

Effects of common centaury (*Centaurium erythraea*) oil and laurel (*Laurus nobilis*) seed oil on full-thickness excisional skin wound healing in rats

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ABSTRACT

The aim of this study was to investigate the effects of common centaury (*Centaurium erythraea*) oil and laurel (*Laurus nobilis*) seed oil in a full-thickness excisional skin wound model in rats. In the present study, 18 adult male Wistar rats were divided into three groups (n=6) the control (CO) group, the common centaury oil (CCO) group, and the laurel seed oil (LSO) group. Under general anesthesia, a full-thickness excisional wound (2.25 cm²) was created on the caudal of the interscapular region on the back of the rats. Treatments were applied topically once a day in all groups. Wound area measurements revealed that the use of CCO accelerated wound healing, while the use of LSO disturbed the healing process (P≤0.001). In the histopathological results, blood vessel formation, fiber synthesis, granulation, and mononuclear cells in the wounds were higher in the CCO group than the other groups and higher in the LSO group than the CO group. Biochemical results revealed differences between groups in TP, GLU, and UREA values (P<0.05). As a result, it was determined that the topical use of common centaury oil accelerated wound healing, while laurel seed oil adversely affected wound healing in the experimental excisional full-thickness skin wound model in rats.

Introduction

Wound healing is a complex physiologic process that consists of different cell types and cellular phenomena or reactions. It includes three intricate stages of inflammation, tissue regeneration, and remodeling of new tissue (maturation). These stages may take different timescales, from several days to months or years. The aims of the treatment are to support wound healing and prevent any failure leading to nonhealing wounds (42, 45). Chronic wounds may lead to severe morbidity and mortality, especially in older individuals, particularly those with concurrent diseases such as diabetes mellitus and vascular diseases. Nonhealing wounds require high costs for treatment and significantly affect the quality of

life (15, 45). Also, surgery is a potential wound complication cause (4). Nearly 234 million surgeries are performed worldwide every year, which is an important threat to public health and the economy. Although many studies have been conducted on wound healing, medical plants and herbal mixtures are needed to be further investigated considering their properties, such as being easily accessible, inexpensive, effective, and having limited adverse effects (42, 45, 51). In order to improve wound healing processes, promising therapeutics based on the active components have been used (8).

Natural product-based compounds are preferred over synthetic products to improve wound healing (7, 31). Researchers have been exploring herbal medicines and

mixtures for wound treatment for years. A wide range of herbs have been investigated so far. *Laurus nobilis* Linn. (bay) has been used traditionally, and its neuroprotective, antioxidant, antiulcerogenic, anticonvulsant, analgesic, anti-inflammatory, antimutagenic, antiviral, antibacterial, antifungal, and anticholinergic effects have been reported (1-18, 20). Common centaury herb and oil are known in traditional medicine for their tonic, sedative, digestive, antipyretic, and antipyretic properties and have been used in diabetes, hepatitis, gout, indigestion, gastritis, and inflammation. Its external use is known for inflammation, wound treatment, snake bites, and eczema-like conditions (50). There are many in vivo and in vitro studies on the medical effects of *C. erythraea*. Anti-inflammatory, antipyretic, antidiabetic, diuretic, and hepatoprotective effects have been reported in vivo studies, as have gastroprotective, antidiabetic, antioxidant, antibacterial, cytotoxic, antimutagenic, and insecticidal effects in in vitro studies (11, 25, 50).

The aim of this study was to evaluate the wound-healing activity of common centaury (*Centaureum erythraea*) oil and laurel (*Laurus nobilis*) seed oil on the excisional full-thickness skin wound model in Wistar rats in terms of wound healing, clinical, histopathological, and biochemical changes.

Materials and Methods

Chemical Analysis of Herbal Oils Used in Treatment: Common centaury (*Centaureum erythraea*) oil, Laurel (*Laurus nobilis*) seed oil, and corn (*Zea mays*) oil were purchased from a local traditional herbal oil vendor (in Türkiye). GC-MS analyses were performed to reveal the chemical components of the oils. For this purpose, each oil was diluted 1/20 with high-purity ethanol, and aromatic components were analyzed using a GC-MS (Shimadzu GCMS QP 2010 ULTRA) analyzer. Capillary column (RTX-5MS; 30 m; 0.25 mm; 0.25 μ m) and helium were used as carrier gas for the analysis. Column furnace, interface, ion source, and injection temperatures were adjusted to 40°C, 250°C, 200°C, and 250°C, respectively. The injection volume was 1 μ l, and the split (1/5) method was used for injection. During analysis, 3 min at 40°C, 4°C/min increment from 40°C to 240°C, 10 min at 240°C, 4°C/min increment from 240°C to 260°C, and 10 min at 260°C, a total of 78 minutes of oven cycle were applied (21). Chromatograms and ingredient lists of the chemical components of the oils were obtained.

