Original Article

Healing Effect of *Hypericum perforatum* in Burn Injuries

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ABSTRACT

Background: Burn injury is still the leading cause of mortality and morbidity in burn patients. We comapred healing effect of *Hypericum perforatum*, silver sulfadiazine and alpha ointments on burn injuries in rat model.

Methods: Sixty female Sprague-Dawley rats in an animal experimental study were randomly divided to 5 equal groups as *H. perforatum*, silver sulfadiazine and (SSD), alpha, gel base and the burn injury left untreated. Wounds were assessed macroscopically and histologic after burn injury and on days 7th, 14th and 21st after treatments.

Results: Burn wounds decreased in size on day 7th in *H. perforatum* group (P<0.01). Regarding scoring the inflammation, re-epithelialization, angiogenesis, formation of granulation tissue and number of macrophage, the best scores were visible in *H. perforatum* group, and the worst in the gel base and the burn injury left untreated (P<0.01).

Conclusions: *H. perforatum* was shown to significantly induce re-epithelialization, angiogenesis and granulation tissue and decrease the inflammation resulting into a healing process in burn wounds. As *H. perforatum* is inexpensive and an easily available herbal medicine, it can be considered as a therapeutic of choice to ameliorate burn injuries.

KEYWORDS
Burn; *Hypericum perforatum*; Silver sulfadiazine; Alpha ointment; Wound healing

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INTRODUCTION

Burn injury is still the leading cause of mortality and morbidity in burn patients as burn patients are at high risk of infection [1]. Burn can also pose a high cost on health care system due to hospital stay, expensive medications, multiple operative procedures and prolonged period of rehabilitation[2-4]. Therefore, to reach the best dressing in burn injuries to accelerate the healing process and decline the bacterial burden is of great importance [5] causing many researchers to study about appropriate treatments in order to decrease the risk of burn infections and to shorten the period of treatment too[6].

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Among therapeutic choices of burn, silver sulfadiazine (SSD) has been a gold standard in burn wounds with many advantages such as easy and convenient use, not creating pain, having low toxicity and sensitivity, and with anti-bacterial effects [7]; but, it may cause several side effects such as leukopenia, neutropenia, methemoglobinemia, erythema multiform, renal toxicity and delay in wound healing [8]. So in health care practice, there is a high demand for new medications in treatment of burn injuries with less complications and better efficiency [9].

The use of herbals in wound healing has been investigated worldwide . Alpha burn ointment is a herbal medication in burn wounds that has active ingredients such as lawsone, available in *Lawsonia inermis* plant)from henna Lythraceae intermis [7]. *Hypericum perforatum (Hypericaceae),* known as Saint John's wort (SJW) has been used in different systems of traditional medicine and has been isolated in Europe, West Asia, North Africa, Madeira, and the Azores and is a member of the genus *Hypericum* family. It contains ingredients such as naphthodianthrones, phloroglucinols, flavonoids, bioflavonoids, and phenylpropanoids with antifungal, anti-inflammatory, antimycobacterial, and antiviral properties [10]. *H. perforatum* role in diabetes [11], as anti-depressant, antimicrobial, antineoplastic, analgesic, improving metabolic syndrome, and healing of wounds has been investigated [10, 12, 13].

This study was carried out to macroscopically and histologic assess the effect of *H. perforatum* in healing of burn injuries in rat model and in comparison to silver sulfadiazine and alpha burn ointments that have been applied in remedy of burns.

METHODS

Compliance with Ethical Standards

Animal selection, care, sacrifice, protocols and procedures in the study followed the Helsinki Declaration (1964). This study was financially and ethically approved by National Institute for Medical Research Development of Iran Ministry of Health, Treatment and Education (IRB: 963474).

Ethical Approval

All experimental procedures used in this study that involved laboratory animals were approved by the Ethics Committee of National Institute for Medical Research Development of Iran Ministry of Health, Treatment and Education (IRB: 963474).

