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Investigation of the Antiulcer Effect of Xsanthoparmelia Somloensis in Rats Induced with Indomethacin

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Abstract *— The gastroprotective effect of Xsanthoparmelia somloensis was investigated in an experimentally in rats. This study was planned to investigate the biochemical changes in ulcer-induced mice. 24 wistar rats were divided into four different groups of 6 rats each. The indomethacin (IND), lichen extract and ranitidine were given orally at appropriate doses to the rats which were fasted for 24 hours before the experiment. The IND was administered orally again 5 minutes after the end of all treatments. The mice were sacrificed with high dose anaesthetic after a 6-hour waiting period. Biochemical parameters and antioxidant activity were determined in the stomach tissues. The catalase (CAT), myeloperoxidase (MPx), superoxide dismutase (SOD), glutathione peroxidase (GPx) enzyme activities and glutathione (GSH) and lipid peroxidase (LPO) levels were measured in gastric tissues removed from mice. In the data obtained, a decrease in CAT, MPx enzymes and an increase in SOD and GPX enzyme activities were determined when compared with IND-treated tissues. GSH level increased while LPO level decreased. The protective effect of the extract on ulcerated tissues caused by IND was assessed, and it can be concluded that it provides protection more than ranitidine utilized as a positive control at the given dosage.*

Keywords *— **antioxidant enzymes, lichen, lipid peroxidation, ulcer, Xsanthoparmelia somloensis***

I. INTRODUCTION

Today, NSAIDs are widely used for their anti-inflammatory and analgesic properties, making them effective in treating conditions like arthritis, muscle pain, and headaches. However, they can also cause gastrointestinal side effects, including the development of ulcers, due to their inhibition of cyclooxygenase (COX) enzymes, which play a role in protecting the stomach lining [1]. However, its high toxic effects indicate that its anti-inflammatory properties have left its anti-inflammatory properties behind and it is the basis of some gastro intestinal system disorders [2,3]. Although it is mainly based on increased acid secretion and consequent damage to the gastric mucosa; smoking, diet, alcohol, stress, Helicobacter pylori (H. pylori) infection, use of various drugs and genetic predisposition are also considered side effects [4,5]. It is also known that ulcer is induced by blocking prostaglandin synthetase (PG) enzyme and preventing cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes from working [3]. Because PGs stimulate the release of mucus and bicarbonate, maintain blood flow and provide regeneration of gastric mucosal cells. In addition to these, the use of NSAIDs, apoptosis, tissue and lipid peroxidation are

also factors that contribute to ulcer formation [6,7]. The indomethacin inhibits COX enzymes, leading to a decrease in PG levels and consequently to disorders such as ulcers, bleeding and platelet dysfunction [8,9]. The antioxidant enzymes and their protective mechanisms attract attention in the treatment of these damages in gastric mucosa [10,11]. Reactive oxygen species (ROS) can cause significant damage to cells, but organisms have evolved various antioxidant mechanisms to mitigate this. The enzymes you mentioned like SOD, CAT, GST, GR, and GPx play vital roles in detoxifying ROS and protecting cellular components.Antioxidant vitamins (such as vitamins C and E) and GSH also contribute significantly to this defense. In the context of ulcer-induced models, studying these enzymatic and non-enzymatic antioxidants can provide insights into the oxidative stress involved in gastric injury and the potential for therapeutic interventions [12-15].

Lichens are plant structures formed by algae and fungi. Since ancient times, it has been the subject of many studies in many diseases (antiviral, antibacterial, antiherbivorous, antitumor, allergen, cream and perfume industry) [16-20]. The tallus surface of Xanthoparmelia somloensis is yellowish green leafy. On the upper surface there are finger-shaped projections and pycnidia, usually in the form of black dots. The lower surface is covered with a dark brownish-colored clinging organ. It grows mostly in warm, sunny areas. It grows on rocks in acidic or basic silicate places. It spreads to the south of the Mediterranean basin. In our country, it is especially widespread in the Eastern Black Sea region. In addition to these effects, investigating the antiulcerogenic effect of lichens may expand the pharmacological uses of lichens and offer new treatment options.

