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Effect of oral *Calendula officinalis* on second-degree burn wound healing

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Abstract

Background: Treatment of wounds and burn injuries is very important. Nowadays, the tendency to research complementary medicine has increased.

Method: In this clinical trial, 60 patients hospitalized in the burn ward who met the inclusion criteria were randomly assigned to two groups: intervention (n = 30) and control (n = 30). In addition to treatments, the intervention group received one capsule (2 g) of *Calendula officinalis* daily, for two weeks, and the control group received the placebo. Wound status was assessed with the Bates-Jensen Wound Assessment Tool (BWAT) on the 1st, 7th, and 15th days of the study in both groups.

Results: The mean total score of wound status using BWAT at the 1st, 7th, and 14th days in the intervention group was 48.23, 35.93, and 22.97, respectively, and in the control group was 48.90, 42.57, and 37.8. Statistically, wound condition on the first day was at the same level for both groups. Wound healing scores in the two groups increased during the 1st to 15th days of the study ($P < 0.001$). However, in the intervention group, the range of wound healing changed on days seven and 15 and was greater than in the control group.

Conclusion: Based on the results of this study, *C. officinalis* may have beneficial healing properties and be effective in accelerating the healing of second-degree burn wounds and can be used as a supplement to treat wounds.

Keywords

Oral *Calendula officinalis*, wound healing, second-degree burns

Introduction

Burns are a type of damage to the body caused by heat, electricity, chemicals, friction, or radiation. These conditions are classified into three degrees as superficial or first-degree burns, partial thickness or second-degree burns, and full thickness or third-degree burns.[1,2] Burns are a worldwide health problem. An estimated 180,000 people die annually due to burns.[3]

In the second half of the 20th century, many advances have been made in the field of regenerative medicine, burn therapy, and pharmacotherapy. However, treating burn wounds is still a challenge.[4] There are still challenges that need to be addressed to improve current burn care, especially research in the field of accelerating wound healing.[2]

Many indigenous and biological medicines have been reported to accelerate wound healing.

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Table 1. Demographic characteristics of the two groups.

Variables	Groups		P- Value
	Intervention	Control	
Age			0.49
Mean	30.35	33.6	
SD	11.9	9.67	
Gender			0.79
Male	18 (60)	19 (63.3)	
Female	12 (40)	11 (36.7)	
Marital status			0.79
Single	13 (43/3)	14 (46/7)	
Married	17 (56/7)	16 (53/3)	
Employment status			0.093
Worker	9 (30)	2 (7/6)	
Employee	3 (10)	7 (3/23)	
Housewife	7 (3/23)	4 (3/13)	
Non-governmental	4 (3/13)	10 (3/33)	
University student	4 (3/13)	4 (3/13)	
Unemployed	3 (10)	3(10)	
Education			0.91
Elementary	5 (16.7)	5 (16.7)	
Middle school	5 (16.7)	8 (26.7)	
Diploma	7 (23.3)	6 (20)	
Associate Degree	6 (20)	5 (16.7)	
BMI			0.15
Intervention	24.81	3.53	
Control	26.16	3.79	

Calendula officinalis belonging to the Asteraceae family, commonly known as Pot Marigold or English Marigold, is used in traditional medicine for treating herpes, wounds, ulcers, skin damage, blood purification, scars, and frostbite.[5] It is mainly used because of its various biological activities, like anti-diabetic, analgesic, anti-inflammatory, and anti-ulcer effects to treat many diseases.[6,7]

C. officinalis has many pharmacological properties. It is used for the treatment of skin disorders and pain, and also as an anti-inflammatory, antiseptic, and bactericide agent. Butanoic fraction of *C. officinalis* possesses a significant free radical scavenging and antioxidant activity.[8] *C. officinalis* flowers are useful in reducing inflammation, and accelerating wound healing. As an antiseptic agent, it is used to treat skin diseases, ranging from eczema to skin ulcerations and burns. In addition, *C. officinalis* is used for the treatment of inflammation and ulcers of the stomach . Besides the flavonoids found in *C. officinalis* that are

Table 2. Indicators related to the etiology and percentage of burns in the two groups.

Variable	Groups		P-Value
	Intervention	Control	
Etiology			0.64
Fire	6 (20)	11 (7/36)	
Gas	11 (7/36)	7 (3/23)	
Boiling water	7 (3/23)	7 (3/23)	
Electricity	2 (7/6)	2 (7/6)	
Acid	4 (3/13)	3 (7/11)	
Percentage of burns			0.11
Mean	34.13	38.17	
SD	9.10	10.22	

Table 3. Comparison of wound healing index in the two groups.