Collection of Plant Material

The plant was collected from the Department of Pharmacognosy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

Preparation of H. perforatum Extract

To provide the extract of *H. perforatum*, all parts of the plant were used and dried during 4-7 days at room temperature. It was ground to powder and subsequently, the extract was provided using a mixture of water: ethanol (1:1, v/v) during a 3 days period. The extract was later filtered and evaporated to reach a dark hydroalcoholic product yield (24.25%). To prepare 5% *H. perforatum* gel 5 mL of the plant was dissolved in 2 mL of distilled water and was later transferred to 2% carboxymethylcellulose (CMC, 2 g dissolved in 98 mL of distilled water).

Experimental Animals

In an experimental animal research to evaluate the effect of *H. perforatum* in treatment of burn wounds, sixty female 8-12 weeks old Sprague-Dawley rats weighing 180-220 g were randomly divided to 5 equal groups of receiving 5% *H. perforatum*, silver sulfadiazine ointment (1% SSD, Shafa Co, Tehran, Iran), alpha burn ointment (33% Henna leaf extract, Sina Daru, Tehran, Iran)[7], the gel base and the control groups with burn injury left untreated. The gel base was prepared by producing 2% CMC gel in absence of *H. perforatum* component. The animals were purchased from Comparative and Experimental Medicine Center of Shiraz University of Medical Sciences, Shiraz, Iran. The rats were kept one per cage at 21±2°C and 65-70% RH and had free access to a balanced diet and water.

All burn wound injuries were standard 3rd degree burn wounds created identically by a steel hot plate (1×1.5 cm) at 69 °C placed on the skin for 3 s. Intramuscular injection of ketamine (100 mg/kg, GmbH, Germany) and xylazine (10 mg/kg, Alfasan, Netherlands) was performed for sedation before induction of any burn injuries, while the animal's

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back hairs were shaved and the skin was scrubbed with povidone iodine solution and wiped later with sterile water.

Macroscopic Evaluation

Assessment of wounds was undertaken for any change in the color, appearance, smell, discharge and the time of scar separation. The debridement and medications of necrotic tissues were done instantly and repeated every 12 hours. If burned animal was lethargic, the activity was recorded. Photography was undertaken by a digital camera on days 7th, 14th and 21st. Five rats were excluded from the study due to infection in induced burn injuries (n=2) and un-standard state of established wounds (n=3).

Histologic Assessment

The animals were euthanized for histological evaluation using score of inflammation (counting polymorphonuclear: PMN cells), re-epithelialization (formation of new epithelium), angiogenesis (counting new vascularization), presence of macrophages (counting the cells) and formation of granulation tissue (Table 1). The macrophages were identified by vesicular nuclei, small nucleolus and abundant amount of cytoplasm. Other inflammatory cells including PMN cells were identified based on their segmented nuclei and the lymphocytes upon their small size and scant cytoplasm. All tissue sections were stained by hematoxylin and eosin (H&E).

Statistical analysis

The data were analyzed by Statistical Package for the Social Sciences (SPSS) software (Version 20, Chicago, IL, USA) using non-parametric tests of Kruskal-Wallis and Mann-Whitney with Bonferroni correction for multiple comparisons. A $P<0.05$ was considered statistically significant.

RESULTS

Macroscopic Evaluation

Grossly, the burn wound injuries showed a prominent decrease in size on day 7th in *H. perforatum* group ($P<0.01$) (Figure 1).

Histologic assessment

Table 2 demonstrates comparison of histological healing scores on different days after burn injury. Regarding the epithelialization, angiogenesis, formation of granulation tissue, number of macrophages and inflammation, the highest scores were in *H. perforatum* group ($P<0.01$), followed by alpha, silver sulfadiazine, gel base and control group on days 7th, 14th and 21st.

