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RESEARCH ARTICLE

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The effects of *Quercus* (Oak) acorn on cutaneous wound healing in rats

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ABSTRACT

Quercus spp. (Oak) has been used in traditional medicine due to its medicinal properties for centuries. However, its effect on wound healing in the skin is well unknown. This experimental trial was performed to evaluate in vivo wound healing of Oak acorn in the skin of rats. In the present trial, 24 Wistar albino rats were allocated to three groups equally, control (n = 8), Madecassol® (n = 8), and Oak acorn (n = 8). The circular excision wound models by biopsy punch device were applied in the interscapular region in rats. Oak acorn and Madecassol® pomade have been applied to experimental groups per day and normal saline solution and glycerin have been given to the control group locally as placebo. Blood and skin tissue were collected to evaluate histopathological and biochemical alterations on days 7th and 15th. In comparison with the control group, the topical administration of Oak acorn showed definite effects on epithelization, proliferative impacts on fibroblast cells, and enhancing effect on collagen formation by reducing inflammation and edema. Biochemical investigations of skin and blood tissues exhibited that fluctuated malondialdehyde and antioxidant defense system components were rehabilitated in the Oak acorn group. This experimental study revealed that pomade obtained from the Oak acorn displays remarkable wound-healing activity.

1. Introduction

The skin of vertebrate animals is a body part that has a protective barrier, sensory, and homeostatic roles (Agyare et al., 2016; Bradshaw et al., 2014; Maver et al., 2015; Muthukumar et al., 2014). When this barrier is injured, miscellaneous complex procedures are needed to recuperate the initial functionality of the skin (Valero et al., 2014). Wounds may be chemical, thermal, or physical lesions that result from the disruption of the skin integrity (Iyyam Pillai et al., 2010).

In the wound healing process, the injured tissue is repaired and tissue integrity is ensured. This process necessitates crucial elements such as the extracellular matrix, blood and parenchyma cells, and some other mediators (Latif et al., 2015). There are four different stages of wound healing which are "coagulation or hemostasis, inflammation, proliferation or formation of granulation tissue, and re-modeling or scar formation phase" (Demidova-Rice et al., 2012; Öztaş, 2021; Sanjari et al., 2015). All these stages are very complex biological processes that bring about the restoration of tissue integrity (Hunt et al., 2000). Additionally, this biological process prevents pathogens from entering the injured tissue (Latif et al., 2015). In this healing process, various cell types including keratinocytes, inflammatory cells, fibroblasts, fibrocytes, and epithelial and endothelial cells as well as extracellular proteins interrelate to restore the da-

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mage in the dermis and epidermis layers of the skin (Riordan et al., 2015).

Oak is a worldwide plant that is grown in many mountainous regions, especially in Europe, Asia, North Africa, and America (Aldrich & Cavender-Bares, 2011). The fruits (acorn) of this plant; due to their antimicrobial, antiulcer, antidiabetic, antihelmintic, anti-inflammatory, and antioxidant activities, have been reported to be used as a burn and wound healer in hemorrhoids, diabetes, and kidney stone ailments in traditional medicine (Kaur et al., 2004; McCune & Johns, 2002; Popović et al., 2013; Şöhretoğlu & Renda, 2020; Şöhretoğlu et al., 2012). Traditionally, people also have long been using them as a remedy against tumors, bleeding, dysentery, and swelling and to inhibit the effect of various poisons (Bratianu, 2015).

Recent investigations on the phytochemical structure and biological activity of oak have revealed the presence of many compounds in the fruit, bark, and leaves of the plant. In a recent study, 41 different compounds were detected in the fruit and leaves of the plant, mainly gallic acid derivatives, saccharides, and flavonoids (Molina-Garcia et al., 2018).

Therefore, this research study was conducted to evaluate the effect of oak acorn extract on wound healing in the skin of rats by using histopathological and biochemical methods.