Wound Healing	Groups		P-Value
	Control Mean + SD	Intervention Mean + SD	
1st Day	48.90 ± 5.92	48.23 ± 5.51	0.65
7th Day	42.57 ± 5.58	35.93 ± 6.58	<0.001
14th Day	5.62 ± 37.8	22.97 ± 4.31	<0.001

responsible for its anti-inflammatory activity, it also contains carotenoids.[9,10]

The mechanism of the local effects of this plant is not exactly known, but according to studies, the anti-inflammatory properties of this plant are due to its flavonoids and carotenoids. The flavonoids of this plant have high anti-inflammatory properties and prevent the release of harmful enzymes and histamine that cause sensitivity and swelling and improve redness and pain. This plant has a vasoprotective effect and reduces capillary permeability, and is useful for the treatment of capillary fragility. Carotenoids, especially beta-carotene, are the precursors of vitamin A biosynthesis, which along with its manganese cause a healing and anti-inflammatory effect. Also, considering its antimicrobial effect, especially against *Staphylococcus aureus* and *Enterococcus faecalis* bacteria, it can also prevent wound infection.[11]

However, the effect of this medicinal plant in humans has not been evaluated; accordingly, the aim of this study was to evaluate the efficacy of oral *C. officinalis* on wound healing.

Material and methods

Study population and setting

This study was a triple-blind clinical trial that was performed on 60 patients with second-degree burns admitted to Valiasr Hospital in Arak to investigate the effect of oral *C. officinalis* on their wounds. In order to control confounding factors, in addition to inclusion and exclusion criteria, patients were divided into intervention and control groups using block randomization.

Measurements

Inclusion criteria were as follows: second-degree burn wound, burn percentage of between 15 and 50% (based on Lund Browder Chart), age range of 18 to 55 years, no more than 48 h having passed since the burn occurred, hospitalization in the burn ward, willingness to participate in the research, no pregnancy and breastfeeding, no underlying diseases, such as diabetes, cancer, or infectious diseases and non-abuse of drugs (alcohol, drugs, and sedatives). Exclusion criteria were the lack of cooperation to participate in study, patient discharge, transfer to another medical center, and death of the patient. After obtaining informed consent and filling out a demographic data form (age and gender) by

Table 4. Changes in the three stages of wound healing scores.

Groups	Day	Day	Mean difference	SD difference	P-value
Intervention	1	7	12.3	0/68	0/001>
	7	14	12.96	0/65	0/001>
	14	1	−25.26	0/67	0/001>
Control	1	7	6.33	0/69	0/001>
	7	14	4.76	0/51	0/001>
	14	1	−11.1	0/61	0/001>

the researcher (SR), the cases were randomly (four blocks) assigned to two groups: intervention (n = 30) and control (n = 30). At the beginning of the study, the wound condition was assessed by the researcher using the standard Bates-Jensen Wound Assessment Tool (BWAT).

Then, in addition to the usual treatments received in the burn ward, the patients in the intervention group received a capsule containing 2 g of marigold extract for 14 days, and those in the control group received a similar capsule containing a placebo given them by the researcher. Thus, both the patient and the researcher were blinded in the study (Figure 1). Marigold flower was prepared from the Arak Kuhsar Arak Nature Elixir Company and then extracted by the Karaj University Jihad Medicinal Plants Research Institute and turned into a capsule. At the end of the first week, the wound condition was re-evaluated by the researcher with the Bets-Jensen instrument in both groups, and also at the end of the second week of the study. In the end, parameters related to the wound condition were analyzed by statistical software.

Ethical considerations

The study group adhered to the principles of medical ethics introduced by the Health Ministry and the Declaration of Helsinki and legislation in the Medical Ethics Committee of the Arak University of Medical Sciences. In addition, the ethical committee of Arak University of Medical Sciences approved the protocol of the study (IR.ARAKMU.REC 1396.44). It was also registered at the Iran Clinical Trials Center with the code IRCT2017070334880N1.

Statistical analysis

Data were analyzed by SPSS 21 software . Descriptive statistics were used for quantitative data with mean and standard deviation and for qualitative data, frequency and percentage were used. At first, the Kolmogorov-Smirnov test was used to select parametric or nonparametric tests. Due to the normality of the data, parametric tests were used. We used paired t-test, independent t-test, and repeated measures ANOVA to analyze the quantitative variables.

