



*Determination of Indomethacin-Induced Gastric Ulcer Healing Effects of  
Several Propolis Extracts and Compared with Omeprazole*

*Çeşitli Propolis Ekstraktlarının İndometasin ile İndüklenen Mide Ülserine  
Karşı İyileştirici Etkilerinin Belirlenmesi ve Omeprazol ile Karşılaştırılması*

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Received/Geliş Tarihi: 03/03/2025

Accepted/ Kabul Tarihi: 12/05/2025

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Doi: 10.35206/jan.1650125

e-ISSN: 2667-4734

## Abstract

Gastric ulcers are an essential problem for both human and animal health. Several medications are used to treat peptic ulcers. Long-term use of these drugs also causes various complications. For this reason, using natural products to treat ulcers has become very popular in recent years. Propolis is an important bee product used in apitherapy, which has various biological activities due to its many active ingredients. Due to its phenolic compounds, it is effective in preventing ulcer formation and accelerating healing. Varying the propolis content according to the solvent used naturally alters its efficiency. This study aimed to compare with omeprazole and to investigate the efficacy of hydro-alcoholic, water, DMSO, and olive oil propolis extracts in a mouse model of indomethacin-induced gastric ulcer. On histopathological examination, epithelial loss, erosion, bleeding, oedema, and inflammatory cell infiltration were scored separately and concerning the overall clinical score. Olive oil and DMSO extracts of propolis

were found to be almost as effective as omeprazole. In contrast, water extract was found to be weak, and hydro-alcoholic extract had no effect, which even worsened some parameters. The results showed that the ulcer healing potential of propolis could be statistically different depending on the solvent. It was also found that DMSO and olive oil extracts of propolis have the potential to heal peptic ulcers.

**Keywords:** Gastric ulcer, Honey bee, Apitherapy, DMSO, Olive oil, Propolis.

## **Özet**

Gastrik ülser birçok sebeple ortaya çıkan hem insan hem de hayvan sağlığı açısından önemli bir sorundur. Gastrik ülserin medikal tedavisinde farklı ilaçlar kullanılmaktadır. Bu ilaçların uzun süreli kullanımları da çeşitli komplikasyonlar oluşturmaktadır. Bu sebeple son yıllarda ülser iyileşmesinde doğal ürünlerin kullanımı oldukça popüler hale gelmiştir. Bunların içerisinde önemli bir arı ürünü olan ve apiterapide kullanılan propolis gelmektedir. Propolis içerisinde bulunduğu birçok aktif bileşen nedeniyle farklı biyolojik aktivitelere sahip önemli bir arı ürünüdür. Özellikle içeriğindeki fenolik bileşikler nedeniyle yara iyileşmesi hızlanması ve ülser oluşumunun engellenmesi gibi etkinlik gösterdiği belirlenmiştir. Propolis içeriğinin çözücülere bağlı değişmesi doğal olarak etkinliğinin de değişmesine neden olmaktadır. Bu çalışmanın amacı, indometazin ile indüklenen gastrik ülser fare modelinde hidroalkolik, su, DMSO ve zeytinyağı propolis ekstraktlarının etkinliğini araştırmak ve omeprazol ile karşılaştırmaktır. Histopatolojik incelemede epitel kaybı, erozyon, kanama, ödem ve inflamatuvar hücre infiltrasyonu ayrı ayrı ve total klinik skor açısından değerlendirilmiştir. Propolisin zeytinyağı ve DMSO ekstraktları neredeyse omeprazol kadar etkin bulunurken su ekstraktının zayıf, alkol ekstraktının ise etkisinin olmadığı hatta bazı parametreleri daha da kötüleştirdiği belirlenmiştir. Sonuç olarak propolisin çözücüye bağlı ülser iyileştirme potansiyelinin istatistiksel olarak değişebileceği tespit edilmiştir. Ayrıca propolisin DMSO ve zeytinyağı ekstraktlarının gastrik ülser iyileştirmede potansiyellerinin olduğu belirlenmiştir.

