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Original Article

Investigating the effect aerials part of *Stachys Lavandulifolia ointment* on 2nd degree burns compared to silver sulfadiazine on male rat

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Abstract: Objective: Skin burns can occur due to exposure to heat, chemicals, electricity, or sunlight, and can cause significant damage to the skin. Burns are classified based on their severity. Research has indicated that herbal extracts may help treat burns. This study aimed to assess the effectiveness of Stachys Lavandulifolia extract ointment in healing burn wounds in rats. Methods: In this study, the efficacy of Stachys Lavandulifolia ointment was evaluated in treating second-degree burns by comparing it with silver sulfadiazine ointment. The study involved preparing Stachys Lavandulifolia extract in 2% and 4% concentrations. Thirty Wistar rats were divided into six groups, including a negative control group, a positive control group, and groups treated with silver sulfadiazine ointment, Stachys Lavandulifolia extract at 2% and 4% concentrations, and Eucerin ointment. Results: The study found that applying 2% Stachys Lavandulifolia ointment is effective in treating second-degree burns. Biochemical analysis revealed significant differences in tissue FRAPS levels between the normal control group and the groups treated with 2% Stachys Lavandulifolia, 4% Stachys Lavandulifolia, and 1% silver sulfadiazine ointment. Statistical analysis indicated that on day 21, the burn area in the 2% and 4% Stachys Lavandulifolia ointment groups was significantly smaller than in the positive control and Eucerin groups. Conclusion: The Stachys Lavandulifolia ointment, with its antioxidant ingredients, can potentially prevent oxidative damage, lower inflammatory factors, and speed up the healing process for burns.

Keywords: *Stachys Lavandulifolia*, silver sulfadiazine, rats, burns, skin

Introduction

A burn is an injury to the skin or tissue caused by heat, electricity, chemicals, friction, or radiation [1]. The severity of the burn depends on the extent of the damage to underlying tissue layers, which humans can experience inflammation and pathological damage [2]. In severe cases, burns can cause death, or if the injuries caused by the burn are healed, they can leave physical and emotional scars that may significantly alter a person's life [3]. Each year, approximately 100,000 people are admitted to hospitals due to burn injuries, and more than 10,000 of these patients die due to burn complications, making it the fourth leading cause of death from accidents and motor vehicle incidents [4]. However, recent advancements in healthcare and burn treatment have improved life expectancy and reduced the mortality rate among burn patients [5]. Burns are classified by the extent of damage and injury severity. Superficial burns, or first-degree burns, only affect the skin's surface [6]. Partial-thickness burns, or second-degree burns, occur when the underlying layers of the skin are damaged. Third-degree burns damage all skin layers, while fourth-degree burns extend deeper, impacting muscles and bones [7]. Burn injuries can be quite painful, and various methods exist for pain management and treatment. Simple pain relievers like ibuprofen and acetaminophen can be effective, as well as opioids like morphine [8]. However, burn injuries often lead to several complications, the most common being infection. Burn infections are a primary

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cause of mortality in patients with extensive burns. To combat this, topical antimicrobial agents, such as silver sulfadiazine 1%, have been developed to reduce burn-related mortality Nonetheless, these medications can have side effects, including decreased white blood cell counts, necrosis of the epidermis, increased skin pigmentation, heightened bacterial resistance, and failure of the skin to heal properly [9]. To alleviate the physical and emotional burdens on burn patients and their families [10], special attention to outpatient treatment is crucial to lowering treatment costs associated with hospitalization. Consequently, developing new drugs that can effectively manage burn wound infections [11], related shock, and other aspects of burn care minimizing complications, accelerating wound healing, and reducing patient mortality is a global research priority [12]. Many advanced dressings, such as paraffin gas, biosynthetic dressing, hydrocolloid dressing, and silicone sheets, are utilized to treat burns and minimize complications from injuries [13]. The ideal dressing aims to reduce pain, protect or isolate the burn wound, and heal [14]. An alternative method for treating burns and minimizing complications is the use of medicinal plants and their natural products, highlighting their significance in the global economy [15]. Essential oils are complex mixtures of volatile, low molecular weight, and hydrophobic compounds derived from various parts of aromatic plants [15]. Stachys lavandulifolia is a medicinal plant commonly used in traditional Iranian medicine [16]. The essential oils from these plants possess antimicrobial and anti-inflammatory properties, making them a promising natural treatment for burn wounds.

Materials and methods

Materials

The study used an MDA kit (Zist Azma Parseh, Iran), a NO kit (Cib Biotec Co., Iran), a FRAP kit (Kavosh Aryan Azma Co., Iran), and Eucerin cream (Iran).

Ethics approval

An experimental study conducted in 2023 at Yasuj University of Medical Sciences (ethics code IR.YUMS.AEC.1402.007) involved 30 male Wistar rats, each weighing between 200 and 250 g. The study protocol was approved by the Ethics Committee for Animal Experimentation at the university.

Preparation of Stachys Lavandulifolia extract

To make the extract, 1 kg aerials part of Stachys Lavandulifolia (Herbarium No. 1887) were combined with four liters of 70% alcohol and distilled water solution in suitable containers [2]. The mixture was then soaked for 48 hours. After this, the mixture was filtered using filter paper and then concentrated using an oven at 40°C. Once concentrated, the extract was dried before being stored. 2% and 4% Stachys Lavandulifolia ointment was prepared based on Eucerin.

Animal groups

In this experimental study, we used thirty male Wistar rats weighing between 200 and 250 grams, sourced from the animal colony at Yasuj University of Medical Sciences. The rats were randomly divided into six equal groups for the purposes of the experiment. These groups were as follows: 1. Negative control group: no burns and no treatment. 2. Positive control group: daily recipient of normal saline. 3. Group receiving 2% Stachys Lavandulifolia ointment on a daily basis. 4. Group receiving 4% Stachys Lavandulifolia ointment on a daily basis. 5. Group receiving Eucerin ointment a daily basis. 6. Group receiving 1% silver sulfadiazine ointment on a daily basis. The treatment groups were treated for 21 days.