Histological evaluation of *H. perforatum* in burn injuries on days 7th, 14th and 21st and in comparison to other groups on day 21st has been demonstrated in Figure 2. On day 21st in *H. perforatum* group; absence of inflammation, absence of ulcer, mild collagen deposition, presence of mature granulation tissue, and formation of a complete epidermis was visible. In silver sulfadiazine group; severe inflammation, ulceration, vascular proliferation, absence of granulation tissue and re-epithelialization were noted. In alpha group, moderate inflammation, ulceration, vascular proliferation, absence of collagen deposition, granulation tissue and re-

Table 1: Histologic scoring system used for burn wound healing

Score	4	3	2	1	0
Re-epithelialization	Complete, keratinized 100% wound covered	Approximately complete 75 to <100%	Moderate 50 to <75%	Thin 25 to <50%	Absent to very thin <25%
Granulation tissue	Completely organized = 80% of tissue	Thick with well-formed collagen matrix = 60% of tissue	Moderate remodeling = 40% of tissue	Thin immature and inflammatory tissue	Immature and inflammatory tissue
Inflammatory cells/HPF	1-4 None	5-7 Few	8-10 Moderate	11-13 Many	>14 Abundant
Macrophages/HPF	(0-15)	(16-30)	(31-45)	(46-60)	(>61)
Angiogenesis	None, 0	1-5	6-10	11-15	>16

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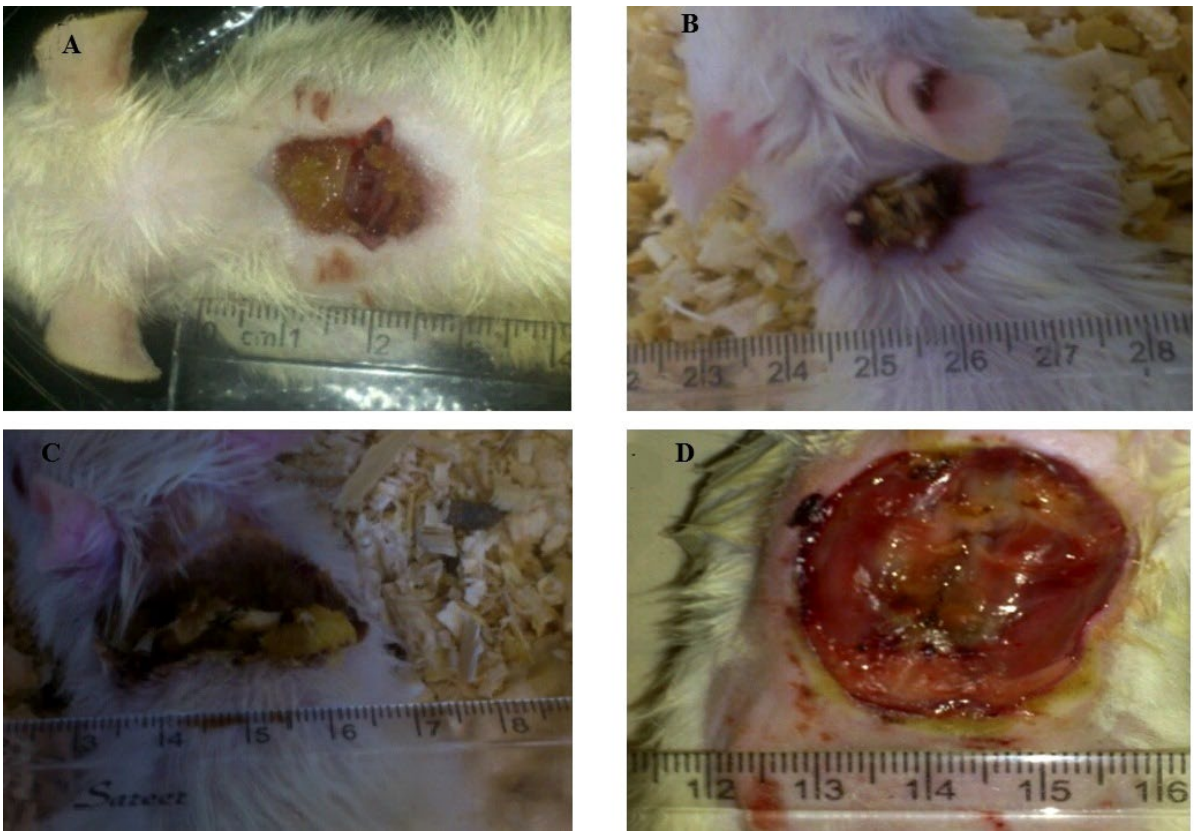