Animals and Experimental Design: The ethical approval of this study was obtained from the Local Ethics Board of Animal Experiments of Hatay Mustafa Kemal University (Decision No: 2020/04-34). Experiments were performed in accordance with the Turkish Code of the Welfare and Protection of Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on the

protection of animals used for scientific purposes. In total, 18 healthy adult male Wistar rats (400–550 g) were purchased from the Hatay Mustafa Kemal University Experimental Research and Application Center. One week prior to the study, the animals were taken to the study site to undergo routine health checks, and time for adaptation was provided. All rats were maintained individually in standard cages with water and food provided ad libitum on a 12:12-h light-dark cycle in a climatically controlled room. Following general anesthesia induction (Ketamine HCl 50 mg/kg and Xylazine HCl 5 mg/kg, i.m.), the dorsal neck area of each animal was shaved, disinfected, and a 1.5x1.5 cm (2.25 cm²) sized square full-thickness excisional wound created. The animals were separated into the three experimental groups (n=6) randomly. Group 1 was treated with corn (*Zea mays*) oil as a control group (CO), group 2 with common centaury oil (CCO), and group 3 with laurel seed oil (LSO). All the treatments were applied topically, covering all wound areas (~1 ml), once a day for 14 days in total. No other drugs were used post-surgically.

Clinical Examinations and Wound Area Measurement:

Before topical treatment, local examinations of wound areas and general clinical examinations of animals were conducted daily. The body weight, feed, and water consumption of each animal were determined weekly. The wound areas of each animal were photographed individually by a digital camera at 0, 1, 4, 7, 11, and 14 days after wound creation. The wound surface area (cm²) was measured using Image J software.

Collection of Tissue: 14 days after applying the treatment, the rats were deeply anesthetized with the combination of xylazine HCl (10 mg/kg, i.p.) and ketamine HCl (100 mg/kg, i.p.) and sacrificed. The wound tissues were removed with a surgical blade and scissor. The wound samples of each animal were preserved in 10% formalin separately until histopathological analysis.

Histopatological Analysis: The specimens were fixed in 10% neutral buffered formalin for 24 hours and dehydrated in a series of graded ethanol solutions (60, 70, 80, 90, and 100%). Following xylol treatment, embedded in paraffin wax. Paraffin-embedded sections were sequentially sliced at a thickness of 4 μ m by a microtome (Leica RM2235®, Almany), stained with hematoxylin and eosin and further evaluated under light microscopy (Olympus BX50-F4, Tokyo, Japan). Histopathological evaluation of inflammatory processes and healing in the scar tissue was scored by examining the number of blood vessels, granulation, fiber synthesis, and mononuclear cells. In this scoring, the relevant parameters were evaluated as absent/unformed (0), low (1), moderate (2), high (3), and severe (4).

Biochemical Analysis: Blood samples were centrifuged (3000 rpm, 10 min), and their serums were separated. Serum samples were analyzed for ALP, AST, CRE, UREA, GLU, and TP values individually by a biochemistry autoanalyzer.

Statistical Analysis: Statistical analyses of the results were performed with the SPSS (Statistical Package for Social Sciences, 26.0) program. The sample size of the study was determined by reference to recent similar scientific studies (19, 36). Descriptives of the results were presented as mean \pm standard error of mean. After the normality tests, one-way ANOVA and post-hoc Tukey tests were used to evaluate the differences between the groups. Repeated measured variance analysis following the Bonferroni test was applied for the wound area alterations by time comparisons between groups. The significance was set at $P < 0.05$.

Results

GC-MS Analyses: The highest component of CCO was determined to be octadec-9-enoic acid (25.57%), LSO's oleic acid (22.44%), and CO's oleic acid (26.09%). The GC-MS analysis results of CCO, LSO, and CO used in the wound treatments are presented in Table 1 by specifying the substances with the highest ratio. GC-MS chromatogram images are presented in Figure 1.

