesses antibacterial properties. The objective of the current study was to evaluate the anti-ulcer and antioxidant effectiveness of Osyris quadripartita Decne in rats. At doses of 75, 150, and 300 mg/kg, p.o., the effects of the methanolic extract of Osyris quadripartita Decne leaf extract on gastric secretion, gastric ulcers in pylorus-ligation, and ethanol-induced injury to the gastric mucosa in rats were studied. The ulcer indices in both animals were greatly decreased, and the gastric juice pH was increased. Although its efficacy has not been established, Ethiopian traditional medicine has employed Osyris quadripartita (OQ) to treat peptic ulcer disease. The goal of the current study was to measure the anti-ulcer activity of OQ leaf extract in 80% methanol in rats. The effects of OQ extract on rat stomach ulcers caused by pylorus ligation, ethanol, and repeated dosing (200 mg/kg for 10 and 20 days) were studied using single dose (75, 150, and 300 mg/kg) and repeated dosing (150 mg/kg for 10 and 20 days) approaches. Sucralfate (100 mg/kg) and ranitidine (50 mg/kg) were the usual treatments. Results were measured using ulcer score, ulcer index, and ulcer index inhibition percentage, depending on the model. Other outcome metrics included ulcer score, overall acidity, and the volume and pH of stomach fluid. The findings of this study showed that OQ contains one or more secondary metabolites with pharmacologic activity against ulcers. This study consequently supports the use of it as an ulcer preventive in Ethiopian traditional medicine. To identify specific phytochemicals and elucidate their modes of action, more investigation is needed.

Key words: Anti-ulcer; Antioxidant; Lipid peroxidation; Superoxide dismutase; Catalase; Reduced glutathione

INTRODUCTION:

One of the most prevalent gastrointestinal disorders is the peptic ulcer. A massive quest has been conducted in recent years to find novel antiulcer medications derived from natural sources. The gastric mucosal defence and repair system is disturbed in peptic ulcer disease (PUD). PUD recurrence rates are high and have been linked to a number of variables, such as ongoing Helicobacter pylori infection, ongoing exposure to mucosal-damaging agents (such as use of non-steroidal anti-inflammatory medicines), and weakened mucosal defence mechanisms [1]. The degenerative diseases hypercholesterolemia, atherosclerosis, carcinogenesis, diabetes mellitus, ischemic reperfusion cardiac injury, and disorders of the digestive system like hypersecretion and gastric mucosal damage have all been linked to reactive oxygen species (ROS), which include superoxide anions and hydroxyl radicals as examples [2]. The alteration in antioxidant status that occurs after ulceration suggests that free radicals are responsible for the pylorus-ligation-induced and ethanol-produced. ulcerations in rats. One step towards minimising tissue damage in human disease may be provided by drugs with various protective mechanisms, such as antioxidant capacities. Many herbs are useful at preventing and treating PUD [3], according to animal research. Traditional methods of treating ulcers have long used chemical and herbal extracts. More than 34 species make up the genus Osyris, which is a member of the Santalaceae family. Osyris quadripartita (OQ) also known as qeret in Amharic and wato in Afaan Oromo, is an evergreen, dioecious tree or shrub with numerous branches, some of which are sometimes dangling, and growing to a height of 1–7 metres. [4] Although it can freely grow and live, it is hemiparasitic and may opportunistically tap into the root systems of surrounding plants and parasitize them. It grows between 1600 and 2900 metres above sea level in scrub, degraded woods, and rocky slopes. The plant's popular name is "wild tea plant," and it is indigenous to Africa, Southwestern Europe, and Asia. It has historically been used to cure a number of ailments, including peptic ulcer disease, cancer, toothaches, malaria, skin sores, abdominal pain, and urinary problems. It is widely available in Ethiopia4. The pharmacologic effects of OQ have been investigated in studies ranging from 7 to 12. In addition to lowering capillary permeability connected to inflammation (13), antibacterial and antifungal (14), and antifungal (6) actions, it has antioxidant, antibacterial, antifungal, and antimalarial6 characteristics. There are phytochemicals like polyphenols (flavonoids, lignans, and coumarins), sesquiterpene lactones, and anthracene derivatives, among others. OQ has a variety of pharmacologic effects but no immediate dangers [5]. Peptic ulcer disease and its sequelae continue to be a significant global cause of morbidity and a significant financial burden on healthcare systems. Although there are numerous effective anti-ulcer drugs on the market, the bulk of them have a variety of toxicities, emphasising the need for creative alternatives.2 Up to 80% of people worldwide utilise herbal medicines as their primary form of healthcare, which lends credence to the notion that plant extracts may be effective for creating new drugs. Ethiopia is characterised by a wide range of climatic and ecological conditions, as well as a large diversity of flora and animals, including a wide range of potentially useful medicinal herbs. The genus Osyris, which belongs to the Santalaceae family, has more than 34 species.