Figure 1: Histological changes in different days after burn injury following treatment. The picture denotes to typical changes during wound contraction on day 7th after inducing burn injury (A: Silver sulfadiazine ointment group after 7 days, B: Alpha ointment group after 7 days, C: *Hypericum perforatum* group after 7 days, D: Gel base group after 7 days). As shown here, the burn wound injuries showed a prominent decrease in size

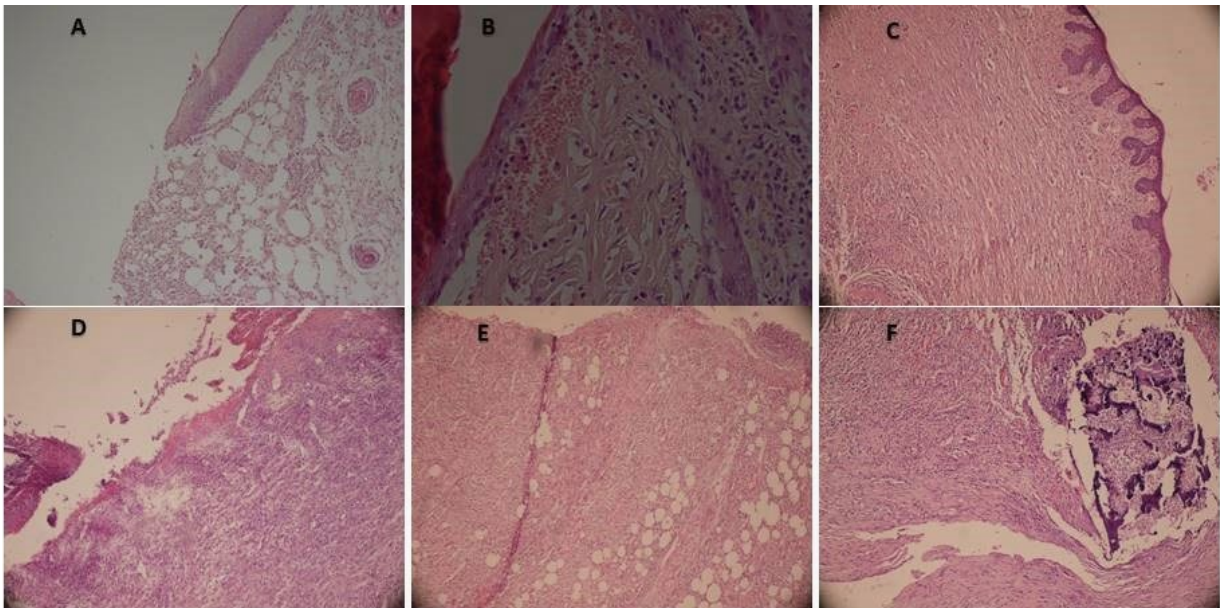


Figure 2: The healing effect of *Hypericum perforatum* in burn injuries on days 7th, 14th and 21st and in comparison to other groups on day 21st (H&E, x40). **A.** *H. perforatum* group after 7 days: Ulceration, severe inflammation and vascular proliferation. **B.** *H. perforatum* group after 14 days: Thin epidermis, maturing granulation tissue, small amount of collagen deposition, inflammation and vascular proliferation. **C.** *H. perforatum* group after 21 days: Complete epidermis, mature granulation tissue, mild collagen deposition, mild inflammation. **D.** Control group after 21 days: Ulceration, marked inflammation, vascular proliferation. **E.** SSD group after 21 days: Ulceration, severe inflammation, vascular proliferation. **F.** Alpha group after 21 days: Marked inflammation, necrosis, vascular proliferation. As illustrated here, a significant healing effect of *H. perforatum* in burn injuries in comparison to other groups was exhibited

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Table 2: Comparison of histological healing scores on different days after burn injury

