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Investigation of the Protective Effects of *Capparis Spinosa* Extract in Indomethacin Induced Ulcer Model in Rats

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Abstract: Capparis spinosa is a genus of the Capparaceae family. In the literature, it has been found that the main components of Capparis buds, quercetin and kaempferol were found to be effective in many diseases. In this study, the protective effects of Capparis spinosa on damaged rat stomach tissue induced by indomethacin and some antioxidant parameters were investigated. A total of 36 female Sprague Dawley rats weighing 200-220 grams were used in the study and six groups were formed. Groups were: healthy group; positive control group (famotidine 20 mg/kg+indomethacin 25 mg/kg); negative control group (distilled water+indomethacin); low-dose study group (125 mg/kg Capparis spinosa+indomethacin); medium dose group (250 mg/kg Capparis spinosa+indomethacin); and high dose group (500 mg/kg Capparis spinosa+indomethacin). Six hours after indomethacin was given to the groups by gastric lavage, all rats were killed under general anesthesia. The stomachs of all rats were removed, the ulcerated areas on the stomach surface were evaluated macroscopically, and the ulcer areas were measured on mm2 paper. In addition, blood and stomach tissues of all rats were biochemically examined, and malondialdehyde, superoxide dismutase and glutathione parameters were measured. The antiulcer activity of CS was compared with all groups. When the ulcer area and histopathological evaluation were examined, it was determined that the group applied 250 mg/kg Capparis spinosa had an appearance close to the healthy group. It was also found that plant extracts at all concentrations decreased the level of MDA in rat gastric tissue and increased SOD activity and GSH levels statistically. It was obtained that Capparis spinosa has antiulcer activity. ©2024 NTMS.

Keywords: Capparis spinosa; Indomethacin; Antiulcer; Antioxidant.

1. Introduction

It is known that peptic ulcer is a polyethiological chronic disease [1]. Disruption of the balance between protective and aggressive factors, trauma, stress, sepsis, hemorrhagic shock, pulmonary and liver diseases,

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smoking, alcohol, steroid and nonsteroidal drug use have been shown in the etiopathogenesis of gastric ulcer [2-6]. Although the aggressive factors that because ulcers are different, there is an increase in the amount of reactive oxygen species (ROS) in the mechanism of gastric damage caused by all of them. This supports that ROS are closely related with ulcer pathogenesis [7]. The significance of the difference between oxidant and antioxidant levels in damaged tissue and undamaged tissue [8] shows the importance of these parameters in the development and treatment of ulcers. Although there are many antiulcer drugs used in the treatment of peptic ulcer, a complete cure cannot be achieved with these drugs. Therefore, researches that can provide permanent treatment of the ulcer are still ongoing.

Capparis, which grows in natural environment in the west of Azerbaijan, is a thorny plant with a bushy structure. As a plant that loves clay soils rich in phosphorus, calcium and potassium and enjoys the sun, it grows spontaneously in sunny areas. The buds of *Capparis spinosa* flower are very rich in mineral substances. In 100 g of edible dry matter: 65 mg of phosphorus, 67 mg of calcium, 9 mg of iron, and 24 g of protein were found. Being from the Capparaceae family, the plant has varieties such as *Capparis spinosa*, *Capparis ovata*, *Capparis scula* and *Capparis orientalis*. The buds and fruits of plants belonging to the Capparidaceae family are used partially as flavoring in meals. In addition, their anti-inflammatory, expectorant and anti–hepatotoxic usage in alternative medicine has also been reported [9].

In a study conducted on Capparis buds, it was determined that the main constituents were quercetin–3–rutinoside, kaempherol–3–rutinoside and kaempferol–3–rhamnosyl-rutinoside. In that study, it was also stated that 10 grams of capparis buds contain 65 mg of flavonoid glycoside, and this antioxidant content can make a significant contribution to human nutrition [9].

In our literature review, there is no study investigating the effectiveness of *Capparis spinosa* in protection from gastric ulcers. In this study; by investigating the protective effect of *Capparis spinosa* against stomach ulcers caused by indomethacin, we examined its connection with oxidant-antioxidant parameters in the stomach tissue.

2. Material and Methods

2.1. Ethical Approval

The experiments adhered to ethical standards approved by the Ethics Committee of the Experimental Animal Teaching and Research Center (E.1800039863). Rats were procured from the Medicinal and Experimental Application and Research Center in Erzurum, Turkey (ATADEM).