II. MATERIAL AND METHODS

Chemicals

The all chemials used in all biochemical measurements were obtained from Sigma Chemicals Company (Germany). For ulcer experiments: Indomethacin (IND): Endol capsule, 20 mg (Deva Pharmaceuticals), Ranitidine (RAN): 150 mg (Deva Pharmaceuticals).Plant material and extraction of plant material Xsanthoparmelia somloensis specimens were collected from Giresun province in the Eastern Black Sea region in Türkiye in June-September 2005 at various time intervals by Dr. Ali Aslan (Van Yüzüncü Yıl University, Faculty of Pharmacy, Department of Pharmaceutical Botany in Türkiye) and identified using international identification methods [21,22]. After the lichen samples were collected, they were cleaned from foreign materials and dried at room temperature. The dry samples were pulverized by grinding with liquid nitrogen in a mortar and pestle. 700 g of ground lichen samples were kept in a water bath with shaker for two days to extract Xsanthoparmelia somloensis with ethanol (ethanol 60oC 200 ml x8). The extracts were then removed and concentrated in a rotary evaporator under reduced pressure. The concentrated extracts were used in animal models. The herbarium specimens of the species were deposited in Atatürk University-Kazım Karabekir Faculty of Education Herbarium.

Experimental procedure

Animals and treatments

The male Wistar rats weighing 180-190 g were used in the study. These rats were obtained from Atatürk University Faculty of Medicine, Experimental Research Center, Experimental Animals Laboratory. The rats were separated into 6 animals in cages as determined before the experiment and kept under the same conditions. The compliance of the studies with ethical principles was approved by Atatürk University Animal Experiments Local Ethics Committee (HADYEK) with the letter dated 14.12.2023, numbered E-36643897-000-2300404445 and decision number 211.

Indomethacin-induced gastric damage

The experiment designed to evaluate the effects of ethanol extract from Xsanthoparmelia somloensis, ranitidine and tap water on gastric tissues after indomethacin administration was designed with 6 rats per group;

- Group 1 was designated as control and given only tap water.
- Group 2 was designated as IND and given orally to rats at a dose of 20 mg/kg.

- Group 3 was designated as ethanol extract of Xsanthoparmelia somloensis and given orally at a dose of 200 mg/kg.
- Group 4 was determined as positive control RAN and given to rats at a dose of 150 mg/kg. 5 minutes after the end of all treatments, 20 mg/kg dose of IND was administered to all rats. The animals were sacrificed 6 hours after the end of the experimental procedures using high doses of anesthetic (thiopental sodium, 50 mg/kg). To determine the gastric lesions, rat stomachs were cleaned with physiological water and the area widths were calculated with the help of millimetric paper after macroscopic evaluation.

Antiulcer effect (%) was calculated according to the formula =IG-DG/IG X 100

(IG indicates the ulcer area of the IND group and DG indicates the ulcer area of the experimental groups). After macroscopic examination for visible lesions or abnormalities, gastric tissues were stored at -20 °C for biochemical analyses [23,24].

Biochemical investigation of stomach tissues

For the analysis of various enzyme activities and biochemical markers, stomach tissues were ground in liquid nitrogen to a fine powder. The ground tissues were transferred to homogenization buffer according to the appropriate literature for each parameter. The mixture was homogenized to completely clarify the tissues and supernatants were obtained. The supernatants were used to evaluate CAT, SOD, MPx, GPx activities and GSH and LPO levels.

Preparing the tissue homogenates

The gastric tissue samples were quickly frozen in liquid nitrogen and then pulverized using a porcelain mortar and pestle to create a fine powder. Approximately 0.5 g of the powdered tissue was accurately weighed and placed into sterile eppendorf tubes. The mixture was homogenized using a homogenizer for 10 minutes to ensure thorough mixing and cell lysis. The homogenized samples were centrifuged at 4°C in a refrigerated centrifuge. The centrifugation speeds and times were adjusted according to the standards described in the literature. The supernatants obtained were used for biochemical enzyme activities [23,24].

CAT activity: The decomposition of H_2O_2 was monitored at 240 nm. This wavelength is commonly used because H_2O_2 absorbs UV light around this region, and its breakdown can be tracked by a decrease in absorbance. Catalase activity is defined as the amount of enzyme required to decompose 1 nmol of H_2O_2 per minute at 25°C and pH 7.8. The results of the catalase activity are expressed as mmol/min/mg tissue. This means that the activity is quantified based on the amount of H_2O_2 decomposed per minute per milligram of tissue [25].

