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Original Article

Burn Wound Healing Effect of a Sterilized Traditional Formulation of *Boswellia carteri* vs. Silver Sulfadiazine Cream 1% in Patients Presenting Second-degree Burn Wounds: A Randomized, Double-blind Clinical Trial

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What's Known

- Natural compounds such as oleo-gum-resins have been traditionally applied to treat burn wounds.
- The topical application of a cream containing *Boswellia* on excision wounds affected different phases of wound healing, including collagen synthesis and wound contraction, leading to a faster healing process.

What's New

- In the treatment of burn wounds, the healing effect of a 40% *Boswellia carteri* formulation containing 0.72 mg of β-boswellic acid per 100 g was compared to silver sulfadiazine.
- On each day of the study, both healing time and healing indices were statistically comparable between the groups.

Abstract

Background: Burn wounds rank among the most serious healthcare issues. Many studies reported the effectiveness of natural products in the wound-healing process. The present study compared the effects of a standardized herbal formulation derived from *Boswellia carteri* (*B. carteri*) and silver sulfadiazine (SSD) cream 1% on the healing of burn wounds.

Methods: This randomized double-blind clinical trial was conducted at Shiraz Burn Hospital (Shiraz, Iran) between July 2012 to August 2013. A sterilized formulation comprising *B. carteri* 40% was prepared. 54 second-degree burn patients of both sexes with age ranges of 20 to 60 were invited to participate in this double-blind, randomized clinical trial. They were randomly divided into two groups and given either the *Boswellia* formulation or SSD cream. The healing index was determined based on the wound area assessment using the planimetry technique. The Kaplan-Meier survival analysis was used to assess the primary outcome, which was the amount of time until complete healing.

Results: The trial was completed by 17 patients from the SSD group and 15 patients from the *Boswellia* group. During the study period, both groups showed a progressive healing trend. The mean (95% CI) healing time in the SSD group was 10.94 (9.03-12.85) days and 10.73 (9.23-12.23) days in the *Boswellia* group (P=0.71), indicating no significant difference. On the 17th day, the healing index of all patients in the *Boswellia* group reached 1.

Conclusion: *Boswellia* topical formulation had a burn wound healing effect comparable to that of the standard SSD 1% treatment. Based on the findings of this study, the likelihood of contact dermatitis with *Boswellia* should be taken into consideration.

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Keywords ● *Boswellia* ● Burns ● Wound healing ● Clinical trial ● Medicine, traditional

Introduction

Acute thermal injuries requiring medical care and surgical treatment are prevailing and burdensome. Burns cause the loss of around 18 million disability-adjusted life years and more than

250,000 fatalities annually.[1] The prevalence is higher in low-income and developing countries. Children, women, and the elderly are high-risk groups, followed by people with comorbid conditions such as epilepsy, blindness, deafness, and diabetes. Patients with mental and psychiatric disorders or drug abusers are more likely to have self-inflicted burns. Large families, single parents, illiteracy, and unemployment are familial and social risk factors.[2, 3] Unprivileged victims face increased complications and risks of permanent damage due to a lack of access to appropriate management, such as split-thickness skin grafting, fluid and electrolyte repletion, and infection control.[4]

Traditional medical practices offer a wealth of information regarding the prevention, diagnosis, and treatment of illnesses. These holistic therapy modalities, which focus on the overall health of the entire body, are practiced broadly worldwide.[5] Due to their indisputable importance to public healthcare, the World Health Organization (WHO) encourages evidence-based research on the safety, efficacy, and quality of traditional medicines.[6] Moreover, natural products are considered respected choices in drug discovery for research on challenging diseases, such as cancer, pain, and acquired immunodeficiency syndrome (AIDS).[7] Burn injuries have historically caused severe damage to humans due to the inevitable exposure to intense sunlight and fire. Therefore, natural products have long been used to treat burn wounds.[8] The availability of medicinal plants in each region is a key factor in applying them for wound healing. For instance, *Aloe vera* gel, *Carica papaya* products, *Lawsonia inermis* formulations, and coconut oil are a few African folk remedies for burns.[9] Plants that promote the natural skin healing process can be helpful in wound treatment. Because of the complexity of the process, numerous mechanisms are involved during healing. For instance, the flowers of *Achillea* have anti-inflammatory and antibacterial effects. *Camomilla recutita*, as a mild astringent, promotes epithelialization and stimulates granulation tissue formation. *Jasminum auriculatum* leaves boost the tensile strength during the early phases of healing and accelerate mucopolysaccharide accumulation. *Rosmarinus officinalis* promotes granulation tissue regeneration, angiogenesis, and collagen deposition.[10]