2. Materials and methods

2.1. Experimental animals

In this study, 24 male Wistar albino rats, 4-5 months old and weighing 200-250 g obtained from the Experimental Animals Production and Experimental Research Center of YYU were used. All animals were housed at 21-23 °C and 50-60% humidity with a 12 h light,12 h dark cycle during the trial. The rats were left for 7 days at room conditions for acclimatization. They were fed with fresh water and a standard pellet diet ad libitum during the trial. All applications and post-operative care were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

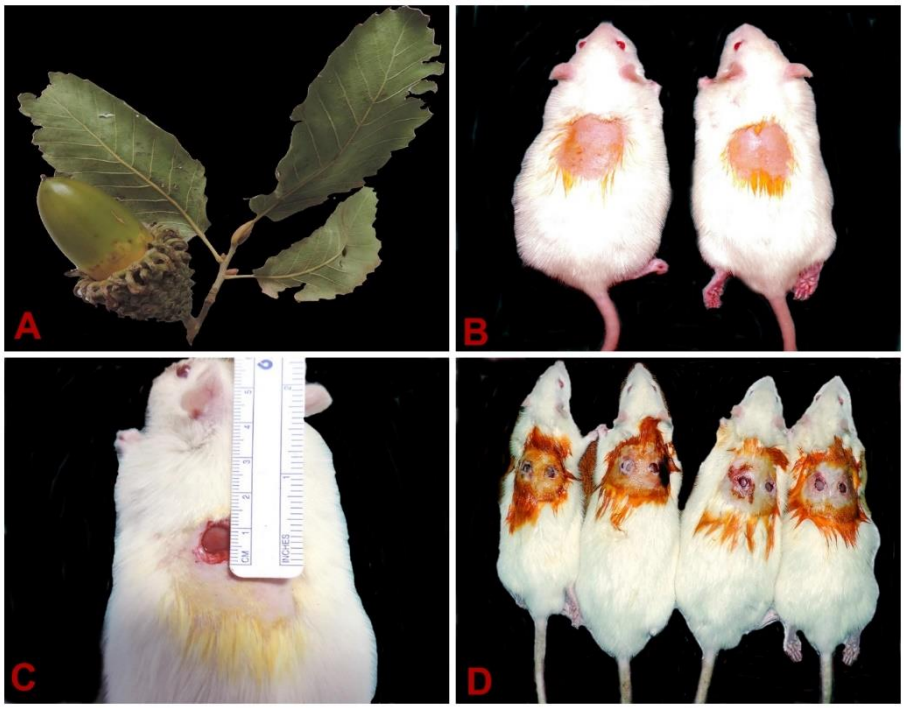

Figure 1. The appearance of process of the experiment
A: Oak acorns used in the experiment, B: Before wound creation, C: Wound size measurement, D: After postoperative treatment

2.2. Collection of plant samples and preparation of ointment

Fresh oak acorns (*Quercus infectoria* subsp. *boissieri*) were collected from Bektaşlı village, Kırıkhan, Hatay-Türkiye (450 m., 36° 39' 15.08"N 36° 24' 25.33"E) and identified (Herbarium number: 2017 HMKUH) by Dr. Ahmet İlçim (Hatay Mustafa Kemal University) **(Figure 1A)**. The acorns were dried and powdered with the help of an electric meat grinder. 50 g powdered samples for extract were subjected to successive solvent extraction in a soxhlet device (Elektromag 6MX25, Turkey) with 500 ml methanol solvent at room temperature for 24 h. At the end of extraction, the solvent was eliminated from the evaporator (Heidolph Laborota 4001 Digital). The attained extract was weighed and a 10% cream was prepared with glycerin (Dardmah & Farahpour, 2021). Then, it was stored in boxes with labeling at –20 °C (Ötün & Yücel, 2019).

2.3. Experimental design

Animals were randomly separated into three groups of eight.

Control group (n = 8): The wounds of rats in this group were medicated with physiological saline solution and glycerin for 15 days on time per day.

Madecassol® group (n = 8): The wounds of rats in this group were medicated with Madecassol® (Bayer) as reference ointment for 15 days on time per day.

Oak acorn group (n = 8): The wounds of rats in this group were medicated with the pomade which is produced from oak acorn with glycerin for 15 days on time per day.

2.4. Circular excision wound model

The shaved and disinfected state of the back skin of the rat before the wound formation, the measurement of the wound size, and the appearance after the postoperative treatment were presented in Figure 1B-D. Each group of rats was anesthetized by 50 mg/kg b.w. ketamine hydrochloride and 10 xylazine hydrochloride mg/kg b.w. cocktail solution. The back hairs of the rats were shaved. The wound areas were cleaned and sterilized (Figure 1B). The circular wound was generated on the dorsal interscapular area of each rat by excising through the full thickness of the skin with an 8 mm biopsy punch device and then the wounds were left open (Figure 1C). Test samples, the reference drug (Madecassol®, Bayer), and the pomade base were administered topically once a day for 15 days (Figure 1D) (Akkol et al., 2012; Süntar et al., 2011).