Animal tests

Rats were anesthetized intraperitoneally with Ketamine (50 mg/kg) and Xylazine (50 mg/kg) according to their weight. The fur on the lumbar region was shaved, and the skin was sterilized with 70% alcohol. A heater set to 100 degrees for 10 seconds was then used to create a second-degree burn measuring 3.14 square centimeters on the back of the animal's neck [2]. After the burns, 2 cc of sterile saline was injected intraperitoneally to prevent hypovolemic shock. In the treatment groups, the ointment was applied daily to the burn site with a sterile swab until the wound was covered. All animals were kept on a 12-hour light/dark cycle at 22± 2 degrees Celsius with adequate food and water. At the end of the treatment period, the rats were anesthetized with ether, and 1 to 3 cc

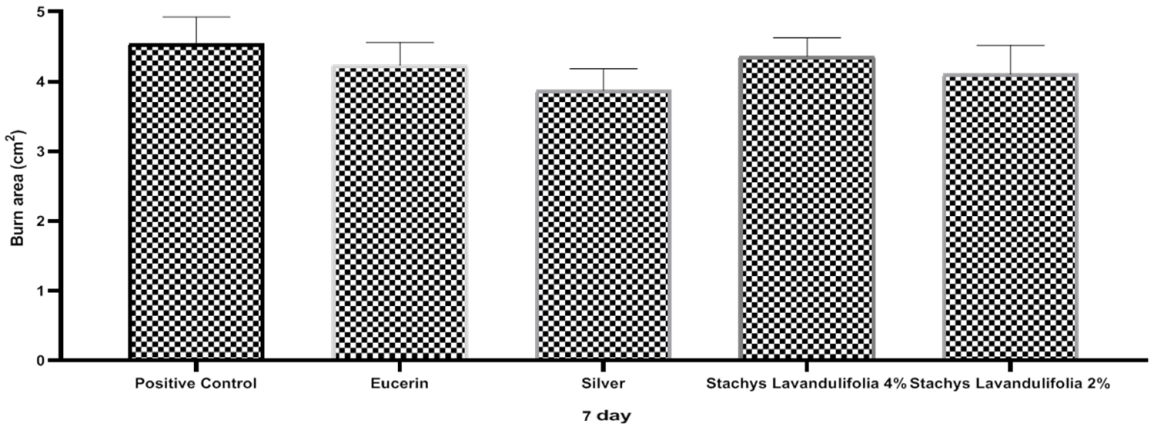

Figure 1. The burn area in the Stachys Lavandulifolia (S.L) ointment group was not significant in all study groups (P>0.05).

of blood was collected from their hearts for serum separation, which was then stored at -80 degrees Celsius for biochemical testing. All groups were sacrificed by cervical dislocation after deep anesthesia on the 21st day. Wound closure was assessed through photography at 7, 14, and 21 days, while healing quality was evaluated histologically.

Histology method

After blood sampling, the rats were anesthetized and dissected. One part of the tissue was stored in a micro tube for homogenization, while another portion was placed in 10% formalin for 24 hours, then washed with physiological serum and transferred to 5% formalin for an additional 24 hours. Subsequently, 0.5 × 0.5 cm^2 samples were cut and processed in a tissue processing machine. Tissue blocks were created, and 5-micron sections were prepared using microtomes and stained with Hematoxylin-eosin dye. Examination was performed using a Nikon light microscope and camera [2].

Measurement of malondialdehyde

In this method, malondialdehyde (MDA) reacts with thiobarbituric acid (TBA) to form a pink complex. A sample (serum or homogenized tissue) was mixed with 900 µl of distilled water and 100 µl of TBA reagent, which was prepared by combining 100 ml of distilled water, 0.5 g of sodium hydroxide, 0.67 g of thiobarbituric acid, and 100 ml of acetic acid. The mixture was heated to 90°C for one hour, cooled, and centrifuged at 4000 g for 10 minutes. The supernatant was collected, and its light absorption was measured at 535 nm using a spectrophotometer. MDA levels in µM/ml were calculated by comparing the results with a standard curve [17].

Nitric oxide assay

To degrade proteins using acetonitrile, 300 µl of the sample (serum or homogenized tissue) was mixed with 300 µl of the solvent. Nitric oxide was evaluated through a grease reaction via the microplate method. For nitrite and total nitrate measurement, 100 µl of the degreased sample was combined with 100 µl of an 8 mg/ml vanadium chloride solution in an ELISA microplate to convert nitrates to nitrites. Then, 100 µl of a 1:1 mixture of sulfonamides and NEDD was added and incubated for 30 minutes at 37°C. After the reaction, the optical density of the color complex was assessed at 540 nm using an ELISA reader, with concentrations determined from a standard curve [18].

FRAP assay (ferric reducing antioxidant power)

A mixture of 125 ml acetate buffer, 12.5 ml TPTZ, and 12.5 ml ferric chloride was prepared. Then, 1000 µl of this solution and 37 µl of the sample (serum or homogenized tissue) were added to 96-well plates, and absorbance was measured at 539 nm [19].