SOD activity: The method used to measure SOD activity is based on the principle that superoxide radicals react with NBT to form formazone. Xanthine is converted to uric acid by xanthine oxidase enzyme. During this process, O_2-'s are formed. NBT (nitrobluetetrazolium) present in the medium reacts with these superoxide radicals and forms blue formazone dye. Formazone gives maximum absorbance at a wavelength of 560 nm [26].

MPx activity: To measure MPx activity using hypochlorous acid (HOCl) production in tissues; 0.1 g of tissue is homogenized in 10 ml of 50 mM phosphate buffer (pH 6.0). The homogenate was centrifuged to obtain the supernatant. Prepare the mixture by adding 100 µl of the supernatant to 1.9 ml of 10 mmol/l phosphate buffer (pH 6.0) and 1 ml of o-dianisidine hydrochloride containing 0.0005% hydrogen peroxide. Absorbance is recorded at 30-second intervals for a total of 5 minutes [27].

GPx activity: For GPx activity based on NADPH consumption in reactions involving GPx and GR; 0.5 g of stomach tissue was homogenized in 4.5 ml KH_2PO_4 buffer (50 mM, pH 7.8). The homogenate is centrifuged to obtain supernatant. 300 µL of hydrogen peroxide solution (0.25 mM) is added to the mixture. absorbance is recorded at 340 nm at 15 second intervals for 5 minutes [28].

GSH determination: Measurements were performed by the method developed by Sedlak and Lindsay (Sedlak and Lindsay, 1968). 0.5 g of tissue was homogenized by adding 4.5 ml of 50 mM Tris-HCl (pH 7.4). The supernatants obtained by centrifugation were homogenized by adding 1500 µl of measurement buffer and reagents according to the literature. The yellow color obtained after incubation was measured spectrophotometrically at 412 nm [29].

LPO determination: The level of LPO was determined using the Ohkawa method. Homogenized by adding 0.5 g of tissue and appropriate homogenate to obtain a mixture. The mixture was centrifuged at 5000 × g for 20 min at 4°C and mixed with reagents described in the literature. After incubation for a certain time, n-butanol was added to the mixture and measured [30].

Statistical analysis: The results of the analysis were given as the mean ± standard deviation. SPSS software was used for data analysis. Data were analyzed with Duncan test and oneway analysis variance (ANOVA) for multiple comparisons. $p < 0.05$ was considered statistically significant.

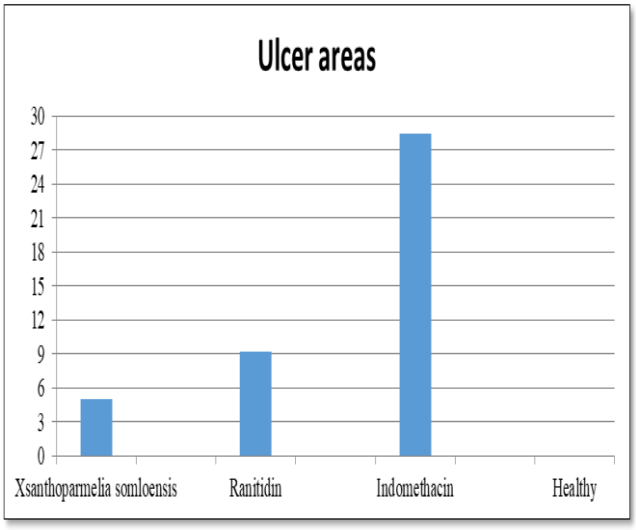

Fig. 1: Figure 1. Effects of gastric injury induced by IND

III. RESULTS

Gastroprotective effect of Xsanthoparmelia somloensis on indomethacin-induced gastric damage

The protective effects of ethanol extract against IND-induced damage in rats are illustrated in Table 1 and Figure 1. The IND group exhibited significant tissue damage, while the rats treated with ethanol extract showed considerable protection, comparable to the results observed in the RAN group. When the ulcer areas were compared, the damage caused by IND was 28.5±1.1, whereas it was significantly reduced in the treatment groups (RAN=9.2±1.2 and X. somloensis extract=5±1.5).