2.5. Wound area

The changes in the healing area of the skin were observed by macroscopically each following day. The wound areas were calculated by detecting the wound boundaries using millimeter-scale translucent graph paper with a permanent marker. In addition, the progressive reduction in the wound region was evaluated via the AutoCAD program on days 0, 4, 7, 12, and 15th. The degree of wound healing was determined using the following formula (Sadaf et al., 2006):

$$Degree\ of\ wound\ healing\ (\%) = 1 - \frac{Wound\ area\ on\ the\ corresponding\ day\ (cm^2)}{Wound\ area\ on\ day\ zero\ (cm^2)} x\ 100$$

2.6. Histopathological analysis

All animals were euthanized by administration of intramuscularly (i.m.) 100 mg/kg ketamine hydrochloride and 10 mg/kg xylazine hydrochloride for investigations on days 7th and 15th. Then, at the end of the experiment necropsies were performed. Full thickness of skin samples from each rat were taken. Half of the skin samples were fixed in 10% buffered formaldehyde solution for 24 hours, dehydrated through a series of alcohol (70, 80, 90, 100%), cleared xylene and embedded in paraffin, and then sectioned into 5 µm sections by microtome (Leica RM 2135) stained with hematoxylin-eosin (HE) for general morphological observation. All slides were examined and microphotographed by using a light microscope (E-400; Nikon, Tokyo, Japan) attached to a video camera (DXM1200F, Nikon, Tokyo, Japan) and graded as absent (-), mild (+), moderate (++), and severe (+++) for re-modeling. Fibroblast proliferation, mononuclear and/or polymorphonuclear cells, neo-vascularization, and collagen deposition were investigated to score the epidermal or dermal remodeling. Finally, all the wound healing processes were staged for wound healing phases as inflammation, proliferation, and re-modeling in all groups (Akkol et al., 2012).

2.7. Biochemical analysis

Blood samples for some biochemical examinations were collected from heart punctures and transferred into serum tubes before euthanasia. The samples were centrifuged at 10.000 x g at 4 °C for 15 min. The serum samples were stored at –20 °C. For lipid peroxidation and antioxidant activity analysis, half of the skin samples were analyzed using a spectrophotometer. Malondialdehyde (MDA) concentrations in the skin tissue samples obtained from the wound region were detected via the method defined based on thiobarbituric acid reactivity (Jain et al., 1989). The level of reduced glutathione (GSH) concentrations was determined by using the method identified by Beutler et al. (1963). Superoxide dismutase (SOD) activity was calculated at 505 nm and 37 °C by using inhibition of formazan dye formation (McCord & Fridovich, 1969).

2.8. Statical analysis

The statistical analyses were accomplished via SPSS 20.0 package program for Windows. One-way analysis of variance (ANOVA) was used to detect the differences between the two treatments and the control groups accepting the significance level at $p \leq 0.05$. As the histopathological findings were determined to be nonparametric, no statistical tests were conducted.

3. Results and discussion

3.1. Wound healing activity

The effects of Oak acorn on wound healing areas are seen in Table 1. As summarized in Table 1, the wound healing area did not differ notably among all groups on the 0th day. In the experimental study, the impact of oak acorn was appeared from the 4th day of the trial. On the 4th day, there was a remarkable decrease in wound area contraction in the groups administered Oak acorn ($p \leq 0.01$) and Madecassol® ($p \leq 0.05$) in comparison with the control group. In the 8th and 12th days of the experiment, the Oak acorn caused a significant ($p \leq 0.05$) decrease in the wound area contraction according to the control group. The Madecassol® drug also exhibited the same effect. Notable ($p \leq 0.01$) wound contraction was detected on the 15th day of the trial in the groups with Oak acorn and Madecassol® drug when compared to the control group.

Table 1. The measurement of wound area contraction according to the different days in experimental groups

Day	Wound area contraction (mm²) ± S.E.M.		
	Control	Madecassol®	Oak acorn
0th day	784.23 ± 1.12	784.65 ± 0.73	785.54 ± 0.48
4th day	411.33 ± 72.00	332.33 ± 2.065*	281.83 ± 72.00**
8th day	148.83 ± 15.3	104.00 ± 11.4*	83.83 ± 19.98*
12th day	45.83 ± 4.91	28.66 ± 2.5*	27.83 ± 1.47*
15th day	31.33 ± 1.03	7.66 ± 1.211**	8.83 ± 2.56**

Values are expressed as mean ± S.E.M. *$p \leq 0.05$, **$p \leq 0.01$. It shows a statistically significant difference compared to the control group within the same column.

