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Gastroprotective effects of *Taraxacum officinale* (Dandelion) extract indomethacin-induced gastric ulcer model

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Abstract

In this study, it was aimed to investigate the gastroprotective and anti-inflammatory effects of the extract (TO) obtain from the leaves of *Taraxacum officinale*, which is used in the treatment of many diseases including gastric ulcers in traditional medicine, in an indomethacin-induced gastric ulcer model. Forty rats, which 10 animals in each group, were divided into four groups (Control (C), TO + Indomethacin (TO+IND), Indomethacin (IND) and Omeprazole + Indomethacin (O+IND) groups). Respectively the group C was given isotonic saline, the group TO+IND was given 100 mg/kg TO extract, group IND was given isotonic saline and the group O+IND was given 5 mg/kg omeprazole orally. On the 11th day of the study, a single dose of 100 mg/kg indomethacin was administered orally to the TO+IND, IND and O+IND groups. It was determined that cyclooxygenase-2 (COX-2), C-reactive protein (CRP) and Interleukin-6 (IL-6) levels were significantly increased in the IND group compared to the K group ($p<0.001$). However, these markers were significantly decreased in both the TO+IND (respectively $p<0.05$, $p<0.001$, $p<0.05$) and O+IND ($p<0.05$, $p<0.001$, $p<0.001$, respectively) groups when compared with the IND group. No significant changes were observed in tumor necrosis factor-alpha (TNF-α) levels. Depending on the administration of indomethacin, it was found that the ulcer index of gastric tissue increased significantly compared to the C group but it decreased significantly as a result of TO and Omeprazole administrations ($p<0.001$). As a result, it was determined that *Taraxacum officinale* leaf extract showed significant gastroprotective effects by reducing COX-2, CRP and IL-6 levels and ulcerative area formation in gastric tissue.

Keywords: Gastric ulcer; *Taraxacum officinale*; Omeprazole; Inflammation

1. Introduction

In the formation of gastrointestinal ulcers; excessive acid and pepsin secretion, decrease in gastric mucosal blood flow, decrease in mucus and bicarbonate secretion, ethanol, smoking, oxidative stress and *Helicobacter pylori* are held responsible [1-3]. It is stated that non-steroidal anti-inflammatory drugs (NSAIDs), which are among the most prescribed drugs worldwide in the treatment of pain, fever and inflammation, even surpass *Helicobacter pylori*, which is the main factor in causing gastric ulcer formation [4]. Indomethacin, one of the most commonly used NSAIDs worldwide, causes mucosal damage by affecting prostaglandin synthesis and increasing gastric acid secretion and hydrogen ion diffusion. In addition, it further increases this damage by causing overproduction of leukotrienes and other substances in the 5-lipoxygenase pathway [5, 6]. Indomethacin prevents the repair of damage to occur by preventing the secretion of protective factors such as prostaglandin E2 (PGE2), Cyclooxygenase 1 (COX-1), bicarbonate and mucus, in addition to these damages in the gastric system [7]. Cyclooxygenase 2 (COX-2) is almost never seen in healthy individuals. Expression of COX-2 occurs rapidly due to proinflammatory stimuli such as cytokines, bacterial toxins, growth factors and necrotic agents. Prostaglandins, product of COX-2, play an important role in inflammation. However, they are also responsible for the development of symptoms such as pain, fever, swelling, redness and loss of

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function [8,9]. It is also known that activated neutrophils in gastric ulcers play an important role in the formation of gastrointestinal lesions by increasing the production of pro-oxidative and pro-inflammatory enzymes that cause oxidative stress, free radicals and pro-inflammatory cytokines such as TNF-α and IL-6 [10].

