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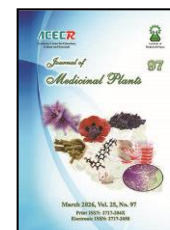

Research Article

Effect of herbal cream made by frankincense (*Boswellia serrata* Roxb. Ex Colebr.) and yarrow (*Achillea millefolium* L.) on the incisional wound healing model in rats

Arman Zargaran[1], Sayid Mahdi Mirghazanfari[2], Katayoun Ziari[3], Samaneh Soleymani[4,5,*]

[1] *Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Department of Physiology and Persian Medicine, School of Medicine, AJA University of Medical Sciences, Tehran, Iran*
[3] *Department of Pathology, School of Medicine, AJA University of Medical Sciences, Tehran, Iran*
[4] *Institute for Studies in Medical History, Persian and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran*
[5] *Department of Traditional Pharmacy, School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran*

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ABSTRACT

Background: *Boswellia serrata* Roxb. ex Colebr and *Achillea millefolium* L. are two main plants cited in Persian medical manuscripts for wound healing. **Objective:** This animal study was planned to assess the effectiveness of a topical cream of *B. serrata* and *Achillea millefolium* propylene glycolic extract on the incisional wound healing model in Wistar rats. **Methods:** An incision wound was created on the dorsal part of 48 male Wistar rats (randomly divided into four groups of 12 each) after anesthesia with intra-peritoneal injection. Cream 5 % (group 1), cream 10 % (group 2), phenytoin (group 3) and placebo (group 4) were applied topically in each group for 14 days. Histopathological assessments and wound contraction percentage were documented on days 3, 7, 10, and 14. Furthermore, quality control and standardization of cream were performed. **Results:** Significant accelerated wound closure and increased re-epithelialization and fibroblasts was detected in the group 1 (cream 5 %) compared with group 3 (phenytoin) and group 4 (placebo) on 7th day. The difference between two groups 1 and 2 was not significant. On the 10th of the experiment, all treated groups demonstrated significant wound closure in comparison to placebo group. **Conclusion:** Significant effects of topical semisolid formulation on improving wound could be incredibly promising for accelerating wound healing as potential natural remedy. However, future clinical studies are suggested to consider the precise effectiveness of this formulation in human.

Abbreviations: IL, Interleukin; TNF- *α*, Tumor necrosis factor- α; COX-2, Cyclooxygenase-2; NO, Nitric oxide; PGE2, Prostaglandin E2; TGF-*β*, Transforming growth factor-*β*; MMP, Matrix metalloproteinases; ROS, Reactive oxygen species; MAPK, Mitogen activated protein kinases; NaHCO3, Sodium hydrogencarbonate; NaOH, Sodium hydroxide; V_b, volume (ml) of standard; HCl required for the blank; V_s, volume (ml) of standard HCl required for the sample; HCl, Hydrochloric acid; FDA, Food and Drug Administration

*Corresponding author: Soleymani.Sa@iums.ac.ir

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1. Introduction

Wound is defined as breakdown or laceration of the skin tissues due to damages induced via biological and physical-chemical agents that causes disturbance in the anatomy and function of normal skin and loss of epithelium continuity and underlying connective tissue [1]. Current estimates demonstrate approximately 8.2 million people suffer wounds with or without infections and Medicare cost for acute and chronic wounds are ranged from $28.1 billion to $96.8 billion worldwide [2]. The skin lesion usually enhances fluid loss and results in hypothermia, compromised immunity, developing life-threatening infections and scars [3, 4]. The wound closure process involves a cascade of biomolecular and cellular events that happen after the beginning of a tissue lesion so as to restore the damaged tissue [5]. The cascade of wound healing is divided into four consecutive and overlapping phases including coagulation or hemostasis, inflammation, proliferation and remodeling or maturation [6]. Several topical pharmacological interventions have been applied for wound healing that each other having frequent deficiencies and limitations. In view of high prevalence of ulcers, high rate of infection and sepsis in patients with chronic wounds, antibiotic resistance, high cost of treatment, concerns about the quality of life of patients, interest in phytochemicals and medicinal plants for wound healing has been progressively increased [7, 8]. In this regard, the use of traditional, complementary, and alternative medicine is promising. Persian medicine dates back to more than 7,000 years ago as one of the oldest and most important traditional and complementary medical systems worldwide [9].