2.2. Animals

For this study, a total of 36 female Sprague Dawley rats weighing between 200-220 grams were sourced from the experimental animal laboratory at the Atatürk University Experimental Research and Application Center (ATADEM). Throughout the experiment, the rats were provided with ad libitum access to both water and standard rat chow and were accommodated in a laboratory environment maintained at a regular room temperature of 22°C. The rats were randomly allocated into six groups, each consisting of six animals. The experimental groups were established as follows:

Group 1: Healthy

Group 2: Famotidine (20 mg/kg)+Indomethacin (25 mg/kg) (positive control group)

Group 3: Distilled water+Indomethacin (25 mg/kg) (negative control group)

Group 4: Low dose *Capparis spinosa* (125 mg/kg)+Indomethacin (25 mg/kg)

Group 5: Medium dose Capparis spinosa (250 mg/kg)+Indomethacin (25 mg/kg)

Group 6: High dose *Capparis spinosa* (500 mg/kg)+Indomethacin (25 mg/kg)

Capparis spinosa 125, 250, 500 mg/kg and famotidine 20 mg/kg were administered orally by gavage to the rat groups, after fasted for 24 hours. The same volume of distilled water was given to the control group. Five minutes after the drugs were administered, indomethacin was administered orally at a dose of 25 mg/kg to all rat groups by the same method. Six hours after indomethacin administration, all rat groups were euthanized by injection of high dose thiopental sodium (50 mg/kg). The rat stomachs were accessed through the greater curvature and rinsed with physiological saline. In this process, each stomach was immobilized on a flat surface, covered with a cellophane sheet, and the contours of both the stomach and the ulcerous regions were traced onto the cellophane. Subsequently, the stomach and ulcer areas were quantified by superimposing the cellophane sheet onto millimeter squared paper. The cumulative surface area of the ulcerous regions was then represented in terms of mm^2. Additionally, blood and stomach tissues were taken and oxidant and antioxidant parameters were biochemically measured. The antiulcer activity of *Capparis spinosa* was evaluated by comparing them with the results obtained from famotidine and the control group.

2.3. Biochemical Analysis

Following the macroscopic analysis of the stomach tissues taken from the rats after the experiments, the tissues were immediately frozen under liquid nitrogen and stored at -80 ° C until the experiments were carried out. For all biochemical analyzes, measurements were made according to the protocols suggested by the manufacturer companies, taking into account two different serum and tissue measurement protocols with Elisa test kits specially purchased for rats.

Superoxide dismutase (SOD), Malondialdehyde (MDA) and glutathione (GSH) levels and/or activities were determined in the stomach tissues. Measurements of SOD, GSH and MDA levels and/or activities in tissues were made in accordance with the protocols in the literature [10-13]. These measurement protocols are

generally similar. In principle, the levels of the relevant parameters were determined by comparing the color reactions that would occur with the standards. Tissue samples kept at -80 °C were pulverized one by one with a mortar under liquid nitrogen and stored at -20 °C. Then, approximately 100 mg of each tissue was weighed and homogenate buffer of the relevant parameter was added onto it. Then the mixture was homogenized for two minutes with a tissue lyser mixer and homogenizer. After the homogenized mixture was centrifuged at the relevant speed according to the measurement protocol included in each kit, the level of oxidant-antioxidant parameters in the supernatant section was determined by Elisa in two or three repetitions for each tissues. Then the amount of protein was determined according to the lowry method. Finally, statistical differences between groups were determined by one-way analysis of variance.

2.4. Histological Examination

Histological examinations were carried out in histology laboratory in Atatürk University Faculty of Medicine, Histology and Embryology Department. Stomach tissues taken from rats in all groups were given code numbers and left in bottles containing 4% formaldehyde. Then, tissue follow-up procedures were started. The tissues were then embedded in paraffin blocks and made ready for sectioning procedures. Staining process was carried out after 5 µm sections of paraffin blocks were taken on glass slides with microtome (Leica RM2125RT). The sections, which were ready to be examined, were examined under the Olympus BH 40 camera attached light microscope and photographs of all relevant groups were taken.

2.5. Preparation of Capparis Spinosa Extracts

Capparis spinosa buds samples collected from Azerbaijani Ganja region of Azerbaijan State Agricultural University, and after drying at room temperature in an environment without sunlight, were brought to Turkey. Then, they were ground with a grinder, pulverized and sieved using a 300 mm diameter 50 mesh sieve in the Department of Pharmacology of Atatürk University Faculty of Medicine. The capers powder sample obtained was extracted with ethanol at 50 °C. For this, 500 g powder sample was treated with 2 liters of ethyl alcohol for 3 days with back cooler, and the solvent was changed every 24 hours. By combining the filtrates, the ethanol in the total extract was removed in the evaporator at 40 °C. Then, the water in the extract was removed by means of a lyophilizer and the pure extract was obtained as a powder. Thus, the extract was dissolved in water and applied.

