Original Article https://doi.org/10.47748/tjvr.1376617

TJVR 2024; 8 (1): 53-61

Turkish Journal of Veterinary Research

https://dergipark.org.tr/tr/pub/tjvr

e-ISSN: 2602-3695

Investigating wound healing and antimicrobial activity of terebinth extract and terebinth extract+oxytetracycline mixture in experimental wounds in mice

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Received: 16.10.2023 Accepted: 21.12.2023

ABSTRACT

Objective: The aim of the study is to investigate the wound healing and antibacterial activity of terebinth extract and the mixture of terebinth+3% oxytetracycline in experimental back skin wounds

Materials-Methods: The animal material of the study consisted of 18 mice. The animals were divided into 3 groups as control group (group I, n:6), terebinth group (group II, n:6), terebinth+oxytetracycline group (group III, n:6). Wounds with a 1 cm^2 diameter were induced on the back of the mice and infected with *Staphylococcus aureus* ATCC® 25923 reference strain. Treatment protocols for the groups were applied daily, once a day. Total aerobic mesophilic bacteria and *S. aureus* count was performed in the swab samples taken on days 3, 7, and 14 of the healing process.

Results: In the study, it was found that wound healing process was completed the earliest in Group III (mean duration of 15.67±0.609 days), which was followed by Group II (18±0.73) and Group I (24.67±0.919), respectively. The healing period was statistically significantly shorter in Group II and Group III than in Group I ($p<0.001$). In the evaluation of aerobic mesophilic bacteria and *S. aureus* load, much less live bacteria were found in Group III compared to the other groups. In addition, the number of bacteria measured in group II, in which terebinth extract was used, was found to be significantly lower than the number of bacteria measured in the control group.

Conclusion: Consequently, it was concluded that the extract of terebinth plant grown in Siirt region reduced the bacterial load in the wound area and accelerated the healing process.

Keywords: *Mice, Wound healing, Terebinth extract, Oxytetracycline, Antibacterial*

INTRODUCTION

Wound is defined as the deterioration of the skin integrity and mucous membranes as a result of various diseases, trauma, bites, or stings (Ayyanar and Ignacimuthu, 2009; Sorg et al., 2017). Wounds classified as open or closed can show an acute or chronic course (Biswas and Mukherjee, 2003). As a result of injury, tissue loss and loss of sensation and function as well as bleeding, redness, pain, contraction of tissues and discharge can be observed (Dhifi et al., 2012). Based on the extent of the injury, some cases can heal spontaneously; whereas, serious cases need a rapid and effective intervention. Especially in open wounds, complications characterized by pus may be seen due to bacterial infections (Wang et al., 2018; Balestrin et al., 2022).

Wound healing is a pathophysiological condition that occurs to restore dermo-epidermal integrity (Wang et al., 2018). Various cells of the immune

system play a role in hemostasis, inflammation, neovascularization, fibroplasia and re-epithelialization stages of wound healing (Taş et al., 2003., De Almeida et al., 2022; Wallace et al., 2022). As well several cytokines, released by cells of the immune system, have a critical importance in the wound healing process, (Darby et al., 2014; Chitturi et al., 2015; Darwin and Tomic-Canic, 2018; De Almeida et al., 2022). Infections, some diseases, and medical treatment can affect the healing process positively or negatively (Wernick et al., 2022).

Numerous studies have examined the effects of various plant extracts on wound healing (Budovsky et al., 2015; Yuan et al., 2016; Sharma et al., 2021; De Almeida et al., 2022). These effects of plants are caused by alkaloids, iridoids, flavonoids, tannins, saponins and phenolic compounds they contain in their structures (Thangapazham et al., 2016). The fact that plant extracts contain various combinations of phytocomponents involved in various pathophysiological steps of wound healing (angiogenesis, fibroplasia, and wound contraction) is one of the most important reasons behind why they are used to treat wounds (Ibrahim et al., 2018; De Almeida et al., 2022).