Clinical Results and Wound Healing: Respiration and vital behaviors were observed as normal in all experimental animals. However, a stressed and mildly depressed appearance was observed in four individuals in the LSO group. The body weight, feed, and water consumption alterations of the groups are presented in Table 2. Local wound sensitivity was increased in animals in the LSO group, and the animals were observed to be irritated by LSO. The wound area results on certain days in all groups are presented in Table 3 and Figure 2. And the time-group wound area comparisons are presented in Table 4.

Table 1. Most-to-lowest-ordered components from GC-MS analysis results of the CCO, LSO and CO.

%	Common Centaury (<i>Centaurea erythraea</i>) Oil
25.57	Octadec-9-enoic acid
15.04	9,12-Octadecadienoic acid (Z,Z)-
10.66	Palmitic acid
8.33	Di-(9-octadecenoyl)-glycerol
7.60	Octadecanoic acid
7.58	Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester
25.22	Other components*
%	Laurel (<i>Laurus nobilis</i>) Seed Oil
22.44	Oleic acid
10.38	3H)-one, 3a,4,6a,7,8,9,9a,9b-octahydro-6-methyl-3,9-bis(methylene)-, [3aS-(3a.alpha.
7.07	-ethenylhexahydro-6-methyl-3-methylene-7-(1-methylethenyl)-, [3aS-(3a.alpha.,6.
6.85	1,1'-Bis(cyclooct-2-en-4-one)
6.74	Palmitic acid
6.00	Eucalyptol
5.58	Cycloisolongifolene, 8,9-dehydro-9-formyl-
34.94	Other components*
%	Corn (<i>Zea mays</i>) Oil
26.09	Oleic acid
14.18	9,12-Octadecadienoic acid (Z,Z)-
13.08	Tributyl acetyl citrate
9.94	Hexadecanoic acid, 1-(hydroxymethyl)-1,2-ethanediyl ester
8.29	Palmitic acid
28.42	Other components*

*Components below 5% are included in 'Other components'.