2.6. Statistical analysis

The statistical analyzes and comparisons were made by using SPSS Statistic 19.0 program (IBM, NY, USA). The experimental results were presented as Mean±Standard deviation (SD), and p-values less than 0.05 were regarded as statistically significant. To determine the significance of differences among the groups, Duncan's post-hoc multiple comparative test was employed in conjunction with the one-way ANOVA test. Each different letter shows that it is statistically different from the other group, and the same letters are meaningless.

3. Results

When we examined the ulcerated areas in the stomach tissues of rats sacrificed, it was observed that *Capparis spinosa* extract at a concentration of 250 mg/kg showed an antiulcer activity of 83% ($p<0.05$) and the famotidine group showed an antiulcer activity at a rate of 88% ($p<0.05$). The ulcer areas of *Capparis spinosa* extracts (125, 250, 500 mg/kg doses), famotidine (20 mg/kg dose) and control group are shown in Figure 1. It was observed that all Capparis spinosa extract doses had a significant anti-ulcer effects ($p<0.05$).

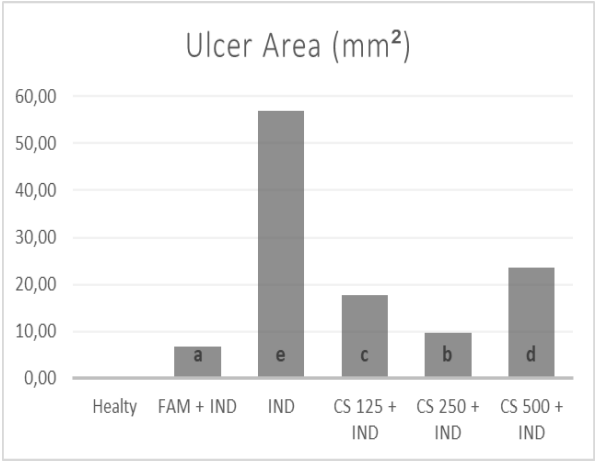

Figure 1: Average gastric ulcer areas of the groups.
*Each value represents a Mean±SD. The different letters given on the bars show a significant difference ($P<0.05$). Famotidine (FAM), Indomethacin (IND), Capparis Spinosa (CS).

3.1. Biochemical Analyzes Results

When the results of the biochemical analyzes performed within the scope of the study were evaluated, *Capparis spinosa* extract at all doses significantly increased SOD activity ($p<0.05$) and GSH levels ($p<0.05$) in the stomach tissues of rats. The extract at a concentration of 250 mg/kg increased the SOD activity and GSH levels at the highest rate. All extract doses significantly reduced MDA ($p<0.05$). The most effective decrease was observed at a dose of 250 mg/kg. The SOD activity, GSH and MDA levels of all samples are shown in Figures 2, 3 and 4.

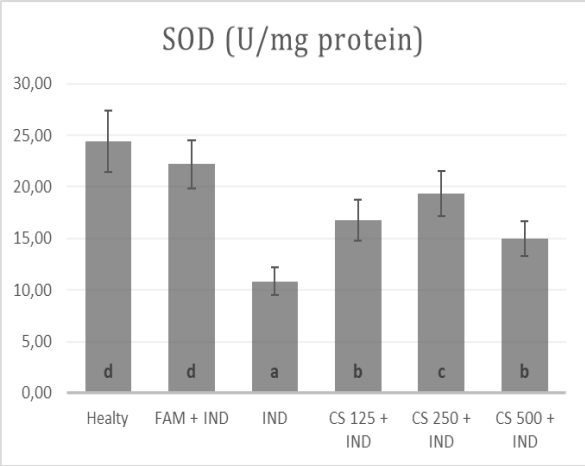

Figure 2: Superoxide dismutase (SOD) activities of the groups.
*Each value represents a Mean±SD. The different letters given on the bars show a significant difference (P<0.05). Famotidine (FAM), Indomethacin (IND), Capparis spinosa (CS).