The phenomenon of bacterial antimicrobial resistance poses problems in effectively treating infectious diseases. This situation necessitates searching new alternatives to antimicrobial agents. In this sense, it has been reported that in recent years there has been an increasing interest in the use of plants known to have antimicrobial effects in the treatment of infectious diseases in both humans and animals (Khalil et al., 2007; Tohidi and Hayran, 2011).

Since ancient times, terebinth plant has been used as an antispasmodic, antipyretic, antibacterial, antiviral and stimulant in eczema treatment, throat infections, kidney stones, asthma and stomach diseases in human medicine and is known to contain phenolic compounds and triterpenoids (Kusmenoglu et al., 1995; Tohidi et al., 2011; Dhifi et al., 2012). In addition, terebinth plant has antioxidant, anti-inflammatory, anti-pyretic, antiparasitic, neuroprotective, and anticholinesterase activity properties (Göçer, 2013; Hacıbekiroğlu et al., 2015).

In the treatment of infected wounds, the use of both topical and systemic antibiotics has been shown to be beneficial (Saco et al., 2015; Gerçeker Türk, 2020). Oxytetracycline is a second-generation tetracycline group antibiotic produced by *Streptomyces rimosus*. Oxytetracycline, which has a broad spectrum, is effective against Gram positive and Gram-negative bacteria and mycoplasma species and inhibits protein synthesis in bacterial agents (Augusto and Alves, 2015; Demirseren, 2020).

The aim of the study is to investigate the wound healing and antibacterial activity of the extract of terebinth plant, which is ecologically grown in Siirt region, and the mixture of terebinth extract+3% oxytetracycline in Experimental back skin wounds in mice.

MATERIALS and METHODS

Material

Animal material and selection: The animal material of the study consisted of 30-day-old, 18 male dormouse mice (*Mus musculus*) obtained from Van Yüzüncü Yıl University Experimental Animals Research and Application Center. The mice were divided into three groups and housed in individual mouse cages. They were fed standard feed and water ad-libitum.

Ethics committee approval: The current study was approved by Siirt University Experimental Animals Local Ethics Committee with the decision dated 10.02.2017 and numbered 2017/01/21.

Method

Preparation of the drug material: Terebinth extract was obtained from the Laboratory of Siirt University Research Center. The mixture of terebinth extract+3% oxytetracycline was obtained by mixing 1 gr terebinth extract and 30 mg oxytetracycline in a sterile glass beaker until a homogenous mixture was obtained. The prepared drug material was stored in a light-proof sterile plastic container. The drug material was prepared originally without considering any cream formulation.

Study groups: The study consisted of 3 groups; control group (C) with no drug administration (group I, n:6), terebinth group (T) (group II, n:6), terebinth extract+3% oxytetracycline group (TO) (group III, n:6).

Group I: No treatment was applied on the wound in mice in this group.

Group II: Terebinth extract (0.5 ml) was applied to the wound once every day until healing took place.

Group III: A mixture of terebinth extract+3% oxytetracycline (0.5 ml) was applied to the wound once a day, every day until healing took place.

Wound formation and care: Food intake of the mice was stopped 3 hours before wound was induced. 10 mg/kg dose of xylazine HCl (2% Rompun, Bayer) and 100 mg/kg dose of ketamine (10% Alfamine, Egevet) were administered Intraperitoneal for anesthesia. Shaving and asepsis-antisepsis procedures were performed in the area where the wound was to be induced on the back of the animals. To ensure standardization of the wound size in animals, a template was created by opening a 1x1 cm square area on an A4 paper. An experimental wound with an approximately 1 cm^2 diameter containing skin and subcutaneous connective tissue was induced by using this template with a scalpel on the animals in each of the 3 groups. From the day the wound was induced, the follow-up process was carried out by performing the prescribed applications specific to the groups until healing was formed. Wound dressing placed and renewed daily wound dressing placed and renewed daily.

Measurement of the wound area: In each group, photographs of the wound line were taken before the dressings on days 0, 2, 4, 7, 10, 12, 14, 16, 18, 20, and 24, and the wound areas were measured and recorded on the photographs using ImageJ program on the computer.