Boswellia serrata Roxb. ex Colebr (Frankincense) from the family Burseraceae and *Achillea millefolium* L. (Yarrow) from the family Asteraceae are two of medicinal plants that commonly cited in Persian medicine documents for accelerating wound healing [10]. *A. millefolium* is the most widespread species and most frequently used plant in conventional and folk medicine to treat inflammation, bleeding, wounds, pains, headache and gastrointestinal disorders for over 3000 years. The ancient Europeans named it military herb and a topical formulation made from this plant was applied as vulnerary medication on battle wounds [11, 12]. A diversity of pharmacological properties of aerial parts of this plant are including skin rejuvenating, skin lightening, anti-inflammatory, strong antioxidant, wound healing, shooting and refreshing agents, cholagogue, anti-inflammatory, hemostatic, antiseptic, analgesic and antitumor due to the presence of several phytochemicals such as phenolic compounds sesquiterpenes and essential oils [13, 14]. *B. serrata* has been used in religious ceremonies and also as a medicinal herb since the prehistoric time to treat acute and chronic disease such as inflammatory diseases [15]. *B. serrata* oleo gum resin and its chemical constituents such as boswellic acids have demonstrated a wide range of pharmacological properties such as anti-inflammatory. *B. serrata* oleo gum resin and its chemical constituents such as boswellic acid have shown a wide range of pharmacological properties including anti-inflammatory, skin whitening, reducing wrinkle, psoriasis, analgesic activity, antimicrobial, anti-asthmatic, anti-cancer, antinociceptive, clastogenic activity [16 - 18].

This animal study was designed to evaluate the efficacy of a semi-solid formulation (topical cream of *B. serrata* and *A. millefolium* propylene glycolic extract) on the incisional wound healing model in Wistar rats.

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2. Materials and Methods

2.1. Preparation of extract and semisolid formulation

The adequate amount of *B. serrata* oleo gum resin and *A. millefolium* aerial part was purchased from a traditional herbal shop in Tehran. These plants were identified and approved by botanists at the Herbarium Center of the School of Pharmacy, Tehran University of Medical Sciences (voucher number: PMP-789 and PMP-1398 respectively). A 1000 g amount of oleo gum resin and 1000 g amount of aerial part was pulverized with an electric mill and extracted by maceration with propylene glycol–water mixture (80 %, v/v) for 72 hours, at room temperature in the dark. Then, the extract was separated and vacuum filtered, and the milestone was pressed until exhaustion. Therefore, the liquid glycolic extract of frankincense and yarrow was collected. Two formulations containing different concentrations of the glycolic extract were prepared. Oil in water (o/w) emulsion-based cream was composed of mixture of cetostearyl alcohol 1.5 %, cetyl alcohol 5 %, stearic acid 10 %, liquid paraffin 10 %, emulsifier (polysorbate 80 and sorbitan monostearate) as the oil phase and glycolic extract (10 % and 5 %), glycerin 5 %, preservatives (mixture of parabens 0.2), pH neutralizer (triethanolamine 2 %) in sufficient water to fill 100 mL aqueous phase. Separately, both oil and aqueous phase were heated at 72 °C. Then, aqueous phase was mixed into oil phase with continuous stirring until cooling. The product was packed and kept under ambient conditions (25 °C). The placebo cream consisted of eatable color, and very low essential oil and all components of the cream without the glycolic extract.

2.2. Standardization and quality control of cream

2.2.1. Total phenolic content

Total phenolic content was estimated by Folin-Ciocalteau spectrophotometric assay. Samples were diluted into ethanol solvent to a final concentration of 1 mg/mL and the reaction mixture was used by mixing ethanol solution (0.5 ml), 7.5 % $NaHCO_3$ (2.5 ml) and 10 % Folin Ciocalteu's reagent (2.5 ml) and incubated at 45 °C for 45 min. The absorbance was measured spectrophotometrically at 765 nm against prepared blank. Gallic acid was used as standard to construct the standard curve. The total phenolic content was expressed as mg gallic acid per milliliter of preparation [19].