Taraxacum officinale, a member of the Asteraceae family, is a plant with green leaves and yellow flowers spreading in the northern hemisphere [11]. *Taraxacum officinale,* also known as Dandelion, has a wide variety of bioactive components such as flavonoids, phenolic acids, terpenes, carbohydrates, proteins, fatty acids, vitamins and minerals [12]. Some of these components are; taraxinic acid, cichoric acid, mono-caffeoyl-tartaric acid, caffeic acid, p-coumaric acid, ferulic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, syringic acid, taraxasterol and quercetin. In addition, there is plenty of chlorogenic acid in the aerial parts and inulin, a short-chain fructooligosaccharide, in abundance in the roots. Again, both the root and aerial parts contain vitamins A, B, C, D and plenty of potassium [11]. Thanks to this rich composition, *Taraxacum officinale* is stated to have anti-inflammatory, antimicrobial, antiatherosclerotic, antitumor, immunostimulating, anticoagulant and antioxidant properties. It is reported that with these properties, it can be effective in preventing or reducing the risk of many diseases such as cancer, obesity, hepatitis, arthritis and cardiovascular disease. It is already used in traditional folk medicine in many societies for the treatment of bladder, spleen, liver, gout and diarrhea [13]. In addition to these properties, its flowers, leaves and roots can also be consumed as food. Salad can be produced from its fresh leaves and coffee from its dried roots, while the obtained extract can be used as a flavoring additive [14]. *Taraxacum officinale* extracts are on the American Food and Drug Lists and are considered safe as food and food additives. It has also been reported that it did not cause any adverse effects in human trials [15]. *Taraxacum officinale*, which is a rich herbal source due to the bioactive components, vitamins and minerals it contains, makes it a potential herbal source because it can be easily obtained and consumed without causing any side effects. In this study, it was aimed to determine its possible gastroprotective and anti-inflammatory activity by determining the efficacy of *Taraxacum officinale* ethanol extract on proinflammatory cytokine levels and COX-2 and CRP levels, which play an important role in the pathogenesis of inflammation.

2. Material and methods

2.1. *Taraxacum officinale* supply and Extraction

Taraxacum officinale plants were collected from the coordinates of 41°04'26.3"N 39°23'51.3"E from Çarşıbaşı district of Trabzon province. After drying in the shade, the aerial parts were ground into powder, and then the ethanol extract was extracted by the soxhlet method. Then, the plant extract was obtained by evaporating the ethanol used as a solvent in the evaporator at 50 °C under reduced pressure. 17 g of extract was obtained from 100 g of plants.

2.2. Experimental Design

Forty female Wistar albino rats, 2-3 months old, were used in the study. All substance applications were carried out at the Experimental Animals Application and Research Center of Kafkas University. Rats were fed ad libitum under standard conditions (12 light and 12 hours dark), in cages that were cleaned daily. The groups were created as follows; Control (C), Indomethacin group (IND), *Taraxacum officinale* + Indomethacin group (TO+IND), Omeprazole + Indomethacin group (O+IND).

100 mg/kg *Taraxacum officinale* and 5 mg/kg omeprazole (standard drug) were administered by oral gavage to the TO+IND and O+IND groups, respectively, for 10 days. During the same period, physiological saline was applied to the C and IND groups to ensure standardization. After fasting for 8 hours on the 11th day of the study, 100 mg/kg indomethacin was administered as a single dose to rats in the IND, TO+IND and O+IND groups.

2.3. Biochemical and Macroscopic Analysis

After 24 hours after indomethacin administration, rats under pentobarbital sodium anesthesia were euthanized by cervical dislocation, and gastric tissues were removed. The stomach tissues taken were homogenized in phosphate buffer (1:9, pH 7.4). Then, the homogenates were centrifuged at 5000 x g for 5 minutes in accordance with the kit procedure and the supernatant portions were taken for analysis. TNF-α, IL-6, COX-2 and CRP levels of these homogenate were determined with commercial ELISA kits (Elabscience-USA).

After the stomach tissues were taken, they were washed in flowing water and photographed. In order to calculate the ulcer score, primarily ulcerated areas and total areas in all stomach tissues were calculated as mm^2. Then, ulcer index and ulcer inhibition index were determined according to the formulas below [16].

$$\% \text{ Ulcer index} = [\text{ulcerative area} / \text{total stomach area}] \times 100$$

% Ulcer inhibition (U.I) = [U.I. in control − U.I. in test] × 100/U.I. in control

2.4. Statistical analysis

SPSS 18 package program was used for statistical evaluation of the data. One-Way Analysis of Variance (ANOVA) and Tukey test were applied to evaluate the variables between groups. Values with $p<0.05$ were considered statistically significant. All values in the study were given as mean ± standard deviation.

3. Results

In the macroscopic examinations of the stomach tissues, it was determined that the C group did not contain ulcerative areas and had a completely normal appearance (Figure 1). It was observed that ulcerative areas were formed in the indomethacin administered groups and these ulcerative areas were much higher in the IND group (Figure 1). As a matter of fact, it was determined that ulcerative areas increased by 18.1% in the IND group compared to the C group ($p<0.001$). Significant reductions in the % of ulcerative areas were detected in both the TO+IND group and the O+IND group compared to the IND group ($p<0.001$) (Figure 2). The ulceration in both *Taraxacum officinale* and Omeprazole groups was significantly lower when compared to the IND group, which was accepted as the ulcer control group. Accordingly, it can be said that *Taraxacum officinale* extract has a similar effect to the standard drug omeprazole in preventing ulcer formation (Figure 3).