**Anahtar Kelimeler:** Gastrik ülser, Bal arısı, Apiterapi, DMSO, Zeytinyağı, Propolis.

**Abbreviations:** OMP, Omeprazole; WEP, water extract propolis; W, water; EEP, hydro-alcoholic (70%) extract propolis; EW, ethanol (70%)-water (30%); DMSOEP, dimethyl sulphoxide extract propolis; DMSO, dimethyl sulphoxide; OOEP, olive oil extract propolis; OO, only olive oil; NSAIDs, non-steroidal anti-inflammatory drugs.

## **1. INTRODUCTION**

Gastric ulcers are open wounds caused by damage to the stomach lining (Khan et al., 2023; RaviKKumar et al., 2023). These wounds are usually caused by damage to the stomach lining by stomach acid and digestive enzymes (RaviKKumar et al., 2023). The stomach lining or mucosa is protected from the damaging effects of stomach acid and digestive enzymes by various mechanisms. However, in some cases, these protective mechanisms weaken, and ulcers occur on the mucosa under the influence of the acidic environment. In addition, oxidative stress is caused by various chemicals, infections, and nutritional disorders; the parasympathetic system is involved in acid release, and histamine-induced disorders cause gastric ulcer

formation. Among the most important causes of gastric ulcers are NSAIDs, which interfere with prostaglandin synthesis and are widely used. Ulcers are usually treated with drugs that reduce acid production and neutralise stomach acid (Khan et al., 2023; RaviKKumar et al., 2023). In addition to medical therapy, dietary changes and the use of natural products have become very popular.

Propolis is one of the natural products. It has many biological activities among bee products and is widely used. Propolis is an essential product, generally used as a building material in the hive, obtained by honeybees by collecting the secretions and resins of surrounding plants (Simone-Finstrom & Spivak, 2010). Propolis contains more than 300 compounds and has a wide range of biological activities, particularly its flavonoids and phenolic acids (Huang et al., 2014). Because of its antioxidant and anti-inflammatory properties, which accelerate wound healing, many studies have been carried out on the digestive system, suggesting that propolis may be effective against various ulcers (Martinotti & Ranzato, 2015; Ruiz-Hurtado et al., 2021a). In these studies, there were differences due to the fact that the chemical content of propolis varied in relation to the surrounding vegetation (Ali Sorucu & Oruç, 2019). Although the chemical content of propolis depends on the vegetation, it has been found that the solvent of the extract used as the final product varies according to the solvent used and that its biological activity is significantly affected (Sorucu & Ceylan, 2021; Oruç et al., 2023).

Previous studies have shown that propolis accelerates ulcer healing (Pillai et al., 2010; Silva et al., 2018; Costa et al., 2020; Boeing et al., 2023; Mokam et al., 2024; Oyetayo et al., 2023). However, it is predicted that the content of propolis will have an effect on the antiulcer activity of propolis due to various factors.

The most commonly used solvent for propolis is ethanol. However, there are studies on different solvents of propolis for both health and religious reasons. Water extracts of propolis dissolve less phenolic substances, which is a negative aspect of efficiency. In addition, studies have shown that phenolic acids, particularly, dissolve in water extract, while flavonoids dissolve in organic solvents such as alcohol. In addition, propolis is extracted in solvents such as DMSO, known as green solvents. The green solvents can be used for both health and cell culture studies. In recent years, several studies have been conducted on olive oil. It is especially preferred to use natural, easily consumable, and religious terms. In addition, the best phenolic content solvent is still alcoholic solvents (Pujirahayu et al., 2014; Kekeçoğlu & Sorucu, 2021; Sorucu & Ceylan, 2021). It is predicted that there will be changes in the biological activity of propolis due to the significant change in its content depending on the solvent.

Therefore, this study aimed to determine the effect of extraction solvent on gastric ulcer healing of propolis. The present study aimed to determine the efficacy of hydro-alcoholic, water, DMSO, and olive oil propolis extracts and compared them with omeprazole in a mouse model of indomethacin-induced gastric ulcers.