2.2.2. Total flavonoid content

Total flavonoid content was measured by a colorimetric method. Samples consisting 1 ml of ethanol solution of extract (1 mg/ml) and 1 ml of 2 % Aluminium chloride solution dissolved in methanol were prepared. After 1 h of incubation at room temperature, absorbance was measured at 415 nm. The calibration curve was plotted using standard quercetin. Total flavonoid content was expressed as mg quercetin equivalent per milliliter of preparation.

2.2.3. Determination of pH

The pH meter was calibrated using standard buffer solution and measured the pH by inserting the electrode directly into the beaker containing 20mg of the cream [20].

2.2.4. Determination of organoleptic properties:

The test formulations were visually analyzed for appearance, color and odor [21].

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2.2.5. Determination of homogeneity

Homogeneity of cream formulation was tested by visual observations and by touch [22].

2.2.6. Determination of viscosity

The viscosity determinations were carried out using a Brookfield Viscometer at 20 rpm at a temperature of 25 ºC [20].

2.2.7. Type of emulsion (Dye solubility test)

In this test, the red dye was mixed with the cream then place a drop of cream was placed on a slide and covered with cover slip, observed under microscope. If the continuous phase appears red color the cream was o/w type and if the dispersion phase appears in red colored globules the cream was w/o type [20].

2.2.8. Smear type

After application of cream on the skin, the type of film or smear formed (oily or aqueous in nature) were checked [23].

2.2.9. Acid value

For this test, 10 g of cream accurately was weighed and dissolved in 50 ml distilled water and mixed with equal volume of solvent ether and alcohol. The flask was connected to reflux condenser and slowly heated, until the sample was dissolved completely. Then 1 ml of phenolphthalein added and titrated with 0.1N NaOH until faintly pink color appears after shaking for 30 seconds. The acid value was calculated using following formula [24]:

$$\text{Acid value} = [N \times 5.61]/W$$

N = the number of ml of NaOH required

W = the weight of substance

2.2.10. Saponification value

In this procedure, 2 g of prepared cream was weighted into a conical flask (200 ml) with 25 ml of KOH in ethanol (0.5 mol/L) for 30 min. To the solution, 1 ml of phenolphthalein indicator was added and was titrated immediately, with 0.5 N HCl. The same procedure was performed for the blank (without cream sample). Finally, saponification number was calculated via below formula [24]:

$$\text{Saponification value} = 28.05 \times (V_b\text{-}V_s)/W$$

V_b: volume (ml) of standard HCl required for the blank

V_s: volume (ml) of standard HCl required for the sample

W: wight (g) of the sample

2.2.11. Spreadability test

The spreadability of cream was assessed through measuring the spreading diameter of 5 g of the cream between two flexi plates after 3 min. Then 500-g sinkers were frequently placed the upper plate frequently and the diameter change was measured. The diameter of spreading was considered as an indication of spreadability of cream [8].

2.3. In vivo experiment

2.3.1. Animals

In this experimental study was conducted on 48 male Wistar rats with weight ranging 150 -200 g. Animals were housed in a conventional vivarium with a temperature of 25 ± 1 °C, a relative humidity of 60 %, and 12-hour light/dark cycles. They were fed standard laboratory pellets and water *ad libitum*. The protocol of this animal study was approved by the Ethical Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.594).

2.3.2. Induction incision wound model and treatment

All the animals were shaved at the dorsal part and disinfected with alcohol (70 %) under anesthesia with intra-peritoneal injection of xylazine (10 mg/kg) and ketamine (80 mg/kg).

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Two centimeters long full-thickness incision wound was created in the median portion of the dorsal vertebrae using a scalpel blade. The wounds were photographed and left open and the day of the surgery was considered as day 0.