Statistical analysis

Statistical analysis was conducted using SPSS software, with data presented as mean and

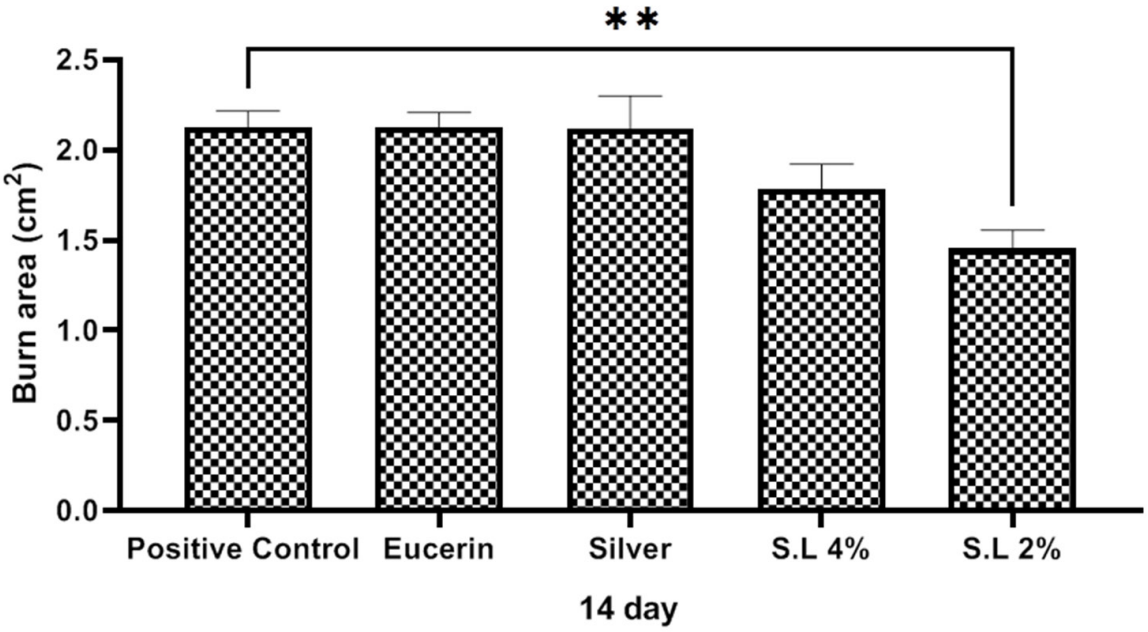

Figure 2. The Burn area level in the Stachys Lavandulifolia ointment 2% group decreased significantly compared to positive control and Eucerin groups (**P<0.01).

standard deviation. One-way ANOVA and Tukey tests were performed after verifying normality, considering results significant at P<0.05.

Results

Comparison of burn area in the studied groups

The burn area chart was created on day 7 for all groups based on statistical analysis. On this day, the wound area in the Stachys Lavandulifolia ointment group showed no significant difference compared to other groups (P>0.05; **Figure 1**). By day 14, the burn area in the 2% Stachys Lavandulifolia ointment group decreased significantly compared to the positive control and Eucerin groups (**P<0.01; **Figure 2**). On day 21, the burn area in the 2% and 4% Stachys Lavandulifolia ointment groups was significantly reduced compared to the positive control and Eucerin groups (****P<0.0001, *P<0.05, respectively; **Figure 3**).

Serum nitrite oxide metabolites (Serum NO)

The results show that the NO level in the tissue samples of rats on the 21st day after the burn, in all groups did not significantly (P>0.05; **Figure 4**), but in the serum samples of rats in control positive and Eucerin groups compared to other groups were increased significantly (***P<0.001,**P<0.01; respectively; **Figure 5**).

Comparison of serum malondialdehyde (MDA)

Figures 6 and **7** show that the MDA level in the serum and tissue samples of rats on the 21st day after the burn, in all groups did not significantly (P>0.05; **Figures 6**, **7**).

FRAP assay (ferric reducing antioxidant ability)

The results show that the FRAP level in the tissue samples of rats on the 21st day after the burn, in control positive, Eucerin, Stachys Lavandulifolia ointment 2% and 4% groups were decreased significantly (**P<0.01; **Figure 8**), but in the serum samples of rats in all groups were not significantly (P>0.05; **Figure 9**).

Comparison of epidermal and dermal thickness

On the 21st day, the groups treated with 2% and 4% Stachys Lavandulifolia ointment showed a significant increase in epidermal thickness compared to the positive control and Eucerin groups (*P<0.05; **Figures 10**, **12**, **13**). Additionally, the same groups, along with the silver sulfadiazine ointment group, exhibited a significant decrease in dermal thickness com-