Table 1: The measurements showing the results of X. somloensis and ranitidine in indomethacin-induced gastric damage

Treatments	Dose (mg/kg)	N	Ulcer area (mm^2)	Ulcer rate (%)	P
X. somloensis	200	6	5.0±1.5	17.6	P<0.05
Ranitidine	150	6	9.2±1.2	32.3	P<0.05
Indomethacine	20	6	28.5±1.1	100	P<0.05
Healthy	-	6	0.0±0.0	0	-

The comparison of enzyme activities in rat stomach tissues

The activity of biochemical enzymes in rat stomach tissues was measured to assess the functioning of the antioxidant defense system. The results are presented in the accompanying figures, illustrating the enzyme activities and their implications for antioxidant defense. According to these; CAT enzyme activity was quite high in the IND treated group, while it was significantly decreased in the ethanol extract administered with RAN. Similarly, MPx enzyme activity was increased by IND and decreased by treatment groups. In the SOD and GPx enzyme activities, there was a significant decrease in the animals induced by IND, while the extract group and RAN increased this activity almost to the rate of the healthy group. In the measured LPO levels, tissue damage was very well evident and the IND group was found to be at a very high level. Likewise, GSH levels were very low in the IND group but increased significantly inthe treatment groups (Figure 2).

IV. DISCUSSION

NSAIDs used in the treatment of various inflammatory diseases have very harmful side effects in long-term use. In particular, IND and many NSAIDs, which are well known for their strong anti-inflammatory effects, trigger the formation of ulcers in the stomach. Among the reasons for the damage to the gastric tissue caused by these drugs are that they

disrupt the protective effect of prostaglandins present in the stomach, inhibit bicarbonate secretion, and weaken protective systems such as surface epithelial hydrophobicity and mucosal blood flow. When the balance of these protective mechanisms is disturbed, stomach acid leaks from the damaged area and damages cells and blood vessels. This causes hemorrhagic ulcer disease [31-33]. The use of IND at doses of 10, 20 and 25 mg/kg causes considerable damage in experimental animals [34,35]. At high doses, it has been shown that there is a very significant and severe gastric damage [36]. In our study, the damage in the gastric tissues treated with IND was shown as % inhibition and it was determined that exarction applied together with IND eliminated 17.6% of the damage and RAN eliminated 32.3% of the damage. The fact that it has more side effects compared to other NSAIDs used is due to the inhibition of prostaglandin (PG) synthesis [37].

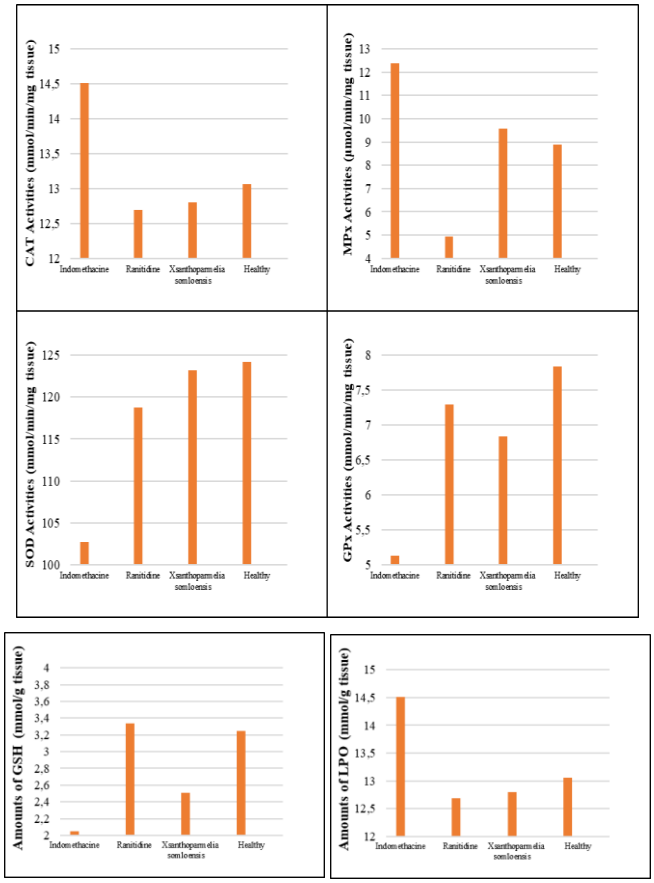

Fig. 2: The results of CAT, MPx, SOD, GPx activities, GSH and LPO levels in stomach tissues obtained from Xsanthoparmelia somloensis, ranitidine, indomethacin and control groups.