MATERIALS AND METHODS:

Chemicals and Drugs:

Glacial acetic acid (Neelkanth college of pharmacy , Meerut), benzene ((Neelkanth college of pharmacy , Meerut), chloroform ((Neelkanth college of pharmacy , Meerut), ethanol ((Neelkanth college of pharmacy , Meerut), ferric chloride (Super Tek Chemicals), lead acetate trihydrate (Guangdong Chemical Reagent Engineering, Guangdong, People's Republic of China), mercuric chloride (Super Tek Chemicals), methanol (Nice Chemicals, Kochi, India), potassium iodide (Super Tek Chemicals), ranitidine (Cadila Pharmaceuticals, Bengaluru, India), sucralfate (Moraceae Pharmaceuticals Pvt. Ltd, Lucknow, India), sulfuric acid (Hi Media Laboratories Pvt. Ltd, Mumbai, India), hydrochloric acid (Nice Laboratory Reagent), sodium hydroxide (Rankem, Mumbai, India), and phenolphthalein (Fine Chemicals, Mumbai, India) were used**.**

Plant material collection and identification:

In January 2016, fresh OQ Salzm. ex Decne. (Santalaceae) leaves were collected in Ethiopia's Gondar region. The voucher specimen was deposited at the National Herbarium of Addis Abeba University (AAU) with voucher number Mattawa 001 after taxonomic identification by Mr. Melaku Wildfires, an ethnobotanist in the Department of Biology and Biodiversity Management [5,6].

Preparation of plant extract:

The extraction procedure was carried out as directed by Girma et al.10 with a small amount of modification. OQ leaves that had just developed were thoroughly washed, let to air dry at room temperature in the shade, and then pulverised with a mortar and pestle into a coarse powder. The powder was stored up until extraction in a dark bottle with a secure lid. Thereafter, 600 g of this coarsely crushed plant were macerated for 3 days at room temperature while intermittently stirring in 80% methanol to create the hydroalcoholic crude extract. The filtrate and marc were divided using a filter paper after 72 hours. The marc was re-macerated twice. The filtrates were combined, and the alcohol was allowed to evaporate in a 40 °C oven. The yield was found to be 35.83% w/w as a percentage. Until the experiment, the dried extract was stored in desiccators [7].

Experimental Animals:

For the testing, albino female Wistar strain rats weighing 180–225 g were used. The animals were bought from the National Toxicology Institute in Pune. The animals were kept in tidy cages made of polypropylene, with a 12:12 light: dark cycle, at a temperature of 22°–3°C and a relative humidity of 45–55%. The animals received regular pellet meals and unrestricted access to water (Amrut laboratory animal feed, Sangli, India). The guidelines set forth by the regional animal ethics committee were followed in the approval and execution of all experiments. The study was carried out according to the National Research Council Guide for the Care and Use of Laboratory Animals and Organization of Economic Co-operation and Development (OECD) guidelines. Approval from the Research Review Committee of the Department of Pharmacology was also obtained. [8].

Experimental method

The animals were divided into six groups, each with six rats. As the normal control group and the Pylorus-ligated control group, respectively, Groups 1 and 2 received 5 ml/kg of vehicle

(1% gum acacia, p.o.). Groups 3 through 5 received 75, 150, and 300 mg/kg of body weight, respectively, of a methanolic extract of Osyris quadripartita Decne indica leaf orally. Ranitidine (2.5 mg/kg) was given to Group 6, the control group [9].

Study of anti-ulcer and antioxidant activity using pylorus ligation method:

It was done using the Shay rat ulcer method (Shay et al., 1945). The rats were deprived for 48 hours. A methanolic extract of Osyris quadripartita Decne leaf material was administered to the animals. During the trial, food was withheld, but the animals were given full access to water. After a one-hour pre-treatment period, the animals were administered anaesthetic ether. In order to access the abdomen, a small midline incision was made below the xiphoid process. The pylorus region of the stomach was then slightly elevated and ligated. Precautions were taken to avoid traction on the pylorus or damage to its blood supply. The wound was sewn shut with interrupted sutures after the stomach was carefully positioned inside the abdomen. The rats' stomachs were removed and killed 19 hours after the pylorus was tied. The stomach contents were separated by centrifuging. The gastric fluid's volume, pH, total acidity, and pepsin activity were all measured. Afterwards, the stomach's wider curvature was cut open to check for ulcers. The ulcers were tallied, and a Vernier calliper was used to measure each ulcer's diameter. The ulcer index was established by Suzuki et al. using their system [10].