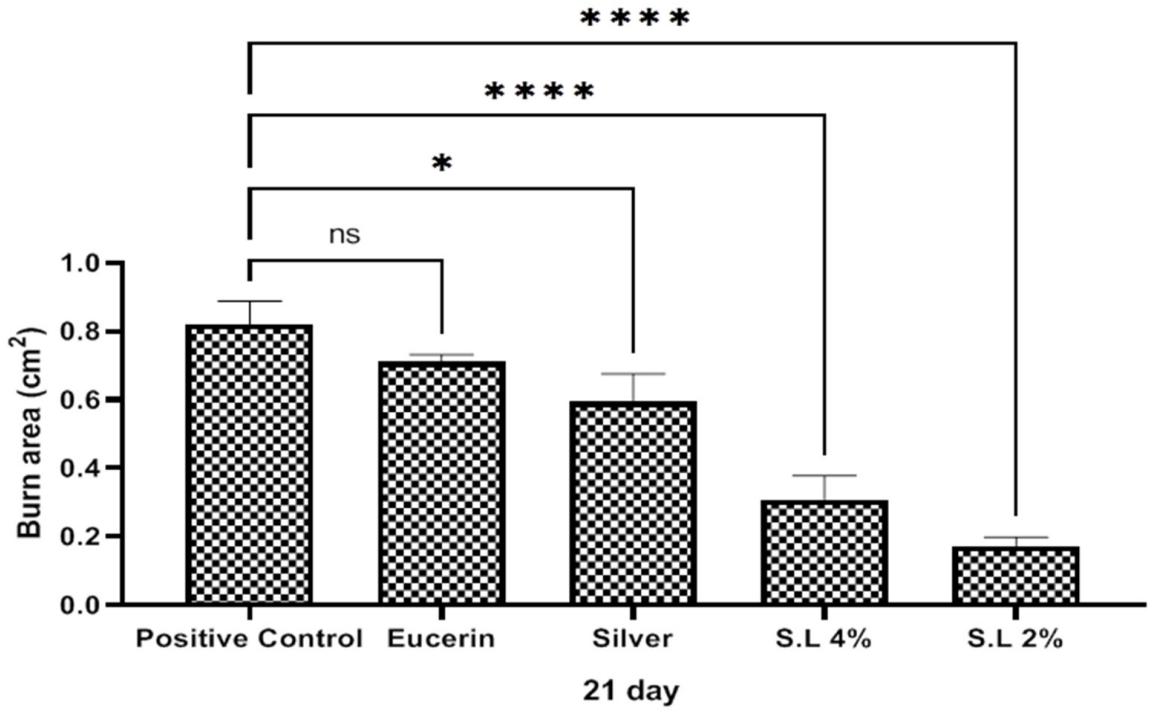

Figure 3. The burn area in the Stachys Lavandulifolia ointment 2% and 4% group was significant compared to positive control and Eucerin groups (****P<0.0001 and *P<0.05; respectively).

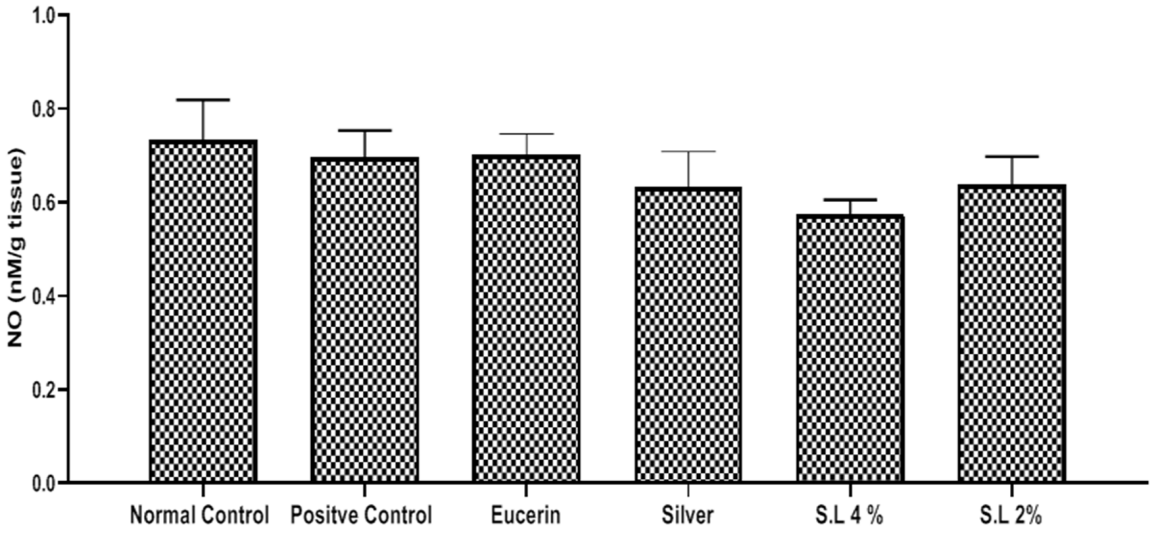

Figure 4. The NO (nitrite oxide) level in the skin tissue chart was not significant in all study groups (P>0.05).

pared to the positive control and Eucerin groups (**P<0.01; **Figures 11-13**).

Discussion

Skin lesions are becoming more commonly treated using plant medicines in addition to therapeutic groups, cellular-molecular medicine, and traditional medicine [20]. The objective of all these treatments is to quickly heal skin lesions. A recent study aimed to compare the effect of Stachys Lavandulifolia extract with 1% silver sulfadiazine cream on skin healing in second-degree burns [21]. The study showed that various harmful factors, such as heat, chemicals, and radioactive substances,

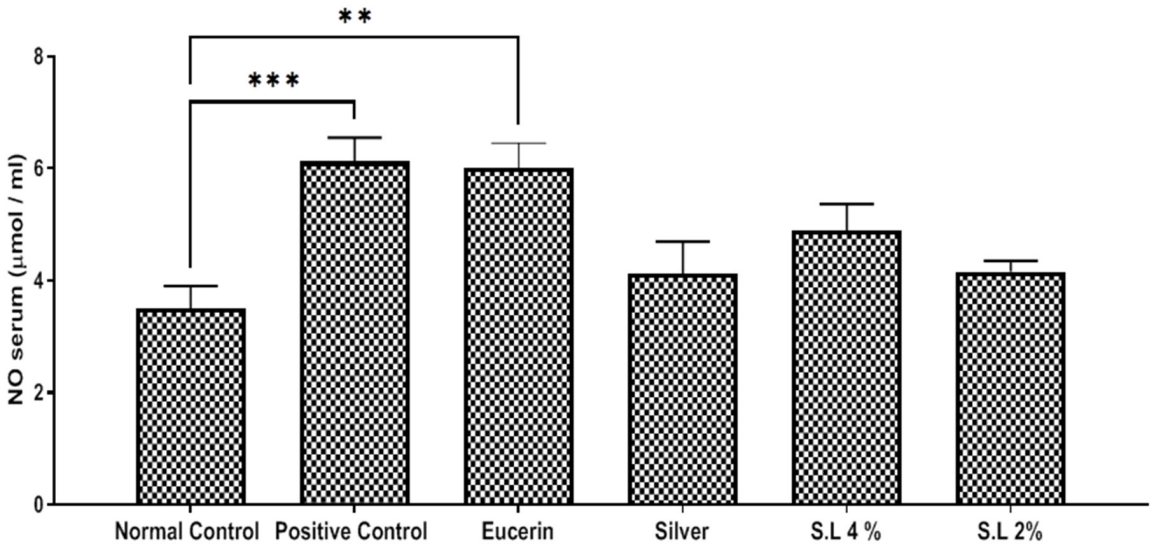

Figure 5. The NO level in the serum sample chart was significant in the positive control and Eucerin groups compared to the other study groups (***P<0.001 and **P<0.01; respectively).