In a study conducted by Naito Y. et al. it was shown that ROS play a role in the etiopathogenesis of gastric damage induced by IND [38]. Enzymatic and non-enzymatic defense mechanisms (antioxidant mechanisms) develop in tissues against these damaging ROS [12,13]. SOD, CAT, GPx, GST and GR (enzymes of glutathione metabolism) are important enzymatic antioxidant systems. Non-enzymatic antioxidant defense systems are expressed as GSH, E-vitamin, ascorbic acid, A-vitamin and phenolic substances [32,39]. GSH is an important antioxidant that protects cells against oxidative damage by reacting with ROS. Melatonin, some vitamins and GSH protect the tissue against damage by keeping the amounts of ROS formed as a result of oxidative damage at a low level [40]. In the present study, which is consistent with other studies, our extract increased the low level of GSH in the IND-treated tissue and provided protection against ROS. We can say that Xsanthoparmelia somloensis prevented the balance from shifting to the oxidant side by increasing the amount of antioxidants.

SOD is an enzyme that converts superoxide radical into hydrogen peroxide and molecular oxygen. Physiologically, the function of SOD is to protect oxygen-metabolizing cells against O2 ·- radical damage such as lipid peroxidation. Antioxidant enzymes such as SOD and GPX are good protective factors in reducing the damage in tissues treated with IND [41]. The data in our study are in parallel with these literatures. The fact that the extract increased the decrease in SOD activity measurements caused by IND and provided a significant increase up to the level of healthy tissue is evidence that the results were successful. Although prostaglandin release decreases with IND, the antioxdian defense system is activated and SOD and similar enzyme activities play an important role in gastric protection [42]. Another important antioxidant enzyme that renders hydrogen peroxide formed by SOD harmless by converting it into water and molecular oxygen is CAT. In order to prevent the damage in tissues, CAT activity increased with the application of IND, the extract and RAN showed its protective properties. The increase in CAT activity in damaged tissues is an expression of the increase in H2O2 in tissues. The increase in H2O2 is expressed as an indicator of oxidative damage. CAT enzyme increases its activity in

response to this increase. In parallel with this, the data obtained are aimed at reducing the level of hydrogen peroxide. The increase in CAT and GR enzyme activity by IND has been reported in some literatures [43,44]. The results of the present study are in line with the literatures. It was also reported in the literature that GPx activity was decreased in IND-treated tissues [45,46]. The decrease in GPx activity while CAT activity increased in these tissues may be due to the fact that both enzymes compete in the utilization of hydrogen peroxide [27]. CAT and GPx enzymes eliminate the radical effect by converting H2O2 to H2O. Another marker of oxidative damage is MDA. MDA is the end product of LPO in blood and urine. It forms the basis of many disorders by damaging membrane structure and cell components [47]. In tissues exposed to reactive oxygen species, toxic molecules are ready to initiate MDA formation and LPO. The high level of MDA in damaged tissues has been recorded in some studies [48,49]. The results of the present study are also consistent with the literature. High MDA levels were detected in the stomach tissues treated with IND. The extract and RAN showed their protective effect by significantly reducing this increase. One of the parameters measured to explain the mechanism of gastroprotective effect is MPx enzyme activity. It is an enzyme bound to the heme group in the cytoplasm of phagocytosing cells. During tissue damage, neutrophils in the defense system move to the damaged area. It has been supported in some studies that NSAIDs increase MPx activity in gastric mucosal damaged tissues [50]. This means that when neutrophil release is high in gastric tissues, MPx enzyme will be synthesized in large amounts and consequently damage will occur. The migration of neutrophils to the damaged area is accepted and evaluated as a harbinger of damage (50). The results of the present study are consistent with the mentioned literatures.

V. CONCLUSION

In the present study, the antiulcer effects of lichen species named Xsanthoparmelia somloensis were investigated in an experimentally induced ulcer model. In line with the results obtained, it was determined that the lichen species had a protective effect compared to the ranitidine drug used. In the research supported by biochemical parameters, it was determined that it had a protective effect close to the drugs used continuously. The results obtained with these data show that it can be used as an alternative treatment method in gastroprotective effect.

FUNDING

The authors declare that there are no commercial or financial interests associated with this research. All costs related to the study were funded by the researchers themselves.

CONFLICTS OF INTEREST

All authors declare that there are no conflicts of interest.

ETHICS APPROVAL

The ethical approval was obtained from Ataturk University Animal Experiments Local Ethics Committee for the applications (2023/211).

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