Score 1: an ulcer of maximal diameter of 1 mm.
Score 2: an ulcer of maximal diameter of 1 - 2 mm.
Score 3: an ulcer of maximal diameter of 2 - 3 mm.
Score 4: an ulcer of maximal diameter of 3 - 4 mm.
Score 5: an ulcer of maximal diameter of 4 - 5 mm.
Score 10: an ulcer over 5 mm in diameter.
Score 25: a perforated ulcer

The method was applied to calculate the amount of mucus in the stomach. The stomachs of the rats in groups 1 (normal control), 2, and 3 (which received Osyris quadripartita Decne treatment) were weighed and homogenised in cooled tris buffer (10 mm, pH 7.4) at a concentration of 10% w/v after being visually inspected. The homogenates were spun at 10,000 g for 20 minutes at 0 °C in a Remi C-24 high-speed cooling centrifuge. The clear supernatant was used for the lipid peroxidation (MDA concentration), endogenous antioxidant enzymes (SOD and CAT), and reduced glutathione tests (GSH). The silt was suspended in a 10 mm, pH 7.4 tris buffer at a final concentration of 10% to calculate the amount of total proteins present [11].

Investigate the anti-ulcer and antioxidant activities using the ethanol-induced ulcer technique:

The strategy was applied. The rats received the methanolic extract of Osyris quadripartita Decne leaf once daily for ten days. On the tenth day, an hour after receiving their final dosage of the methanolic extract of Osyris quadripartita Decne leaves, the overnight-fasted rats of all groups were given 96% ethanol (5 ml/kg, p.o.). One hour after the ulcerogen injection, the animals were killed. The stomach was then removed, the bigger curvature was cut out, and the size of the lesion was measured to determine the degree of mucosal erosion at random. The overall area was represented by the ulcer index (mm2). The stomach was then measured and processed for antioxidant estimations as described in the earlier section [12].

BIOCHEMICAL PARAMETER:

Superoxide dismutase (SOD) was examined using the Mishra and Fridovich method (1972). described Hugo Abebi's method for estimating catalase (1984). Reduced glutathione was found using the method. Using the Slater and Sawyer method, malondialdehyde (MDA) generation from lipid peroxidation was measured. The total number of proteins was determined [13].

Statistical Analysis: The outcomes of each of the aforementioned estimations are shown as mean SEM. Difference The Tukey-Kramer Multiple Comparison Test and Analysis of Variance (ANOVA) were used to statistically compare the drug-treated groups to the control group, with the significance level set at P 0.05 [14] .

Table 1. Effect of Osyris quadripartita Decne on the various gastric parameters of Pylorus-ligated rats

Parameters	Control Group	Osyris quadripartita Decne (75 mg/kg)	Osyris quadripartita Decne (150 mg/kg)	Osyris quadripartita Decne (300 mg/kg)	Ranitidine (2.5 mg/kg)	F-value
Ulcer index	97.16 ± 4.19	79.33 ± 3.06** (18.35%	41.50 ± 1.74*** (57.28%)	17.59± 2.35*** (80.61%)	9.16 ± 1.64*** (90.57%)	189.01
Volume of gastric fluid (ml)	16.41 ± 0.68	13.58 ± 0.80	11.91 ± 1.24*	8.75 ± 0.49	7.25 ± 0.35*	422.27
PH of gastric fluid	2.16 ± 0.27	2.58 ± 0.27N	3.75 ± 0.21	4.41 ± 0.30	4.75 ± 0.35***	15.23
Total acidity(mEq/l/100 g)	78.33 ± 4.31	63.16± 2.92*	48.83 ± 4.01	25.66 ± 2.03	24.46 ± 2.03	73.271
Pepsin (µg tyrosine/ml)	124.25 ± 4.70105.21 ± 6.02N	105.21 ± 6.02N	97.66 ± 5.57	69.66 ± 6.05	39.75 ± 4.62	37.328
Mucin (µg Alcian blue/g wet tissue)	8.54 ± 0.40	12.67 ± 1.09NS	19.52 ± 1.41*	26.15 ± 1.75	32.99 ± 2.93	32.569

To express values, utilise the mean S.E.M. Comparisons were done between the drug-treated and control groups. *P 0.05, **P 0.01, ***P 0.001, and NS stands for non-significant. The proportion of the ulcer index that was decreased in comparison to the control group is shown in the numbers in parenthesis.