3.2. Gross findings

All animals remained alive throughout the study. No infection was found in all three groups. The macroscopic view of the wound size on the 7th and 15th days is presented in Figure 2. In the macroscopic examinations performed on the 4th and 7th day of the study, a mild irregular scab and exudate in the wound areas were observed in the control group (Figure 2A) compared to other groups. In comparison

with the control group, the scab in both the Madecassol® group (Figure 2B) and Oak acorn group (Figure 2C) had a more regular appearance and the crusting phase was almost complete. On the 12th day, it was detected that the improvement in the control group started to slow down compared to the Oak acorn and Madecassol® groups. Cracks on the scab were formed in the control group and a serous exudate leaked out of. On the 15th day, it was defined that the wound healing was completed and the scars disappeared in the Madecassol® and Oak acorn groups (Figure 2E-F, respectively). On the other hand, the healing in the wound areas of the rats in the control group was delayed and the scars were not completely closed (Figure 2D).

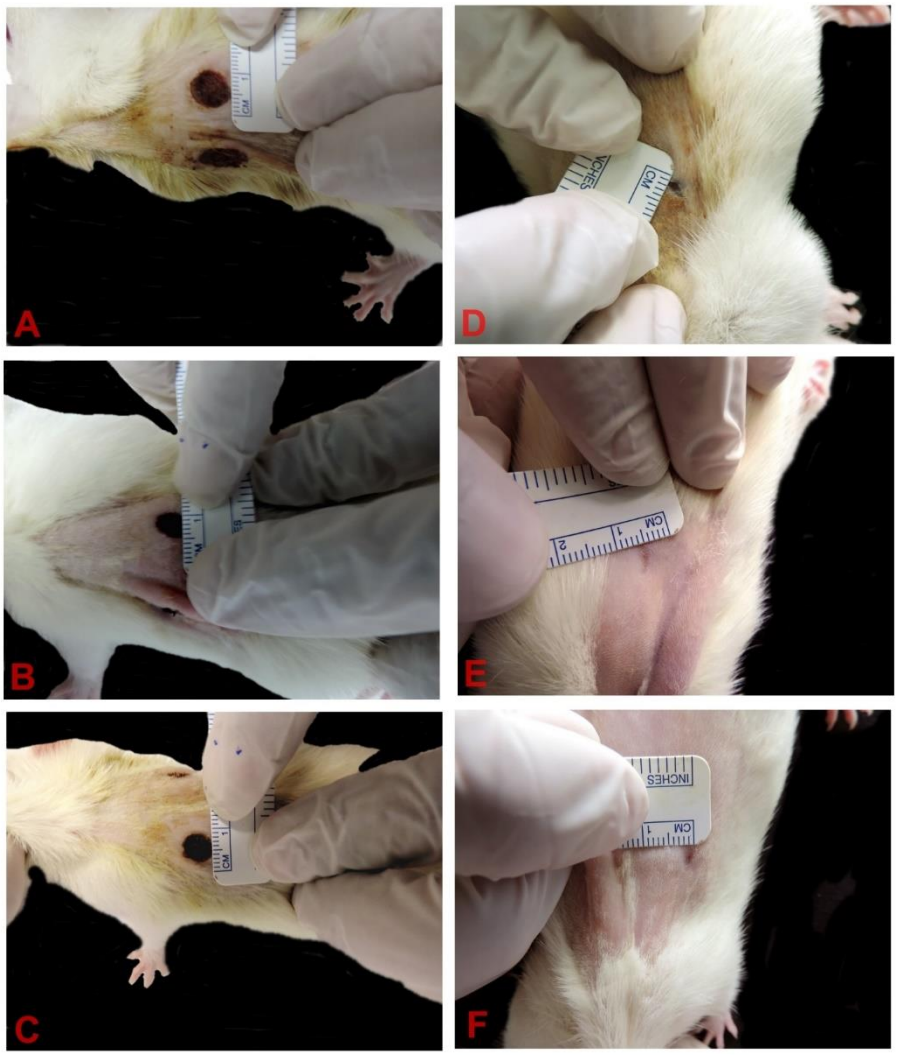

Figure 2. Macroscopic appearance of wound healing on days 7th and 15th
A: Control group 7th day, B: Group Madecassol 7th day, C: Group Oak acorn on day 7th, D: Control group 15th day, E: Group Madecassol 15th day, F: Group Oak acorn on day 15th

