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Investigation of the curative effects of *Hypericum perforatum* (St. John's Wort) and *Rosa spinosissima* (Black rosehip) on rats in an indomethacin-induced gastric peptic ulcer model

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Abstract

In this study, histopathological and immunohistochemical evaluations were made on the damage to the gastric tissue in the gastric peptic ulcer model induced by indomethacin, and it was investigated whether the plants *Hypericum perforatum* and *Rosa spinosissima* have a therapeutic effect. In order to create an ulcer model, 25mg/kg indomethacin was administered orally to the rats in the other groups, except the sham control group, in 2 doses, 24 hours apart. In the treatment groups, the first dose of indomethacin was given an hour after the second dose, and the second dose of plant oils was given orally 24 hours later. Then, 1 hour later, the rats were sacrificed. In the histopathological evaluation, sections belonging to the indomethacin control group showed intense degeneration of both epithelial and mucosal glands in the gastric mucosa. Edema and bleeding were also present in the lamina propria and submucosa layers. These observed damages were significantly reduced in the RS+HP-1 and RS+HP-2 groups. As a result of the immunohistochemical evaluations, it was observed that the group with the highest Bax immunoreactivity was the indomethacin control group, and the groups with the lowest were RS+HP-1 and RS+HP-2. It was determined that the group with the lowest Bcl-2 immunoreactivity was the indomethacin control group, and the groups with the highest were RS+HP-1 and RS+HP-2. The results showed that *Hypericum perforatum* and *Rosa spinosissima* plants have therapeutic and anti-apoptotic effects on gastric injury.

Keywords: Ulcer; Indomethacin; *Hypericum perforatum*; *Rosa spinosissima*

1. Introduction

Peptic ulcer disease, which is commonly seen in the gastrointestinal tract, occurs with the deterioration of the balance between the aggressive factors in the gastric mucosa and the mechanisms known as defense factors [1]. Aggressive factors include stress, helicobacter pylori, gastric acid, reactive oxygen species, and NSAIDs (Non-steroidal anti-inflammatory drugs); among the defense factors are the mucus-bicarbonate barrier, prostaglandins, and mucosal blood flow [2]. While indomethacin, which is one of the NSAIDs, increases acid secretion and pepsin enzyme activity, it causes a decrease in the mucus layer and bicarbonate secretion. At the same time, it triggers the formation of ROS with the increase in lipid peroxidation and, in this way, damages the gastric mucosa [3]. In the case of peptic ulcers, the erosion of the mucosa can progress to the underlying tissue layers with the digestive effect of gastric and duodenal secretions [4].

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Today, besides the existence of many anti-ulcerative drugs, to avoid the possible side effects of these drugs and to prevent the recurrence of the disease, there has been an increased tendency towards polymers with less toxic properties and natural ones [5, 6].

Hypericum perforatum (St. John's Wort) is a plant containing flavonoids, tannins, carotenoids, choline, and various amino acids found in the natural vegetation of the Asian and European continents [7, 8]. Although its effects on mild or moderate depression are more commonly known, it has also been discovered to have antipyretic, antispasmodic, analgesic, and antimicrobial effects. There are also studies showing its therapeutic effects on neurological diseases such as migraine, respiratory and urogenital system inflammations, some skin diseases, and diseases such as ulcers [9-11].

Rosehip (*Rosa spinosissima*) is widely researched because it contains carotenoids, bioflavonoids, natural antioxidants, minerals, vitamin C, pectin, tocopherol, fruit acids, tannin, and various amino acids that are beneficial to human health [12]. It has been reported that rose hips are used in folk medicine in many countries around the world against diabetes, stomach disorders, kidney disorders, and gingival bleeding [13].

In the present study, it was aimed to investigate the curative effects of *Hypericum perforatum* and *Rosa spinosissima* in the gastric peptic ulcer model induced by indomethacin.

2. Material and methods

2.1. Animal procedure

A total of 96 Wistar male rats with an average weight of 250-300 g obtained from the Atatürk University Experimental Research and Application Center (ATADEM) were used. Before the experiments, animals that were adapted to the environment were grouped and fed ad libitum water and pellet food throughout the study. The animals were housed in a laboratory environment at an average room temperature of 22 °C and humidity of 45-50%, with 12 hours of light and 12 hours of darkness.