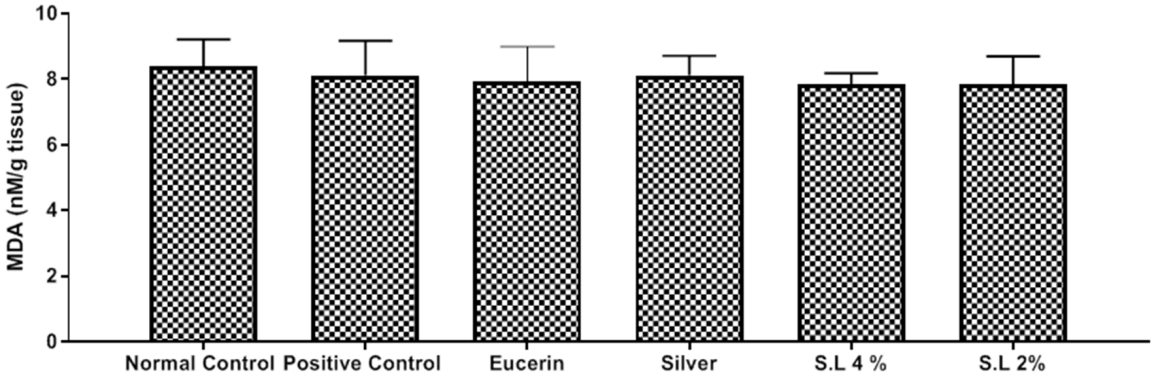

Figure 6. The MDA (malondialdehyde) level in the skin tissue chart was not significant in all study groups (P>0.05).

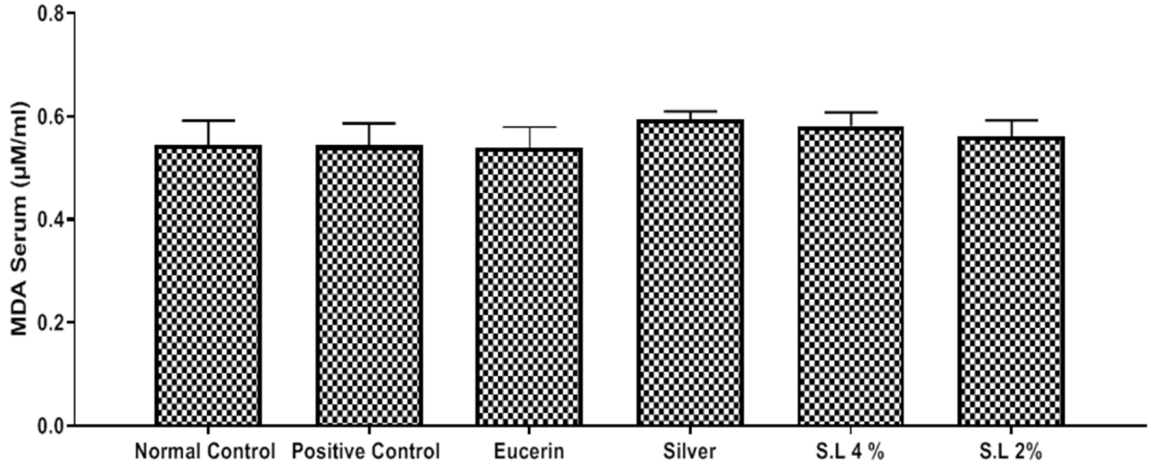

Figure 7. The MDA level in the serum sample chart was not significant in all study groups (P>0.05).

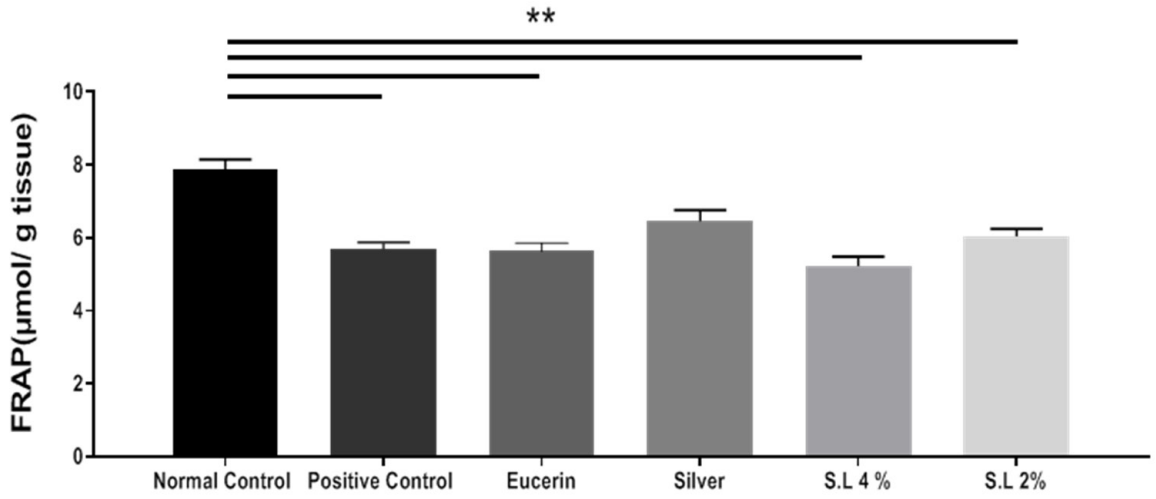

Figure 8. The FRAP (ferric reducing antioxidant ability) level in skin tissue chart was significant in the positive control, silver, Eucerin, S.L 4% and S.L 2% groups compared to normal control group (**P<0.01).