Numerous studies indicated that plant exudates such as gum-resins and oleo-gum-resins can heal wounds. *Picea abies* exudate also known as coniferous tree exudate was used to treat complicated surgical wounds.[11] *Pistacia atlantica* resin oil and extracts were shown to considerably reduce wound size.[12] The very valuable oleo-gum-resin of *Boswellia* (family Burseraceae), frankincense or olibanum, is obtained from the bark of the trees during dry seasons and contains 3-9% volatile oil, 60-70% resin, and 27-35% gum.[13] *Boswellia* oleo-gum-resin, which has antimicrobial, antioxidant, anti-inflammatory, and analgesic properties, is widely used for skin disorders, rheumatism, and central nervous system diseases. The topical application of a single-dose cream containing *Boswellia* on excision wounds affects various phases of wound healing, including collagen synthesis and wound contraction. Additionally, this product boosts the tensile strength of the wound, leading to a faster healing process.[14] Traditional Iranian Medicine (TIM) manuscripts mentioned *Boswellia* oleo-gum-resin as a burn wound healing agent.[15] In this study, one traditionally-originated and pharmaceutically-evaluated formulation from *Boswellia carteri* (*B. carteri*) was developed. Then, in a randomized clinical trial, the effectiveness of the sterilized *B. carteri* formulation (BCF) versus silver sulfadiazine (SSD) cream 1% in the treatment of second-degree burns was compared.

Material and Methods

Study Design and Patients

This double-blind, randomized clinical trial was conducted on 54 patients with second-degree burn wounds at Shiraz Burn Hospital, (Shiraz, Iran), from July 2012 to August 2013. Patients of both sexes aged 20 to 60 years old who had second-degree burn wounds of thermal origin affecting up to 5% of total body surface area (TBSA) were invited to take part in the study. Patients with known malignancy, collagen vascular disease, peripheral vascular disease, immunosuppressive disorders, cardiovascular diseases, diabetes mellitus, G6PD deficiency, electrical and respiratory burns, known allergy to the agents used, pregnancy, or breastfeeding were excluded. A further exclusion criterion was taking any medications that interfere with the wound healing process or affect the healing pace such as glucocorticoids, non-steroidal anti-inflammatory drugs, and chemotherapeutic drugs.

Eligible participants were randomly allocated into two groups. One group received SSD cream 1% produced by Sobhan Pharmaceutical Company (Iran), while the other received BCF 40%. The sample size for each group was determined using the means-comparison formula, with the mean healing time in the SSD group being 10±0.9 days. Using the below

formula, and also considering α=0.05 and β=0.90, a sample size of 15 was calculated for each group.[16] Blocked randomization with a block size of two was applied. Time until complete healing was considered the primary outcome in the statistical analysis.

$$n_1 = n_2 = \frac{(S_1^2 + S_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (CT-90-5981) and also was registered in the Iranian Registry of Clinical Trials (IRCT201208041605N14). The participants were informed about the goals of the research as well as the whole process of the study. Written informed consent was obtained from the patients before participation. The study was carried out in agreement with the principles of the Helsinki Declaration and Iranian research ethical codes.