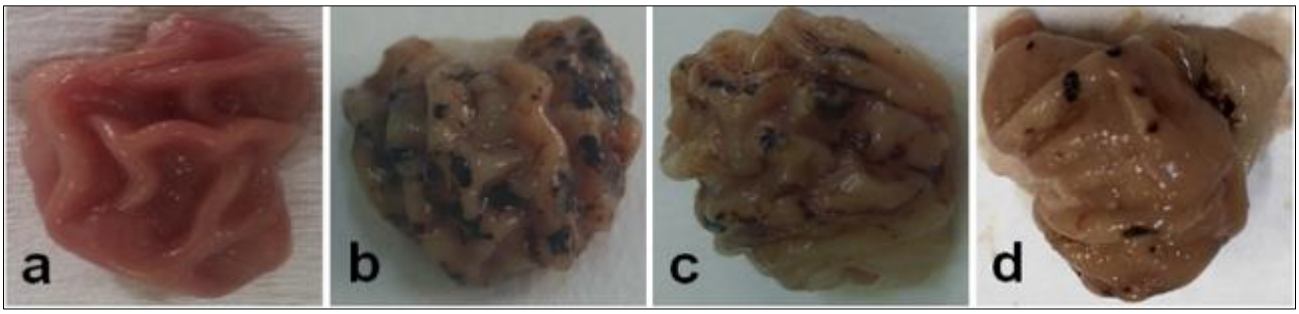

Figure 1 Macroscopic views of ulcerative areas in stomach tissues (a: C, b: IND, c: TO+IND, d: O+IND)

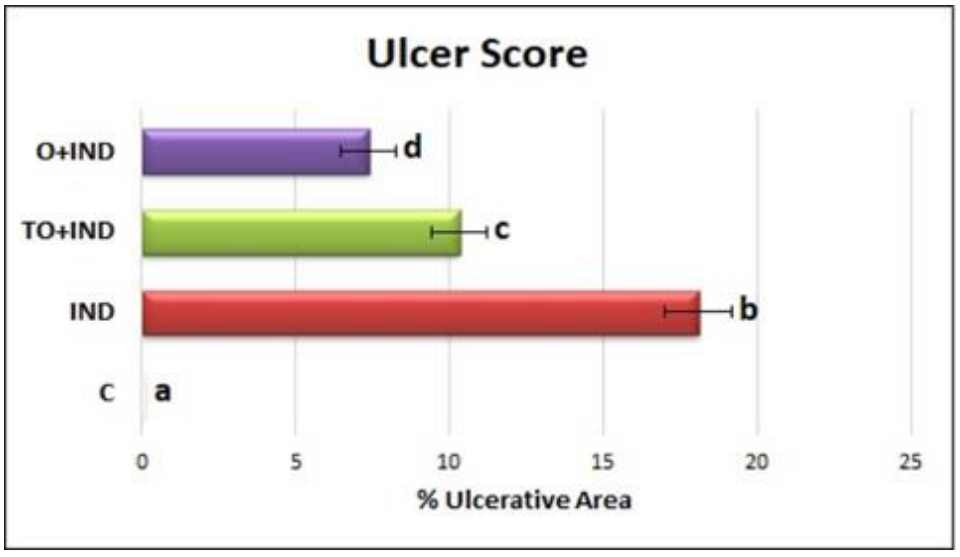

Figure 2 Ulcerative area levels of control and experimental groups (%). Mean ± SD. a-b, a-c, a-d, b-c, b-d, c-d: $p<0.001$