RESULTS

Study of anti-ulcer and antioxidant activity using pylorus ligation method

The ulcer index in the vehicle-treated control group was discovered to be 97.16 4.19, with ulcer scores 4 and 5 being the most prevalent. Furthermore, observed in the rats of this group were several perforated ulcers (score 25).

The ulcer index was shown to be greatly decreased by the methanolic extract of Osyris quadripartita Decne a in all three doses; the corresponding percentage reductions were 18.35, 57.28, and 80.61%. At doses of 75 mg/kg (P 0.01), 150 mg/kg (P 0.001), and 300 mg/kg, a

substantial reduction in ulcer index was seen as compared to the pylorus ligated control group (P 0.001). All of the ulcers had scores of 1, 2, 3, and 4, and there were no perforations Osyris quadripartita Decne also markedly reduced the volume of gastric fluid, as well as the total acidity and pepsin content of the stomach, in compared to the pylorus-ligated control group. By significantly increasing the pH of gastric fluid and the amount of stomach mucus compared to the pylorus-ligated control group, it showed its anti-ulcer efficacy (Table 1) [15]. These results were comparable to the protective effect caused by ranitidine. Ranitidine (2.5 mg/kg, intravenously) was seen to significantly (P 0.001) lower the ulcer index, by 90.57%. It also considerably increased the mucin content and pH of the gastric fluid while significantly lowering the volume of gastric fluid, total acidity, and pepsin content of the stomach when compared to the pylorus ligated control group. Pylorus ligation was found to increase lipid peroxidation and decrease SOD, catalase, and reduced glutathione in the pylorus ligated control group, resulting in oxidative stress. Administration of methanolic extract of Osyris quadripartita Decne at dosages of 75, 150, and 300 mg/kg significantly reduced lipid peroxidation while significantly raising the quantity of reduced glutathione in comparison to the pylorus-ligated control group. It was found that the antioxidant enzyme SOD's activity had significantly increased at a level of 300 mg/kg. At the doses of 150 and 300 mg/kg, catalase activity was revealed to be significantly higher when compared to the pylorus ligated control group (Table 2) [16].

Table 2. Effect of Osyris quadripartita on the antioxidant parameters in stomach of pylorus-ligated rats

Parameters

Groups	SOD Unit/mg protein)	Catalase (µmoles of H2O2 consumed/ min/mg protein)	Reduced glutathione (µg of GSH/mg protein))	Lipid peroxidation (nM of MDA/mg protein)
Normal Control	97.16 ± 4.19	79.33 ± 3.06** (18.35%	41.50 ± 1.74*** (57.28%)	17.59± 2.35*** (80.61%)
Control Group	16.41 ± 0.68	13.58 ± 0.80	11.91 ± 1.24*	8.75 ± 0.49
Osyris quadripartita Decne (75 mg/kg)	2.16 ± 0.27	2.58 ± 0.27N	3.75 ± 0.21	4.41 ± 0.30
Osyris quadripartita Decne (150 mg/kg)	124.25 ± 4.70105.21 ± 6.02N	105.21 ± 6.02N	97.66 ± 5.57	69.66 ± 6.05
Osyris quadripartita	8.54 ± 0.40	12.67 ± 1.09NS	19.52 ± 1.41*	26.15 ± 1.75

Decne(300 mg/kg)				

Values are expressed as mean ± S.E.M. Control group was compared with Normal Control group. Drug treated groups were compared with Control group. *P < 0.05; ** P < 0.01; *** P < 0.001; NS = non-significant.

Study of anti-ulcer and antioxidant activity using ethanol-induced ulcer method:

Substantial ulcers in the control group were brought on by the administration of ethanol (273.33 6.47). The ulcer index was dramatically lowered by all three Osyris quadripartita Decne ice doses and by ranitidine in the group (Table 3). It was found that ethanol administration decreased SOD, catalase, and reduced glutathione in the control group while increasing lipid peroxidation in comparison to normal control rats [17]. Substantial Osyris quadripartita Decne administration SOD levels rose and lipid peroxidation was decreased at all dose levels, but at 150 and 300 mg/kg dose levels, catalase and reduced glutathione levels sharply increased (Table 3).