Experimental animals, after being recovered from anesthesia, were housed separately (1 in each cage) and were casually allocated into 4 groups (12 rats in each group) receiving: group 1: (A: placebo cream); group 2: (B: phenytoin cream); group 3: (C: cream 5 %); group 4: (D: cream 10 %). The treatments were topically applied to cover the wound area once daily until the 14th day.

Wound closure process was checked and measured on days 3, 7, 10, and 14 by a digital caliper as scale and the wound contraction rate was assessed as the percentage reduce in wound size using the following equation:

Wound closure (%) = 100× [(first day wound size – specific wound size) / first day wound size]

2.3.3. Histological analyses

Three rats from each group in days 3, 7, 10 and 14 were used for histopathologic studies. Rats were sacrificed and the thick sections of skin tissue was retrieved and preserved in buffered 10 % formalin. 5 μm- paraffin embedded tissues were stained by H&E to create microscopic slides [25]. The slides were observed under a light microscope (Nikon, Alphaphot-2-YS2, with JENUS camera) and microscopic photographs were captured under × 400 magnifications, and the parameters, containing macrophage, fibroblast, re-epithelialization, neovascularization and PMN were blindly scored by a pathologist. Scores were as follow: 0 (-) = no evidence, 1 (+) = minimal, 2 (++) = slight, 3 (+++) = moderate and, 4 (++++) = severe (6).

2.4. Statistical analysis

After data collection, IBM SPSS statistics version 25 was used for the statistical calculations (one-way ANOVA and Tukey's Post hoc test). P value less than 0.05 was considered statistically significant in all tests.

3. Results

3.1. Standardization and quality control of the cream

The pH of formulation was 6.5, which is within the normal pH range of skin. After the visual and organoleptic evaluation, it was verified that the formulations submitted to the stability tests did not display changes in appearance, odor and color (yellowish green color) after three months. It was detected that the cream was consistent, smooth and homogeneous in nature. The viscosity was 27085 cP that demonstrated a desirable non-Newtonian shear thinning pseudo plastic type of flow, that is, viscosity declines at enhancing angular velocity. Dye test outcome established that the formulation was o/w type emulsion cream. Also, non-greasy film on the skin area was demonstrated in smear type test. The outcomes of saponification and acid value were 5.3 and 26.4 respectively and demonstrated satisfactorily values. The diameters of spreading cream were 5.65 ± 0.16 (cm ± SD) which indicates cream is simply spreadable via small quantities of shear.

3.2. Total phenol and flavonoid contents of the preparation

A standard curve with gallic acid at concentrations of 50, 100, 150, 200 μg/ml was used to quantify total phenolics. The line equation was obtained by linear fitting of the calibration curve ($y = 0.0099x + 0.056$; $R^2 = 0.9988$) and the total amounts of phenol of the

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cream was: 47.92 ± 3.94 mg gallic acid equivalent/ ml. A standard curve with quercetin at concentrations of 20, 40, 80, 100 µg/ml was used to quantify total flavonoid. The line equation was obtained by linear fitting of the calibration curve ($y = 0.0481x + 0.0906$; $R^2 = 0.9983$) and the total amounts of flavonoid of the cream was: 18.61 ± 0.04 mg quercetin equivalent/ ml of cream.

3.3. In vivo assessment of wound healing activity

The percentage of wound contraction for each group on every experimental day has been presented in Table 1. There was no significant difference between treated groups on 3rd day. The highest wound healing was observed in the group C (cream 5 %) on day 7 and was significant compared with placebo ($P < 0.001$). The difference in healing percentage between two groups C and D (cream 10 %) on 7th day was not significant ($P = 0.16$). Also on this day, the difference in wound area in group C and D compared to the group B (phenytoin) was significant ($P = 0.001$ and $P = 0.01$ respectively). On the 10th of the experiment, all treated groups demonstrated significant wound closure in comparison to placebo group ($P < 0.001$). There was no evidence of complete wound healing in the placebo group until the end of the experience (day 14th). The results of healing process are displayed in Figure 1.