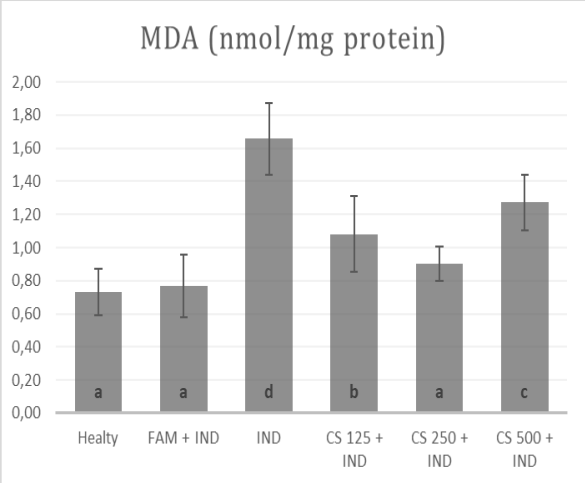

Figure 3: Malondialdehyde (MDA) levels of the groups.
Each value represents a Mean±SD. The different letters given on the bars show a significant difference (P<0.05). Famotidine (FAM), Indomethacin (IND), Capparis spinosa (CS).

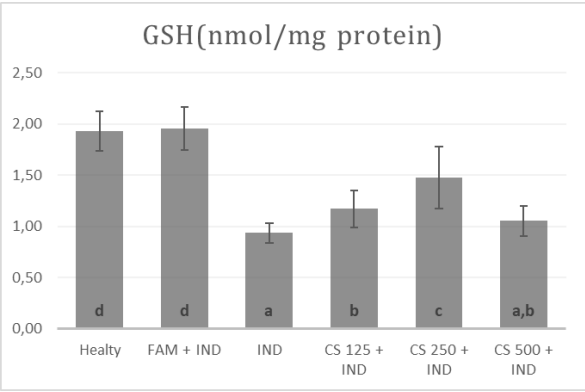

Figure 4: Glutathione (GSH) levels of the groups.
*Each value represents a Mean±SD. The different letters given on the bars show a significant difference (P<0.05). Famotidine (FAM), Indomethacin (IND), Capparis spinosa (CS).

3.2. Histopathological Results

The histopathological evaluation of our study performed with hematoxylin and eosin staining (H&E) was based on the gastric mucosa layer. As per the findings, in the healthy group, it was observed that the gastric cavities of the stomach exhibited a normal appearance, and both the parietal and mucous cells appeared healthy (Figure 5A).

The positive control group, consisting of famotidine+indomethacin (FAM+IND), exhibited a resemblance to the healthy group in terms of appearance. No necrotic alterations in the surface mucous cells were observed (Figure 5B).

In the negative control group, distilled water+indomethacin (IND), epithelial losses and irregular gastric pits were observed in the superficial mucosa, while especially surface mucous cells were observed to have necrotic appearances. However, the increase in lymphatic cells in the lamina propria was also remarkable. In addition, an increase in eosinophilia was observed in some parietal cells (Figure 5C).

In the low-dose *Capparis spinosa* group (125 mg/kg: CS 125), epithelial losses were severely reduced, but surface-facing mucous cells had necrotic appearances (Figure 5D).

In the medium dose *Capparis spinosa* group (250 mg/kg: CS 250), an appearance similar to the healthy group was dominant. However, spills were still observed in some epithelial cells (Figure 5E).

In the high-dose *Capparis spinosa* group (500 mg/kg: CS 500), in addition to necrotic-looking surface mucous cells, increased inflammatory cells in the near-surface lamina propria were remarkable. In addition, some parietal cells showed an increase in eosinophilia (Figure 5F).

In order to better understand histopathological evaluations, epithelial cell loss, histopathological damage based on the presence of hemorrhage and necrotic cells; they were scored as - (none), + (little damage), ++ (moderate damage), +++ (severe damage) (Table 1).

Table 1: Average histopathological damage score of all groups.

	Necrotic cell	Haemorrahage	Epithelial cell loss
Healty	-	-	-
FAM+IND	-	-	-
IND	+++	+	+++
CS 125+IND	+	-	-/+
CS 250+IND	-	-	-
CS 500+IND	+	+	+

4. Discussion

Peptic ulcers, characterized by mucosal erosions or ulcers in the stomach or duodenum, are significant gastrointestinal disorders that can lead to various complications if left untreated. A multitude of factors, including the use of nonsteroidal anti-inflammatory drugs like indomethacin, stress, and bacterial

infections, have been implicated in their pathogenesis [14-19]. The pathophysiology of peptic ulcers is complex, involving an intricate balance between aggressive factors such as acid secretion, pepsin activity, and oxidative stress, and protective mechanisms including mucus and bicarbonate secretion, mucosal blood flow, and antioxidant defenses [20].