2.2. Treatment preparation

Dried 400 grams of *Hypericum perforatum* were placed in natural olive oil (Taris, Erzurum, Turkey) and kept at room temperature for 1 year. Dried 400-gram *Rosa spinosissima* was placed in natural olive oil (Taris, Erzurum, Turkey) for 1 year. The two extracts were filtered. We used combinations of oils we had prepared for the experiment (Figure 1).

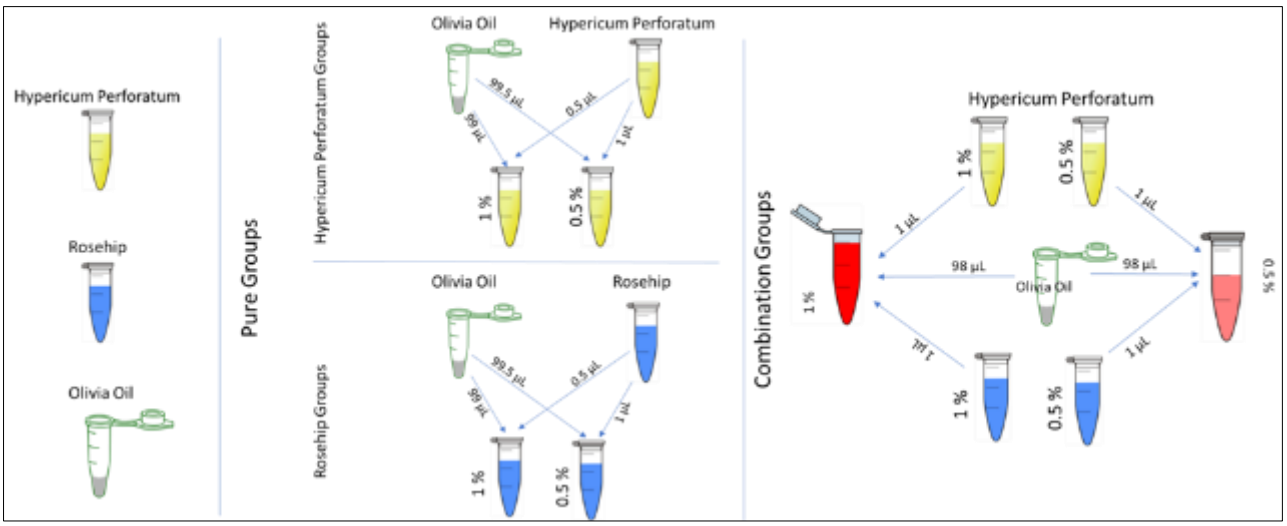

Figure 1 Preparation process of oils prepared for *Hypericum perforatum* and *Rosehip* groups

2.3. Animal groups and experimental procedure

Rats subjected to standard care and feeding conditions were divided into 8 groups with 12 animals in each group. The groups and drug doses created are as indicated in the table below:

Table 1 Experimental groups, drug doses and number of animals

Groups	Drug doses	Number of rats
Sham control	-	12
Indomethacin control	25 mg/kg	12
Hypericum perforatum-1 (HP-1)	%0.5	12
Hypericum perforatum-2 (HP-2)	%1	12
Rosa spp-1 (RS-1)	%0.5	12
Rosa spp-2 (RS-2)	%1	12
RS+HP-1	%0.5	12
RS+HP-2	%1	12

Of these groups, no application was made to the sham control group during the experiment (for 3 days). All of the substances applied to the other groups were given by oral gavage. Indomethacin was given to the experimental groups twice, as one dose every 24 hours. For the treatment groups, treatment was started 1 hour after the second dose of indomethacin and the first doses were given. The second dose of the treatment was given 24 hours later, and the rats were sacrificed 1 hour later under general anesthesia by administering 4% sevoflurane. After sacrification, some of the gastric tissues taken from the animals were taken into 10% neutral buffered formaldehyde for use in routine histopathological procedures.