Table 2. Wound healing processes and healing phases of the control, Madecassol® and Oak acorn administered groups

Groups	Wound healing processes							Healing phases		
	S	Re	FP	Cd	MNC	PMN	Nv	I	P	R
Control	++/+++	-	+	-/+	++/+++	++/+++	-/+	+/++	+/++	+/++
Madecassol®	+/++	-	+/++	+/++	+	+/++	+/++	-/+	+	++/+++
Oak acorn	+/++	+	++/+++	+/++	-/+	+	++	-/+	+	++/+++

HE stained sections were scored as negative (-), mild (+), moderate (++) and severe (+++) for epidermal and/or dermal re-modeling. S: Scab, Re: Re-epithelization, FP: Fibroblast proliferation, Cd: Collagen depositions, MNC: Mononuclear cells, PMN: Polymorphonuclear cells, Nv: Neovascularization, I: Inflammation phase, P: Proliferation phase, R: Re-modeling phase

3.3. Histopathological results

At the end of the experiment, the wounded areas of skin were collected from each rat and the samples of healing tissue were evaluated histopathologically. The phases in wound healing processes (inflammation, proliferation, and re-modeling) with varying degrees were detected within the experimental groups. Table 2 and Figure 3 which are stained with H.E. represent score and microscopical findings according to the groups on the 7th and 15th days for the exhibition of wound healing process and healing phases, respectively.

On the 7th day, epithelial regeneration had not started in the wound area of the epidermis of the control group rats. There was edema

and exudate in the wound area. Intense inflammatory cell infiltration consisting of lymphoplasmacytic and neutrophil leukocytes was also seen. Scab was not in a compact structure and did not completely cover the wound area. Angiogenesis was not evident. It was only observed that epithelial cells came together in the epidermis of the wound area of Oak acorn group rats to initiate epithelization. Angiogenesis was evident in the dermis Madecassol® and Oak acorn group rats. In both of these groups, inflammatory cell infiltration consisting of lymphoplasmacytic and neutrophil leukocytes was observed relatively less than in the control group. A loose connective tissue cell proliferation was observed in the dermis. On the 15th day, epithelial regeneration was completed in the epidermis in the wound region of the control group rats. However, in this group, a loose connective tissue proliferation rich in fibroblasts was observed. Limited wound healing phases were determined in the control group. On the 15th day, epidermis regeneration was completed in the wound area of Madecassol® and Oak acorn group rats. In both groups, the stratum basale was prominent. In the dermis, granulation tissue was poor in vessels but rich in fibrocytes, and mature connective tissue was observed. In comparison with the control group, better the re-modeling, principally and better re-epithelization was detected in Madecassol® and Oak acorn-treated groups. The re-modeling and re-epithelization were observed at similar levels in both Madecassol® and Oak acorn-treated groups.