The present study has shed light on the potential therapeutic utility of *Capparis spinosa* extract in countering the damaging effects of indomethacin-induced gastric ulcers. Indomethacin, a widely used nonsteroidal anti-inflammatory drugs, is known to disrupt the mucosal barrier and enhance oxidative stress within the gastric mucosa, leading to the development of ulcers [16, 17]. The observation that *Capparis spinosa* extract, particularly at a medium dose of 250 mg/kg, exhibited a substantial reduction (83%) in ulcer formation in the rat model suggests that this natural extract may hold promise as a protective agent against nonsteroidal anti-inflammatory drugs -induced gastric ulcers. These findings are consistent with the hypothesis that *Capparis spinosa* may exert its effects by bolstering the gastric mucosa's defenses against oxidative damage.

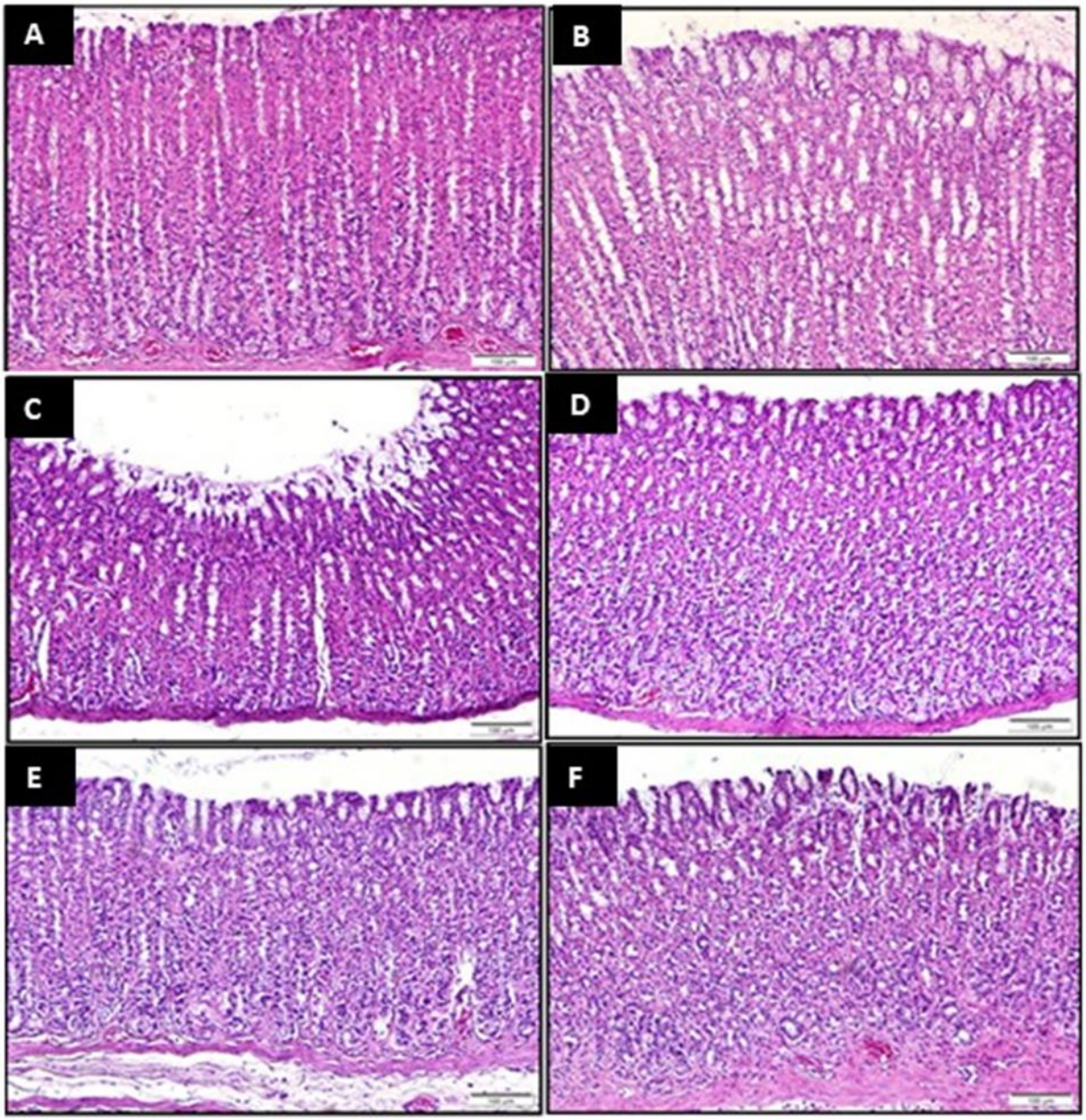

Figure 5. Histopathological results of rat stomach tissues (A: Healthy group; B: FAM+IND; C: IND; D: CS 125 mg/kg+IND; E: CS 250 mg/kg+IND; F: CS 500 mg/kg+IND).