2.4. Histopathological analysis

After the fixed gastric tissue samples were passed through graded alcohol and xylol series, they were embedded in paraffin blocks. Serial sections of 5 µm thick were taken from paraffin blocks (Leica RM2125 RTS). Sections of all groups were stained with the Crosman's Modified Mallory's Triple Staining procedure for histopathological evaluations. Tissues on poly-l-lyzed slides were used for nuclei staining. It was kept in hematoxylin solution for 3 minutes and then washed with distilled water for 5 minutes to remove excess dye. Then it was kept in sodium thiosulfate solution for 2 minutes. The preparations were washed with distilled water. The preparations, which were kept in acid fuchsia for 1 minute in order to stain the cytoplasm, were washed with distilled water and kept in phosphotungstic acid for 5 minutes, and the connective tissue was whitened. The sections, which were washed with distilled water again, were kept in aniline blue dye solution for 30 seconds to stain the connective tissue. The preparations, washed with distilled water, were kept in 96% alcohol for 5 minutes, in absolute alcohol for 5 minutes twice, and then in xylol for 3 times for 5 minutes, then covered with entellan and a coverslip.

2.5. Immunohistochemical analysis

The streptavidin-biotin complex method was used for immunohistochemical staining. Antibodies used in immunohistochemical staining: Bax (sc-7480), Bcl-2 (sc-7382). Primary antibodies used were diluted at the ratio of 1:50. After staining pretreatment, antigen retrieval treatment was applied to the tissues on positively charged slides, and they were kept in EDTA for 20 minutes in an oven set at 110 °C (with the mouth closed). (EDTA buffer; 0.37 grams of EDTA was weighed and dissolved in 1000 mL of distilled water, and its pH was adjusted to 8. It was mixed well, and 0.5 mL of tween 20 was added.) After 20 minutes, the chalet was removed from the oven and kept at room temperature for 5 minutes. Then the slides were placed in a vertical chalet and washed with distilled water. It was then soaked in 3% hydrogen peroxide for 18 minutes. After PBS (phosphate buffered saline) the preparations, which were kept in for 10 minutes, were scratched with a PAP pen and treated with protein block for 10 minutes. Meanwhile, antibodies were prepared by diluting with PBS at a ratio of 1:50. After protein blocking, 100 microliters of antibody were dropped on each preparation and incubated for 1 hour in the dark. Then they were washed twice for 5 minutes with PBS. They were treated with secondary antibody for 20 minutes. They were washed twice for 5 minutes with PBS. Streptavidin-biotin was dripped and waited for 20 minutes. DAB solution dripped after washing three times with PBS for five minutes. The preparations were waited until browning was observed and washed with PBS. Preparations treated with Mayer's hematoxylin for 2 minutes were washed again with PBS. Then, the preparations were kept for 1 minute in 96% alcohol, 2 times for 5 minutes in absolute alcohol, and twice for 5 minutes in xylol, and closed with entellan.

Slides of all stainings were examined under a light microscope (Nikon Eclipse i50. Tokyo, Japan), and photographs of the sections were taken. Semi-quantitative scoring method was used in the immunohistochemical evaluation of the

study. According to this method, scoring was performed by taking into account the average staining intensity of at least five different regions from each stomach tissue. If there is little or no staining – (0%), if low intense + (0–30%), if moderately intense ++ (30–60%), if intense staining is +++ (60–100%).

2.6. Statistical analyzes

Statistical differences between groups will be evaluated by SPSS 21 program. The difference between the groups of semi-quantitative data obtained in histopathological and immunohistochemical examination will be analyzed with the Kruskal Wallis test and results with a p value <0.05 will be considered significant.