3.4. Histopathological analyses

The outcomes achieved from the histopathological assessment are presented in Table 2 and Figure 2. On the 3rd day, there was no significant difference in histopathological parameters between the groups. On days 7, re-epithelialization in the treated samples either group C was significantly higher than the placebo group ($P < 0.05$). Also, the significant difference in fibroblasts was observed in groups C and phenytoin compared with placebo ($P < 0.01$) however fibroblasts in group C have significant difference with phenytoin group in this day ($P < 0.05$). On the 10th day, significant difference in re-epithelialization and fibroblasts was recorded in groups C, D and phenytoin compared with placebo ($P < 0.001$). There is a significant difference in the number of PMNs in groups C and phenytoin compared with placebo ($P = 0.01$). Macrophage levels in all three groups displayed significant differences with the control group on the 14th day ($P < 0.01$).

Also in neovascularization, there were no significant differences between groups throughout the test period.

Table 1. Comparison of wound contraction rate (%) in different experimental groups on each experimental day.

	3-Day	**7-Day**	**10-Day**	**14-Day**
Placebo (A)	3.20 ± 0.60	28.41 ± 0.53	49.12 ± 0.14	84.15 ± 1.32
Phenytoin (B)	5.31 ± 0.58	52.12 ± 0.63	100.00	100.00
Cream 5% (C)	7.02 ± 1.60	67.73 ± 1.51	100.00	100.00
Cream 10% (D)	5.52 ± 1.12	60.23 ± 0.08	100.00	100.00

Data are shown as means ± SD

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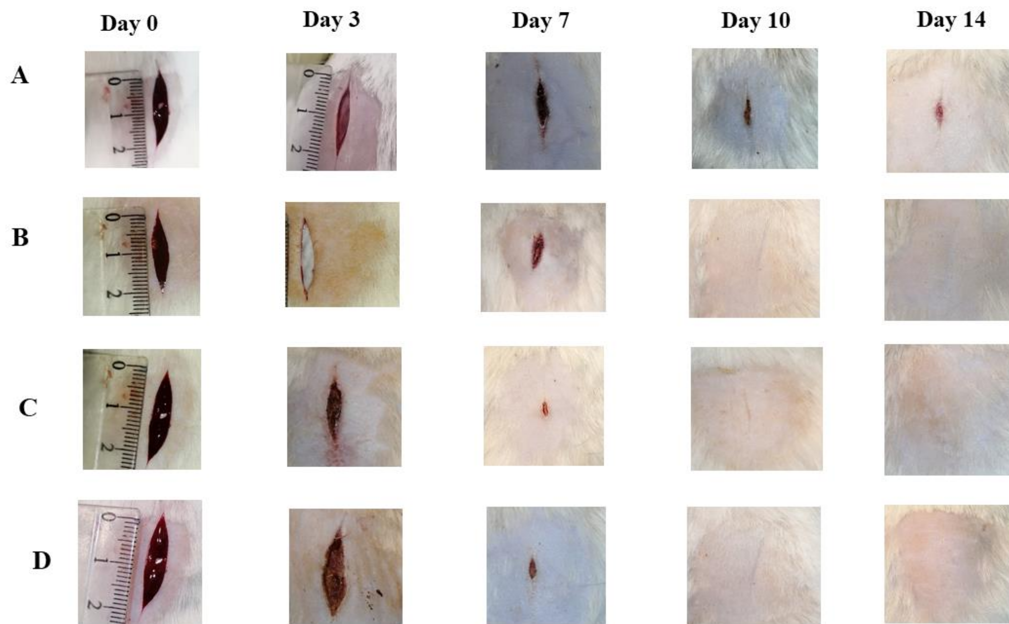

Fig. 1. Macroscopic view of the wounds on days 0, 3, 7, 10, and 14. A: placebo; B: phenytoin; C; cream 5 %; D: cream 10 %.

Table 2. Histopathological parameters in different treatments on days 3, 7, 10, and 14.