Day	Epithelialization (Mean±SD)	Macrophage (Mean±SD)	Angiogenesis (Mean±SD)	Granulation tissue (Mean±SD)	Inflammation (Mean±SD)
			H. perforatum		
7	2.00±0.63	2.33±0.82	2.33±0.82	2.17±0.41	2.17±0.75
14	3.00±0.63	3.00± 0.63	3.17±0.75	3.17±0.41	3.00±0.63
21	3.67±0.52	3.83± 0.41	3.83±0.41	4.00±0.01	3.83±0.41
Total	2.89±0.90	3.06± 0.87	3.11±0.90	3.11±0.83	3.00±0.91
			Silver sulfadiazine		
7	0.50±0.55	1.00±0.00	1.17±0.41	0.17±0.41	0.17±0.41
14	1.33±0.52	1.50±0.55	1.50±0.55	0.67±0.52	0.67±0.52
21	1.67±0.52	1.67±0.52	1.67±0.52	1.33±0.52	1.33±0.52
Total	1.17±0.71	1.39±0.50	1.44±0.51	0.72±0.67	0.72±0.67
			Alpha		
7	1.67±0.52	2.00±0.63	2.17±0.41	2.33±0.52	2.00±0.63
14	2.33±0.52	2.50±0.55	2.83±0.41	2.67±0.52	2.83±0.41
21	3.33±0.52	3.17±0.75	3.33±0.52	3.50±0.55	3.00±0.01
Total	2.44±0.86	2.56±0.78	2.78±0.65	2.83±0.71	2.61±0.61
			Gel base		
7	0.33±0.52	0.50±0.55	0.50±0.55	1.00±0.63	0.50±0.55
14	0.67±0.52	1.33±0.52	1.50±0.55	1.33±0.52	1.17±0.75
21	1.17±0.75	1.67±0.52	1.67±0.52	1.50±0.55	1.50±0.55
Total	0.72±0.67	1.17±0.71	1.22±0.73	1.28±0.57	1.06±0.72
			Burn injury		
7	0.17±0.41	0.33±0.52	0.33±0.52	0.67±0.52	0.33±0.52
14	0.50±0.55	1.00±0.63	1.17±0.75	1.17±0.41	0.83±0.75
21	0.83±0.75	1.50±0.55	1.50±0.55	1.33±0.52	1.50±0.55
Total	0.50±0.62	0.94±0.72	1.00±0.77	1.06±0.54	0.89±0.76
			***P* value**		
7	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001
14	≤0.001	≤0.001	≤0.014	≤0.001	≤0.001
21	≤0.001	≤0.001	≤0.014	≤0.001	≤0.001

As demonstrated here, the highest scores were in *Hypericum perforatum* group, followed by alpha, silver sulfadiazine, gel base and control group.

epithelialization were observed. In control group; Severe inflammation, ulceration, necrosis, vascular proliferation, absence of collagen deposition, granulation tissue and re-epithelialization were noticed (Figure 2).

Briefly sorting by groups, it was shown as follows: *H. perforatum* group: Severe inflammation, ulceration, vascular proliferation, absence of collagen deposition, granulation tissue and re-epithelialization after 7 days. *H. perforatum* group: Mild inflammation, absence of ulcer, presence of small amount of collagen deposition and granulation tissue, mild inflammation, vascular proliferation, and thin epidermis after 14 days. *H. perforatum* group: Absence of inflammation, absence of ulcer, mature granulation tissue, mild collagen deposition, and complete epidermis after 21 days. Silver Sulfadiazine group: Severe inflammation, ulceration, vascular proliferation, absence of granulation tissue and re-epithelialization after 21 days. Alpha group: Moderate inflammation, ulceration, vascular proliferation after 21 days, absence of collagen deposition, granulation tissue and re-epithelialization. Control group: Severe inflammation, ulceration, necrosis, vascular proliferation, absence of collagen deposition, granulation tissue and re-epithelialization after 21 days (Figure 2).