Table 3. Effect of Osyris quadripartita Decne on the ulcer index in stomach of ethanol-treated rats

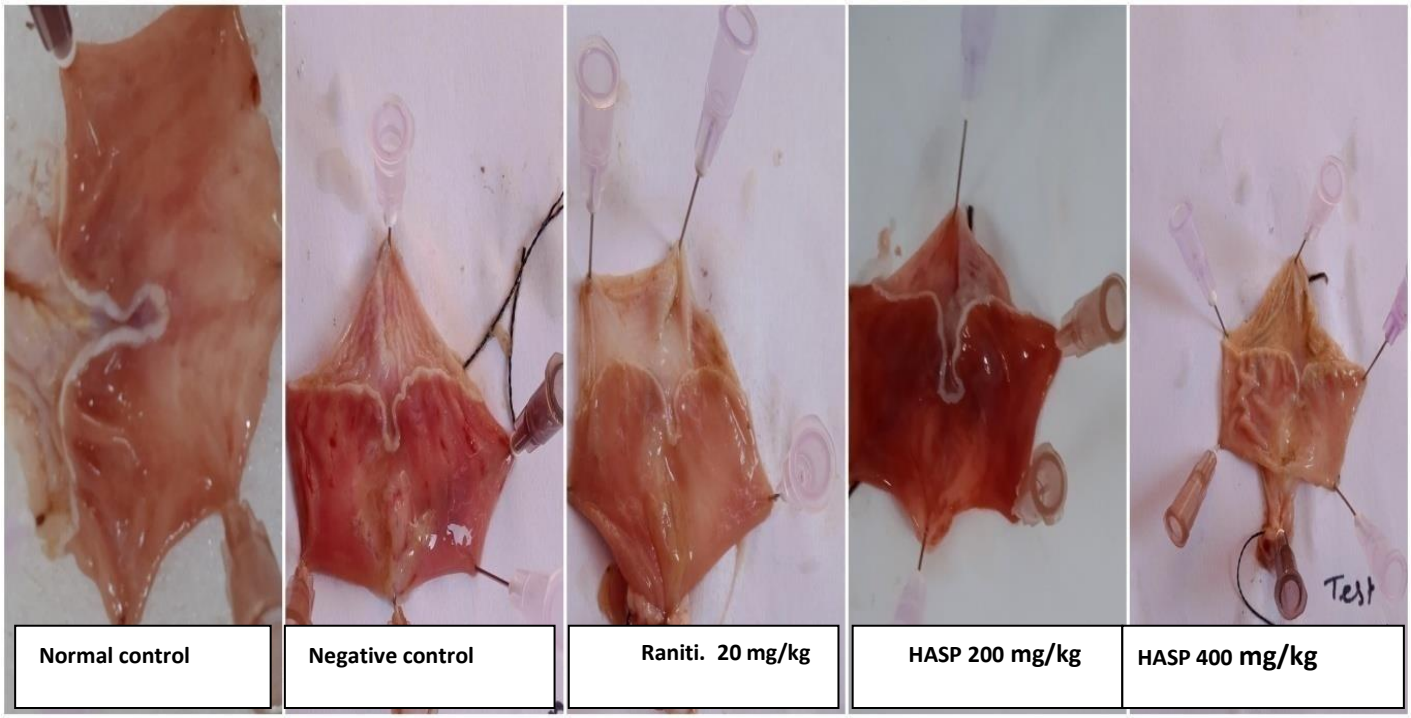
GROUPS	Ulcer index
Control Group)	273.33 ± 6.47
Osyris quadripartita Decne (75 mg/kg)	98.83 ± 3.34***(63.84))
Osyris quadripartita Decne (150 mg/kg)	52.28 ± 2.40*** (80.87)
Osyris quadripartita Decne (300 mg/kg)	21.23 ± 1.36*** (92.23
Osyris quadripartita Decne (2.5 mg/kg)	19.25 ± 1.30*** (92.95)

Table 4. Effect of Osyris quadripartita Decne on the antioxidant parameters in stomach of ethanol-treated rats

Groups	SOD Unit/mg protein)	Catalase (µmoles of H2O2 consumed/ min/mg protein)	Reduced glutathione (µg of GSH/mg protein))	Lipid peroxidation (nmoles of MDA/ mg protein)
Normal Control	5.78 ± 0.42	8.82 ± 0.19	2.42 ± 0.16	2.78 ± 0.27
Control Group	2.17 ± 0.12**	5.52 ± 0.34***	0.72 ± 0.26**	7.69 ± 0.64***
Osyris quadripartita Decne (75 mg/kg)	3.58 ± 0.18*	6.23 ± 0.23N	1.01 ± 0.16NS	4.48 ± 0.82**
Osyris quadripartita Decne (150 mg/kg)	5.03 ± 0.38***	7.31 ± 0.17***	1.68 ± 0.14**	2.67 ± 0.36***

