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Effect of Herbal Bioactive Compounds on the Angiogenic Factors and Modulation of Inflammatory Mediators in the Patients with the Deep Second-Degree Burn: A Single-Blinded, Randomized Clinical Trial

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Abstract

Background: Inflammation is the first response to tissue damage. A hematoma occurs when blood leaves the damaged vessels, and platelets play an important role in this process. This study aimed to investigate the effect of herbal bioactive compounds on the angiogenic factors and modulation of inflammatory mediators in deep second-degree burn patients.

Methods: In a randomized clinical trial, 54 patients were divided into two groups :Swalin ointment (n=31) and silver sulfadiazine (SSD) (n=23). Ointments were administered every other day for 28 days. The concentration of compounds in ointment oils was measured using the GC-MS technique. Serum levels of TNF-α and IL-6 were measured on days 3, 7, and 14, and tissue levels of VEGF, FGF, and PDGF variables were measured on day 14 by ELISA method. Student t-test was used to compare the mean in 2 groups, depending on the type of normal/abnormal distribution. The chi-square test was also used to check the relationship between qualitative variables.

Results: The most common compounds in Swalin ointment were Linoleic acid (41.37%), Elaidic acid (37.45%), and Palmitic acid (9.45%), respectively. The tissue level of VEGF, FGF, and PDGF on the 14th day was higher in the Swalin group compared to the SSD group (P<0.001). The serum level of IL-6 and TNF-α in both groups increased until day 7, but gradually decreased on day 14, which was significant in the Swalin group. IL-6 serum level was significant in the Swalin group (P<0.001). The serum level of TNF-α was also significant in the Swalin group (P<0.001).

Conclusion: The present study showed that Swalin ointment, due to the presence of a wide range of fatty acids, especially linoleic acid, leads to the modulation of systemic tissue inflammation. The ingredients of the ointment, especially hemp and sesame oil, increase the tissue level of angiogenic factors and accelerate remodeling and wound healing.

Keywords: Burns, Angiogenesis, Vascular Endothelial Growth Factors

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↑What is "already known" in this topic:
Skin repair occurs in four stages: inflammation, cell proliferation, angiogenesis, and regeneration. Accelerating these phases leads to faster healing. In burn recovery, fibroblasts, inflammatory factors, and keratinocytes coordinate to promote cell division, differentiation, migration, and collagen deposition. Medicinal plants enhance burn healing by regulating TNF-alpha, cytokines, nitric oxide, ROS, and inflammatory mediators.

→What this article adds:
This study found that Swalin ointment, rich in fatty acids like linoleic acid, helps modulate systemic tissue inflammation. Its key ingredients, particularly hemp and sesame oil, enhance angiogenic factors, promoting faster tissue remodeling and wound healing.

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Introduction

Burn injuries represent a significant global health issue, accounting for an estimated 180,000 deaths each year (1-13). These injuries are characterized by damage to the skin or other organic tissues, primarily resulting from exposure to fire, electricity, radiation, or chemical agents (14-30). The consequences of burn injuries are extensive and long-lasting, affecting not only the physical health of individuals (31-46) but also their mental well-being and overall quality of life (47-66). The impact of these injuries extends beyond the individuals directly affected, placing considerable stress on their families and healthcare systems worldwide (67-84). Furthermore, burns are recognized as the fourth most common type of accident, impacting around 11 million people globally and leading to approximately 300,000 deaths annually (85).

Skin repair includes four stages: inflammatory phase, cell proliferation, angiogenesis, and regeneration (86). Any substance that can reduce the duration of these phases leads to faster repair (87). To heal burns, several cells and factors such as fibroblasts, inflammatory factors, and keratinocytes cooperate and promote cell division, cell differentiation, and cell migration in an organized manner, which stimulates the deposition of collagen and connective tissue and angiogenesis (88). Inflammation represents the initial response to tissue injury. Its primary objective is to quickly restore homeostasis and trigger a cascade of biological reactions that facilitate tissue repair. A hematoma forms when blood escapes from injured blood vessels, with platelets being crucial to this process. The release of cytokines and growth factors from activated platelets and surrounding cells initiates various events, including cell migration, proliferation, differentiation, and the synthesis of the extracellular matrix (89-92).

Neutrophils, as the first inflammatory cells that infiltrate the wound area, provide rapid defense against infections and also remove tissue debris (89-91, 93, 94). After monocytes reach the wound area, they differentiate into macrophages and become the predominant cell types. Macrophages, whose lifespan is limited to a few days to 1 month, support neutrophil functions and increase the secretion of factors from them (89-91, 93). The endothelium of the blood vessel near the site of injury proliferates to form new capillaries, and these new vessels extend toward the wound. These events are considered as the first stage of angiogenesis (89, 91, 92).

In the proliferative stage, as the second stage of wound healing, damaged and necrotic tissue is removed from the surrounding area and replaced by living tissue that matches the original tissue structure (such as bone, cartilage, and fibrous tissue) (92, 95). The regeneration phase is the final stage of wound healing, in which the newly produced tissue is reshaped and reorganized (92). Numerous proteins located within the alpha granules of platelets play a significant role in the wound-healing process. Among these proteins are transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), platelet-derived endothelial growth factor (PDEGF), platelet-derived angiogenic factor (PDAF), platelet factor 4 (PF4), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), interleukin-1 (IL-1), osteocalcin, osteonectin, vitronectin, fibrinogen, fibronectin, and thrombospondin (TSP) (89, 95, 96).

Platelets initiate the active secretion of these mediators within 10 minutes following the onset of clotting, with over 95% of the pre-synthesized growth factors being released within a one-hour timeframe (96). In the treatment strategy of burn wounds, the multiple mechanisms related to microvascular dysfunction should be understood. The three main mechanisms include vascular thrombosis due to vascular injury, upregulation of inflammatory factors, and pro-apoptotic factors (97). Macrophages are the most important secretors of proinflammatory mediators (i.e., prostaglandin E2, reactive nitrogen mediators, IL-6, and TNF-α). In addition, thermal injury increases the production of these mediators by macrophages (98). TNF-α is partly responsible for inducing apoptosis in various cellular elements. TNF-α plays a significant role in the induction of apoptosis across a range of cellular components. Additionally, there is an upregulation of proapoptotic factors, including Bax, Bcl-xl, and caspase-3. Furthermore, epidermal burn injuries frequently lead to considerable apoptosis in organ cells, potentially instigated by a pronounced systemic inflammatory response resulting from the burn. TNF-α also enhances antimicrobial defense mechanisms by activating neutrophils and monocytes while promoting the release of other proinflammatory mediators such as IL-1 and IL-6 (99).