3. Results

3.1. Histopathological Results

When the histopathological evaluation of the stomach sections of the sham control group was performed, it was determined that the sections had a normal histological structure and no pathological condition was present (Figure 2 A). In the group in which ulcers were formed with indomethacin, very intense damage was observed. In the sections belonging to this group, it was observed that the gastric surface epithelium was shed due to intense cellular damage in the gastric mucosa, the mucosal gland structures were deteriorated, and there was intense edema and bleeding in the lamina propria and submucosa (Figure 2 B). In the RS-1, RS-2, and HP-1 groups, the damage to the mucosal epithelial tissue was partially reduced compared to the Indomethacin group; epithelial formation started, and bleeding areas in the connective tissue were observed. It was determined that the edema, which was the first, continued in some places (Figure 2 C, D, E). On the stomach sections of the HP-2, RS+HP-1, and RS+HP-2 groups, it was observed that the mucosal epithelium and glandular structures developed more smoothly, the level of healing was quite good, and the edema and bleeding in the connective tissue completely disappeared (Figure 2 F). The groups with the best recovery levels were the RS+HP-1 and RS+HP-2 groups (Figure 2 G, H).

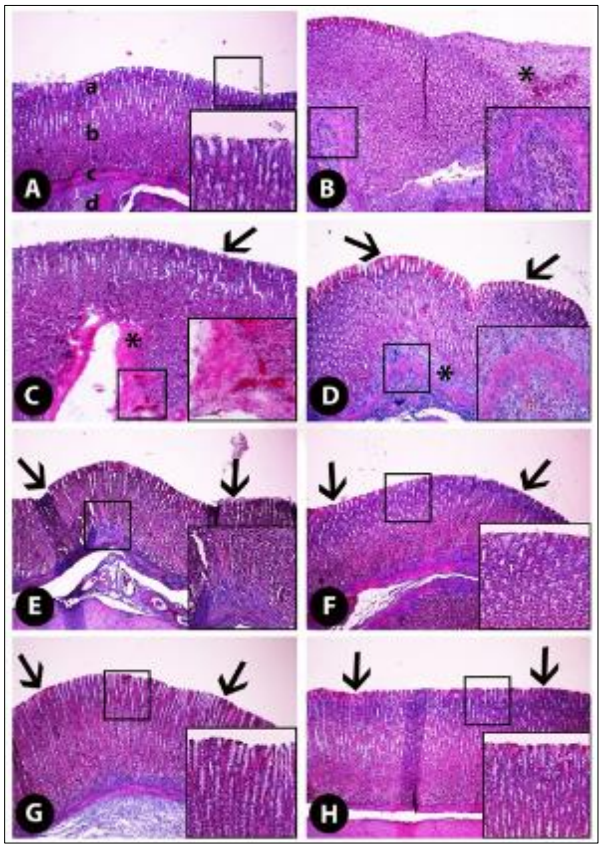

Figure 2 Histopathological structure of gastric tissue sections in rats with ulcers created with indomethacin. A: Sham control group, B: Indomethacin control group, C: RS-1 group, D: RS-2 group, E: HP-1 group, F: HP-2 group, G: RS+HP-1 group, H: RS+HP-2 group rats. a: T. mucosa, b: T. submucosa, c: T. muscularis, d: T. serosa, arrow: developing epithelial layer, star: edema and hemorrhagic areas. Staining: Crossman's Triple Staining

3.2. Immunohistochemical Results

Bax and Bcl-2 antibodies were used for immunohistochemical staining. As a result of the immunohistochemical staining made by the Bax antibody, the immunoreactivity intensity was high (+++) in the Indomethacin control group, moderate (++) in the RS-1, RS-2, and HP-1 groups, and low (+) in the HP-2, RS+HP-1 groups, while no immunoreactivity (–) was observed in the RS+HP-2 and sham control groups. As a result of the immunohistochemical staining made by the Bcl-2 antibody the immunoreactivity intensity was high (+++) in the sham control group, moderate (++) in the RS+HP-1, RS+HP-2 groups, and low (+) in the RS-1, RS-2, HP-1, HP-2 groups, while no immunoreactivity (–) was observed in the Indomethacin control group. All immunohistochemical stainings are presented in Figures 3 and 4.