Infection of the wound area: *Staphylococcus aureus (S. aureus)* ATCC® 25923 reference strain obtained from culture collection of Van Yüzüncü Yıl University, Faculty of Veterinary Medicine, Department of Microbiology was used for bacterial contamination of the wounds. For this purpose, 1 ml of the bacterial suspension prepared in physiological saline (PS) at a density of 10^8 cfu/ml was inoculated into the wounds in the control and experimental groups. For 24 hours, no treatment protocol was applied, and bacterial colonization was ensured.

Total aerobic mesophilic bacteria and *S. aureus* count: Swab samples were taken from a 1 cm^2 area of the wounds induced in the control and experimental groups on days 3, 7, and 14 of the study. While taking the samples, care was taken to ensure that 12 hours had elapsed since the application of the preparation. The swab samples were sent to the microbiology laboratory in Stuart transport medium in accordance with cold chain requirements. For total aerobic mesophilic bacteria count and *S. aureus* count, samples were placed in tubes containing 10 ml sterile PS and vortexed for a few minutes. One ml of the suspension was taken and transferred to tubes containing 9 ml of PS. Dilution was continued until 10^{-8} dilution.

One ml of each dilution was transferred to two separate petri dishes and 15 ml of Plate Count Agar (Merck, Darmstadt, Germany), which was sterilized and cooled to 45-50°C, was poured into each dish and mixed. After the media was solidified, they were inverted and incubated at 37°C for 48 hours in aerobic environment. At the end of the incubation period, bacterial counts were made in the petri dishes in which 30-300 colonies grew. The geometric mean of the number of bacterial colonies detected in 2 petri dishes of the same dilution was taken and the total count of aerobic mesophilic bacteria in the samples was evaluated as cfu/cm^2 (TS, 2014).

Method given in ISO 6888-1 was used for *S. aureus* count (TS, 2001). For the verification processes of the counted *S. aureus* colonies, typical and/or atypical 5 colonies were selected from the petri dishes and Gram staining, catalase, and coagulase (M43 Microgen™ STAPH, Italy) tests were applied. In the form of Gram-positive cocci, those that gave positive results in catalase and coagulase tests were identified as *S. aureus*.

Statistical analysis: The probability of healing and the mean and median healing periods of the study groups were calculated by Kaplan-Meier survival analysis method. The significance of the difference in healing periods between the study groups was analyzed by Log rank (Mantel Cox) test. To examine the effect of treatment (group) and time on wound healing, a single factor repeated two-way analysis of variance was performed using general linear modelling technique. Treatment (group), time and treatment (group)*time interaction terms were included in the model. Simple effect analysis was performed to analyze the significant interaction terms and Bonferroni correction was applied on the results. SPSS 14.01 software was used for data analysis.

RESULTS

The mean healing time of the subjects was 24.67±0.919 days (95% CI: 18.6-23.4) in group I, 18±0.73 days (95% CI: 21.605-28.395) in group II and 15.67±0.609 days (95% CI: 14.807-17.193) in group III. The healing time was found to be statistically significantly longer in group I compared to group II and group III ($p<0.001$). Although the healing time of the subjects in group III was shorter than group II, no statistically significant difference was found (Table 1, 2) (Figure 1,2).

Table 1. Descriptive statistics of wound areas according to the measuring times.