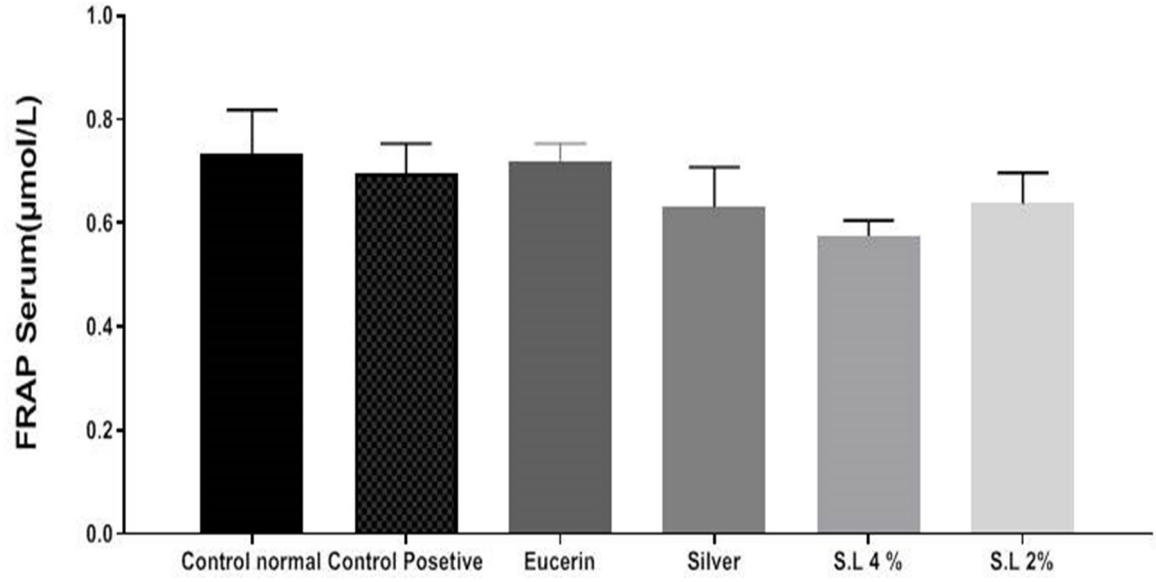

Figure 9. The FRAP level in the serum sample chart was not significant in all study groups (P>0.05).

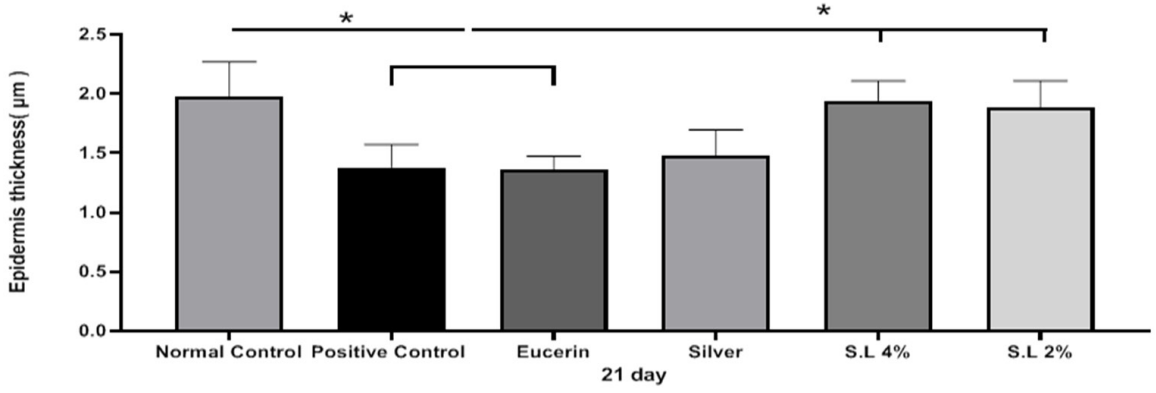

Figure 10. It was significant in positive control and Eucerin groups compared to S.L 2%, 4%, and Normal control groups (*P<0.05).

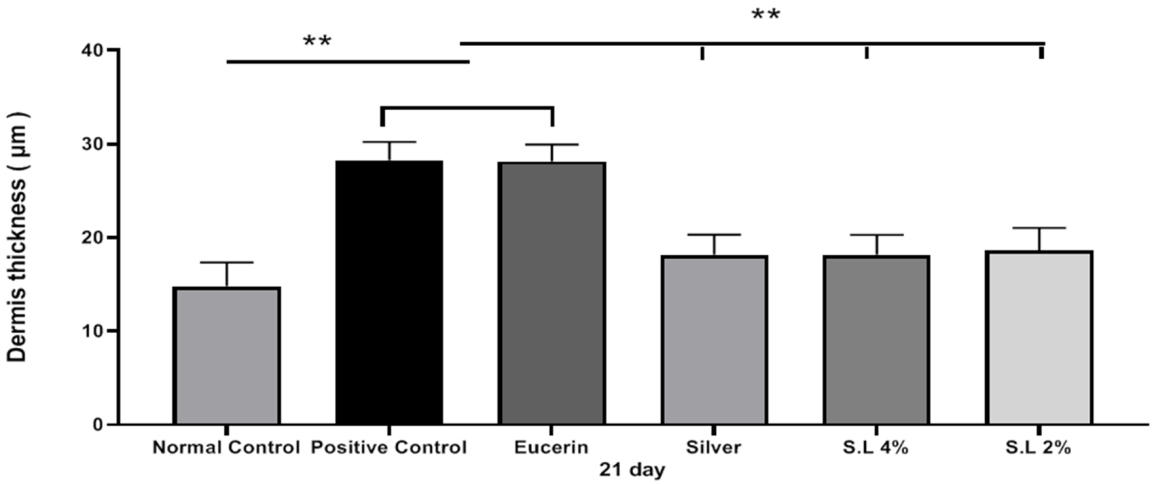

Figure 11. It was significant in positive control and Eucerin groups compared to other groups (**P<0.01).