Preparation of Sterilized B. carteri Formulation

The oleo-gum-resin of *B. carteri* Birdw. was purchased from a local market in Shiraz (Iran). The samples were authenticated and deposited in the herbarium of the Phytopharmaceutical Department of the School of Pharmacy, Shiraz University of Medical Sciences (Shiraz, Iran) under voucher number PM400-5. This medicinal herb was chosen for research based on its market availability, safety, affordable price, and potential for a novel formulation that has not yet been reported. The sample was subjected to quality control tests. According to Food and Drug Administration regulations, any topical medication used to treat burns, wounds, and chronic ulcers must be sterile to avoid introducing exogenous microorganisms.[17] The oleo-gum-resin of *B. carteri* was frozen (-20 °C) for two hours before being powdered in an electric grinder and packaged in double-wrapped plastic bags for gamma sterilization. Based on the initial microbial count, radiation dosimetry was conducted. To prevent any interference with radiation-induced paramagnetic effects, packages were stored at room temperature in darkness for at least 72 hours after radiation (irradiator: 60 Co). We used gas chromatography-mass spectrometry to analyze the essential oils before and after irradiation and then compared the chromatograms to determine the effect of sterilization on the active components.[18] For aseptic preparation, the ingredients of the traditional medicine-based formulation (*B. carteri* oleo-gum-resin 40% in an oily duck fat base) were sterilized along with all devices and instruments using approved techniques and methods.[19]

Standardization of B. carteri Formulation

High-performance liquid chromatography (HPLC) analysis of the formulation was performed by a Cecil (CE 4900) instrument (UK) equipped with an ultraviolet detector set at 210 nm and a C18 Eurospher column (250*4.6 mm, 5 µm) and a C18 Eurospher guard column (40*4.6 mm, 5 µm).[20] The flow rate of the mobile phase (methanol) was 0.8 mL/min. The solvents were of analytical grade. The β-boswellic acid content of the formulation was quantified against standard commercial β-boswellic acid (Sigma-Aldrich, USA). We performed co-chromatography, compared the retention times of the compounds, and used the co-injection method to differentiate the peak of β-boswellic acid.

Burn Care and Assessments

After admission and primary preparation, wounds were washed with normal saline and dried using sterile gauze. Before providing any treatment, an expert emergency burn physician evaluated the general condition of the lesions. According to the related random code for each patient, wounds were covered either with SSD or BCF. Before application, the treatments were coded and packaged in identical containers, and each patient received individualized care.

The dressing was changed every two days until the wound was epithelialized completely. The same expert physician monitored the healing process for all patients. In the case of any drug reaction, the patient was removed from the trial and was given the required conventional care.

A nurse took photographs of the wounds every two days, and the files were coded. For further calibration of the images, a length scale was used. Both formulations were packaged similarly and coded to identify them. The margins of the wound were marked by a surgeon who was not informed of the patient's treatment groups. After digitally scanning the tracings with Sigma Scan Pro 5 software (Systat Software Inc., California), the planimetry technique was used to calculate the wound area.[21] The wound healing index, defined as $(A_{wo} - A_{wn})/A_{wo}*100\%$, was used to calculate the healing rate, where A_{wo} is the initial wound area, and A_{wn} is the wound area on the n^{th} day.[22]

Statistical Analysis

Data were analyzed using SPSS 22.0 (SPSS, Chicago, IL), and the continuous data were expressed as Mean±SD, and categorical data were presented as frequency and percentage. Missing values were replaced

via linear interpolation, which used the valid values before and after the missing value to interpolate. The amount of time until complete healing was considered the primary outcome and was evaluated by Kaplan-Meier survival analysis. The log-rank test was used to compare the survival times of the two groups. The independent samples *t* test was used to compare healing indices and the total number of healed patients between the two groups at each time interval. Cox proportional hazards regression was used to calculate the crude and adjusted hazard ratios (HRs) and 95% confidence intervals. In the analysis, age, sex, weight, cause of the burn, and TBSA were all considered potential confounders. Variables that changed the crude HR by more than 10% remained in the multivariable model. For all statistical analyses, P<0.05 was considered statistically significant.

Results

Standardization of B. carteri Formulation

According to the HPLC standardization procedure, each 100 g of the BCF 40% product contained 0.72 mg of β-boswellic acid (figure 1).