Period	Control							Terebinth							T+O					
	n	Arithmetic Mean	Std. Error	Std. Deviation	Median	Min.	Max.	n	Arithmetic Mean	Std. Error	Std. Deviation	Median	Min.	Max.	n	Arithmetic Mean	Std. Error	Std. Deviation	Median	Min.	Max.
t0	6	98.5	2.51	6.16	97	93	110	6	95.67	2.97	7.28	94	89	110	6	97.33	2.76	6.77	95.5	91	110
t2	6	81.5	1.48	3.62	80	78	87	6	66.17	4.2	10.28	67	51	80	6	59.67	2.19	5.35	60.5	51	67
t4	6	65.67	1.82	4.46	66	59	71	6	54.5	3.79	9.29	55.5	40	68	6	49.17	0.7	1.72	49.5	46	51
t7	6	59.17	1.35	3.31	59.5	54	63	6	45.33	2.03	4.97	46	37	51	6	39.67	0.56	1.37	39.5	38	42
t10	6	58.33	4.65	11.4	55	50	81	6	37.5	2.05	5.01	37.5	30	45	6	27.5	1.78	4.37	27	22	35
t12	6	51	3.28	8.02	48.5	45	67	6	30.33	2.06	5.05	30	24	37	6	17.83	1.45	3.54	17.5	14	24
t14	6	42	3.51	8.6	40.5	32	58	6	25	2.83	6.93	26.5	12	31	4	13.25	1.8	3.59	12.5	10	18
t16	6	33.83	2.06	5.04	33.5	27	42	4	19	2.86	5.72	20.5	11	24	1	10	.	.	10	10	10
t18	6	27.83	1.6	3.92	28	22	34	2	13.5	0.5	0.71	13.5	13	14	0	.	.	.	.	.	.
t20	6	23.67	1.23	3.01	24	19	28	0	.	.	.	.	.	.	0	.	.	.	.	.	.
t22	6	16.67	1.2	2.94	18	12	19	0	.	.	.	.	.	.	0	.	.	.	.	.	.
t25	4	13.5	0.65	1.29	13.5	12	15	0	.	.	.	.	.	.	0	.	.	.	.	.	.

T: Group treated with terebinth extract, **TO:** Group treated with terebinth extract + oxytetracycline. **Min:** Minimum, **Max:** Maximum

Table 2. Mean and Median Healing Periods

Group	Mean				Median				P*
	Probability	Std. Error	95% Confidence Interval		Probability	Std. Error	95% Confidence Interval		
			Lower Limit	Upper Limit			Lower Limit	Upper Limit	
Control	24.67 [a]	0.919	22.866	26.468	25	1.732	21.605	28.395	
Terebinth	18 [b]	0.73	16.569	19.431	18	1.155	15.737	20.263	<0.001
T+oxy	15.67 [b]	0.615	14.462	16.871	16	0.609	14.807	17.193	
General	19.444	1.014	17.458	21.431	18	1.405	15.245	20.755	

** Log Rank (Mantel Cox) test result (Chi square = 18.602; sd=2; p<0.001)*

T: Group treated with terebinth extract, **TO:** Group treated with terebinth extract + oxytetracycline

Table 3. Total aerobic mesophilic bacteria and *S. aureus* count (cfu/cm²).

Animal No	Day 3		Day 7		Day 14	
	TAMB	***S. aureus***	**TAMB**	***S. aureus***	**TAMB**	***S. aureus***
C-1	0.1×10^7	9.6×10^5	1.8×10^5	0.8×10^5	4.5×10^3	3.4×10^4
C-2	0.9×10^4	0.7×10^4	1.6×10^4	1.7×10^4	2.5×10^4	1.6×10^4
C-3	2.0×10^5	2.0×10^5	1.8×10^5	0.8×10^5	8.5×10^3	2.4×10^4
C-4	6.5×10^5	5.6×10^5	1.8×10^5	2.0×10^5	4.5×10^4	1.4×10^4
C-5	3.4×10^5	3.4×10^5	3.5×10^5	3.5×10^5	1.5×10^4	3.8×10^4
C-6	2.3×10^4	1.7×10^4	2.7×10^4	2.0×10^4	6.5×10^3	0.5×10^5
T-1	1.6×10^4	2.7×10^4	1.5×10^3	1.4×10^3	1.5×10^2	1.5×10^1
T-2	1.1×10^4	0.6×10^4	5.8×10^3	0.6×10^3	2.5×10^2	1.5×10^2
T-3	2.0×10^4	1.7×10^4	1.1×10^4	1.0×10^4	1.5×10^3	1.0×10^3
T-4	1.7×10^4	1.2×10^4	3.9×10^3	1.2×10^3	1.6×10^2	1.1×10^1
T-5	1.6×10^5	1.4×10^5	2.0×10^4	1.8×10^4	1.5×10^3	1.3×10^2
T-6	1.4×10^5	1.2×10^5	5.8×10^4	5.5×10^4	1.4×10^3	1.2×10^3
TO-1	0.3×10^3	0	0	0	0	0
TO-2	2.4×10^3	0.9×10^3	0	0	0	0
TO-3	0.2×10^4	0	1.6×10^3	0	3.0×10^1	0
TO-4	0.8×10^3	0.3×10^3	3.0×10^2	0	0	0
TO-5	0.8×10^3	0	3.2×10^2	0	3.0×10^1	0
TO-6	0.8×10^3	1.7×10^4	0.1×10^3	0	3.0×10^1	0