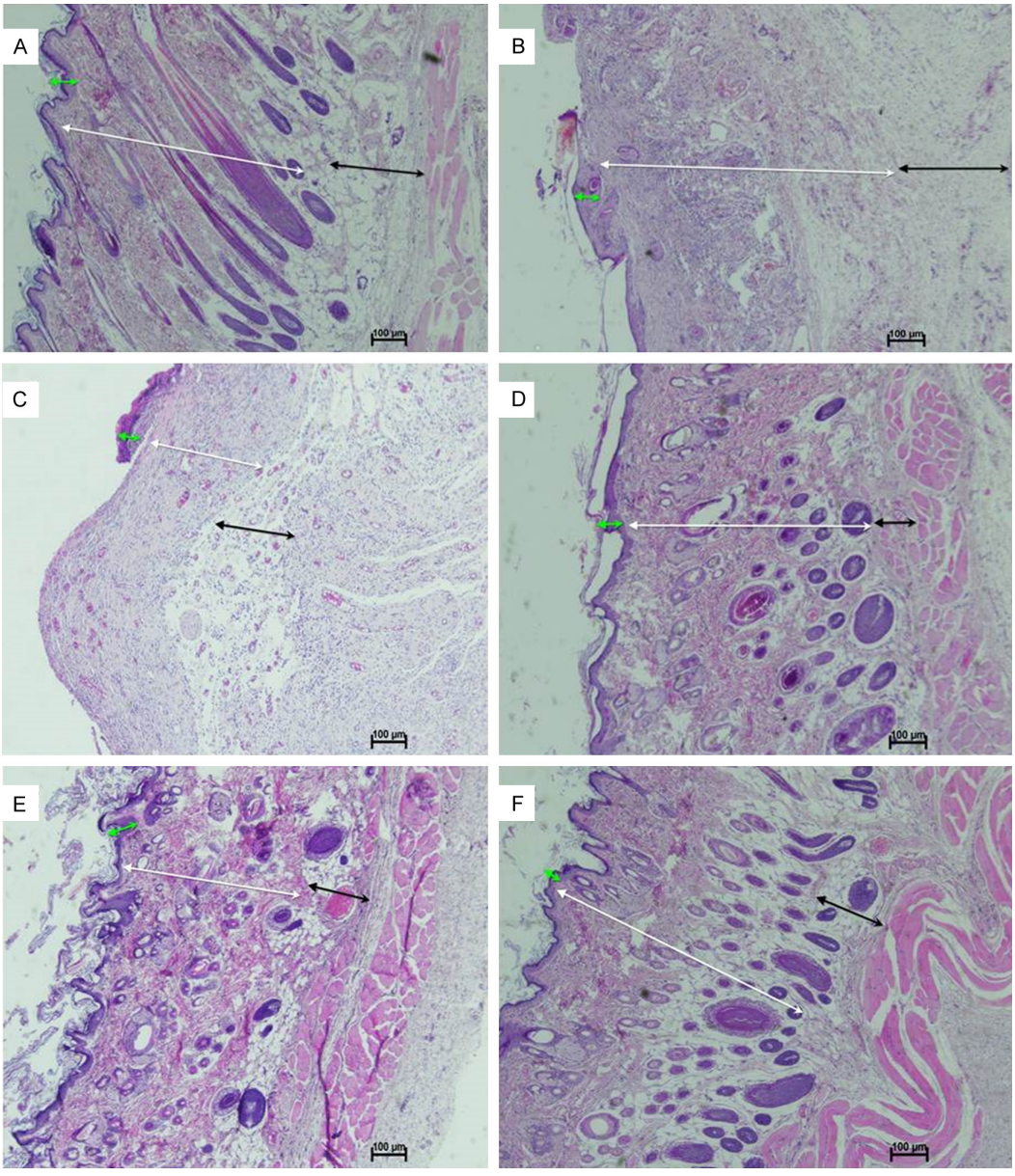

Figure 12. Comparison of skin Burn healing process in different groups studied on the 21st day in rats. (A) Normal control group, (B) Positive control group, (C) Silver group, (D) Group treated with Eucerin, (E) Group treated with Stachys Lavandulifolia 4%, (F) Group treated with Stachys Lavandulifolia 2%. Epidermis layer thickness (green arrow), dermis layer thickness (Whit arrow), and Hypodermis layer thickness (Black arrow) (H&E staining, magnification X100 µm).