Patients' Characteristics

Sixty-one patients were evaluated for eligibility, but seven of them did not meet the inclusion criteria. As a result, 54 patients with second-degree burn wounds participated in this randomized clinical trial (RCT). In total, 26 patients received SSD 1%, whereas 28 patients received BCF 40%. Due to changes in clinical circumstances or a desire to receive another type of treatment such as herbal formulations, eight patients from the SSD group and nine from the BCF group discontinued their treatment. One patient from the SSD group had a resistant infection that did not respond to SSD; thus, he was excluded. Four patients in the BCF group experienced hypersensitivity and had to quit the treatment process. Finally, 17 patients from the SSD group and 15 from the BCF group successfully completed the RCT. The CONSORT flow diagram of the study is shown in figure 2. The baseline characteristics of the patients are presented in table 1. The groups were similar in terms of age (SSD=34.70±13.36 years; BCF=36.20±13.49 years; P=0.75), weight (SSD=67.82±12.17 Kg; BCF=68.80±8.60 Kg; P=0.79), sex (P=0.46), cause of burn (P=0.69), and site of wounds (P=0.05). However, the TBSA burnt for the SSD group was 1.70±0.68%, which was significantly greater than that of the BCF group 1.20±0.41% (P=0.01).

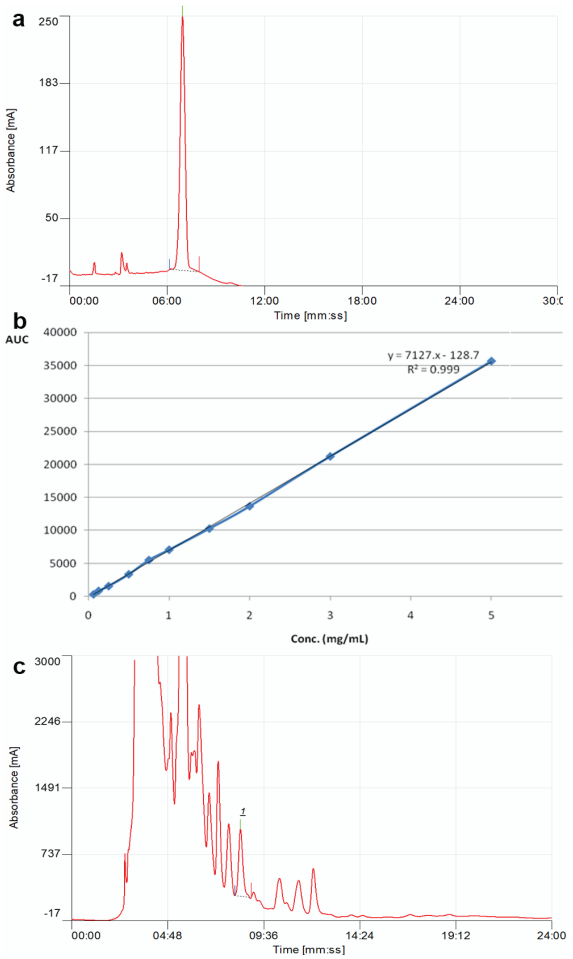

Figure 1: High-performance liquid chromatography (HPLC) chromatogram for the methanolic extract of β-boswellic acid (a); standard curve for β-boswellic acid (b); and HPLC chromatogram for the methanolic extract of *Boswellia carteri* formulation (c) is illustrated.

Wound Healing

In total, 17 patients in the SSD group and 15 patients in the BCF group were included in the final analysis. According to table 2, there was no significant difference between the mean (95% CI) healing times for the SSD group and the BCF group, which were 10.94 (9.03-12.85) days and 10.73 (9.23-12.23) days, respectively (P=0.71). As indicated in table 3, the Cox proportional hazards model revealed no significant difference between BCF and SSD in terms of the healing effect (adjusted hazard ratio=0.9 [95% CI:0.4-1.9]). The healing indices of the patients are compared across the two groups in table 4. The healing index of all patients in the BCF group reached 1 on day 17, but not in the SSD group until day 20. However, the P values revealed no significant differences in healing indices between the groups on any day. Figure 3 demonstrates the trend of healing indices for patients in the two groups. Another variable that was compared in the SSD and BCF groups, was the number of patients who had recovered (figure 4).