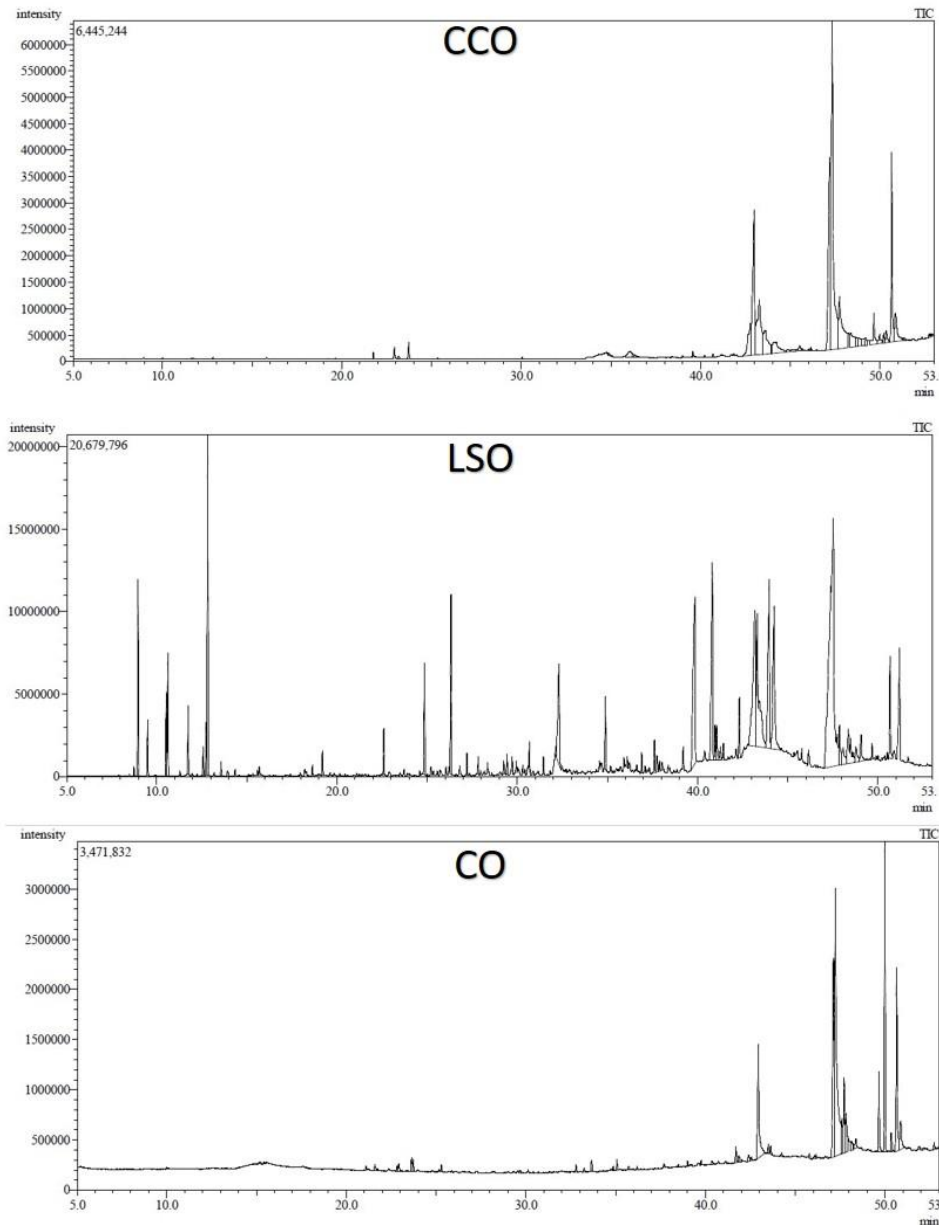


Figure 1. Chromatograms of the CCO, LSO and CO (GC-MS analysis). CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil.

Table 2. Bodyweights, feed and water consumption (mean, standard error) during the experiment according to the groups (gram).

Variable	CO	LSO	CCO	P Value
Bodyweight (day 0)	505.97 ± 17.40	512.52 ± 25.98	507.13 ± 18.45	P>0.05
Bodyweight (day 14)	463.92 ± 7.60	415.00 ± 21.08	456.62 ± 17.55	P>0.05
Feed consumption (day 7)	243.75 ± 5.82	226.83 ± 17.49	234.82 ± 8.85	P>0.05
Feed consumption (day 14)	243.20 ± 6.53 ^a	215.17 ± 8.74 ^b	230.27 ± 7.27 ^{a,b}	P<0.05
Water consumption (day 7)	218.33 ± 8.63	223.33 ± 26.79	204.17 ± 14.52	P>0.05
Water consumption (day 14)	236.67 ± 13.02 ^b	302.50 ± 17.26 ^a	224.00 ± 11.81 ^b	P<0.05

a, b: shows the statistical differences between groups. CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil.