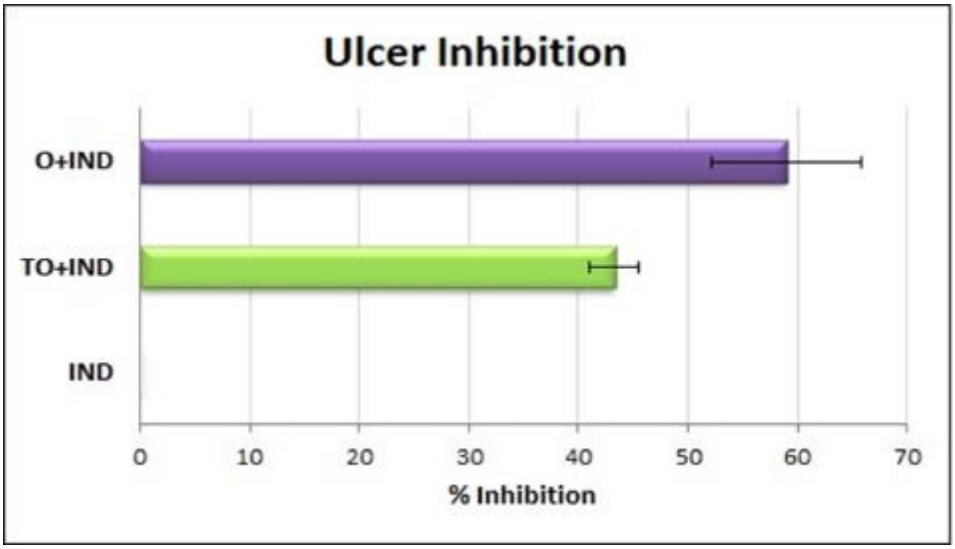

Figure 3 Efficacy levels of *Taraxacum officinale* extract and Omeprazole in preventing indomethacin-induced ulceration (%). Mean ± SD. IND group was accepted as the positive control group

It was determined that the level of CRP, one of the most important inflammation markers, increased significantly in the IND group ($p<0.001$). On the other hand, it was determined that the results of *Taraxacum officinale* extract and omeprazole applications showed statistically significant decreases ($p<0.001$). CRP levels of both the TO+IND group and the O+IND group were statistically similar to the C group (Figure 4).

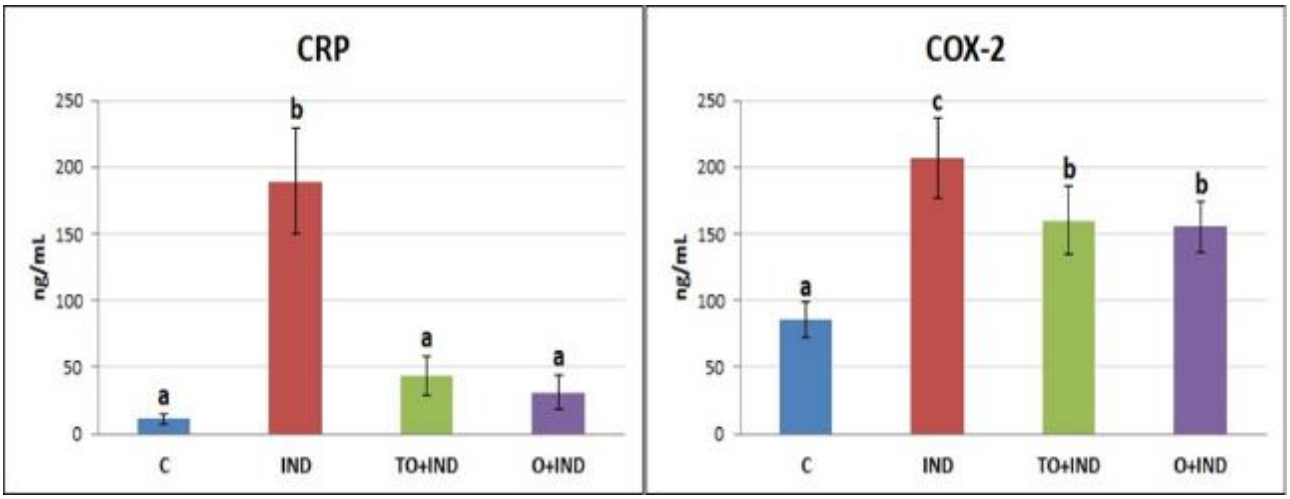

Figure 4 CRP and COX-2 levels of gastric tissue of control and experimental groups. Mean ± SD. a-b, a-c: $p<0.001$, b-c: $p<0.05$

As a result of the analyses, it was determined that COX-2 levels increased due to the inflammation induced by indomethacin. This increase was $p<0.001$ in the IND group compared to the C group. It was established that COX-2 levels, which increased due to indomethacin administration, decreased at a similar level with *Taraxacum officinale* and omeprazole applications ($p<0.05$). However, it was observed that it was still at a higher level than the control group in both groups ($p<0.001$) (Figure 4).