The antioxidative properties of *Capparis spinosa* extract, as evidenced by the significant increases in SOD activity and GSH levels along with a reduction in MDA levels in the stomach tissues of rats, suggest that this extract has the capacity to counteract oxidative stress within the gastric mucosa. Oxidative stress is a pivotal contributor to mucosal damage in the stomach [21]. Excessive production of ROS overwhelms the

endogenous antioxidant defenses, leading to lipid peroxidation and cellular damage [21]. The ability of *Capparis spinosa* extract to enhance SOD and GSH levels while reducing MDA levels underscores its potential as an antioxidant agent. This is consistent with previous research demonstrating the antioxidant activity of *Capparis spinosa* and its flavonoid constituents, such as quercetin and kaempferol [22]. Flavonoids possess free radical-scavenging properties and can mitigate oxidative damage, making them relevant in the context of gastric ulcer prevention [23].

The mechanisms underlying the protective effects of *Capparis spinosa* extract warrant further investigation. It is plausible that the extract exerts its antiulcer and antioxidant actions through multiple pathways. Firstly, as an antioxidant, it likely scavenges ROS generated during the ulcer-inducing process, thereby reducing tissue damage. Moreover, *Capparis spinosa* may modulate inflammatory responses and support the repair of damaged gastric mucosa. Its anti-inflammatory and tissue-healing properties, reported in previous studies [22], may contribute to its overall efficacy in reducing ulcer formation. Additionally, the extract might enhance mucosal blood flow, stimulate mucus and bicarbonate secretion, or directly protect mucosal cells from nonsteroidal anti-inflammatory drugs-induced damage, as observed in some gastroprotective agents [15, 17].

While these findings are promising, it's crucial to recognize that this study was conducted in a rat model, and extrapolating the results to humans requires caution. Further research, including well-designed clinical trials, is needed to evaluate the safety and efficacy of *Capparis spinosa* extract in human subjects. These studies should consider optimal dosages, formulations, and potential adverse effects. Moreover, investigations into the long-term effects of *Capparis spinosa* extract and its comparative efficacy with established antiulcer medications are warranted to establish its clinical relevance.

5. Conclusions

In conclusion, this study provides valuable insights into the potential therapeutic utility of Capparis spinosa extract as a protective agent against NSAID-induced gastric ulcers. Its antioxidant properties, coupled with its significant reduction in ulcer formation in the rat model, suggest its promise as a natural remedy for peptic ulcers. However, further research is essential to validate these findings in human populations and elucidate the precise mechanisms responsible for its therapeutic effects.

Limitations of the Study

To definitively establish the anti-ulcer efficacy of *Capparis spinosa*, clinical studies involving humans are needed. The absence of research conducted on humans in this study represents a limitation.

Acknowledgement

None.

Conflict of Interests

The authors have not disclosed any conflicts of interest.

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Author Contributions

Conception: AA, AA, MA, YB, ZH. Design: AA, AA, MA, YB, ZH. Supervision: AA, AA, MA, YB, ZH. Materials: AA, AA, MA, YB, ZH. Data Collection and/or Processing: AA, AA, MA,YB, ZH, ET. Analysis and Interpretation: AA, AA, MA, YB, ZH, ET. Literature: AA, AA, MA, YB, ZH, ET. Review: AA, AA, MA, YB, ZH, ET. Writing: AA,YB,ZH. Critical Review: AA, AA, MA, YB, ZH, ET.

Ethical Approval

The experiments adhered to ethical guidelines approved by the Ethics Committee of the Experimental Animal Teaching and Research Center (E.1800039863). The rats used in the study were sourced from the Medicinal and Experimental Application and Research Center in Erzurum, Turkey (ATADEM).

Data sharing statement

It is mentioned in the article that all the data supporting the results are provided within the article itself, and there is no need for additional source data.

Consent to participate

None.

Informed Statement

None.

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