Results

We evaluated 60 patients with second-degree burn wounds, of whom 23 cases (38.3%) were female and 37 cases (61.6) were male. In terms of education level, diplomas and bachelor's degrees (comprising 23.3% each), and guidance school (comprising 26.7%) were more common in the samples of the intervention and control groups, respectively. In terms of occupation, manual laborers comprised 30% and 33.3% of the intervention and control groups respectively. In terms of marital status, single and married people comprised 43.3% and 56.7% in the intervention group and 46.7% and 53.3% of the control group, respectively. Thus, 45% of the total sample were single and 55% were married. Also, regarding BMI, this index in the intervention group was 24.81 ± 3.53 kg/m2 and in the control group was 26.16 ± 3.79 kg/m2. Based on statistical evaluations, there was no statistically significant difference between the two groups (P = 0.157) (Table 1).

The most common cause of burns, with a frequency of 36.7%, was a gas explosion in the intervention group and fire in the control group. Regarding burn-related indices, including burn etiology (P = 0.64) and burn surface (P = 0.11), there was no significant difference between the two groups (Table 2). The percentage of burns was 38.17% in the intervention group and 34.13% in the control group.

Concerning wound condition, the healing condition on the first day was the same for both the

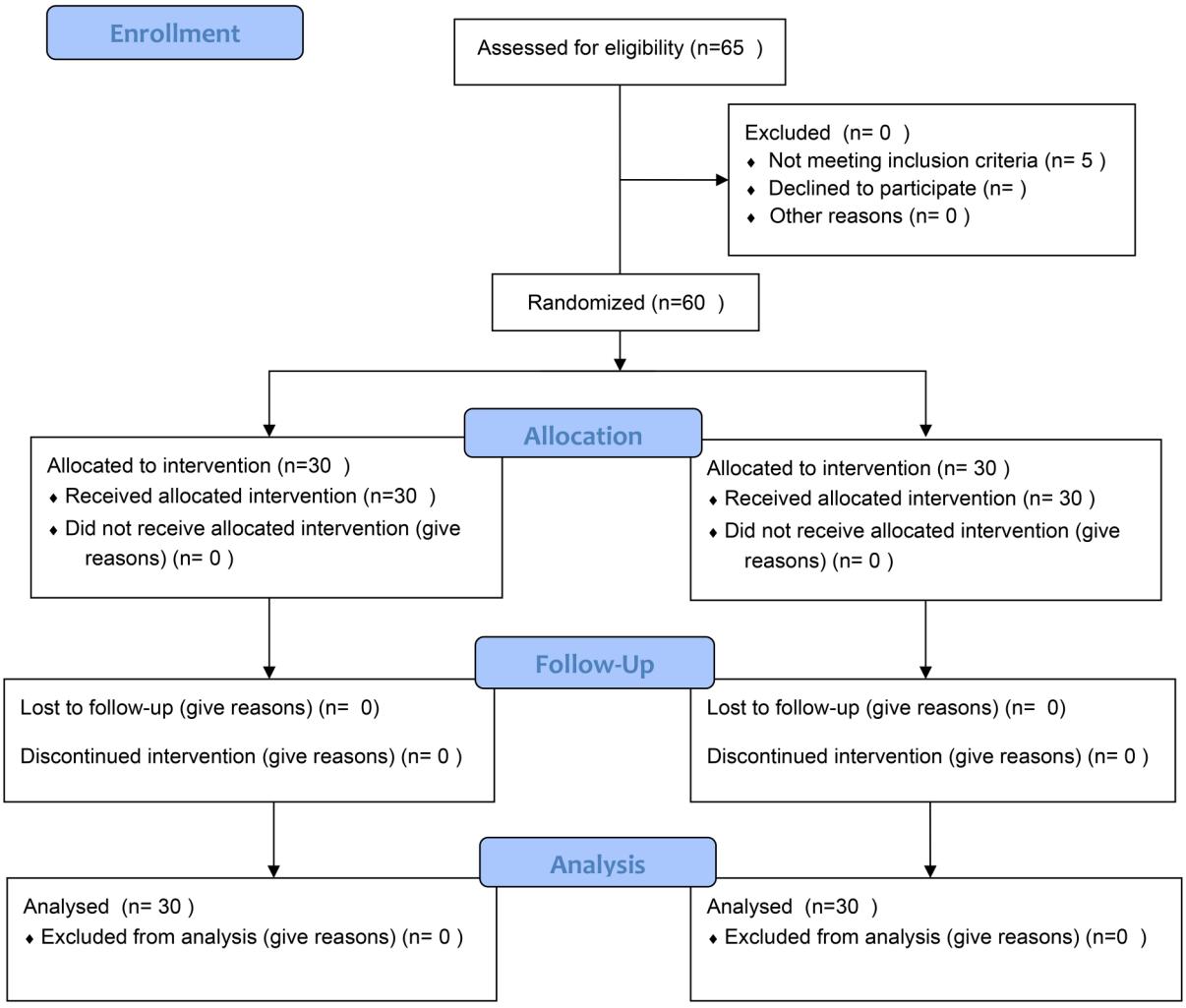

Figure 1. Consort 2010 Flow Diagram.

intervention (48.23 ± 5.51) and control (48.90 ± 5.92) groups; this difference was not statistically significant (P = 0.65). However, the wound healing score on days seven and 14 after treatment was respectively 35.93 ± 6.58 and 22.97 ± 4.31 in the intervention group and lower than the control group (42.57 ± 5.58) (5.62 ± 37.8) and this difference was statistically significant (P <0.001) (Table 3).

The three stages of wound healing in each group were compared in pairs using analysis of variance with repeated measures and showed significant differences (Table 4). Therefore, edible marigold (oral *C. officinalis*) was effective in wound healing in burn patients at all stages.

Discussion

C. officinalis has mainly been used to treat diseases in many studies because of its anti-diabetic, analgesic, anti-inflammatory, and anti-ulcer activities.

In this study, wound condition on the first day was at the same level for both the intervention

and control groups. The wound healing rate in the intervention and control groups increased during the 1st to 15th days of the study (P <0.001). However, in the intervention group, the range of wound healing changed in the second and third periods (days seven and 15) and was greater than the range of wound healing changes in the control group. These results show that the use of *C. officinalis* can be effective in healing second-degree burn wounds.