		Placebo (A)	**Phenytoin (B)**	**Cream 5 % (C)**	**Cream 10 % (D)**
3-Day	Re-epithelialization	+	++	++	++
	Fibroblast	+	+	+	+
	Neovascularization	+	-	+	+
	Polymorphonuclear cells (PMN)	++	+	+	++
	Macrophage	+	++	++	++
7-Day	Re-epithelialization	++	+++	++++	+++
	Fibroblast	+	++	++++	++
	Neovascularization	+	++	++	+
	Polymorphonuclearcells (PMN)	++	++	++	++
	Macrophage	++	+++	+++	+++
10-Day	Re-epithelialization	++	++++	++++	++++
	Fibroblast	++	++++	++++	++++
	Neovascularization	++	++	++	++
	Polymorphonuclear cells (PMN)	+	+++	+++	++
	Macrophage	++	+	+	++
14-Day	Re-epithelialization	+++	++++	++++	++++
	Fibroblast	++	++++	++++	++++
	Neovascularization	+	++	++	++
	Polymorphonuclear cells (PMN)	+	-	-	-
	Macrophage	++	-	-	-

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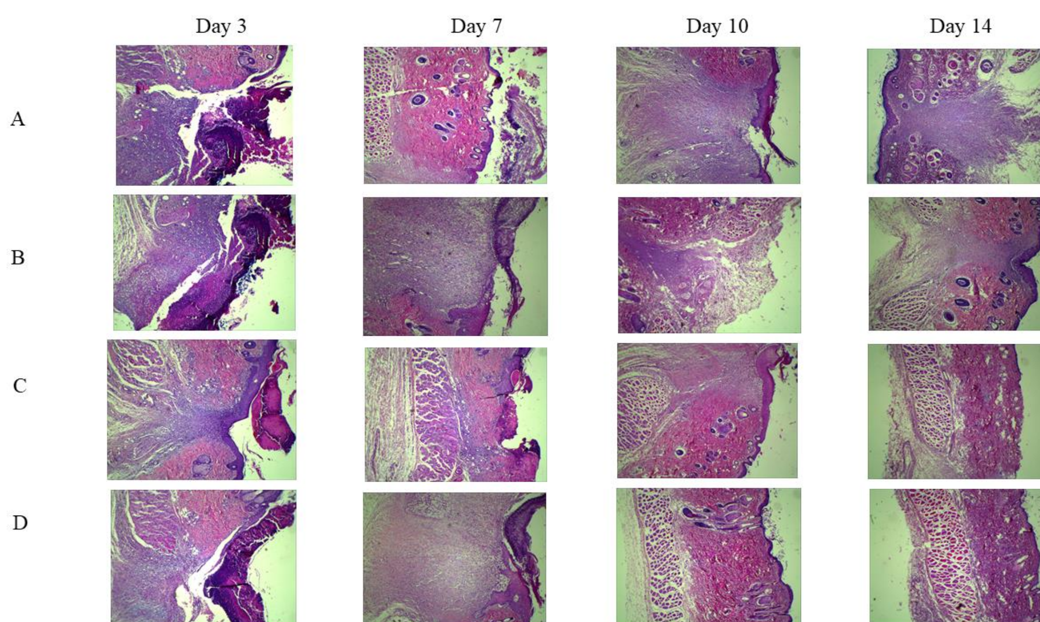

Fig. 2. Photomicrographs of histopathological sections of wound healing on different days of treatment. A: placebo; B: phenytoin; C; cream 5 %; D: cream 10 %.

4. Discussion

Wound healing is a complex of organized cellular, humoral, and molecular mechanisms and active procedure of exchanging missing and devitalized tissue layers and cellular structures [26]. In this study, an assessment of wound healing features of semi-solid formulation (topical cream of *B. serrata* and *A. millefolium* propylene glycolic extract) was performed on *in vivo* incisional wound model, and revealed significant accelerate wound healing process. Propylene glycol absorbs further water and maintains humidity in some cosmetics, medicines and food products and is used by the food, and pharmaceutical industries. FDA has categorized it as a preservative that is GRAS (commonly recognized as safe) for use in food [27]. Also, previous studies demonstrated propylene glycol–water extracts are permanent and condensed in phenolic derivatives, flavonoids and lipophilic substances [28].