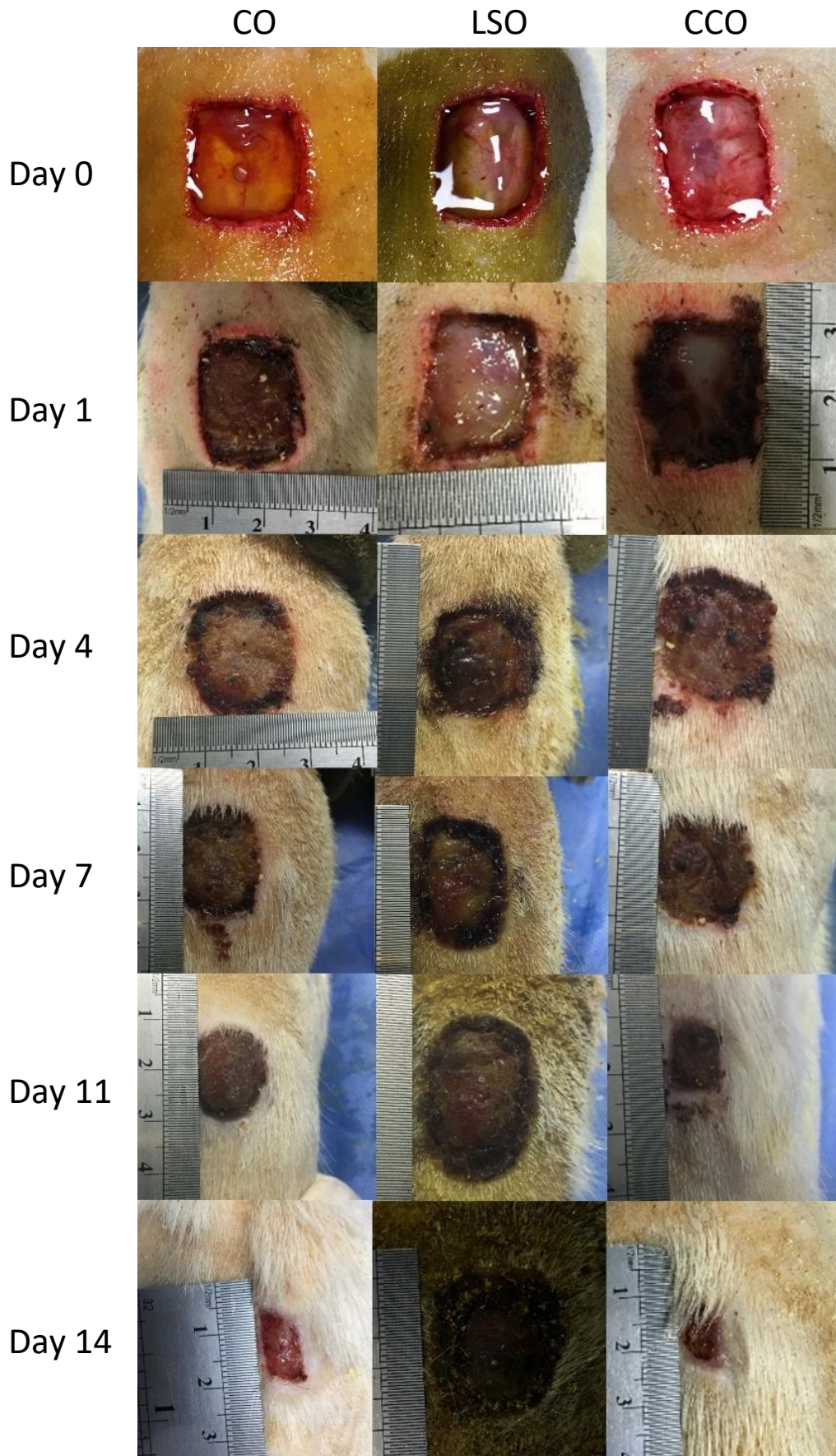


Figure 2. Photographic representation of the short-term (14 days) local clinical follow-up of skin wound healing process on different days by Control (CO: corn oil) group and experimental (LSO: Laurel seed oil, CCO: Common centaury oil) groups.

Table 3. Wound area measurements according to the groups on certain days during the experiment.

Group	Time	Mean	Std. Error
CO	Day 1	3.019	0.068
	Day 4	2.539	0.085
	Day 7	2.084	0.082
	Day 11	1.367	0.080
	Day 14	0.916	0.097
LSO	Day 1	1.983	0.068
	Day 4	2.431	0.085
	Day 7	2.064	0.082
	Day 11	1.943	0.080
	Day 14	1.304	0.097
CCO	Day 1	2.408	0.068
	Day 4	1.822	0.085
	Day 7	1.569	0.082
	Day 11	0.999	0.080
	Day 14	0.560	0.097

CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil.

Table 4. Wound area Time-Group comparison according to the groups on certain days during the experiment.

Time	Group Comparison	P Value	Std. Error
Day 1	CO-LSO	P<0.001	
	CO-CCO	P<0.001	0.096
	CCO-LSO	P=0.001	
Day 4	CO-LSO	P>0.05	
	CO-CCO	P<0.001	0.120
	CCO-LSO	P<0.001	
Day 7	CO-LSO	P>0.05	
	CO-CCO	P=0.001	0.116
	CCO-LSO	P=0.001	
Day 11	CO-LSO	P<0.05	
	CO-CCO	P>0.05	0.113
	CCO-LSO	P<0.001	
Day 14	CO-LSO	P<0.001	
	CO-CCO	P<0.001	0.137
	CCO-LSO	P<0.001	

CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil.

Table 5. Histopathological examination scores (mean, standard error) of wound tissues by groups.

Histopathological Variables	CO	LSO	CCO	P Value
Blood vessels	1.33 ± 0.21 ^b	2.50 ± 0.22 ^a	3.00 ± 0.37 ^a	P<0.05
Granulation	0.17 ± 0.17 ^c	2.67 ± 0.21 ^b	3.50 ± 0.22 ^a	P<0.05
Fiber synthesis	-	2.00 ± 0.26 ^b	2.83 ± 0.17 ^a	P<0.05
Mononuclear cells	0.33 ± 0.21 ^b	2.17 ± 0.17 ^a	2.83 ± 0.31 ^a	P<0.05

a, b, c: shows the statistical differences between groups. CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil.