However, of these pro-inflammatory cytokines, only IL-6 has been shown to increase consistently after burn (13). VEGF is a 45 kDa heterodimeric protein and a potent positive regulator of angiogenesis that stimulates endothelial cell functions required for the formation of new blood vessels, such as proliferation, migration, differentiation, and survival (100, 101). VEGF, which is normally expressed at low levels by epidermal keratinocytes, is upregulated in these cells in damaged skin (102). Studies on human wounds and animal models have shown that VEGF is produced by keratinocytes in the early stages of wound healing, but more recent evidence shows that keratinocytes also produce VEGF in the later stages of healing (103).

Active fibroblasts, mast cells, and macrophages also express VEGF in damaged skin. The use of 1% silver sulfadiazine (SSD) ointment (from the group of sulfonamides), which has a wide range of antimicrobial properties, is common in most burn centers (104). However, due to the toxic effects of SSD ointment on the regeneration of keratinocytes and sticking to the surface of wounds during bandaging, the healing process is delayed (105, 106). Among other side effects of this drug, we can mention the increase in bacterial resistance (107). electrolyte imbalance, skin necrosis, erythema multiforme, skin discoloration, and leukopenia. Considering these conditions, it is very important to find a drug with minimum side effects for the treatment of burn injuries (108).

Medicinal plants as appropriate therapeutic/adjunctive agents for burn wounds, have better potential in burn

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wound healing with various mechanisms such as modulating TNF-alpha, inflammatory cytokines, nitric oxide, ROS, and secretion of inflammatory mediators (109). Swalin ointment, which has a plant base, is a combination of four plant oils, including 60% sesame oil (S. indicum), 20% wild pistachio oil (Pistacia Atlantica), 12% hemp oil (Cannabis sativa), and 8% walnut oil (Juglans regia) (110). Sesame oil is abundant in linoleic and linolenic acids, along with various biologically active compounds, including lignans, natural vitamin E, and phytosterols (111). The predominant unsaturated fatty acids found in sesame oil are linoleic acid, constituting 46.9%, and oleic acid, making up 37.4%. These fatty acids are classified as essential, as they cannot be produced endogenously and must be acquired through dietary sources (112). Additionally, hemp is a significant source of flavonols, specifically kaempferol and quercetin (113). CBD oil is characterized by its diverse composition, which includes a variety of fatty acids, proteins, amino acids, vitamins A, C, and E, beta-carotene, and an array of minerals, particularly phosphorus, potassium, magnesium, sulfur, and calcium. Due to the presence of unsaturated fatty acids, CBD oil accelerates wound healing and reduces inflammation and can be used as a treatment for skin lesions (114).

Gopalakrishnan et al. (2016) showed that quercetin accelerates wound healing in mice by modulating inflammatory and anti-inflammatory cytokines, angiogenesis growth factors, and antioxidant systems, which may be responsible for effective cell proliferation and increased collagen deposition (115). P. Atlantica oil contains saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids (PUFAs) (116). Linoleic acid is an essential fatty acid (EFA) of 18 carbons that cannot be synthesized by humans and gives rise to arachidonic acid (a 20-carbon acid) through an unsaturated process. Arachidonic acid is the precursor of prostaglandins, leukotrienes, thromboxanes, and lipoxins, which mediates platelet function and also inflammatory, vascular, motor, and sensory processes. It has also been shown that linoleic acid participates in cell proliferation and the inflammatory process, whereas the latter has a mediating role in leukocyte function, which stimulates chemotaxis and neutrophils (117).

The study of Shahouzehi et al. (2018) showed that wild pistachio oil significantly increases antioxidant defense, VEGF, and hydroxyproline and decreases MDA levels, which could significantly reduce wound size compared to the control group (silver sulfadiazine). P. atlantica also significantly increased SOD, GPX, TAS, and hydroxyproline compared to sulfadiazine (118). Eleine et al. (2018) conducted a study examining the impact of palmitoleic acid on various phases of the wound healing process. Their findings indicated that palmitoleic acid significantly enhances the rate of wound closure. Additionally, the application of palmitoleic acid to wounds resulted in smaller lesions compared to those in the control group. The observed anti-inflammatory properties of palmitoleic acid are likely to contribute to its efficacy in wound healing, particularly during the granulation and regeneration phases. The compound was found to influence the levels of TNF-α, IL-1β, IL-6, and VEGF-α at the wound site at multiple time points: 24, 48, 120, 216, and 288 hours post-injury. Evaluations of neutrophil migration and exudate production revealed that palmitoleic acid exhibits significant anti-inflammatory effects and effectively inhibits LPS-induced neutrophil migration. The study concluded that palmitoleic acid promotes wound healing primarily through its anti-inflammatory action (119).

Considering the importance of the angiogenic factors and modulation of inflammatory mediators in patients with deep second-degree burns and the limited evidence related to this issue, this study aimed to investigate the effect of herbal bioactive compounds on the angiogenic factors and modulation of inflammatory mediators in the patients with the deep second-degree burn.

Methods

Study design

This investigation is a single-blinded, randomized, controlled trial designed to explore the effect of herbal bioactive compounds on the angiogenic factors and modulation of inflammatory mediators in patients with deep second-degree burns. The study adhered to Consolidated Standards of Reporting Trials (CONSORT) criteria (120) (Figure 1). This research was conducted in Motahari Hospital, affiliated with Iran University of Medical Sciences.

Ethics consideration

The study received approval from the ethics committee at Iran University of Medical Sciences (IR.IUMS.FMD.REC.1401.373) and was registered in the Iranian Registry of Clinical Trials Database (IRCT20220702055349N1). Prior to participation, all participants provided informed consent after receiving a detailed explanation of the study's objectives. Participants were also made aware of their right to withdraw from the study at any time. In this research, the participants were independent in responding. In addition, sampling was done for each participant separately and in a private room with the presence of the researcher.