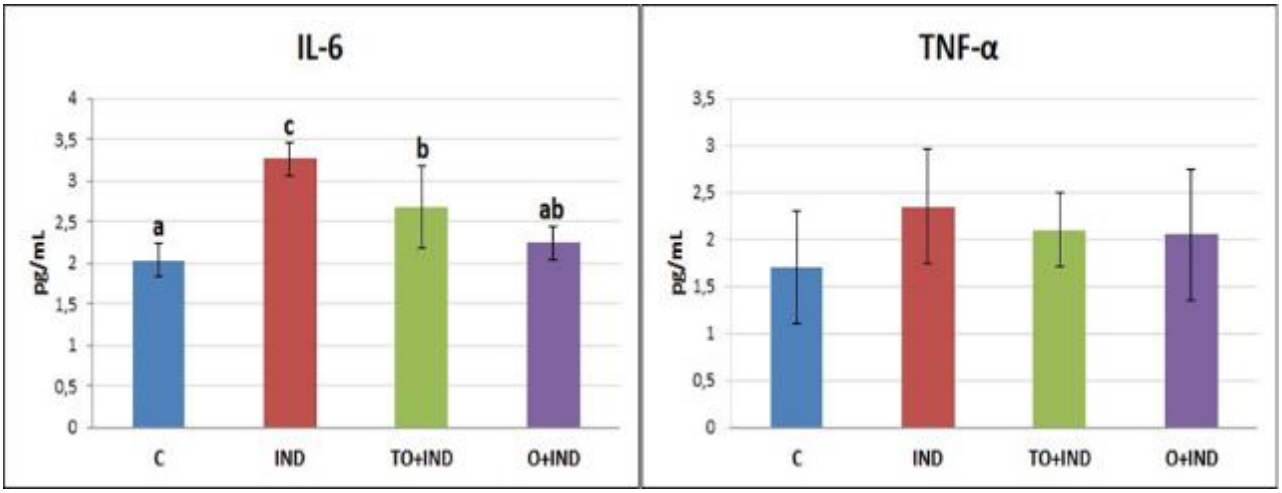

Figure 5 IL-6 and TNF-α levels of gastric tissue of control and experimental groups. Mean ± SD. a-b, b-c: $p<0.05$, a-c, ab-c: $p<0.001$

Proinflammatory IL-6 levels were significantly increased in the IND group compared to group C ($p<0.001$). On the other hand, it was observed that it decreased significantly in both TO+IND and O+IND groups (respectively, $p<0.05$, $p<0.001$) (Figure 6). The changes observed in TNF-α levels between groups were not statistically significant ($p>0.05$) (Figure 5).

4. Discussion

Gastrointestinal ulcers occur as a result of many triggering factors such as excessive acid secretion, decreased mucus secretion, oxidative stress and Helicobacter pylori. However, non-steroidal anti-inflammatory drugs, which are frequently used in the treatment of pain, fever and inflammation today, cause gastrointestinal ulcers at least as much as these factors [2, 4, 17]. In traditional folk medicine, herbal sources are often used to relieve or alleviate many ailments, including gastrointestinal ulcers. One of these plants is *Taraxacum officinale*, which spreads especially in the northern hemisphere [14]. Turkistani (2019) stated that the aqueous extract of the leaves of *Taraxacum officinale* inhibits gastric acid secretion thanks to the antioxidant substances in the plant content. It has also been reported that it reduces ulcerative areas in the stomach wall and can accelerate healing by reducing leukocyte infiltration in the mucosal layers [18]. Berezi et al. (2018) stated that aqueous *Taraxacum officinale* extract increased the amount of mucus with antioxidant levels and also decreased the ulcerative areas in ethanol-induced gastric ulcer [19]. Similarly, Zanata et al. (2021) reported that the aqueous extract of *Taraxacum officinale* increased the levels of SOD, CAT, GSH and GST in rats and decreased the levels of myeloperoxidase. The same researchers stated that *Taraxacum officinale* extract can also prevent the thinning of the gastric wall by decreasing the ulcerative areas and increasing the mucin level [20]. In this study, it was determined that indomethacin caused significant damage to the stomach tissue, whereas *Taraxacum officinale* leaf ethanol extract, given orally to rats for 10 days before indomethacin administration, reduced the formation of ulcerative areas just like a standard drug, omeprazole.

Proinflammatory cytokines are among the main factors that play a role in ulcer development. Proinflammatory cytokines such as TNF-α and IL-6 are involved in the maintenance and regulation of gastric ulcer severity, just as in acute phase inflammations [21]. CRP secreted from liver tissue is an important indicator of inflammatory reactions. CRP production is regulated by proinflammatory cytokines such as TNF-α, IL-1 and IL-6 [22]. Many researchers have reported that mucin levels are decreased in indomethacin-induced ulcers and TNF-α [5,23-27] and IL-6 levels are increased [5,25,27].