C: Control group, **T:** Group treated with terebinth extract, **TO:** Group treated with terebinth extract+oxytetracycline, **TAMB:** Total aerobic mesophilic bacteria.

In the microbiological analysis of the samples taken from the wound line, S. aureus count and total aerobic mesophilic bacteria count were performed in all cases. As a result, total aerobic mesophilic bacteria and *S. aureus* counts per unit area in group III were significantly lower than the other groups. However, the bacterial load in group II, in which terebinth extract was used, was less than the control group. In addition, on the days 7 and 14, the *S. aureus* count was 0 in all subjects in group III (Table 3).

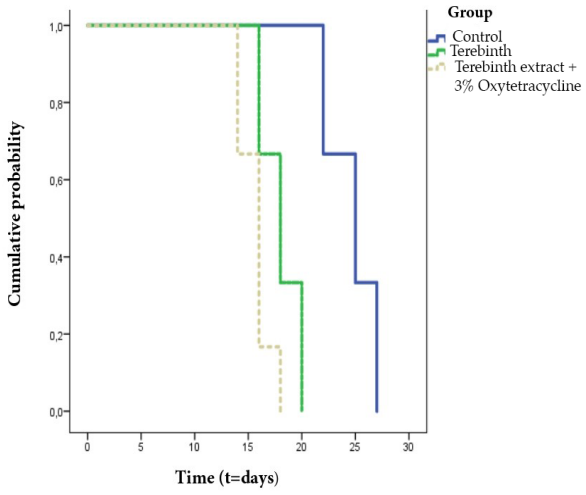

Figure 1. Graph of cumulative survival probability

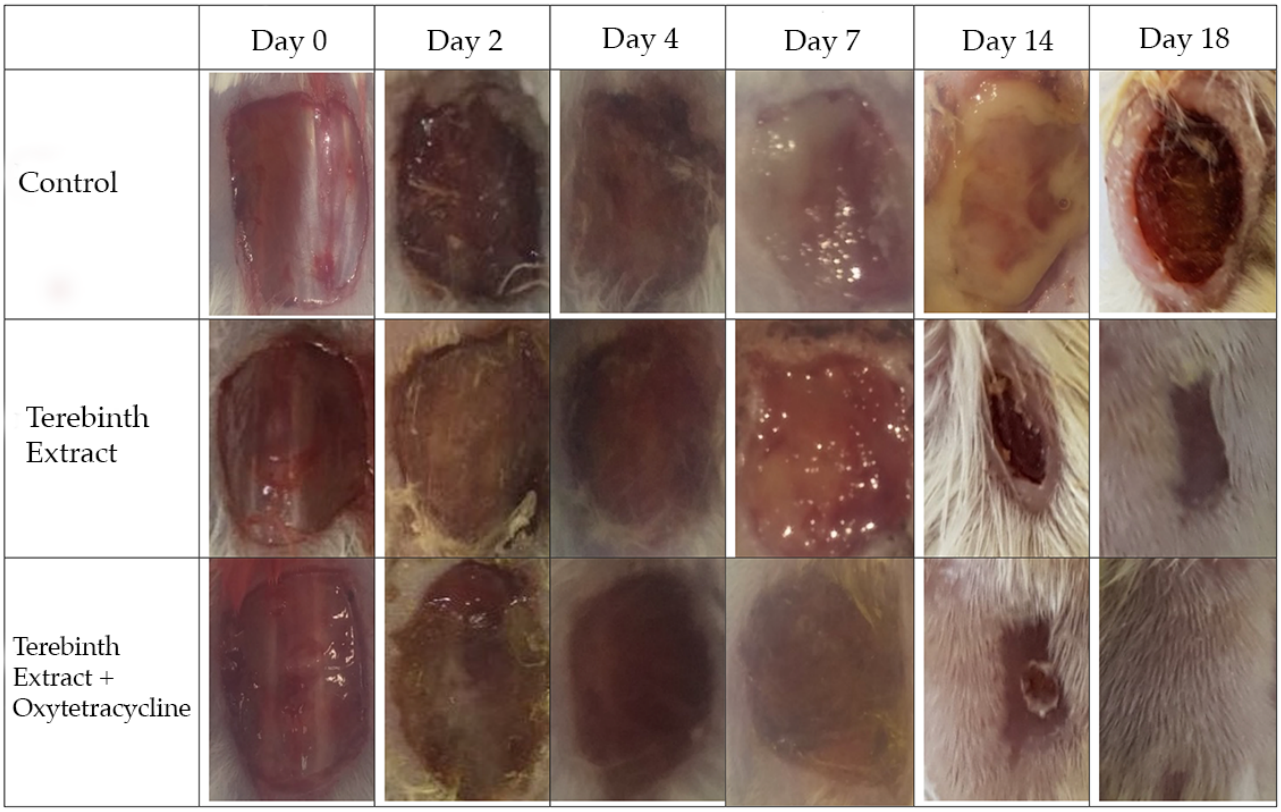

Figure 2. Macroscopic view of the wounds belonging to the groups

DISCUSSION

Wound healing is a pathophysiological condition that includes phases of hemostasis, inflammation, cell proliferation, extracellular matrix synthesis and remodeling; many parts of the process are known in detail, but some parts remain unexplained (Christine and Theoret, 2010; Ayla et al., 2017). The completion of these processes involves various factors such as cytokines, growth factors, proteases, eicosanoids, kinins and cellular metabolites. While in the past years, multiple complications were seen together in wound healing (infection, chronic scarring, etc.), today the frequency of wound healing complications has decreased (Mustoe et al., 2006; Ayla et al., 2017). The aim of wound treatment is to reduce the wound healing times by increasing the effects of factors (inflammatory cells, platelets, cytokines, extracellular matrix, etc.) that are effective in healing and to ensure