## **2. MATERIALS AND METHODS**

### **2.1. Propolis Extraction**

The raw propolis, which is reddish, was obtained from the Apitonic Beekeeping company in Muğla. The extraction was carried out based on the study (Sorucu & Oruç, 2019). Propolis was ground into a powder using a grain mill and then thoroughly mixed to homogenise. 500 g of the homogenised propolis powder was weighed, and 1500 ml of extraction solvents, which were ultrapure water, cold pressed olive oil, 50% DMSO, and 70-30% ethanol-water, were added individually. The extracts were shaken in an orbital shaker for one week. Finally, the solvents were filtered through the Whatman No:1 filter paper to obtain the extracts. After propolis was transferred in 1 ml tared tubes, the solvents were evaporated, and the ratios of the resins were determined. The obtained extracts were stored at +4 C in amber glass bottles.

### **2.2. Animals and Experimental Design**

This study is based on the Ruiz-Huarta (2021b) and Pillai (2010). The study was conducted with the approval of the Local Ethics Committee for Animal Experiments of Muğla Sıtkı Koçman University under the approval number 30/05/2022-22/04. A total of 72 male BALB/c mice weighing 15-25 g were used in the study. The mice were obtained from the Experimental Animal Application and Research Centre, Muğla Sıtkı Koçman University. The experimental study was conducted at this centre. The conditions were appropriate for mice.

Mice were randomised into nine groups of eight. All the applicants were administered oral gavage to the mice. A dose of 100 mg resin/kg of propolis extract was applied. The animals used in the experiment were starved for 24 hours. A 100 mg/kg dose of indomethacin was administered orally by gavage into the stomach to create an ulcer model. After administering indomethacin, the first applications were carried out and then repeated daily for 15 days. Omeprazole was used for the positive treatment control, and extraction solvents were applied for the negative control, such as the volume of propolis extract. The groups are as follows:

**Group 1 (OMP):** Omeprazole 30 mg/kg

**Group 2 (WEP):** Water (high purity from ELGA) extract of propolis (100 mg/kg)

**Group 3 (W):** The only extraction solvent of WEP with the same volume for the negative control

**Group 4 (EEP):** Hidro-alcoholic extract of propolis (ethanol (MERCK) 70%-water 30%) (100 mg/kg).

**Group 5 (EW):** Ethanol-water, the only extraction solvent of EEP with the same volume for the negative control.

**Group 6 (DMSOEP):** DMSO (TEKKİM) (DMSO 50%-water 50%) extract of propolis (100 mg/kg).

**Group 7 (DMSO):** The only extraction solvent of DMSOEP with the same volume for the negative control.

**Group 8 (OOEP):** Cold pressed olive oil (Memecik olive of Milas) propolis extract (100 mg/kg).

**Group 9 (OO):** The only extraction solvent of OOEP with the same volume for the negative control.

Mice anaesthetised with 10 mg/kg xylazine hydrochloride (Rompun®, Bayer, 23.32 mg/ml, Germany) followed by 70 mg/kg ketamine hydrochloride (Ketalar®, Parke-Davis, 50 mg/ml, Germany) were euthanised by cervical dislocation on day 15th. For histopathological examination, the stomachs of the mice were removed and preserved in 10% formaldehyde (Ruiz-Hurtado et al., 2021a).