Participants

Patients aged 15-45 years old with deep 2nd-degree burns were confirmed by a plastic surgeon. Inclusion criteria were as follows: Age of 15-45, having a deep 2nd-degree burn wound covering 1 to 10% of the organ, no diabetes, no history of autoimmune diseases, no history of immune system deficiency, no history of hospitalization in the psychiatric department, and no history of any types of burns. The exclusion criteria included the presence of an infected wound, using any type of substance other than drinking water on the wound before entering the study, untreated active infection in different parts of the body, diabetes, high blood pressure, and also pregnant and lactating women. Each patient could withdraw from the study at any time they wanted. The patients were also excluded from the study in case of serious side effects, such as allergy to the ingredients of the ointment or other systemic diseases, and when there was the need to use antibiotics or immunosuppressive drugs. Intention to treat analysis was done for all samples. This study

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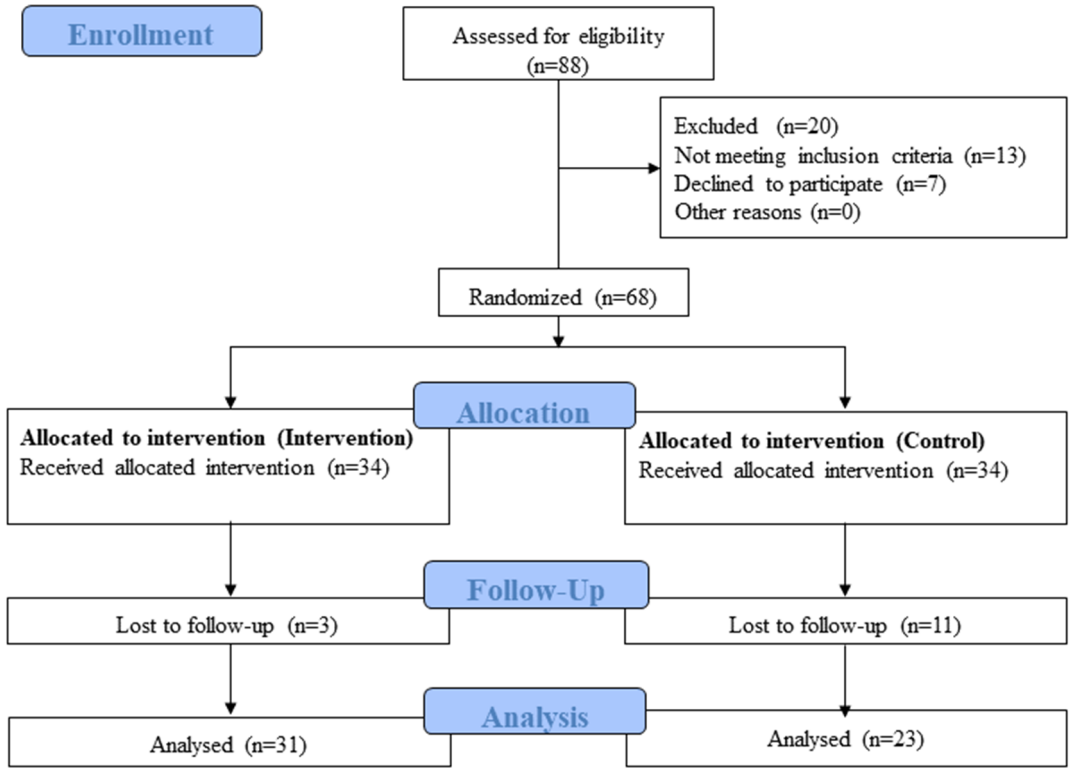

Figure 1. Flow diagram of participants

was conducted by Good Clinical Practice (GCP) guidelines.

Sample size

The determination of the sample size for this investigation was conducted utilizing G-Power software version 3.1. Given the primary objective of this study, which involved comparing the mean dialysis adequacy between two distinct groups, an independent samples t-test was employed. The significance threshold (α) was established at 0.05, while the statistical power (1-β) was set at 0.8, and the effect size (f) was derived from the research conducted by Mehrabani et al. (2016), with a value of 0.7 (110). Consequently, the calculated sample size was 34 individuals for each group, resulting in a total of 68 participants across both groups.

t tests - Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	0.7
	α err prob	=	0.05
	Power (1-β err prob)	=	0.8
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	2.8861739
	Critical t	=	1.9965644
	Df	=	66
	Sample size group 1	=	34
	Sample size group 2	=	34
	Total sample size	=	68
	Actual power	=	0.8116461

Randomization

The patients who fulfilled the specified criteria were allocated into two distinct groups. This allocation was carried out using block randomization, with block sizes of 4 and 6. An online randomization service provided by Sealed Envelope Ltd. in 2019 was utilized to generate the randomization list.

Blinding

This clinical trial had a single-blinded design as the bandages, smeared with swalin ointment or SSD, was prescribed by the nurse on the burn area (patients were unaware of the intervention). It was not possible to perform a double-blinded trial due to the difference in color and smell between swalin and SSD.

Grouping and intervention

Using a blind random method, the patients were divided into two groups of 34 people, and clinical evaluations, histopathological studies, and laboratory molecular tests were performed for them. In the study, there were two types of interventions, so to control the blindness of the trial, ointments were prescribed in the same amount (every other day). The study groups included: 1- patients who received SSD 1% ointment (Soban Daru Company, Tehran, Iran), every other day for 28 days as a control group. 2- patients who received Swalin ointment (Novin Andishan Parsian

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Kavir Karmania Company, Kerman, Iran) every other day as the intervention group.

First, the degree of the burn and then its percentage was determined by an experienced doctor, based on Wallace's rule of nines. Then the basic procedures, including washing with normal saline and drying with sterile gas, were performed. The aims of the research were explained to the patients, and written consent was obtained for participation. In addition, they were allowed to leave the study at any time. Then, the indicators of age, type of burn injury, percentage of burn, burned organs, size of the wound, and drug sensitivity were initially recorded by the researcher based on the patients' statements and visual examinations. The intervention continued until the burn wound was completely healed. Complete epithelialization, defined as the shedding of a crust without a fresh underlying scar, was determined as an indicator of healing by the attending physician.

After explaining the research procedure to the patients, a thin layer of Swalin or SSD (3 mm) was applied to the burn wounds based on the randomization of the patients, and the wounds were covered with sterile gauze and ordinary bandages. In addition, the process of wound care, bandaging, and diet were taught to the patients based on the department's routine. Patients had to go to the hospital every other day to change the bandage, receive examinations during the recovery, and evaluate possible complications during the treatment. Digital images of the burn wounds were checked every time before changing the bandage.