the formation of scar tissue with appropriate neovascularization (Ayla et al., 2017). Thus, studies have been conducted in order to determine whether or not numerous plants have wound healing potential (Ximenes et al., 2013; Ayla et al., 2017; Balestrin et al., 2022; Sharma et al., 2021; De Almeida et al., 2022). The present study was aimed to scientifically demonstrate the wound healing properties of the extract obtained from the seed of the terebinth plant, which has been widely used by the people of Siirt in the treatment of diseases from past to present, and its combinations with oxytetracycline.

The healing process in wounds can be observed by many methods (macroscopic, microscopic, ELISA methods, measurement of some biomarkers) (Lin et al., 2012; Akdoğan et al., 2022). Macroscopic follow-up of wound closure is important. Recently, measurement of wound size on the computer is important in terms of preventing personal errors (Lucas et al., 2021). In the study, the wound line was photographed before applying the dressings on days 0, 2, 4, 7, 10, 12, 14, 16, 18, 20, and 24 in each group and the areas were measured and recorded with the ImageJ program.

Plants contain bioactive phytochemical structures such as alkaloids, iridoids, flavonoids, tannins, saponins and phenolic compounds (Thangapazham et al., 2016). As various combinations of these phytochemical compounds can be found in a single plant extract, the use of that plant extract alone provides the advantage of acting on various stages of wound healing (angiogenesis, fibroplasia and wound contraction) (Ibrahim et al., 2018; De Almeida et al., 2022). The terebinth plant, consisting of phytochemical compounds such as flavonoids and flavonoid glycosides, has a very important place in medical treatments (Kawasty et