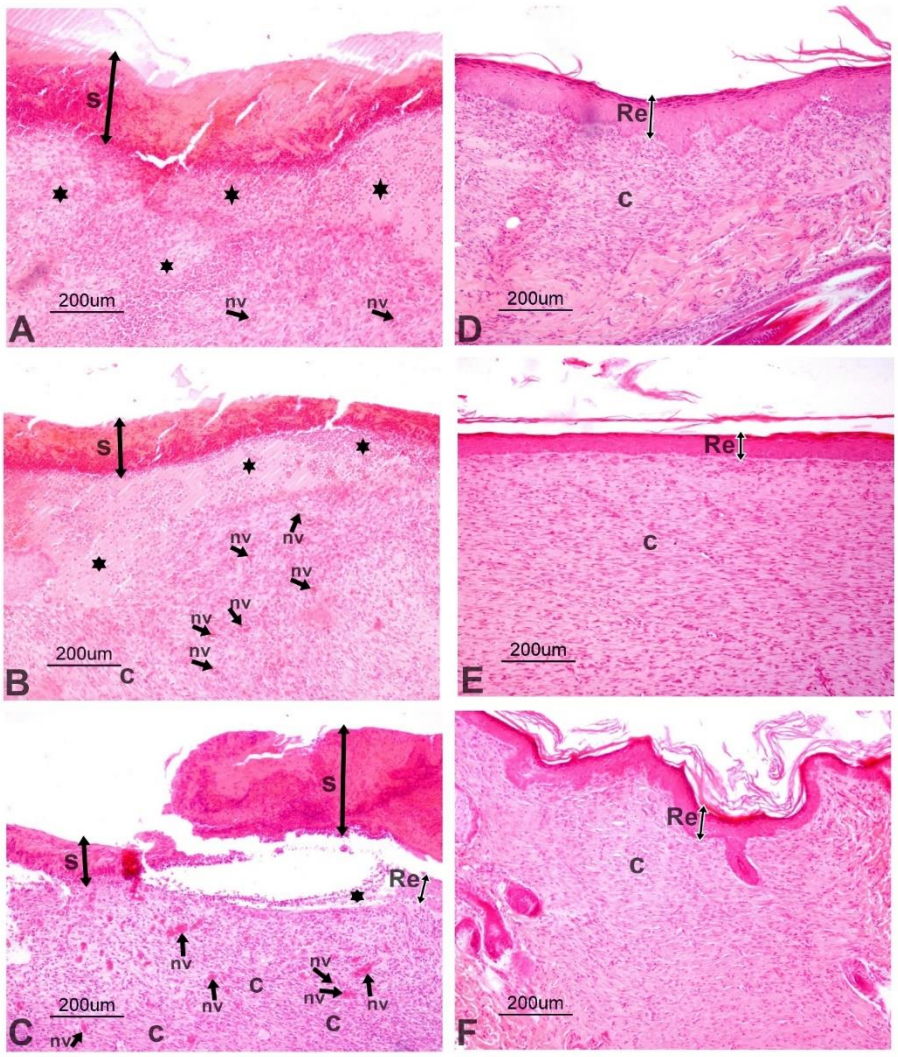

Figure 3. Histopathological view of wound healing and epidermal/dermal re-modeling in the control, Madecassol® and Oak acorn administered animals on days 7th and 15th

Skin sections show the hematoxylin and eosin (HE) stained epidermis and dermis. A: Control group 7th day, B: Group Madecassol® 7th day, C: Group Oak acorn on day 7th, D: Control group 15th day, E: Group Madecassol 15th day, F: Group Oak acorn on day 15th, S: Scab, Re: Re-epithelization, nv: neovascularization, stars: exudate, c: connective tissue

3.4. Biochemical findings

The results obtained from lipid peroxidation and antioxidant defense system activity in the skin of rats according to the groups are summarized in Table 3. A crucial decrease in MDA content and rise in GSH and SOD levels in the Oak acorn and Madecassol® groups was observed according to the control group ($p \leq 0.05$). Additionally, the findings of some biochemical parameters are presented in Table 4.

In traditional medicine, different endeavors have been made to discover management for enhancing dermal wounds and wound repair (Alerico et al., 2015). However, since no specific therapy has been acquainted resulting in the quickening of the recuperating pattern of wounds, research on natural pharmaceuticals, and their impacts on the recovery of wounds is ceaselessly continuing (Firdous & Sautya, 2018). The purpose of this study was to investigate the effect of oak acorn extract on wound healing using in vivo approaches.

Table 3. Lipid peroxidation and antioxidant defense system levels according to the groups

Parameters	Groups		
	Control (X ± SD)	Madecassol® (X ± SD)	Oak acorn (X ± SD)
MDA	163.38 ± 5.50^{b}	112.42 ± 26.62^{a}	117.74 ± 26,74^{a}
GSH	2.51 ± 0.24^{b}	3.81 ± 0.91^{a}	3.40 ± 0.82^{ab}
SOD	2012.37 ± 41.90^{b}	2296.32 ± 21.13^{a}	2275.42 ± 32.51^{a}

Values are expressed as mean ± S.E.M. Different superscript letters (^{a}, ^{b}) within the same column show statistically significant differences among the groups. ($p \leq 0.05$)