Preparation of Swalin ointment and performing GC-MS technique

This herbal ointment is a combination of four plant oils with proportions of 60% sesame oil (S. indicum), 20% wild pistachio oil (P. atlantica), 12% hemp oil (C. sativa), and 8% walnut oil (J. regia). Sesame, wild pistachio, hemp, and walnut oils were obtained by pressing 3 kg of these compounds in a cold press machine (PR500, Germany). One of the analytical methods for identifying fatty acids in plant and synthetic compounds is the gas chromatography-mass spectrometry (GC-MS) technique (121). The active substances of compounds in the GC-MS technique are in the form of distinct peaks (122). In this study, the compounds of sesame, hemp, wild pistachio, and walnut oils used for the production of Swalin ointment were analyzed using the HS-SMPE/GC-MS method. Briefly, 0.1 to 0.5 mL of these oils were poured in a 15cc falcon, and 2 mL of M methanolic potash was added. After adding 1 mL of sodium sulfate, 5 mL of the supernatant was transferred to the GC system. GC-MS analysis was performed using an Agilent 7890B gas chromatograph coupled to a 5977B mass spectrometer (Santa Clara, California, USA) with an ion source temperature of 250 °C, ionization energy of 70 eV, and a scanning mass range of 35-350 aum (123, 124).

Assessment of tissue levels of VEGF, FGF, and PDGF

On the 14th day, in all study groups, a skin sample was taken and sent to the laboratory. For the ELISA method, the samples were homogenized by an Ultrasonic Processor (Hielscher, UP200H) in a cold phosphate buffer solution (PBS, pH = 7.4) and then centrifuged at 4°C and 15000 rpm for 15 minutes. 50 µL of sample was added to 50 µL of dilution buffer. VEGF standard solution was prepared in two tubes 1 hour before the experiment. The biotinylated anti-VEGF antibody solution was prepared before the experiment in a way that in each well, 0.1 ml of solution was diluted with antibody dilution buffer)1:100(and mixed thoroughly. ABC and TMB (TMB color-developing agent) solutions were kept at 37°C for 30 minutes before use. During dilution, samples and reagents were thoroughly and uniformly mixed. The strips were closed with a special cover and incubated for 90 minutes at 37°C. 0.1 ml of biotinylated anti-VEGF antibody solution was added to each well, and the strips were incubated for 60 min at 37°C. Next, 90 µL of TMB staining agent was added to each well, and the strips were incubated at 37°C in the dark for 30 minutes. Then, 0.1 ml of TMB stop solution was added to each well, which led to a change in the color of the samples from blue to yellow. Finally, the optical density of the samples was measured at 450 nm. The same steps were performed for FGF and PDGF.

Assessment of serum levels of TNF-α and IL-6

On the 3rd, 7th, and 14th days, a blood sample was taken to evaluate the serum level of these factors. The Zellbio kit (cat no: ZB-0090-H9648, made in Germany) was used to measure IL-6. First, the standard vial was microfuged so that the lyophilized powder was deposited at the bottom of the container. Then 220 µL of distilled water was added to reach a final concentration of 200 ng/mL. It was allowed to dissolve slowly at room temperature for 30 minutes and was shaken well before dilution. An assay buffer was needed to make the initial dilutions from the standard stock and to dilute and prepare the working solution of biotin and streptavidin-HRP.

Therefore, the necessary amount of this buffer was prepared (20X buffer: to make 4 ml of it, 200 µL of the stock was added to 3800 µL of distilled water). Also, to make 1:100 conjugated biotin, 10µl of conjugated biotin was added to 990µl of assay buffer, and to make 1:100 streptavidin-HRP, 10µl of streptavidin-HRP was added to 990µl of assay buffer. Then, 100µl of diluted standards and 100µl of HRP was added to the wells and incubated at 25°C for 60 minutes. Next, 100µl of TMB substrate was added to the wells and incubated at 25°C for 10 minutes. After adding 100µl of Stop solution into the wells, the absorption of samples was measured at 450 nm using an ELISA reader.

Outcomes

The primary outcome of this study was to evaluate the angiogenic factors (VEGF), growth factors (FGF and PDGF), and serum levels of inflammatory factors (TNF-α and IL-6) in the two groups of swalin ointment and SSD. In addition, the secondary outcome of this research was to compare the angiogenic factors (VEGF), growth factors (FGF and PDGF), and serum levels of inflammatory factors (TNF-α and IL-6) in the two groups of Swalin ointment and SSD. The safety outcome of this study was to compare the function of immune cells in participants in the two groups of Swalin ointment and SSD.

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Data analysis

Statistical evaluations were performed using SPSS 20 software (SPSS Statistics for Windows, IBM Corp., Armonk, NY, United States). Quantitative data were reported using mean (standard deviation) and qualitative data using frequency (percentage). In this research, the missing data did not exist. Student t-test was used to compare the mean in 2 groups, depending on the type of normal/abnormal distribution. The chi-square test was also used to check the relationship between qualitative variables. As the data was normally distributed, repeated measures analysis of variance was used to compare the mean rate of wound closure in two treatment groups through five subsequent measurement time points. Mauchly's test was used to evaluate the sphericity of the dependent variable (wound closure rate), and Bonferroni's test was used for paired comparisons. GraphPad Prism software (GraphPad Software, version 9) was used for graphs and graphic analysis.

Results

Participants

As presented in Figure 1, 54 burn patients participated in this study and were assigned to two intervention (Swalin) (n=31) and control (SSD) (n=23) groups. The average age in the SSD group was 33/83 ± 10/17, and in the Swalin group was 30/68 ± 8/25 years. The most common causes of burns in the SSD group were flame (56.5%), scald (34.8%), and contact (8.7%). However, in the SW group, the causes were flame (51.6%), contact (32.3%), and scald (16.1%). The upper limb was the most common burn site in both the SSD group (73.9%) and the SW group (64.5%). No notable differences were detected in the demographic and clinical characteristics between the two groups (Table 1).

Ointment contents and GC technique

The most important contents in swalin ointment were Linoleic acid (41.37%), Elaidic acid (37.45%), and Palmitic acid (9.45%). The rest included Lauric acid, Myristic acid, Myristoleic acid, Palmitoleic acid, Stearic acid, Linolenic acid, Arachidic acid, Gadoleic acid, Behenic acid, and Lignoceric acid.