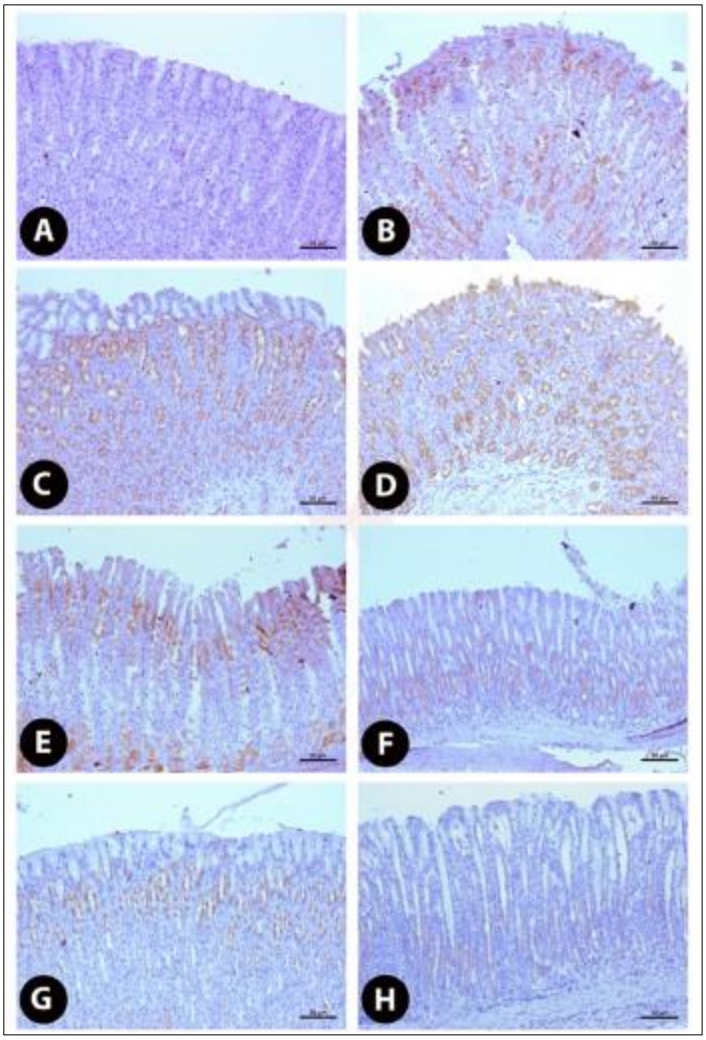

Figure 3 A: Sham control group, B: Indomethacin control group, C: RS-1 group, D: RS-2 group, E: HP-1 group, F: HP-2 group, G: RS+HP-1 group, H: RS+HP-2 group. Bax immunopositivity in stomach sections of rats in all groups. Staining: Streptavidin-Biotin Complex