Osyris quadripartita Decne (300 mg/kg)	6.28 ± 0.34***	7.89 ± 0.29***	2.57 ± 0.15***	2.19 ± 0.14***
F-value	28.237	20.207	19.201	17.202

Values are expressed as mean ± S.E.M. Control group was compared with Normal Control group. Drug treated groups were compared with Control group. *P < 0.05; **P < 0.01; ***P < 0.001; NS = non-significant [15;16].



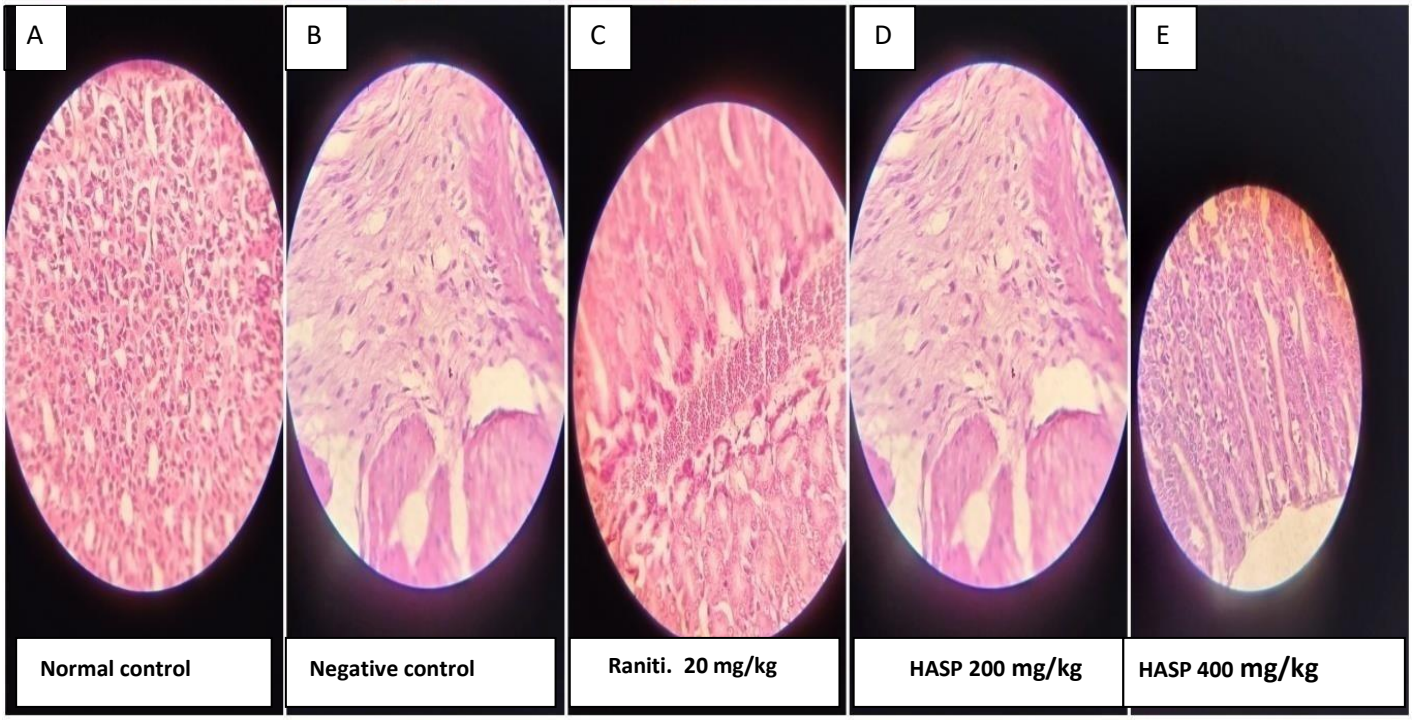
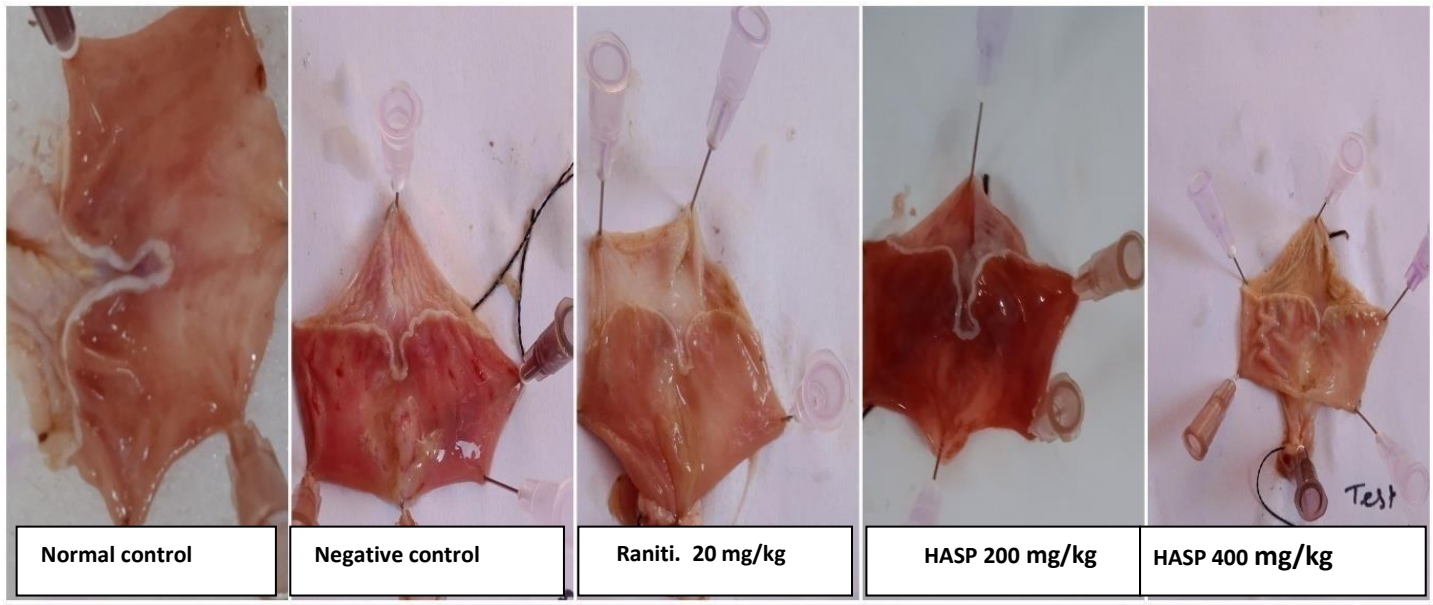