Table 6. Serum (blood) biochemistry results (mean, standard error) by groups.

Biochemical Parameters	CO	LSO	CCO	P Value
AST (GOT)	130.25 ± 4.28	179.07 ± 15.53	1168.07 ± 37.81	P>0.05
ALT (GPT)	69.17 ± 3.38	84.83 ± 3.68	72.50 ± 4.36	P>0.05
GLU	159 ± 15.75 ^a	105.67 ± 7.57 ^b	181.83 ± 10.59 ^a	P<0.05
CRE	0.87 ± 0.10	0.84 ± 0.69	0.80 ± 0.57	P>0.05
TP	6.50 ± 0.77 ^{a,b}	6.13 ± 0.15 ^b	6.75 ± 0.12 ^a	P<0.05
UREA	64.67 ± 3.06 ^b	70.67 ± 3.04 ^{a,b}	78.67 ± 4.18 ^a	P<0.05

a, b: shows the statistical differences between groups. CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GLU: Glucose, CRE: Creatinine, TP: Total protein.

Histopatological Results: In the histopathological results of the wound tissues, an increase in keratinocytes in the stratum basale layer for healing and epidermal regeneration in epithelial cells was determined in the CCO group. It was also revealed that the pilosebaceous contains epithelial stem cells that can regenerate and differentiate into basal keratinocytes and are necessary for the re-epithelialization process. Angiogenesis was observed with increased vascularization of wound healing in the dermis layer. In the LSO group, epidermis-associated hair follicles, pilosebaceous, eccrine, and apocrine glands were found to be normal, and vascularization increased. In the CO group, fiber synthesis and granulation formation were

very low, but sebaceous glands and hair follicles were found in normal amounts. The histopathological scores of the wound tissues according to the groups are presented in Table 5. Histopathological microscopic images of wound tissues are presented in Figure 3.

Biochemical Results: GLU results were significantly lower in the LSO group than in the other groups. TP results were significantly lower in the LSO group than in the CCO group. UREA results were significantly higher in the CCO group than in the CO group. Serum biochemistry findings by groups are presented in Table 6.