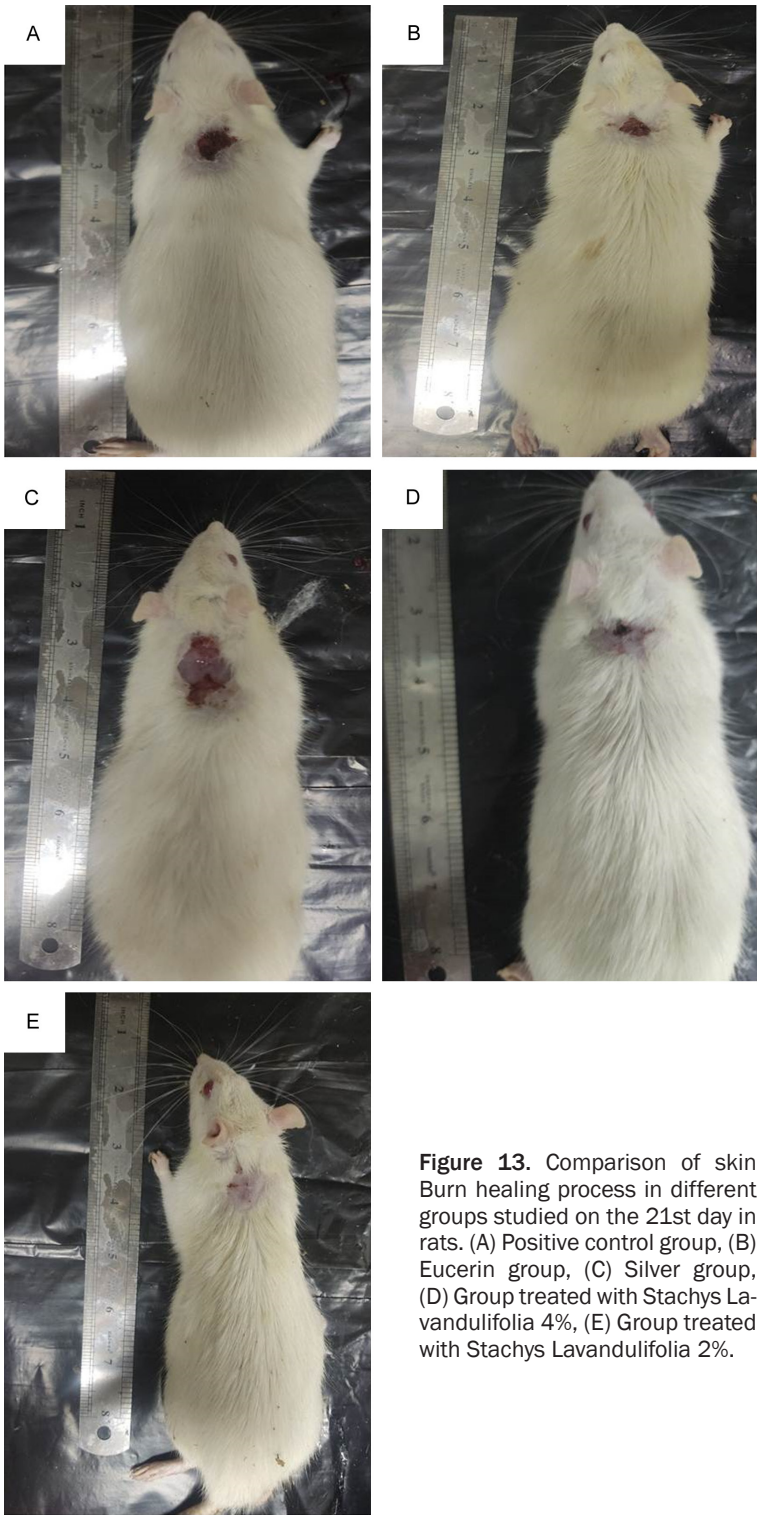

Figure 13. Comparison of skin Burn healing process in different groups studied on the 21st day in rats. (A) Positive control group, (B) Eucerin group, (C) Silver group, (D) Group treated with Stachys Lavandulifolia 4%, (E) Group treated with Stachys Lavandulifolia 2%.

can activate the inflammatory process in the skin, leading to edema, bleeding, and other complications. If left untreated, these wounds can cause severe injuries, infections, and even death [2]. Therefore, it is crucial to treat them immediately with local drug treatment. Skin wound healing is a complex process that involves various factors, including cells, growth factors, cytokines, and hyaluronic acid [1]. Hyaluronic acid plays a critical role in the connective tissue of the dermis layer, which helps in the healing process by absorbing fluids secreted from blood vessels, providing a suitable area for immune and connective tissue cells to function [22]. Other inflammatory factors in skin lesions include cytokines such as TNF-α, IL-12, INF-c, and IL-17, which are effective in the process of inflammation and subsequent repair [23]. The study revealed that Stachys Lavandulifolia extract contains antioxidant substances that can reduce the effect of oxygen radicals generated and the effect of its oxidation on cellular structures. It can also reduce the effect of inflammatory factors, resulting in a gradual process of improvement during optimal use of these antioxidant substances [24]. Moreover, the study showed that Stachys Lavandulifolia extract can increase the rate of angiogenesis [25], which is one of the most effective factors in wound healing. It can also double or intensify the formation of new blood

vessels through biochemical and pharmacological mechanisms [26], change tissue blood circulation in the affected area, and advance the wound healing process. Additionally, it can increase the speed of proliferation of fibroblasts, activate tissue fibroblasts [27], and increase the production of extracellular matrix by activated fibroblasts, reducing the extent of the burning surface and increasing the healing process of the skin epithelium. Lastly, the study showed that Stachys Lavandulifolia extract can increase the thickness of the epidermis layer, the dermis layer, the growth of collagen fibers in the dermis layer, and the growth of hair follicles. These factors can improve the healing process and accelerate the formation of granulation tissue. The presence of tannins [1], terpenoids [28], and flavonoids in Stachys Lavandulifolia extract can also increase the proliferation of fibroblasts, secrete TNF to accelerate wound healing, and regulate the formation of granulation tissue.

Conclusion

According to the information you provided, it seems that Stachys Lavandulifolia extract can help speed up the healing process of burn wounds and reduce the time needed for complete healing. More research is required to fully understand the extract's mechanism of action and appropriate dosage. The clinical application of these findings will also depend on further investigations into potential side effects and safe dosages.

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Disclosure of conflict of interest

None.

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