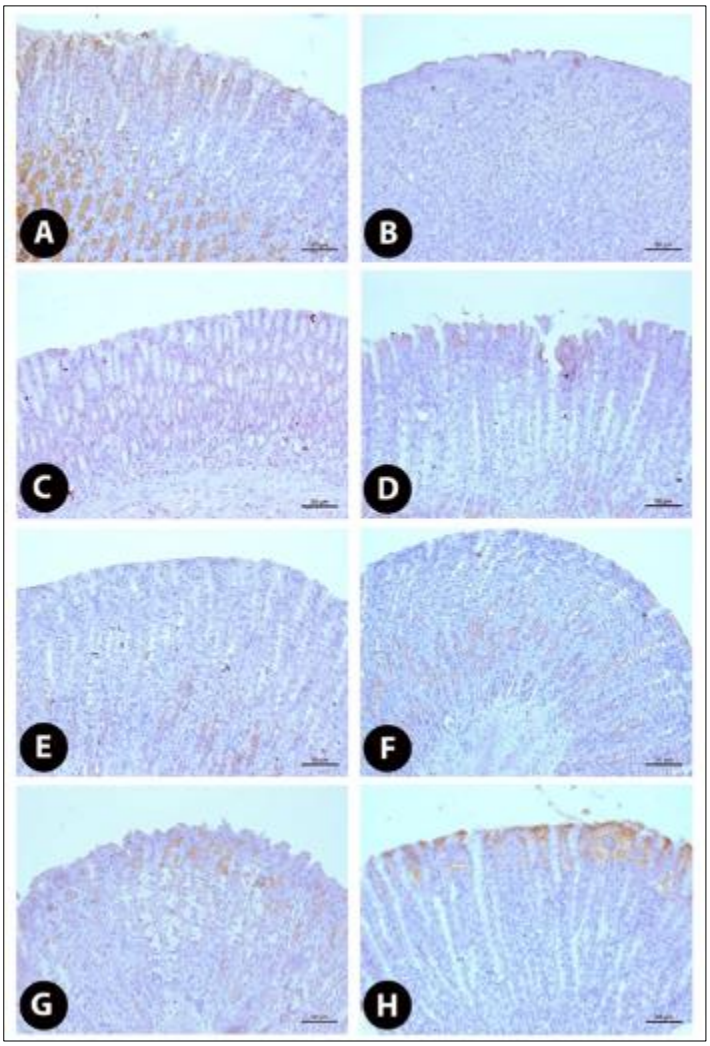

Figure 4 A: Sham control group, B: Indomethacin control group, C: RS-1 group, D: RS-2 group, E: HP-1 group, F: HP-2 group, G: RS+HP-1 group, H: RS+HP-2 group. Bcl-2 immunopositivity in stomach sections of rats in all groups. Staining: Streptavidin-Biotin Complex

4. Discussion

Gastric ulcer is a global disease that is frequently seen in the gastrointestinal tract, with an increasing incidence and prevalence [14]. It is defined as the wounds that occur in the mucosal epithelium as a result of the gastric tissue being exposed to excessive amounts of acid and pepsin activity. Peptic ulcer, which is one of the common gastrointestinal disorders [15], is mostly seen in the duodenum and stomach. In addition, it can be seen in the lower part of the esophagus, jejunum, and anastomosis sites after stomach surgery. The risk of developing a peptic ulcer is around 11-14% in men and 8-11% in women [16].

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used worldwide in the treatment of many diseases such as arthritis, inflammation, and cardiovascular diseases [14, 17]. However, there are some side effects of NSAID use on the digestive system, such as gastric mucosal ulceration, bleeding, perforation, and some more serious complications. It has also been reported that the main factors contributing to the pathogenesis of gastric damage induced by NSAID use are lipid peroxidation, tissue oxidation, and apoptosis [14]. Indomethacin, one of the synthetic NSAIDs with analgesic and antipyretic effects [18], has a higher ulcerogenic potential than other non-steroidal anti-inflammatory drugs; therefore, it is a highly preferred drug in creating an experimental ulcer model [19].

Studies have shown that indomethacin increases gastric acidity and ulcer index [18-20]. In addition, in stomach sections of rats treated with indomethacin gastric erosions, inflammatory cell infiltrates in the lamina propria, muscularis

mucosa, and submucosal layers [19, 21], as well as congestion in the submucosal blood vessels, hypertrophy of the muscular layers, and partial hyalinization have been detected [21]. As a result of the applications in the present study, in the group in which ulcers were formed with indomethacin, it was determined that the gastric surface epithelium was shed due to intense cellular damage in the gastric mucosa, the mucosal gland structures were deteriorated, and there was intense edema and bleeding in the lamina propria and submucosa.

Although many chemical drugs are used in the treatment of gastric ulcers unfortunately, most of them have strong side effects. Therefore, it is important to investigate both safer and more effective gastroprotective agents [22]. Therefore, it is becoming more and more important to use antiulcer drugs obtained from medicinal plants, which may have fewer side effects, as an alternative treatment for peptic ulcer disease [12]. *Hypericum perforatum* (St. John's Wort) is one of the oldest medicinal plant species that has been most researched in traditional medicine of different cultures. It is used as a folk remedy in many diseases such as skin disorders, urogenital system and bronchial inflammations, bladder irritation, colds, biliary disorders, neuralgia, diabetes, hemorrhoids, migraine headaches, sciatica, and ulcers [10]. There are many studies showing that St. John's wort has anti-inflammatory [9, 23], anti-microbial, wound healing [9, 24], antioxidant, and antidepressant properties [11, 25].