Jafarzadeh et al. (2009) reported that serum CRP level was higher in patients with peptic ulcer infected with *Helicobacter pylori* compared to healthy individuals [22]. Kanbay et al. (2005) determined that serum CRP levels were significantly reduced in patients who recovered after *Helicobacter pylori* treatment [28]. Similarly, it has been shown that CRP levels increase significantly in experimental gastric ulcer models created by different methods. It is thought that this increase in CRP levels is likely triggered by elevated proinflammatory TNF-α and IL-6 cytokines [25-27, 29]. Our results showed that CRP levels increased significantly due to ulcer formation, in line with the literature. In contrast, the administered *Taraxacum officinale* ethanol extract reduced CRP levels quite similar to the standard drug omeprazale. This decrease in CRP levels is probably due to the bioactive components of *Taraxacum officinale*, which alleviates ulcer formation and reduces pro-inflammatory cytokine levels.

COX-2 produced from arachidonic acid in biological processes mediates the formation of inflammatory prostaglandins [30]. In our study, we determined that the COX-2 level increased significantly due to increasing inflammation in the gastric ulcer model induced by indomethacin. However, we found that the application of omeprazole (proton pump inhibitor used as a positive control) and *Taraxacum officinale* extract before triggering ulcer formation had a significant protective effect and accordingly prevented the increase in COX-2 levels to a certain extent. COX-2 product prostaglandins cause inflammatory conditions such as pain, fever, swelling, redness and loss of function [8, 9]. While the production of COX-2 is increased by triggering it with traumas, inflammatory stimuli such as IL-1, IL-6 and IL-8, its level is decreased by anti-inflammatory stimuli such as IL-10 [31].

Both experimental and clinical studies have shown that selective COX-2 inhibitors have less gastrointestinal toxicities when compared to conventional NSAIDs [32]. For this reason, selective COX-2 inhibitors are frequently used in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute musculoskeletal pain. In these cases, the human body produces too much prostaglandin, causing inflammation. Selective COX-2 inhibitors act by preventing this inflammation [33, 34]. However, selective COX-2 inhibitors also prevent the production of beneficial prostaglandins, which are responsible for the prevention of gastric ulcer formation. In this respect, they cause serious side effects on the gastrointestinal system, just like classical NSAIDs [9, 35]. As a matter of fact, the drug named Rofecoxib was withdrawn from the market on the grounds that it caused serious cardiovascular problems [36]. Therefore, the search for substances that both create the desired therapeutic effect and cause fewer side effects will always continue. Certainly, in this quest, plants and the active ingredients to be obtained from them will be the first sources to refer to.

Mizuno et al. (1997) found that COX-2 mRNA was not detected in healthy mice, but was highly expressed in acute-phase mice with gastric injury and gastric ulcer [37]. Aziz et al. (2019) reported that COX-2 mRNA level increased significantly in gastric ulcer model induced by ethanol [38]. Similarly, in another study, it was stated that COX-2 expression was induced by gastric ulceration in rats, and the level of COX-2 mRNA decreased with ulcer healing [39]. In addition, many studies have reported that COX-2 levels are significantly increased in gastric ulcer induced by indomethacin in rats [25-27]. In our study, we determined that the COX-2 level increased significantly due to increasing inflammation in the gastric ulcer model induced by indomethacin. However, we found that the application of omeprazole (proton pump inhibitor used as a positive control) and *Taraxacum officinale* extract before triggering ulcer formation had a significant protective effect and accordingly prevented the increase in COX-2 levels to a certain extent.

5. Conclusion

Taraxacum officinale ethanol extract showed a protective effect against indomethacin-induced gastric ulcer in rats by suppressing CRP, COX-2 and IL-6 levels. In addition, it was determined that it provided a significant inhibition in ulceration caused by indomethacin in gastric tissue. We concider that *Taraxacum officinale*, a natural source with a rich bioactive composition, can be an effective source for the prevention of stomach ulcers thanks to its gastroprotective and anti-inflammatory properties.

Compliance with ethical standards

Acknowledgments

Authors are acknowledged for their contributions.

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

Statement of ethical approval

Experiments on animals were carried out in accordance with national guidelines and were approved by the Local Ethics Committee of Animal Experiments of Kafkas University (protocol no: 2017/55).

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