Plants and their phytochemical compositions including phenolic compounds, anthocyanins, terpenes, flavonoids, essential oil and tannins with their antioxidant, astringent and anti-inflammatory properties displayed to be effective in several pathologic conditions such as wounds [29].

According to the phytochemical screening studies, the pharmacological effects of *A. millefolium* are principally due to flavonoids, essential oil, sesquiterpene lactones, proazulenes and dicaffeoylquinic acids [30]. To assess the wound healing influence of *Achillea* at the cellular level, the keratinocyte Ha- CaT cells and fibroblast Hs68 cell line was applied. When the cells were treated with *A. millefolium* ethanolic extract demonstrated strong anti-inflammatory effectiveness by decreasing expression of IL-1β, IL-6, TNF- α, COX-2, NO production and release of PGE2. In addition, extract increased wound healing promotion via stimulating keratinocyte motility and differentiation through inducing keratinocyte and β-catenin differentiation and stimulating collagen expression via activating of TGF-β in Hs68 fibroblasts [31]. According to Benedek et

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al, 2007, *A. millefolium* extract and fraction enriched in flavonoids and dicaffeoylquinic acids showed anti-inflammatory effects by inhibiting activity human neutrophil elastase, MMP-2 and MMP-9 and inhibition of arachidonic acid metabolism [32]. In another study that used mice derived NIH-3T3 fibroblasts treated with *Achillea* extract displayed a clear proliferating effect and an enhanced production of type I collagen and accelerated wound healing and also, strong ROS scavenging and detoxifying action with a high binding capacity [33].

The chemical contents of *B. serrata* include alcohol-insoluble gum, resin and essential oil. Boswellic acid is a pentacyclic triterpenoid and the main composition of *B. serrata* [34]. Gayathri et al., investigated that boswellic acid by block leukotriene biosynthesis and methanolic extract of *B. serrata* by inhibiting mitogen activated protein kinases (MAPK) and cytokines such TNF- α and IL-1β, NO in mouse macrophages and in human peripheral blood mononuclear cells exerts anti-inflammatory property [35]. Several studies have confirmed that methanolic and aqueous extract of *B. serrata* can scavenge DPPH and glutathione, inhibit superoxide free radical generation and nitrite formation due to containing high amount of essential oils (monoterpenes, sesquiterpenes) and total phenolics compound [36]. The wound healing activity of *B. serrata* extract was investigated in a diabetic foot ulcer model of rats that demonstrated wound healing potential through enhanced angiogenesis (Ang-1/Tie2) and collagen synthesis (hydroxyproline and collagen-1), prohibition of oxido-inflammatory indicators (ILs, TNF-α, NF-κB), prohibition of apoptosis (Bcl-2-associated X protein) [37]. According to Mallik et al, 2010, cream formulation of *B. serrata* oleo-gum-resins on the excisional wound healing model as single dose at different percentages, accelerated the wound healing process via impressing the different phases of wound healing including fibroplasias, wound contraction and collagen synthesis, enhancing the tensile strength and reducing the wound surface area [38].

Considering the traditional usage of various *Achillea* and *Boswellia* species in folk and traditional medicine of numerous countries such as Persian medicine since ancient time, the extract of these plants seems to be safe within the effective wound healing effects [39]. However, future mechanistic preclinical investigations, and also, clinical studies would be more beneficial to explain the precise effective and safe dose range of this formulation as a wound healing agent.

5. Conclusion

This study demonstrated significant efficacy of standardized topical semisolid formulation of *B. serrata* and *A. millefolium* propylene glycolic extract in the new formula of cream. Enhanced rapid wound contraction and histopathological observations suggest that this renewed form could be considered as a potential herbal preparation for management of wound healing. Nevertheless, future clinical studies are suggested to examine the effectiveness of this formulation in humans.

Authors' contributions

SS: Project administration, Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Validation. **SMM:** Writing – original draft, Investigation, Writing – review & editing, Data curation. **KZ:** Writing – original draft, Writing – review & editing, Resources, Analysis. **AZ:** Project administration, Methodology, Supervision, Investigation, Writing – review & editing, Validation.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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