Table 4. Comparison with the some biochemical parameters between groups

Biochemical parameters	Groups		
	Control	Madecassol®	Oak acorn
ALT	61 ± 9.16^{ab}	73 ± 4.58^{b}	51.66 ± 6.25^{a}
AST	199 ± 46.8^{a}	176 ± 27.83^{a}	138.50 ± 29.37^{a}
GGT	0.40 ± 0.65^{a}	0.33 ± 0.57^{a}	0.50 ± 0.83^{a}
ALP	359 ± 91.82^{ab}	438 ± 34.11^{b}	268.83 ± 14.35^{a}
UREA	50.36 ± 14.55^{b}	44.06 ± 4.3^{ab}	33.73 ± 1.91^{a}
Ca	12.73 ± 2.13^{a}	14.53 ± 2.59^{a}	11.73 ± 0.77^{a}
Mg	3.75 ± 0.84^{a}	4.013 ± 0.42^{a}	3.42 ± 0.33^{a}
P	12.03 ± 3.21^{a}	10.98 ± 1.58^{a}	9.10 ± 1.18^{a}
TP	6.90 ± 0.87^{a}	9.26 ± 2.10^{a}	7.58 ± 0.81^{a}
ALB	4.09 ± 0.95^{a}	4.49 ± 0.60^{a}	3.88 ± 0.16^{a}
CK	1044.3 ± 209.4^{b}	634 ± 97.01^{a}	378.0 ± 214.34^{a}
Fe	47.36 ± 16.11^{a}	59.033 ± 5.68^{a}	43.78 ± 9.53^{a}

Values are expressed as mean ± S.E.M. Different superscript letters (^{a}, ^{b}) within the same column show statistically significant differences among the groups. ($p \leq 0.05$)

The regular and quick development of granulation tissue is an important sign in the wound healing process (Kirsner & Eaglstein, 1993). The development of granulation tissue is obvious in open wound healing, and it has been detected to begin 72-96 hours after injury (Heinze & Clem, 1988; Kirsner & Eaglstein, 1993). Granulation tissue is formed by the embedding of collagen, fibronectin, and hyaluronic acid in the extracellular matrix, angiogenesis, and the combination of fibroblasts and inflamed cells (Arnold & West, 1991; Swaim & Henderson, 1990). In experimental studies, it has been observed that 3-4 days after the wound formation, the fibrin threads of the clot in the wound are directed vertically to the wound surface. 6 days later, the capillaries, fibroblasts, and collagen fibers between the incisional wound take a horizontal structure on the wound surface and bring the wound lips closer to each other (Swaim & Henderson, 1990). In this study, even though it was detected that the scab started to develop from the wound edges to the middle in all groups in the first 4 days, it was observed that there was still a large ulcer area in the wound areas. In the continuation of the healing process, it was determined that this opening was more clearly covered with scabs on the 7th day in the Madecassol® and Oak acorn groups according to the control group, and the wound area was reduced. On the 15th day, it was determined that the re-epithelization developed completely and the scars almost disappeared in the Madecassol® and Oak acorn groups. However, although epithelization was observed to a large extent in the control group, it was observed that there were scars in the wound area. Like Madecassol® ointment, a more significant difference was observed in the Oak acorn group than in the control group, suggesting that this herb is effective in wound healing. Epithelization is a process including the proliferation, organization, and keratinization of epithelial cells to regain the barrier property of the skin after injury (Calvin, 1998). Epithelization proceeds from the free wound edges and continues until it encounters cells from another direction (Theoret, 2005). If a scab has formed, epithelization continues to form under this scab. The wound is considered healed when epithelization is complete (Kirsner & Eaglstein, 1993; Rigler, 1997). The final phase in the wound healing process is the maturation phase. This phase is the longest period of the wound healing process involving the transformation of granulation tissue into scar tissue and the maturation of the extracellular matrix (Heinze & Clem, 1988; Rigler, 1997). In the maturation phase, a decrease in the number of fibroblasts in the wound area, reaching the equilibrium in collagen production, completion of epithelization, pale wound color, increase in wound tension resistance, and decrease in the volume of scar tissue are observed. At this stage, scar tissue with few cells and vascular structure forms (Heinze & Clem, 1988; Rigler, 1997). In this study, in the histopathological examination of the rats slaughtered on the 7th day of the experiment, inflammatory cells and fibroblasts were detected in the wound area of all groups, while it was observed that the collagen had not yet developed in bundles. In addition, neovascularization and a more prominent and regular crust formation were observed in the wound area in the Madecassol® and Oak acorn groups compared to the control group. At the end of the 15-day trial, although epithelization was observed in the control group, it was determined that the vascular structure had not yet disappeared compared to the treatment groups. Additionally, a loose connective tissue rich in terms of fibroblasts, fibrocytes and collagen threads was formed together with the inflammation of cells in the wound area. In the treatment groups, on the other hand, it was observed that the epithelization was completely formed and more mature connective tissue rich in terms of fibrocyte and collagen fibers was formed in the wound area compared to the control group. According to these results, it was concluded that Oak acorn, like Madecassol®, increased fibroblastic activity and collagen formation in the wound area.