Tissue levels of VEGF, FGF, and PDGF

The tissue level of all three factors in day 14 was higher in the Swalin group compared to the SSD group. Statistical analysis with the Mann-Whitney test showed that the tissue level of VEGF, FGF, and PDGF on day 14 had a statistically significant difference between the two groups (P<0.001) (Figure 2 and Table 2).

Serum levels of inflammatory factors: TNF-α and IL-6

The serum levels of IL-6 and TNF-α in both groups increased until day 7, but gradually decreased on day 14, which was significant in the Swalin group (Table 2). The Mauchly test indicated that the assumption of sphericity was contravened for IL-6 (P=0.085), so the degrees of freedom were corrected using the Greenhouse-Geisser estimate of sphericity (ε<0.7). The results show that the IL-6 serum level was significant in the Swalin group (P<0.001) (Figure 3 and Table 3). Mauchly's test indicated that the assumption of sphericity was contravened for TNF-α (P=0.008), so the degrees of freedom were corrected using the Greenhouse-Geisser estimate of sphericity (ε<0.7). The results show that the serum level of TNF-α was significant in the Swalin group (P<0.001) (Figure 4 and Table 3).

Table 1. Characteristics of the participants (N=54)

Variable	Total (N=54)	Groups		*P*-value
		SSD (Mean±SD) (N=23)	Swalin (Mean±SD) (N=31)	
Age	32.25 (SD=9.21)	33.83 ± 10.17	30.68 ± 8.25	0.443
Sex				
Male	35 (64.8)	13 (56.5)	22 (70.9)	0.740
Female	19 (35.2)	10 (43.5)	9 (29.1)	
Burn cause				
Flame	29 (53.7)	13 (56.5)	16 (51.6)	0.873
Contact	12 (22.2)	2 (8.7)	10 (32.3)	
Scald	13 (24.1)	8 (34.8)	5 (16.1)	

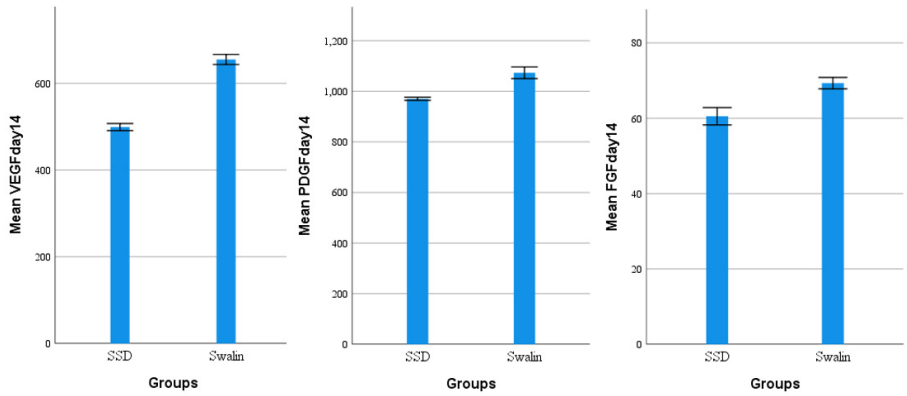

Figure 2. Comparison of the mean tissue level of VEGF, FGF, and PDGF on day 14, in the two study groups

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Table 2. Serum levels of IL-6, TNF-α, VEGF, FGF, and PDGF in the two study groups

Study groups Day/Variable		SSD (Mean±SD)	Swalin (Mean±SD)
3	IL-6 (ng/mL)	196.93±5.01	142.48±5.61
	TNF-α (ng/mL)	310.86±6.51	396±10.95
7	IL-6 (ng/mL)	239.21±5.8	182.3±3.52
	TNF-α (ng/mL)	218.04±7.21	260.96±13.80
14	IL-6 (ng/mL)	132.79±13.84	52.74±5.91
	TNF-α (ng/mL)	159.79±10.37	111.91±19.40
	VEGF (pg/ml)	499±18.75	654.87±31.51
	FGF (pg/ml)	60.52±5.33	69.32±4.11
	PDGF (pg/ml)	970.22±14.25	1073.23±62.79

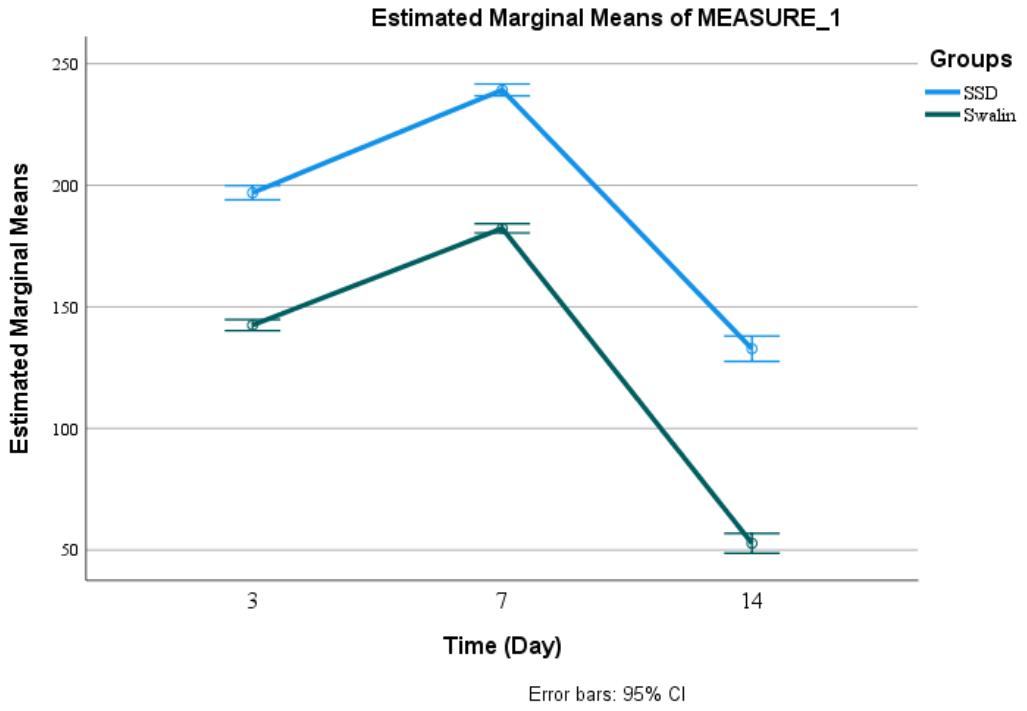

Figure 3. Comparison of the mean IL-6 serum levels in SSD and Swalin, at three time points of day 3, 7, and 14