### **2.3. Histopathologic Analyses**

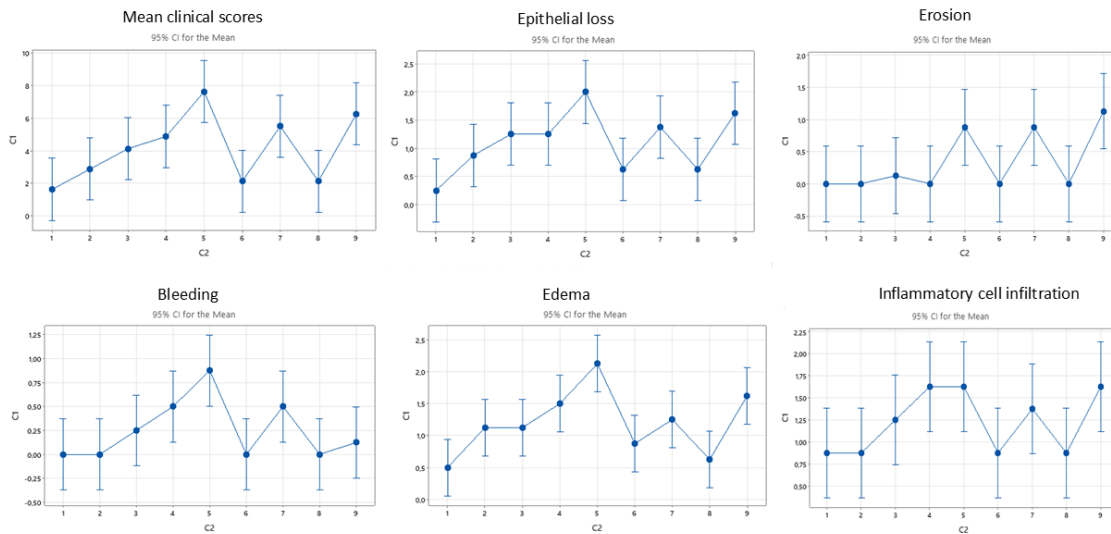
Histopathologic examination was carried out at the Adnan Menderes University, Faculty of Veterinary Medicine, Department of Pathology. The tissues fixed in formaldehyde solution were processed through tissue tracing with alcohol and xylol and then embedded in paraffin blocks. Sections of 3-5 µm thickness were cut from the paraffin blocks and transferred to microscope slides. Finally, the samples were stained with haematoxylin-eosin, and a microscopic examination was performed. In the histopathologic examination, the groups were scored semiquantitatively with slight modification in terms of (1) epithelial cell loss (score: 0-3), (2) haemorrhage (score: 0-3), (3) inflammatory cell infiltration (score: 0-3), (4) mucosal erosion of the lamina propria (score: 0-3), (5) oedema (score: 0-3). The scores were evaluated as follows: 0: none, 1: light, 2: medium, and 3: violent (Yang et al., 2017).

## 2.4. Statistical Analysis

Firstly, the normal distribution of data was checked using the Kolmogorov-Smirnov test using SPSS 16 software (SPSS, Inc., Chicago, IL). The test result was  $p=0.01$ . Since the  $p$ -value was less than 0.05, it was decided that the distribution was non-normal. Non-normal statistical analyses of the results were performed using Minitab 21.0.1 software, in which the following procedures were used. The Kruskal-Wallis test was used to compare the means of each group, and the post-hoc Dunn's test was used to determine the source of the difference. The Chi-square test was used to evaluate the total clinical score categorical variables. The assessment of significance levels was assessed according to  $P \leq 0.05$ .

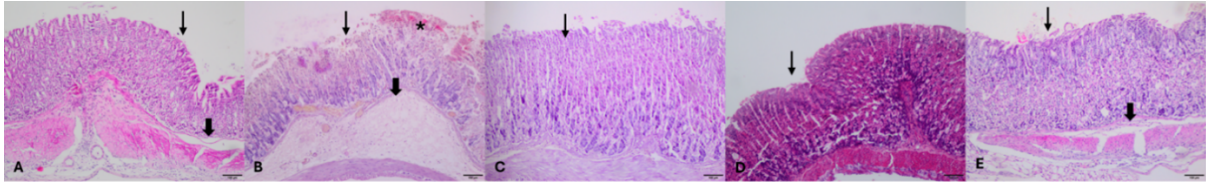
## 3. RESULTS AND DISCUSSION

Histopathological examination was scored for epithelial cell loss, haemorrhage, inflammatory cell infiltration, lamina propria mucosal erosions, and oedema (Table 1 and Figure 1).