Any wound that may occur in a tissue that does not have a blood circulation problem initiates healing in a normal time. However, insufficiency in blood flow may cause chronic wounds depending on the degree of ischemia. Although the oxygen demand of the injured tissue increases, hypoxia occurs in the wound as a result of damage to the vessels. This hypoxia in the wound delays wound healing. Reactive oxygen species (ROS) occur, which causes tissue damage due to ischemia for any reason (Mustoe, 2004; Rees et al., 1995). ROS cause decreased protein synthesis, inflammatory cell infiltration, and increased metalloproteinase level in tissue. These pathological changes due to ischemia alter the normal course of wound healing due to impaired extracellular matrix production and prolonged inflammatory response (Saarialho-Kere, 1992). In injuries, damage and functional disorders may occur both in the wound area and in distant tissues and organs due to lipid peroxidation caused by

the increase of free radicals (Çavdar et al., 1997). For this reason, factors that free radicals or oxidants occur in the wound area may impair the healing process by causing tissue injury. Among these factors, hydroxyl radical and O– anion can change the adhesion, proliferation, and viability of fibroblasts by breaking down hydroxyproline and proline in the collagen structure. Similarly, hydrogen peroxide (H_2O_2) formed in injuries both inhibits the migration of keratinocytes and causes significant damage to fibroblasts by preventing Epidermal Growth Factor (EGF) signal communication (Yager et al., 2007). High levels of ROS also delay wound healing due to cytotoxicity. Therefore, it is necessary to eliminate ROS during the healing process of wounds (Aksoy & Özakpınar, 2014). Antioxidant defense systems against free radicals catalyze the reduction of H_2O_2 or hydroperoxides to organic water or alcohols (Herbette et al., 2007). Thus, lipid peroxidation is prevented and cell membranes are protected from oxidative damage (Czuczejko et al., 2003). Antioxidant defense system components appear intensely through the inflammatory phase of wound healing. In this way, this system stimulates the proliferation of keratinocytes by creating resistance against ROS products in cases of intense oxidative stress (Munz et al., 1997). At the end of this study, lipid peroxidation (MDA) was lower and antioxidants (GSH and SOD) were higher in the groups of Madecassol® and Oak acorn compared to the control group. Due to the high antioxidant and free radical scavenging capacity of the plant (Galvez et al., 2003; Gezici & Sekeroglu, 2019), it has been thought that it can prevent oxidative damage in the wound area and perform rapid and proper wound healing.

Detecting the length and width of the wound area is an important factor in the evaluation of wound healing. In determining the healed wound, the surface area of the wound can be detected via ultrasound, magnetic resonance, or stereo photometry. Clinically, the technique with wound ruler and transferring wound sizes to acetate is mostly used. Although it has been reported by some researchers (van Rijswijk & Braden, 1999) that the measurements made using the wound area measurement ruler are not very reliable in irregular and very wide wounds, this method is seen as the most accurate wound measurement method by some researchers (Thomas & Wysocki, 1990). In our study, the oak acorn extract triggered a notable decrease in wound area. According to these findings, the extract has revealed a remarkable positive effect on the wounds from the 4th and following days. In this study, it was also found that wound area values, which is an important sign of wound healing, were significantly lower than in the control group in the Oak acorn and Madecassol® groups. These results obtained in this study are clinically important, therefore, bioactive constituents in Oak acorn can be considered and evaluated as new alternative drug-like molecules for wound healing.

4. Conclusions

In the light of findings of this study, it was seen that the use of Oak acorn in wound treatment accelerated wound healing, increased fibroblast and myofibroblast activation or migration, and caused a regular and intense increase in collagen synthesis. The results of this experiment also have provided a scientific basis for the traditional use of Oak acorn as a wound healing agent.

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Conflict of interest

The authors confirm that there are no known conflicts of interest.

Statement of ethics

Ethical approval for this study was obtained from the Animal Experiments Local Ethics Committee of Yuzuncu Yil University (YYU), Van, Türkiye (Approval no: 2015/09).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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CRediT authorship contribution statement

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Supplementary File

None.

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