Fig.1 Histopathology of ethanol induced ulcer: Normal Control **(A)**, Negativecontrol **(B**), Ranitidine 75 mg/kg **(C)** HASP 150 mg/kg **(D**) and HASP 300 mg/k**(E).**



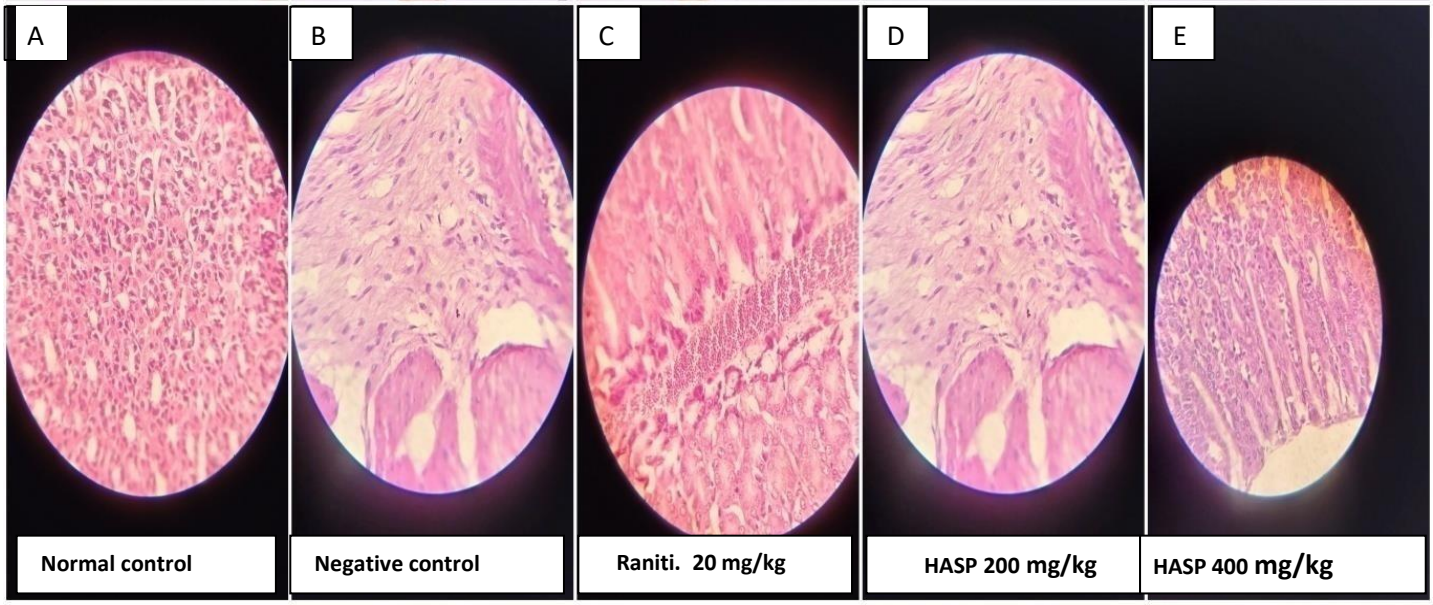


Fig.2 Histology of pylorus ligation induced ulcer: Normal Control **(A)**, Negative control **(B**), Ranitidine (75 mg/kg) **(C)** HASP 150 mg/kg **(D**) and HASP 300 mg/k**(E).**

DISCUSSION:

The current study's findings showed that administration of rats with Osyris quadripartita Decne methanolic extract exhibited gastroprotective and ulcer-healing benefits, most likely as a result of the drug's antioxidant action.

Although the precise origin of peptic ulcers is sometimes unknown, it is generally accepted that they are brought on by an imbalance between aggressive forces and the capacity of the

endogenous defence mechanisms to maintain the integrity of the mucosa. In order to restore the balance, a variety of therapeutic approaches, including herbal medicines, are employed to reduce gastric acid secretion or to improve the mucosal defence mechanism by increasing mucus production. Two experimental models for the development of lesions involving the production of reactive species—pylorus ligation and ethanol—were used to test the anti-ulcer effects of Osyris quadripartita Decne Pylorus ligation causes ulcers because pepsin and gastric acid accumulation cause the gastric mucosa to digest itself. Furthermore, to According to this theory, gastric ulcer development may be significantly influenced by stomach acid secretion, reflux, or the neurogenic effect. Methanolic extract from Osyris quadripartita Decne leaf shielded the mucosal lesion caused by ethanol and pylorus ligation. The Osyris quadripartita Decne also reduced the ulcer index and pepsin content in the stomach, demonstrating the suppression of aggressive forces, in addition to a significant drop in acid secretory markers such as total acidity and amount of gastric fluid. A rise in the pH of the gastric fluid and an increase in the amount of mucus in the stomach were signs of Osyris quadripartita Decne cytoprotective activity. In vivo pylorus ligation and ethanol-induced stomach mucosal injury are both caused by ROS. The results of the present investigation likewise suggest analogous alterations in the antioxidant status after ulcers brought on by pylorus ligation. Recently, ROS content has drawn a lot of interest, including singlet oxygen, hydroxyl radicals, and super oxide. ROS encourage lipid peroxidation in membranes by destroying unsaturated fatty acids. As a result, having a strong antioxidant defence system that comprises anti-oxidant enzymes, foods, and drugs is essential. Preventive antioxidants like SOD and CAT enzymes are the first and greatest defence against reactive oxygen species. GSH is a significant low molecular weight scavenger of free radicals in the cytoplasm in addition to being a significant inhibitor of free radical-mediated lipid peroxidation. In comparison to control mice, SOD, CAT, and GSH levels considerably rose after receiving a methanolic extract of Osyris quadripartita Decne leaves, demonstrating the extract's potency in minimising the harm brought on by free radicals.

The study's findings showed that Osyris quadripartita Decne leaves exhibited ulcer-preventing qualities, which may be connected to its antioxidant mechanism of action. More research is required to identify the active ingredient(s) that are accountable for such an impact.

CONCLUSION:

The findings of this study show that OQ has anti-ulcer pharmacologic effect and that at the doses utilised, there is no oral acute toxicity. Numerous administrations are preferable to a single dose and its efficacy is comparable to that of common medications. One or more of the newly found phytochemicals may have cytoprotective and antisecretory properties that support their anti-ulcer effects. As a result, the current study supports the traditional Ethiopian medical practise of using OQ to treat gastrointestinal ulcers. Subsequent studies will focus on isolating specific phytochemicals and elucidating their modes of action.

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