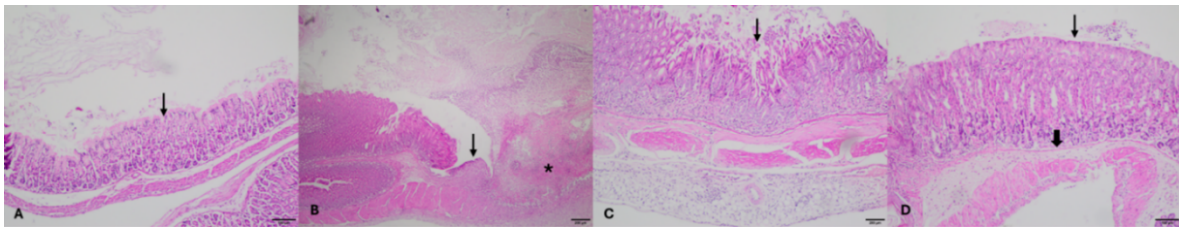


**Figure 1.** Means of pathology scoring results of the gastric tissue (n=8). The pooled standard deviation is used to calculate the intervals. C1 is the mean of pathological scores  $\pm$  SD, C2 is treatment groups which are 1: OMP, 2: WEP, 3: W, 4: EEP, 5: EW, 6: DMSOEP, 7: DMSO, 8: OOEP, 9: OO

Histopathological findings of the treatment and control groups are given in Figures 2 and 3. The statistical parameters were analysed individually, and for more accurate results, the total clinical score was analysed for all values (Table 1 and Figure 1).



**Figure 2.** The histopathology of the treatments of propolis extracts and omeprazole. A; OOEP, B; EEP, C; WEP, D; DMSOEP, E; OMP, Arrow; epithelium (mucosa), Star; bleeding areas, Bold arrow; edema and cell infiltration (H&E staining, 20x).



**Figure 3.** The histopathology of the negative controls. A; OO, B; EW C; W, D; DMSO, Arrow; epithelium (mucosa), Star; Granulation tissue formation (epithelium etc. terminates the inflammatory reaction with the organisation of all layers), Bold arrow; edema and cell infiltration (H&E staining, 20x).

It was determined that the lowest epithelial loss was found in the OMP as a positive control group, and the highest epithelial loss was found in the EEP treatment group (Table 1 and Figure 1). Although epithelial loss was less in the WEP group than in the EW group, it was found to be more prominent than in the other groups (Table 1 and Figure 1). Mild epithelial loss was predominantly observed in the DMSOEP and OOEP treatment groups (Table 1). In addition, regarding epithelial loss, the DMSOEP and OOEP groups were closest to the positive treatment OM (Table 1). Statistical analysis revealed that DMSOEP and OOEP reduced epithelial loss as much as OMP, and the other treatments had no statistically significant effect (Table 1).

**Table 1.** Statistical comparison of positive control omeprazole with other treatments

<b>Treatment groups (n=8)</b>	<b>OMP (+)</b>	<b>WEP (-)</b>	<b>W (-)</b>	<b>EEP (-)</b>	<b>EW (-)</b>	<b>DMSOEP (-)</b>	<b>DMSO (-)</b>	<b>OOEP (-)</b>	<b>OO (-)</b>
<b>Mean clinical scores</b>	P	0.08	0.04	0.03	0.01	0.464	0.03	0.465	0.02
<b>Epithelial loss</b>	P	0.042	0.001	0.005	0.001	0.149	0.026	0.15	0.014
<b>Erosion</b>	P	1	0.335	1	0.089	1	0.14	1	0.1
<b>Bleeding</b>	P	1	0.15	0.019	0.045	1	0.082	1	0.335
<b>Edema</b>	P	0.053	0.053	0.002	0.001	0.224	0.031	0.705	0.001
<b>Inflammatory cell infiltration</b>	P	0.905	0.09	0.004	0.003	0.904	0.227	0.919	0.049

Omeprazole: OMP, water extract propolis: WEP, only water: W, hydro-alcoholic extract: EEP, only water-ethanol: EW dimethyl sulphoxide extract propolis: DMSOEP, only dimethyl sulphoxide: DMSO, olive oil extract propolis: OOEP, only olive oil: OO, (+): Positive treatment control, (-): negative treatment control.