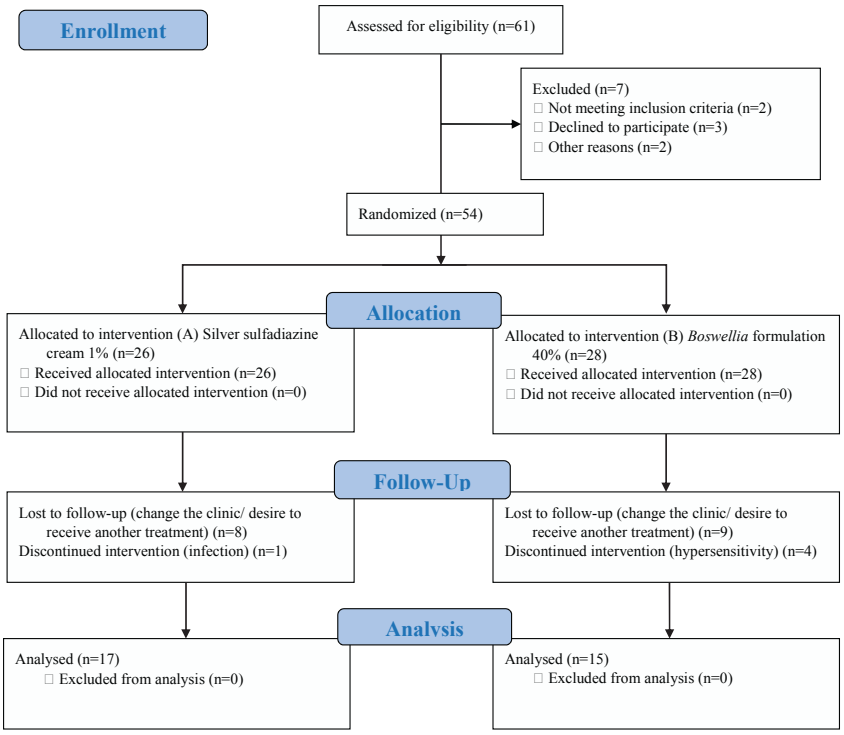

Figure 2: This figure represents the CONSORT flow diagram of the study.

Table 1: Baseline characteristics of patients with second-degree burn wounds that participated in the randomized clinical trial

Variables		SSD (n=17)	BCF (n=15)	P value
Age (year, mean±SD)		34.70±13.36	36.20±13.49	0.75
Weight (Kg, mean±SD)		67.82±12.17	68.80±8.60	0.79
TBSA (%, mean±SD)		1.70±0.68	1.20±0.41	0.01
Sex n (%)	Female, n (%)	9 (52.9%)	6 (40.0%)	0.46
	Male, n (%)	8 (47.1%)	9 (60.0%)	
Cause n (%)	Scald	9 (52.9%)	9 (60.0%)	0.69
	Flame	2 (11.8%)	3 (20.0 %)	
	Explosion	6 (35.3%)	3 (20.0 %)	
Site* n (%)	Trunk	2 (11.8%)	0	0.05
	Shoulder and upper limb	10 (58.8%)	5 (33.3%)	
	Wrist and hand	1 (5.9%)	7 (46.7%)	
	Hip and lower limb	2 (11.8%)	1 (6.7%)	
	Ankle and foot	2 (11.8%)	2 (13.3%)	

Independent samples *t* test and Chi square were used. P<0.05 was considered significant. TBSA: Total body surface area (%); *According to ICD-10 (International Classification of Diseases, 10th revision); SSD: Silver sulfadiazine cream 1%; BCF: *Boswellia carteri* formulation

Table 2: Comparison of healing time between silver sulfadiazine cream 1% and *Boswellia carteri* formulation groups

Group	Healing time (days)		P value*
	Mean (95%CI)	Median (95%CI)	
SSD (n=17)	10.94 (9.03-12.85)	10 (8.67-11.32)	0.71
BCF (n=15)	10.73 (9.23-12.23)	10 (8.11-11.89)	

*Log-rank test was used; P<0.05 was considered significant; SSD: Silver sulfadiazine cream 1%; BCF: *Boswellia carteri* formulation

Table 3: Hazard ratios for complete wound healing in burn patients who used *Boswellia carteri* formulation compared to silver sulfadiazine cream 1%