Pathological study on wound surrounding cells between different groups denoted to the highest scores in *H. Perforatum* group, followed by alpha, silver sulfadiazine, gel base and control group on days 7th, 14th and 21st (Table 3). Comparison of

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Table 3: Pathological study on wound healing cells between different groups

Group	Day	Epithelialization	Macrophages	Angiogenesis	Granulation tissue	Inflammation
H. perforatum	7	2	3	3	2	2
Silver sulfadiazine	7	1	1	1	1	0
Alpha	7	2	2	2	2	2
Gel base	7	0	1	0	1	1
Burn injury	7	0	0	0	0	0
H. perforatum	14	3	3	3	3	3
Silver sulfadiazine	14	1	2	2	1	1
Alpha	14	2	3	3	3	3
Gel base	14	0	1	1	1	1
Burn injury	14	1	1	1	1	1
H. perforatum	21	4	4	4	4	4
Silver sulfadiazine	21	2	2	2	1	1
Alpha	21	3	3	3	3	3
Gel base	21	1	1	2	1	1
Burn injury	21	1	1	1	1	1

As displayed here, the highest scores were visible in *Hypericum perforatum* group, followed by alpha, silver sulfadiazine, gel base and control group.

Table 4: Comparison of means and standard deviation of different groups with each other regarding various wound healing scores

Group	Eepithelialization (Mean±SD)	Macrophage (Mean±SD)	Angiogenesis (Mean±SD)	Granulation tissue (Mean±SD)	Inflammation (Mean±SD)
H. perforatum	2.89 ± 0.13^{b}	3.06 ± 0.13^{b}	3.11 ± 0.13^{b}	3.11 ± 0.11^{b}	3.00 ± 0.13^{b}
Silver sulfadiazine	1.17 ± 0.13^{c}	1.39 ± 0.13^{c}	1.44 ± 0.13^{c}	0.72 ± 0.11^{c}	0.72 ± 0.13^{a}
Alpha	2.44 ± 0.13^{d}	2.56 ± 0.13^{d}	2.78 ± 0.13^{b}	2.83 ± 0.11^{b}	2.60 ± 0.13^{c}
Gel base	0.72 ± 0.13^{a}	1.17 ± 0.13^{ac}	1.22 ± 0.13^{ac}	1.28 ± 0.11^{a}	1.06 ± 0.13^{a}
Burn injury	0.5 ± 0.13^{a}	0.94 ± 0.13^{a}	1.00 ± 0.13^{a}	1.05 ± 0.11^{a}	0.89 ± 0.13^{a}

Alphabetes denote to the statistical significant difference between groups. a: *Hypericum perforatum*, b: Silver sulfadiazine, c: Alpha, d: Gel base. The significance level was considered $P<0.05$. As shown here, the best scores were seen for *H. perforatum* group, followed by alpha, silver sulfadiazine, and gel base group. As displayed here, the highest scores were visible in *H. Perforatum* group, followed by alpha, silver sulfadiazine, gel base and control group

means and standard deviation of different groups with each other regarding various wound healing scores on day 21st was illustrated in Table 4 revealing the best scores for *H. perforatum* group, followed by alpha, silver sulfadiazine, and gel base group.

DISCUSSION

Burn injuries are still a vital public health problem leading to fatal complications and impairment in burnt's social, psychological, physical functioning, aesthetic appearance, and quality of life [14, 15]. In burn treatment, the aim would be to prevent infections and to reach the best functional aesthetic results. Wound healing can be impaired due to pathologic injuries such as burn, frostbite, gunshot, ischemia, diabetes, venous stasis and immune disorders[1, 6, 16]. In burn wound healing, the final

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step is epithelialization that compromise migration, proliferation and differentiation of epithelial cells from wound edges to the injured area. In open full thickness burn wound injuries, epithelialization occurs when granulation tissue is established supporting migration of epithelial cells [9,17].

In severe burn injuries, the conventional therapeutic measures are excision of the injured skin and replacement of epidermis by autologous split-thickness skin graft; while this management is costly, lengthy and risky and can result in further debilitation[18, 19]. So it seems that there is a need for other effective treatments in burn wounds, including regenerative and traditional medicine. Regenerative medicine by employing stem cells and tissue engineering was shown to be a new platform in wound healing through acceleration of wound closure, enhancement of re-epithelialization, increase in angiogenesis, modulation of inflammation and regulation of extracellular matrix (ECM) remodeling, but this treatment modality is expensive, time consuming and needs an equipped laboratory and skilled persons[5]. Herbal products as another alternative in treatment of burn injuries were demonstrated to have therapetic efficacy without any or less toxicity and are less expensive in healing of burn wounds [6, 20], such as *Plantago major* [21], licorice[22], and *H. perforatum*[11] .