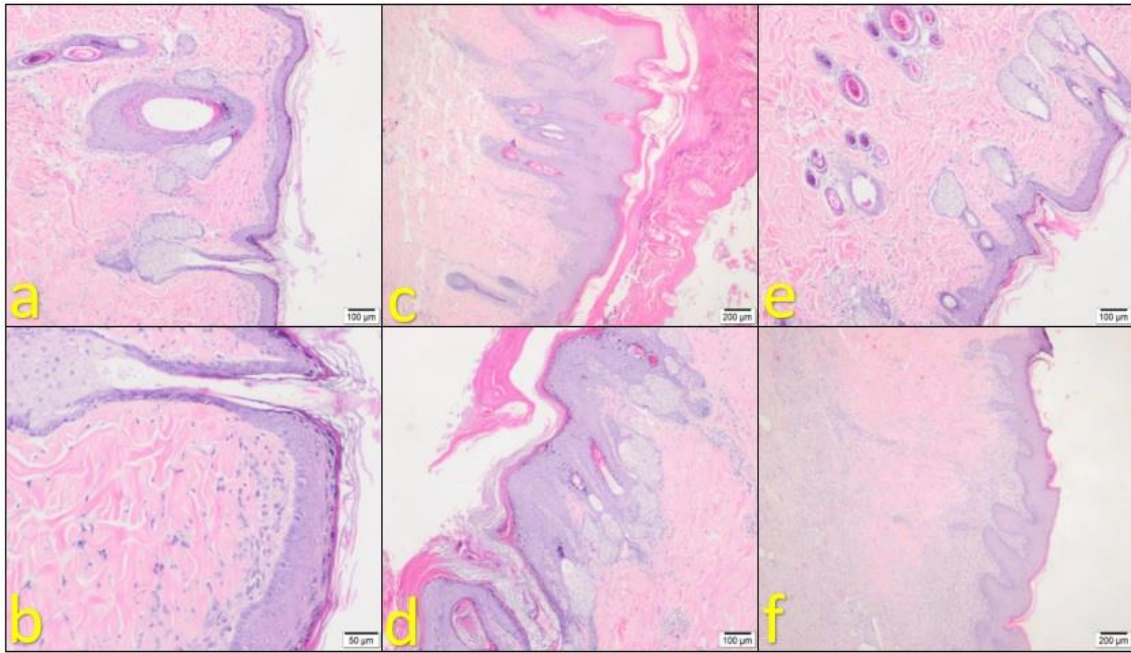


Figure 3. Histopathological (H&E) images of skin wound tissues at day 14: CO group (a, b), LSO group (c, d), and CCO group (e, f). CO: Corn oil, CCO: Common centaury oil, LSO: Laurel seed oil.

Discussion and Conclusion

Ideal wound healing is defined as the successful closure of the wound in the shortest time without any undesirable effects (10). Wound healing involves continuous, active, highly complex processes that may vary depending on many factors (22). Any effect disrupting the natural chain of wound healing may also affect the following stages, resulting in abnormal healing, chronic wounds, or scar tissue formation (13). The course of wound healing is largely associated with the antioxidant activity of the therapeutic agent used. Antioxidants accelerate wound healing by removing free oxygen radicals and increasing colloid synthesis (46).

Topical applications of anti-inflammatory and free radical scavenging products increase wound healing and protect tissues from oxidative damage (6, 21, 29, 48). Open wound treatment is frequently required in many medical branches. There are many studies trying to develop an ideal and faster open wound treatment option. Medicines, biomaterials, and methods that are thought to be more effective in open wound treatment have been tested. The use of natural products or the active substances obtained from them in wound dressings or wound care processes is increasing. In this context, wound healing studies are increasingly continuing.

Common centaury oil (CCO) is a herbal oil that contains over 230 different components, including a wide variety of fatty acids and terpenes in its chemical composition (25). Its antioxidant, antibacterial, and dermatoprotective effects have been reported (11, 24). Laurel seed oil (LSO) is a herbal oil with strong

antibacterial, anti-inflammatory, and antioxidant properties (15, 18). St. John's Wort (*Hypericum perforatum*) plant extract and oil, which can be considered close to CCO, are used in many areas, especially wound healing, and there are many scientific studies about them (2, 3, 12, 21, 47, 49). To our knowledge, there are no studies investigating the effects of CCO on wound healing. Although there are many studies on LSO, there is also no study showing its effects on wound healing. Based on the knowledge of the antioxidant, antimicrobial, and dermatoprotective effects of these oils (11, 24, 37, 50), this study was planned with the hypothesis of their possible wound healing effects. Although the chemical components of the herbal oils used in our study were similar to the results of other studies (14, 25, 41), the percentages were determined to be relatively different. However, as a result of the GC-MS analysis, it is noteworthy that the LSO used in our study contains 6% eucalyptol. It is known that the content of the vegetable oils may vary according to the collection period and region. Because in previous studies eucalyptol ratios of laurel oil and LSOs have been reported to be around 30-60% (14, 41), it was considered that the proportional differences in the content of herbal oils are possibly caused by the harvesting regions. In experimental wound model studies, corn oil has been used as a control group in cases where the treatment group has a different oil-based substance (23, 44). Although some researchers prefer no treatment in the control group (48), in order to get a better oil-based substance comparison, the use of corn oil was considered necessary in our study as a negative control group.

It is noteworthy that the GLU results in the biochemical changes were significantly lower in the LSO group than the other two groups and lower in the CO group than the CCO group. Differences in GLU value are associated with stress and food consumption (32). It was considered that the changes in the GLU values showed the differences in the amount of stress caused by the application of the oils. It's known that a high TP value contributes to reducing inflammation and increasing fibroplasia (38). The fact that the TP value was significantly lower in the LSO group than the other two groups may indicate that the anti-inflammatory events are insufficient. AST, ALT, and CRE values did not differ statistically between the groups. Food and water consumption in experimental animals is an indicator for the evaluation of the welfare and stress (5). In our study, no significant difference was found in the clinical examination, body weight, and feed consumption results of the groups. However, water consumption increased in the LSO group during the second week of wound healing. The reason was considered to be increased stress by LSO treatment irritating animals.