There was no evidence of erosion in any of the treatment groups (Table 1). Statistical analysis for erosion found that all treatments reduced erosion, such as OMP, but the propolis treatment was more effective than the negative controls.

There was a slight occurrence of haemorrhage in the EEP group, but no haemorrhage was detected in the other treatment groups (Table 1). The statistical analysis regarding haemorrhage determined that propolis treatments, apart from the EEP, reduced haemorrhage (Table 1). Only solvents (negative controls) DMSO, W, and OO reduced the haemorrhage weakly, and the haemorrhage was higher in EW than in the others (Table 1).

Oedema was mild in the OMP and OOEP groups and occurred in fewer animals than in the other groups, whereas significant oedema was observed in the EEP group. Statistical analysis of oedema showed that DMSOEP and OOEP reduced oedema as much as OMP, whereas WEP and W application reduced oedema to a lesser extent (Table 1).

In the EEP group, there was a significant inflammatory cell infiltration ranging from mild to moderate, while in the other groups, a mild infiltration was observed. In the statistical analysis in terms of inflammatory cell infiltration, it was determined that propolis applications except EEP had similar effects to OMP, while W, DMSO, and OO reduced cell infiltration at a low level (Table 1). EEP and EW treatments were not statistically effective in treating inflammatory cell infiltration. In the negative control groups (W, EW, OO), the most remarkable results in histopathological changes were observed in the EW group, while epithelial loss was mild in the W group compared to the other groups. It was observed that

epithelial loss was severe in the EW group, haemorrhage was present in 3 animals, and the inflammatory response, although not very severe, continued significantly, especially when oedema was prominent compared to other groups. Erosion was also observed in the OO, EW, and DMSO groups (Table 1).

In the statistical analysis performed with the mean values of the total clinical scores, it was found that WEP, DMSOEP, and OOEP had similar effects to OMP, while the other treatments showed a negative significant difference compared with OMP (Table 1). The results concluded that DMSOEP, OOEP strongly, and WEP weakly contributed to ulcer healing (Table 1). In the statistical analysis, the solvents were worse in terms of healing than their propolis extracts, except for EEP. When examining the pathological evaluation, it was seen that EEP is worse than its solvent EW in all parameters, but this was not statistically significant (Figure 1 and Table 1).

Phenolic compounds have been reported to be beneficial in protecting and healing gastrointestinal disorders, particularly in healing peptic ulcers (Serafim et al., 2020). Propolis has been the subject of research into gastrointestinal disorders due to the high diversity and quantity of phenolic compounds in its content (Silva et al., 2018; Ruiz-Hurtado et al., 2021b). Many studies have demonstrated the gastroprotective properties of propolis with different properties (Abd El-Hady et al., 2013; Costa et al., 2020; de Mendonça et al., 2020; Sahin et al., 2023). However, studies of ulcer healing are very limited (Pillai et al., 2010; Silva et al., 2018; Boeing et al., 2023; Costa et al., 2020; Mokam et al., 2024; Oyetayo et al., 2023).