H. perforatum (St. John's wort, Kantoron) is a Turkish herbal traditionally used as pain reliever, tranquilizer, antidepressant, parasite-lowering, and also for treatment of pediatric nocturnal incontinence[10, 13]. It can exert insulinotropic effects and regulate endogenous glucose production[11]. *H. perforatum* is nearly as effective as esomeprazole to prevent gastric ulcer[23]. It can has the potential as a curative herbal against obesity-associated complications [24]. In our study, we showed wound healing in burn injuries treated with *H. perforatum* that were significantly associated with re-epithelialization, angiogenesis and formation of granulation tissue together with a decrease in inflammation in absence of any side effects.

Several researchers have successfully employed *H. perforatum* in wound healing[10]. The wound healing activity of *H. perforatum* is due to an increase in stimulation of fibroblast migration, collagen production, and reduction of inflammation, which are important in wound healing leading to the closure of the injured area. As a result of fibroblast proliferation, migration, contraction and collagen production, they play an important role in the wound-healing[10, 13, 25]. *H. perforatum* can be effective in wound repair by decreasing the time of reepithelialization from 21 to 12 days [26]. *H. perforatum* has an important impact on healing of cesarean wounds with a faster repair process and a decrease in pain and pruritus [27]. Najafizadeh et al. evaluated the clinical effect of topical *H. perforatum* in plaque type psoriasis vulgaris[28].

H. perforatum extract was shown to have positive effects on diabetic surgical wounds with fast anti-inflammatory property and a successful healing[29]. It has been successfully utilized in care and treatment of pressure sores. *H. perforatum* extract was shown to be effective on inflammation, fibrosis, and necrosis in corrosive stomach and esophageal burns[30, 31]. *H. perforatum* to be effective in protecting the esophagus and stomach in mild to moderate alkali corrosive burns during subacute period[31]. *H. perforatum* extract had anti-inflammatory, anti-angiogenic, and anti-fibroblastic impacts in corneal alkali burns[32]. In another study, Seyhan compared *H. perforatum* and curcumin in healing of burn wounds and demonstrated them to be effective in burn wound healing [33]. Wound-healing effect of *H. perforatum* was assessed on cultured chicken embryonic fibroblasts revealings a wound healing activity [10].

In our study, we focused on healing effect of *H. perforatum* in comparison to silver sulfadiazine and alpha burn ointments and showed a significant wound healing effect for *H. perforatum* when compared to silver sulfadiazine and alpha burn ointments. As SSD among conventional therapeutic choices of burn has disadvantages and side effects such as leukopenia, neutropenia, methemoglobinemia, erythema multiform, renal toxicity and delay in wound healing[6], and alpha burn ointment is expensive and not available in many regions , *H. perforatum* as a cost-effectiveness and available herbal can enhance wound healing. The strength of our study was the quantitative assessment of tissue changes after treatment by utilzing a scoring system to validate our findings and describe the differences between groups significantly presented by a *P* value. However, some limitations were associated in our study that should be considered in *in vivo* researches of burn treatment; such as remarkable native regeneration potential of the skin in rat

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animal model that should be considered when describing histological features. It seems that employing immunohistochemistry in the studied tissue can clarify healing process in more details. The small sample size used in this study can be another limitation of the present study that in future assessments to be included.

CONCLUSION

In our study, the wound healing effect of *H. perforatum* was compared with silver sulfadiazine and alpha burn ointments in burn injury revealing a significant re-epithelialization, angiogenesis and formation of granulation tissue together with a decrease in inflammation in rat model of burn wound. *H. perforatum* could promote healing process in burn wounds in absence of any side effects. As it is inexpensive, easy to find, and easy to use, *H. perforatum*
by fibroblast migration and stimulation of collagen synthesis can be a target herbal and traditional medicine in treatment of burn injuries. These findings can open a new door in treatment of burn wounds when herbals are targetted.

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CONFLICT OF INTERESTS

The authors of the current manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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