In a study, histopathologically, bleeding, congestion, edema, necrosis, and mucosal lesions were detected in gastric sections in an ulcer model created by hypothermic restraint stress. In the same study, it was observed that *Hypericum perforatum* extract given to rats with ulcers had regenerative effects on all these damages [26]. In another study, the protective effects of *Hypericum perforatum* were determined against pathological damage such as mucosal damage, loss of villi, hemorrhage, and ulceration seen in hamsters with intestinal damage by ischemia-reperfusion technique [27]. Turan et al. [7] showed the contribution of St. John's Wort extract, which they applied to one of the treatment groups, to the healing of the gastric mucosa in their indomethacin-induced gastric ulcer model. Zduni´c et al. [10] also proved the gastroprotective effect of St. John's Wort. Sargul et al. [28] also proved that St. John's Wort extract has a gastroprotective effect on the gastric mucosa in their study of ethanol-induced gastric ulcer in mice. Paterniti et al. [29] showed the effects of *Hypericum perforatum* in the rodent periodontitis model, and showed that there was a decrease in the increased Bax expression due to periodontitis in the groups treated with *Hypericum perforatum*. In the same study, it was shown that Bcl-2 expression increased in experimental groups treated with *Hypericum perforatum*. Atalay et al. [30] showed the protective effects of *Hypericum perforatum* application in their hepatic ischemia/reperfusion model, and it was observed that the Bax/Bcl-2 expression rate decreased in the groups in which this extract was applied. This information supports the data from the current study. In the study, the curative effect of St. John's Wort against indomethacin-induced damage to the gastric mucosa is demonstrated.

Rosehip (*Rosa spp*) has become a very popular fruit in recent years with its natural antioxidant properties that are very beneficial for human health [13]. Studies have shown that gastric ulcers were remarkably healed in animals treated with rosehip (*Rosa spp*) extract, and interestingly, all rosehip extracts had a strong anti-ulcerogenic potential [31, 32]. There are some ulcer studies using *Rosa canina* extracts, one of the Rosa species. Gürbüz et al. [32] tried to induce a peptic ulcer model in rats and treat them with *Rosa canina* extracts and were successful. Lattanzio et al. [33] performed a more comprehensive study and showed that the erosion of the gastric mucosa and therefore the formation of hemorrhagic ulcers can be prevented by the treatment of *Rosa canina*. It is known that lipid peroxidation and ROS production have an effect on gastric damage, and according to the results obtained in studies, it is suggested that rosehip extracts can have a protective effect even in gastric acidity.

Valcheva-Kuzmanova et al. [34] gave Aronia melanocarpa juice alone to some experimental groups as a preservative in a study of peptic ulcer induced by indomethacin in rats, while they gave *Aronia melanocarpa* juice together with *Rosa canina* and *Alchemille vulgaris* extracts to some experimental groups and investigated its effects. It was observed that the degree of Bax expression was lower in the groups in which plant extracts were applied as a preservative compared to the group in which only indomethacin was administered. It was determined that Bcl-2 expression level increased in groups pretreated with protective plant extracts. In fact, it was determined that the Bcl-2 expression level in the experimental group, in which *Aronia melanocarpo* juice and *Rosa canina* extract were given together, was even higher than the control group. Koczka et al. [35] analyzed many Rosa species in their study and found that *Rosa spinosissima* had significantly higher total phenolic content and antioxidant capacity than other Rosa species. All this information supports the data in the presented study.

In the current study, it was determined that the damage to the mucosal epithelial tissue was partially reduced in the RS-1, RS-2, and HP-1 groups compared to the indomethacin control group; epithelial formation started, bleeding areas in the connective tissue and existing edema continued in some places. In the gastric sections of the HP-2, RS+HP-1, and RS+HP-2 groups, it was observed that the mucosal epithelium and glandular structures developed more smoothly, the

level of healing was quite good, and the edema and bleeding in the connective tissue completely disappeared. It was observed that the groups with the best recovery level were RS+HP-1, and RS+HP-2 groups.

5. Conclusion

These results show that the oils obtained from *Hypericum perforatum* and *Rosa spinosissima* plants have antioxidant and anti-apoptotic properties, and that their combined use in the treatment of peptic ulcer model may be more effective.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

Compliance of the study with the ethical rules was approved by the decision of Atatürk University Animal Experiments Local Ethics Committee (HADYEK) No. 2018/45.

Foundation

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