Model (BCF vs. SSD)	HR (95%CI)
Crude	1.13 (0.5 to 2.3)
Adjusted for age, sex, TBSA*	0.9 (0.4 to 1.9)

Cox regression was used. *Adjustment for weight, cause and site of burn did not change the crude estimate. HR: Hazard ratio; CI; Confidence intervals; BCF: *Boswellia carteri* formulation; SSD: Silver sulfadiazine cream 1%; TBSA: Total burn surface area

Table 4: Healing indices for patients in groups who received silver sulfadiazine cream 1% or *Boswellia carteri* formulation on consecutive days

Day	SSD (mean±SD)	BCF (mean±SD)	P value
1	0±0.000	0±0.000	-
2	0.021±0.056	0.004±0.018	0.28
3	0.130±0.152	0.095±0.111	0.46
4	0.267±0.248	0.183±0.217	0.32
5	0.371±0.252	0.238±0.240	0.13
6	0.473±0.277	0.337±0.245	0.15
7	0.578±0.298	0.470±0.265	0.29
8	0.688±0.282	0.639±0.254	0.61
9	0.785±0.224	0.769±0.245	0.85
10	0.856±0.204	0.840±0.216	0.83
11	0.883±0.192	0.888±0.192	0.94
12	0.913±0.162	0.929±0.143	0.77
13	0.940±0.144	0.957±0.111	0.71
14	0.953±0.133	0.974±0.068	0.59
15	0.957±0.121	0.990±0.037	0.29
16	0.961±0.109	0.995±0.018	0.23
17	0.965±0.097	1.000±0.000	0.17
18	0.980±0.055	1.000±0.000	0.16
19	0.994±0.020	1.000±0.000	0.33
20	1.000±0.000	1.000±0.000	-

Independent samples *t* test was used. P<0.05 was considered significant. SSD: Silver sulfadiazine cream 1%; BCF: *Boswellia carteri* formulation

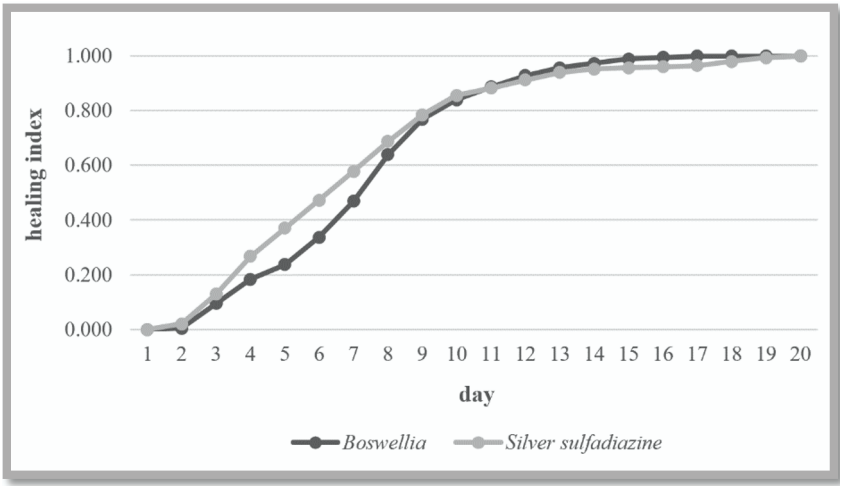

Figure 3: The trends of healing indices for patients in the silver sulfadiazine cream 1% group and *Boswellia carteri* formulation group were compared with each other. P values are mentioned in table 4.

Discussion

In this study, the healing effect of a 40% BCF containing 0.72 mg of β-boswellic acid per 100 g was compared against SSD in the treatment of burn wounds. On each day of the trial, both healing time and healing indices were statistically similar between groups.