In a 14-day study measuring the effects of coconut oil in terms of wound closure time, antioxidants, and biomechanics, it was suggested that coconut oil has an antioxidant effect and accelerates wound healing (35). Another study suggests that *Nigella sativa* oil had stronger antioxidant properties than the *hypericum perforatum* oil and the placebo cream treatments, and *hypericum perforatum* increased wound healing via its effects on epithelialization and granulation (21). In a 14-day rat diabetic wound model study, by measuring the percentage of wound tissues macroscopically, the use of topical bitter melon oil accelerated wound healing (16). In another study of a 14-day experimental rat wound model, although black cumin (*Nigella sativa*) oil and zinc-silver cream in topical use gave poor results in macroscopic findings, zinc-silver cream gave good results in histopathological findings and physical testing. Thus, it has been suggested that it positively affects wound healing (29). Another study examined the effects of ozonated black cumin (*Nigella sativa*) oil, sesame oil, and St. John's Wort (*Hypericum perforatum*) oil on wound closure rate and healing process, both microscopically and macroscopically. Black cumin oil gave better results than other groups (12). Poljšak et al. (38) also reported similar effects and suggested that in-depth studies are needed to gain knowledge about vegetable oils' effects on the skin (38). In our study, macroscopic findings revealed LSO had an irritating effect on the skin and negatively affected wound healing. The increase in stress was at a level that would affect even food consumption. Although such a negative effect was not observed in the CO group, no effect that increased wound healing was observed. In the CCO group,

on the other hand, as a result of macroscopic findings, the amount of wound closure was higher, and thus wound healing accelerated. Based on the results, it was determined macroscopically that CCO enhanced wound healing but LSO delayed it.

In the wound healing study using coconut oil, it was reported that fibroblast proliferation and neovascularization, pepsin-soluble collagen level, and cross-linking increased in the histopathological results, thus revealing the contribution to wound healing (35). The positive effect of bitter melon oil on wound healing was explained by the low inflammation findings in the histopathological examination (16). In the study showing the effects of black seed oil and sesame oil in the experimental wound model in rats, although significantly positive results were observed in macroscopic results, no significant difference was found between groups in histopathological results (12). In our study, histopathological findings revealed the scores in the CCO group were higher than the other two groups in terms of blood vessel formation, fiber synthesis, granulation, and mononuclear cells, and the LSO group had higher scores than the CO group. Additionally, macroscopic (wound area measurements and local clinical findings) and histopathological results support each other, hence showing that the CCO group had significantly better wound healing than the other two groups. However, histopathological results were better in the LSO group than in the CO group, although results that impair wound healing were observed in wound area measurements and local clinical findings in the LSO group compared to the other two groups. The reason for that was considered to be that, although it provides an anti-inflammatory effect at the cellular level, the wound healing process is adversely affected due to the irritating effect of the oil components. Because, in two different studies, the presence of six different cytotoxic components in the Laurel plant (*Laurus nobilis*) extract was identified (9, 18). On the other hand, it has been reported that Laurel plant extract obtained by different extraction methods has antioxidant effects in vitro and in vivo, but different effects may occur depending on the methods and solutions used in the extraction (26). Also, many extraction methods have been reported for medicinal purposes in wound healing (28, 31, 34). In an in vivo wound model study using *Allamanda* and *Laurus nobilis* extracts, the *Allamanda* group gave significantly better results than the *Laurus nobilis*, but still, the *Laurus nobilis* had better results than the control group (34). Although macroscopic findings for LSO in our study do not support this, microscopic findings partially support it.

In conclusion, the topical use of Common centaury (*Centaurium erythraea*) oil accelerated wound healing, while Laurel (*Laurus nobilis*) seed oil adversely affected wound healing in an in vivo experimental excisional full-

thickness skin wound model in rats by a clinical, macroscopic, histopathological, and biochemical investigation. Further investigation may provide original results for these oils if used in diseased wound models, such as infected or diabetic wounds, in future studies.

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Conflict of Interest

The authors declared that there is no conflict of interest.

Author Contributions

MZYD and NS designed the study and animal experiments. MZYD and NS carried out the animal experiments, sample collection, and analyses. MZYD contributed to the interpretation of the results and discussion. MZYD and NS wrote the manuscript.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethical Statement

The ethical approval of this study was obtained from the Local Ethics Board of Animal Experiments of Hatay Mustafa Kemal University (Decision No: 2020/04-34).

Animal Welfare

The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

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