al., 2000; Tohidi et al., 2011;). Flavonoids (alpha pinene, terpinolene, limonene, etc.) are antimicrobial substances that can act on many microorganisms by their binding ability to bacterial cell walls with proteins (Tohidi et al., 2011). Besides, this plant contains phenolic compounds and triterpenoids, and it is reported that such components are active against bacteria (Kusmenoglu et al., 1995). In the study, in order to determine the healing properties of the extract of the terebinth plant grown in the Siirt region in infective wounds, 3 groups were formed as the control group with no treatment (group I, n:6), group treated with terebinth extract (group II, n:6), group treated with terebinth and oxytetracycline combination (group III, n:6). When analyzed in terms of wound healing time; healing time in group I was found to be statistically significantly longer compared to group II and group III ($p<0.001$). Although the healing time of the subjects in group III was shorter than that of group II, no statistically significant difference was found. This was interpreted as the fact that the phytochemical components of the terebinth extract affected wound healing by increasing epithelialization and granulation tissue and thus accelerating wound healing.

In terms of regression of infection, *S. aureus* and total aerobic mesophilic bacteria count was performed in the samples taken from the wound line. As a result, total aerobic mesophilic bacteria and *S. aureus* counts in group III were significantly lower than the other groups. In this case, it can be asserted that terebinth and oxytetracycline combination significantly reduced the bacterial load. In addition, it was observed that the bacterial load in group II, in which terebinth extract was used, was less than the control group. This result shows the antibacterial activity of phenolic compounds and flavonoids in terebinth extract.

The related studies have reported that topical application of antioxidant-containing compounds will be useful for the protection of tissues from oxidative damage (Kumar et al., 2007). In a study investigating terebinth seeds, it was found that they had effective antioxidant properties (Göçer, 2013). When the wound healing time in the study is considered, it was concluded that one of the reasons for shorter healing time in the groups II and III treated with terebinth extract compared to group I was the effectiveness of the antioxidants in the composition of terebinth extract.

In a previous study comparing the effects of topical administration of glycerin solution and terebinth oil on wound healing, it was statistically demonstrated that terebinth oil accelerated wound healing compared to glycerin solution. Histological evaluation in the same study showed increased collagen synthesis and epithelialization in the group treated with terebinth oil, supporting this difference (Akgül et al., 2016). Another study revealed the effects of combinations of terebinth oil with different substances on wound healing. When the healing time was taken into consideration, it was observed that there was a very slight difference between the group treated with terebinth oil only and the group treated with terebinth oil and *Centella asiatica* pomade mixture, but it was observed that the healing time was completed in a much shorter time than all other groups (Şındak et al., 2017). In their study Tohidi et al., (2011) stated that the extract of a species of terebinth plant (*P. khinjuk*) showed faster healing compared to the control groups and its antibacterial activity was very good. In the study conducted by Djerrou et al., (2010) on rabbits by inducing experimentally 3rd degree burn, they reported that *Pistacia lentiscus* oil supported and accelerated the wound contraction and epithelialization process compared to madecassol and Vaseline. In the current study, it was concluded that the extract of terebinth plant grown in Siirt province accelerated the wound healing process and had significant antibacterial activity, which was in parallel with the studies using terebinth plant.

CONCLUSION

Consequently, it was scientifically found that the extract of terebinth plant found in Siirt province has positive effects on wound healing in mice. It was statistically shown that the antimicrobial activity of only terebinth extract and terebinth extract+3% oxytetracycline mixture used locally was higher compared to the control group and shortened the wound healing process. It is thought that the present study would form the basis of studies to convert terebinth extract into a commercial product suitable for topical use in wound treatment.

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ACKNOWLEDGMENTS

Author contributions: NŞ, AG, ÖG and MBA designed the study. NŞ and AG performed surgeries. ÖG performed microbiological analyses. DÖ performed statistical analysis. AG and ÖG participated in drafting and revising the manuscript.

NŞ: Nihat Şindak, AG: Ali Gülaydın, ÖG: Özgül Gülaydın, MBA: M. Barış Akgül, DÖ: Doğukan Özen

Financial Disclosure: This study was supported by Research Fund of Siirt University with project number 2017-SIUVET-24.

Conflict of Interests: The authors declared that there is no conflict of interests.

Additional information: All authors have read and agreed to the published version of the manuscript Correspondence and requests for materials should be addressed to AG.

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