Herbal products are widely available and culturally accepted in many areas, although there is little scientific proof of their safety and effectiveness. Traditional Iranian Medicine (TIM) offers a variety of herbal remedies for wound healing.[8] These products have anti-bacterial, anti-inflammatory, and anti-oxidative properties, which reduce the amount of time needed for healing.[23] Finding evidence to support the rational usage of herbal medicines is receiving more attention from researchers, but the field demands more quantitative evaluations such as evidence-based clinical trials.[10] The SSD, a common treatment for burn wounds, just prevents infections and has no definite effect on the wound healing process. Some studies reported that SSD delayed the wound healing process due to its toxic effects on fibroblasts and keratinocytes.[24, 25] Some of its side effects included silver staining, allergic reactions, and

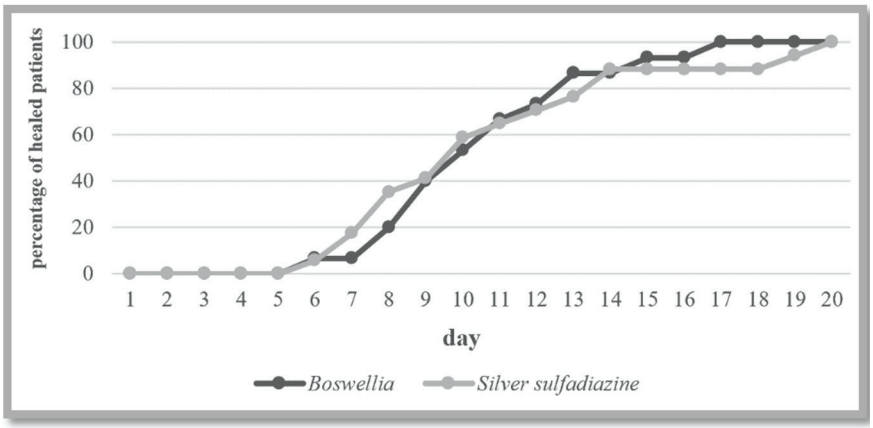

Figure 4: The trends of healed patients (%) in the silver sulfadiazine cream 1% group and *Boswellia carteri* formulation group were compared with each other.

methemoglobinemia, and it is not recommended during pregnancy or infancy.[26, 27] Therefore, looking for an alternative medication that does not have the limitations of SSD seems helpful. The oleo-gum-resin of *B. carteri* consists of boswellic acids and essential oils, composed mainly of octyl acetate, incensole, and incensole acetate.[18, 28] The anti-inflammatory effect of boswellic acids were established in many studies.[29, 30] Furthermore, the essential oils of *Boswellia* species act as antimicrobial agents.[31, 32] Therefore, it is hypothesized that the wound-healing properties of *Boswellia* formulations are mostly due to their anti-inflammatory components such as boswellic acids and essential oils.

To the best of our knowledge, this is the first clinical trial to evaluate the burn wound healing effect of a sterilized product formulated from *B. carteri*. In this study, a topical formulation based on manuscripts from traditional medicine was developed. The main ingredient of the formulation, *B. carteri* oleo-gum-resin, was sterilized using gamma-irradiation to minimize the hazard of pathogenic microorganisms.

In 2004, a case of allergic contact dermatitis was reported in which *Boswellia* oleo-gum-resin was considered a safe herbal medicine.[33] Essential oils are proven to be a potential source of allergic reactions.[34] As *B. carteri* contains essential oils, the reaction may be associated with these compounds. Nevertheless, the findings of the present study indicated that utilizing BCF 40% could lead to the possibility of allergic contact dermatitis. Furthermore, exposure to gamma radiation of *B. carteri* might cause degradation of some components to low molecular weight compounds that penetrate the epidermal barrier faster and trigger hypersensitive reactions. The only limitation of the study was the difference between the TBSA of the two groups (P=0.01).

Conclusion

The findings of the present study indicated that a 40% BCF had healing activity in treating second-degree burn wounds. According to the results of this randomized clinical trial, BCF and SSD, the standard treatment for burn wounds, provide comparable healing times and healing indices. However, the likelihood of allergic reactions to BCF should be taken into consideration. Consequently, further studies on formulations with a lower concentration of *B. carteri* are suggested as products with lower percentages of oleo-gum-resin might not elicit hypersensitivity reactions.

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Authors' Contribution

P.B: conception, study design, acquisition of data, drafting the manuscript; S.A: conception, revising the manuscript critically; H.R.T: analysis and interpretation of data, revising the manuscript critically; A.A.M: study design, revising the manuscript critically; S.D: conception, study design, revising the manuscript critically; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions

related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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