Table 3. Within-subjects and between-subjects analysis of the effectiveness of Swalin on the level of inflammatory factors

Variable	Analysis	F(df)	*P*-value	Partial eta
IL-6	Within-subjects	36.17** (1.76, 61.69)	<0.001*	0.508
	Between-subjects	2277.09 (1, 35)	<0.001	0.985
TNF-α	Within-subjects	225.47** (1.6, 56.21)	<0.001*	0.866
	Between-subjects	123.89 (1, 35)	<0.001	0.780

The results of fibroblast, angiogenesis, collagen deposition, and immune cells

The results of the Mann-Whitney test showed that there was a statistically significant difference between the two groups in terms of fibroblast density (P=0.020) (ε=0.332). The levels of angiogenesis and collagen deposition in the Swalin ointment group exhibited a significant difference compared to the SSD group, with P-values of 0.008 and 0.007, respectively. However, no statistically significant difference was noted regarding the quantity of immune cells, as indicated by a P-value greater than 0.050 (Table 4).

Discussion

The primary components of Swalin ointment include Linoleic acid (41.37%), Elaidic acid (37.45%), and Palmitic acid (9.45%). On day 14, the levels of VEGF, FGF, and PDGF in tissue were significantly elevated in the Swalin group compared to the SSD group (P<0.001). Both groups exhibited an increase in serum levels of IL-6 and TNF-α up to day 7, followed by a notable decline by day 14, particularly in the Swalin group. The reduction in IL-6 serum levels in the Swalin group was statistically significant (F(1.76, 61.69)=36.17, P<0.0001), as was the decrease in TNF-α serum levels (F(1.60, 56.21)=225.47, P<0.0001).

Wound healing is a complex process characterized by a

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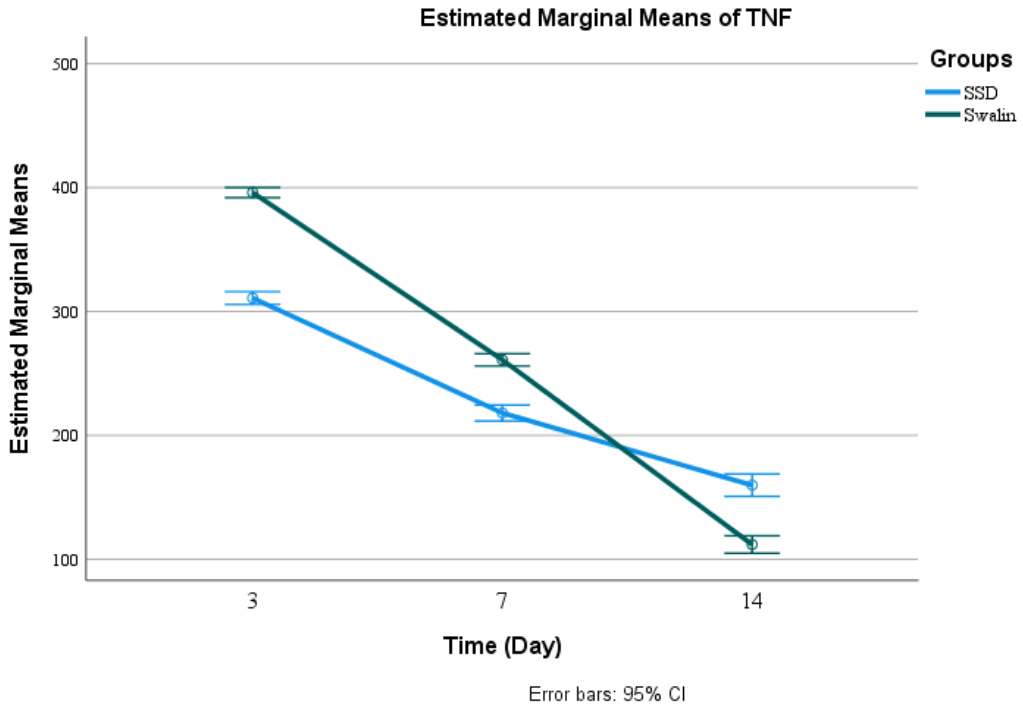

Figure 4. Comparison of the mean serum levels of TNF-α in SSD and Swalin, at three time points of day 3, 7, and 14.

Table 4. The density of fibroblast cells, the number of neutrophil cells, and the amount of collagen deposition and angiogenesis in the two groups of Swalin ointment and SSD.

Variable	Groups		*P*-value
	SSD	Swalin	
Fibroblast cell density (%)			
Mild	30.4%	19.9%	>0.050
Moderate	43.5%	48.4%	>0.050
Marked	17.4%	38.7%	0.020
Angiogenesis (mean±SD)	10.22±1.59	11.68±1.88	0.008
Collagen deposition (mean±SD)	10.78±1.56	12.32±1.93	0.007
Neutrophil cells (mean±SD)	10.22±1.27	11.03±1.44	>0.050

series of intrinsic and coordinated events, which involve interactions among various cell types, including neutrophils, macrophages, endothelial cells, fibroblasts, and keratinocytes. This process is mediated by the release of various substances, such as cytokines (including IL-1β and TNF-α), cytokine-induced neutrophil chemoattractants, reactive oxygen species (ROS), and vascular endothelial growth factors (VEGFs). Most treatment strategies aim to preserve the integrity of the skin barrier and manage infection. Consequently, a variety of bandages containing different compounds, such as silver, growth factors, or fatty acids, have been developed. Silver has historically been utilized for its antibacterial properties; however, some studies indicate that it may exert cytotoxic effects on various cell types, potentially hindering the wound-healing process (125). Tumor necrosis factor-alpha (TNF-α) is a cytokine that promotes inflammation by stimulating the activity of monocytes, macrophages, and natural killer (NK) cells. Additionally, it facilitates vasodilation through the enhancement of nitric oxide synthesis, promotes the chemotactic movement of neutrophils, and triggers both prothrombotic and fibrinolytic mechanisms (6). Serum level of TNF-α is increased post-burn, with higher levels in patients with sepsis (126, 127). The decrease in serum TNF-α levels is associated with improved survival rate in patients with sepsis and has potential prognostic value (128). IL-6 is a multifunctional cytokine that plays a significant role in various immune processes. Its functions encompass the regulation of the acute phase response, the initiation of fever, the enhancement of stress hormone synthesis, the promotion of hematopoiesis, and the maturation and activation of immune cells (129, 130). Higher levels of IL-6 are observed in burn patients with sepsis (131). IL-6 has been identified as a potential prognostic marker for mortality in burn patients and is correlated with burn size (132).