The hydro-alcoholic extract of Brazilian green propolis reduced gastric epithelial damage in gastric ulcer models induced by various methods and accelerated the daily healing process by 71% (Costa et al., 2020). In indomethacin-induced gastric ulcer models, ethanol extract of Cameroon propolis (administered at doses of 200 mg/kg, 400 mg/kg, and 600 mg/kg) was found to show an increasing dose-dependent improvement (Mokam et al., 2024). In acetic acid-induced gastric ulcer models in rats, hydro-alcoholic extract of Nigerian propolis showed both protective and healing properties (Oyetayo et al., 2023). After lyophilisation of the ethanolic extract of Indian propolis, it was dissolved in water and administered at a dose of 300 mg/kg for 15 days to ethanol and indomethacin-induced gastric ulcer models in rats. A statistical improvement was observed (Pillai et al., 2010). Most studies to date have found that treatment with alcohol extract has a positive effect on ulcer healing. In one study, applying water-extracted propolis after alcohol extraction showed positive results. However, the current study found that the water extract had a weak healing effect. The hydro-alcoholic extract did not contribute to the healing of the peptic ulcer. On the contrary, the hydro-alcoholic extract

made the peptic ulcer worse. A study conducted in Türkiye investigated the gastroprotective effect of propolis but not its effect on ulcer healing. This study found that the protective effect of the water extract of Türkiye propolis was even better than that of the alcohol extract (Sahin et al., 2023). Since the phenolic components in propolis are mostly transferred to hydro-alcoholic extract, its biological activity is generally expected to be higher than other solvents. Still, in the present study, the hydro-alcoholic extract of propolis did not show any effect. On the contrary, it caused the ulcer to worsen in some properties (Kekeçoğlu & Sorucu, 2021; Oruç et al., 2023). Some studies have used alcohol in gastric ulcer models so the deterioration may be due to the alcohol used in the extraction of propolis (Costa et al., 2020). However, in some previous studies, hydro-alcoholic extract of propolis was beneficial in terms of both healing and protection, which reduces the possibility (Liu et al., 2002; Pillai et al., 2010; Costa et al., 2020; Boeing et al., 2021). In order to clarify the situation, the amount and variety of phenolic compounds in the content should be analysed and examined in detail.

Many studies have reported that the content of propolis varies depending on the extraction solvent (Kekeçoğlu & Sorucu, 2021; Oruç et al., 2023). This change is reflected in many biological activities. In the present study, the effect of propolis on ulcer healing was noted to change significantly depending on the solvent. The studies which analysed the content of propolis generally reported that many substances, especially flavonoids, were higher in alcohol extract propolis. It is known that the water extract of propolis contains less soluble substances, but the phenolic acids are at a higher level (Kekeçoğlu & Sorucu, 2021; Oruç et al., 2023). Although the alcohol extract of propolis dissolves more substances, it has been determined that the water extract is better in some biological activity studies (Sahin et al., 2023; Sorucu & Ceylan, 2021). This is thought to be due to the higher biological activity of some substances. There are also many substances in propolis. Although these substances give biological activity to propolis, it is challenging to predict which reveals these effects. Therefore, the present study did not carry out a content analysis and did not compare the content with ulcer healing.

#### **4. CONCLUSIONS**

Propolis is an important product in alternative and complementary medicine, and it has become very popular in recent years due to its many properties. In particular, antioxidant, antimicrobial, protective effects on various tissues and organs, and wound healing accelerator ethics are at the forefront. It has been used in various studies of gastrointestinal disorders, with positive results, primarily due to its tissue-protective and wound-healing properties. The beneficial substances

in propolis vary in biological activity due to variability depending on various factors. It is predicted that the phenolic components in its content will show differences in the healing of peptic ulcers due to different levels of passage to different solvents. Therefore, extracts obtained with four different solvents were used, and it was found that propolis extracted with DMSO and olive oil showed almost as much activity as omeprazole. Previous studies have determined that the alcohol extract, through which the phenolic compounds in the propolis content pass the most, causes the ulcer to worsen rather than heal. The present study has concluded that olive oil extract of propolis has the potential to be used in the healing of ulcers, particularly because of its availability and applicability. OOEP has the potential for industrial production and use in apitherapy due to its ease of use and production and the lack of reported toxic effects of olive oil.

### **ACKNOWLEDGEMENTS**

The study was supported by TUBİTAK 1919B012109659 project number. We would like to thank Nurettin Çanakoğlu for the statistical analyses.

### **DECLARATIONS**

The authors declare that they have no conflict of interest in this study.

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