In the hemostasis phase, the coagulation cascade is promptly triggered following an injury, resulting in the formation of a temporary matrix at the wound site. The subsequent inflammation phase encompasses an innate immune response that plays a vital role in the removal of pathogen debris from the injury area. Polymorphonuclear neutrophils (PMNs) are responsible for releasing reactive oxygen spe-

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cies (ROS) and nitric oxide while also facilitating and initiating the process of phagocytosis. Furthermore, PMNs produce significant quantities of PMN collagenase, elastase, and matrix metalloproteinases (MMPs), which are instrumental in the degradation of damaged cells and the extracellular matrix (133). At the molecular level, the inflammatory response engages in a multitude of intricate repair mechanisms that are linked to the innate immune response, skin differentiation, and the restoration of the skin barrier. The process begins with the activation of keratinocytes and various innate immune cells, including leukocytes (such as polymorphonuclear neutrophils, macrophages, and lymphocytes), mast cells, and dendritic cells. The release of cytokines, including IL-1α, TNF-α, and IL-6, promotes chemotaxis, thereby drawing immune cells to the area of injury.

ROS are generated by activated keratinocytes and various immune cells. In addition, immune cells release elastase and proteinase. The inflammatory microenvironment plays a crucial role in facilitating tissue repair and managing infections. Nonetheless, the presence of chemokines can lead to detrimental effects on the skin tissue surrounding the site of inflammation. Consequently, the intensity of the inflammatory response and the rate of tissue repair are critical factors in safeguarding healthy skin from potential damage (134). Fatty acids serve as potent pro-angiogenic agents, encompassing eicosanoids that influence the proliferation, migration, and capillary development of vascular endothelial cells. Compounds such as oleic acid, cholesterol, and linoleic acid may function as key molecular regulators of angiogenesis, modulating the balance between stimulatory and inhibitory signals that govern the vascular microenvironment. Specifically, oleic acid promotes cellular proliferation, the secretion of MMP-9, as well as migration and invasion (135).

Inflammation represents the second stage of the wound-healing process and is characterized by a typical sequence of cellular infiltration that occurs post-injury. Within the initial hours following the injury, polymorphonuclear leukocytes (PMNs)—which encompass various types of white blood cells such as basophils, eosinophils, and neutrophils—migrate into the wound site. This infiltration persists for a duration of up to one week (136). These cells generate significant quantities of reactive oxygen species and play a crucial role in the clearance of necrotic tissue and pathogens within the wound environment. The migration of polymorphonuclear leukocytes (PMNs) into the wound is succeeded by the infiltration of macrophages within a timeframe of 1 to 2 days. Macrophages, along with Langerhans cells and dendritic cells residing in the epidermis, function as antigen-presenting cells that facilitate the presentation of antigens to T cells, thereby initiating an immune response. Additionally, macrophages are instrumental in the synthesis of nitric oxide (NO) and the regulation of various processes, including collagen synthesis, angiogenesis, and the production of chemokines and cytokines such as prostaglandin E2 (PGE2) and transforming growth factor-beta (TGF-β), which are essential for promoting cell proliferation and migration (137). Finally, macrophages are essential for the formation of new tissue in the wound area and transition to the cell proliferation phase.

Angiogenesis, defined as the development of new blood vessels from existing ones, represents a critical feature of the proliferative phase in the wound healing process. This phenomenon results in a temporary surge in the vascular network at the injury site. The provision of oxygen and essential nutrients through these newly formed vessels plays a vital role in tissue repair, and impairments in angiogenesis are frequently linked to prolonged wound healing. Various growth factors, cytokines, and lipid mediators released in response to tissue injury can promote angiogenesis. Among these, vascular endothelial growth factor (VEGF) is recognized as a key regulator of pre-angiogenic activity. Sufficient concentrations of VEGF are considered crucial for effective wound healing (115). Angiogenesis can be divided into phases of quiescence, activation, and resolution. In healthy tissues, blood vessels are in the quiescence phase. These vessels are covered with endothelial cells called phalanx on the inner surface (138). Cell-cell adhesions between these cells create a barrier that helps maintain the blood flow. Mature vessels have a basement membrane mainly composed of collagen IV and laminin covered by pericytes, which promotes endothelial cell survival and helps maintain vascular stability (139).

When quiescent vessels are exposed to a pro-angiogenic stimulator, endothelial cells begin to loosen their cell-cell adhesions. Furthermore, detachment of pericytes, along with enzymatic degradation of the basement membrane by matrix metalloproteinases (MMPs), provides an environment for the development of a new vascular bud (138). Growth of the new vessel is directed by a single endothelial cell called the tip cell. Tip cells direct vascular growth by sensing gradients of pro-angiogenic mediators, such as VEGF (140). Adjacent endothelial cells convert to stalk cells that proliferate and migrate towards the tip cell, leading to a vessel bud. During the resolution phase, vascular buds fuse with adjacent ones to establish blood flow. Moreover, the non-functional buds regress. Finally, blood vessels return to the quiescent phase, the phalanx cell phenotype is restored, a new basement membrane is formed, and pericytes cover the vessel again (138).

In a mouse model of endotoxin-induced sepsis and burn injury, combined inhibition of IL-6 and the IL-6 receptors increased survival, suggesting the role of IL-6 in sepsis and sepsis-induced death (141, 142). In addition, Zhang et al. showed that IL-6 is involved in cardiac dysfunction due to burn injury and sepsis in mice (143).

A recent meta-analysis showed that IL-6 has a similar diagnostic value to PCT, with relatively high specificity (78%), and low sensitivity (68%). These findings support its potential use as a confirmatory test instead of ruling out the diagnosis of sepsis (144). SSD and silver-based wound bandages have been associated with delayed or incomplete re-epithelialization, discolored scars, limited burn scar penetration, hypersensitivity, neutropenia, and ineffectiveness against some pathogens (145). Additionally, these bandages only work when moistened and are relatively expensive. Although these costs partially decrease because of the need for fewer applications, more prospective randomized controlled trials (RCTs) are needed to determine the optimal wound bandage after burn injury (146, 147).

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Linoleic acid reduces TNF-α and causes angiogenesis through specific mediators, including angiopoietin-2 (ANGPT-2), and VEGF (148). In the proliferative stage of wound healing, the number of fibroblasts decreases due to differentiation into myofibroblasts, and the tissue is prepared for remodeling with the help of apoptosis. The regression of granulation tissue through cell apoptosis is a sign of the remodeling phase, in which the mature wound is seen as avascular and acellular (149). In the hemostatic phase, the primary wound repair begins with the invasion of neutrophils, macrophages, and lymphocytes as the source of inflammatory and growth-stimulating cytokines, which causes fibroblasts to migrate and proliferate. Fibroblasts synthesize extracellular matrix components and participate in the formation of granulation tissue. This migration and proliferation must be sufficient and specific so that the natural process of repair occurs (86, 150-152). Therefore, a rapid increase in cell proliferation occurs when the apoptosis is controlled. As the inflammatory process shuts down, cell density is significantly reduced through increased apoptosis as a result of wound closure and scar development (152, 153).

When the granulation tissue is not removed due to the lack of apoptosis or disruption in the apoptotic pathway, tissue repair is abnormal, and a hypertrophic scar or keloid is formed (154). Studies show that the regression of granulation tissue in the proliferative phase is mainly due to increased apoptosis in granulation tissue cells, in which bFGF plays an important role (155). Research has shown that fatty acid deficiency causes impaired wound healing (156, 157). Linoleic acid, as the main fatty acid in the epidermis, has important functions such as maintaining the impenetrability of the stratum corneum, forming and differentiating the stratum corneum, forming and differentiating lamellar bodies, enhancing wound healing, and inducing angiogenesis (62). Successful wound healing is a complex process that requires the interaction of multiple cell types, cytokines, growth factors, and extracellular matrix (ECM)components. During wound healing, several cellular signals are present, including AKT/mTOR (158). Wnt and Notch (159). Mitogen-activated protein kinase (MAPK) (160) and TGF-β (161). are activated in a coordinated cascade. Several cytokines and growth factors are also involved in wound healing, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL- 8), interleukin-10 (IL-10), transforming growth factor(TGF), vascular endothelial growth factor(VEGF), epidermal growth factor(EGF), and platelet-derived growth factor (151, 162, 163). In brief, wound healing is a dynamic and highly regulated process, divided into four main stages: 1- vascular response (coagulation and hemostasis). 2- cellular response (inflammation). 3- proliferation. 4- remodeling. The stages overlap in time and duration (134). The third phase, the proliferative phase, is divided into three sub-phases including a) re-epithelialization. b) angiogenesis. c) formation of granulation tissue. 3 to 10 days after the wound creation, in the proliferation stage, the main focus is on covering the wound surface, the formation of granulation tissue, and the repair of the vascular network. Simultaneously with the migration of local fibroblasts along the fibrin network and the beginning of re-epithelialization from the corners of the wound, angiogenesis is activated by the new capillary buds (134, 164). During wound healing, fibroblasts migrate and proliferate and are involved in several key processes, such as breaking down the fibrin clots, creating a new extracellular matrix (ECM), and maintaining collagen structure, leading to effective wound healing.

Limitations

Among the problems, we can point out the lack of on-time funding, the high cost of diagnostic kits, the delay in transferring from abroad, and the low probability of patient cooperation. In some cases, the patients refused to continue cooperation for personal reasons (according to the principle of written informed consent, there was no compulsion to continue the study), while the ointment was prepared for them, which caused a waste of financial resources.

Implications for clinical practice

Incorporating herbal bioactive compounds in the treatment plan for patients with deep second-degree burns may help to promote wound healing by enhancing angiogenesis and modulating inflammatory mediators. Clinicians should consider the potential benefits of using herbal bioactive compounds alongside conventional treatments for deep second-degree burns to potentially improve patient outcomes. In addition, healthcare providers need to stay informed about the current research on herbal bioactive compounds and their effects on wound healing in order to make evidence-based decisions for patient care. Close monitoring and evaluation of patients receiving herbal bioactive compounds for deep second-degree burns is essential to ensure safety and effectiveness. Also, education of patients on the potential benefits and risks of using herbal bioactive compounds in the treatment of deep second-degree burns is crucial for informed decision-making and compliance with the treatment plan.

Recommendations for Future Research

Further research is needed to investigate the specific mechanisms by which herbal bioactive compounds promote angiogenesis and modulate inflammatory mediators in patients with deep second-degree burns. Studies should explore the optimal dosage, formulation, and duration of treatment with herbal bioactive compounds to maximize their therapeutic effects on wound healing in patients with deep second-degree burns. In addition, comparative studies comparing the efficacy of different types of herbal bioactive compounds in promoting angiogenesis and modulating inflammatory mediators in patients with deep second-degree burns are warranted. Also, long-term follow-up studies are needed to assess the safety and long-term outcomes of using herbal bioactive compounds in the treatment of deep second-degree burns.

Conclusion

The present study showed that Swalin ointment, due to

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the presence of a wide range of fatty acids, especially linoleic acid, leads to the modulation of systemic tissue inflammation. The ingredients of the ointment, especially hemp and sesame oil, increase the tissue level of angiogenic factors and accelerate remodeling and wound healing. Therefore, the effects of herbal bioactive compounds on angiogenic factors and inflammatory mediators in patients with deep second-degree burns show promising results. The compounds have been shown to enhance angiogenesis, leading to improved wound healing and tissue regeneration. Additionally, these compounds have been found to modulate inflammatory mediators, reducing inflammation and promoting a more controlled and efficient healing response. Further research is needed to better understand the mechanisms of action and optimize the use of herbal bioactive compounds in the treatment of deep second-degree burns.

Authors' Contributions

All authors: idea for the review, study selection, data extraction, interpretation of results, writing of the manuscript. All authors read and approved the final manuscript.

Ethical Considerations

The study was conducted under the oversight of the Ethics Committee at Iran University of Medical Sciences (IR.IUMS.FMD.REC.1401.373) and the Iranian Clinical Trial Registration Center (IRCT20220702055349N1).

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Conflict of Interests

The authors declare that they have no competing interests.

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