C. officinalis may facilitate wound healing by increasing both wound angiogenesis, glycoprotein, and collagen metabolism leading to improvements in both local granulation tissue formation and blood circulation.[12,13]

In a study conducted by Shobana et al.,[14] the topical use of herbal ointment containing *C. officinalis* caused significant wound healing, and this result was attributed to the improvement of collagen synthesis, increased wound contraction, changes in interleukin 6, and increased epidermal growth factor (EGF), platelet-derived factor (PDGF), and tumor necrosis factor-alpha (TNF-α) levels.

Hasanoglu et al.[15] mentioned that micronized flavonoid fractions could be used in venous leg ulcer treatment. *Calendula* is effective in improving blood vessel conditions. In addition, they mentioned that lymphatic drainage regulation and reducing edema could be some of the mechanisms for this effect on the healing of wounds.[15–17] Di Perri et al.[18] observed that flavonoid fractions can reduce the complement system activation in vivo and in vitro, which is consistent with our results. In another study, Lonchampt et al.[19] examined the effects of *Calendula* on oxygen radicals in vitro and in vivo and reported its protective effect against active oxygen radicals; but we assessed its effect in vivo.

Recently, a study have demonstrated the effectiveness of micronized flavonoids, found in *C. officinalis* in microcirculation. They have reported that an intact microcirculation is essential for normal healing, and delayed wound healing is tightly attributed to ischemia.[19] Also, in the present study, oral *C. officinalis* consumption was beneficial in wound healing based on evaluations done on days 7 and 14 ($p < 0.05$).

Re et al.[20] showed that some of the components of calendula flower extract in personal care products and cosmetics were not safe and could irritate the skin; however, nothing was mentioned about the safe doses. Yoshikawa et al.[21] observed some gastroprotective effects of its components without mentioning any dose-dependent effects. Also, Andersen et al.[22] indicated that the calendula extract was relatively nontoxic, which is consistent with the present study, in which no side effects were found.

Nikiema et al.[23] also observed that different concentrations of *C. officinalis* gel could promote the proliferation of keratinocytes due to its anti-inflammatory effects and promote wound healing. Also, they mentioned that different concentrations of this gel had significant positive effects on wound healing on days 14 and 21, especially on day 14,[23] but the present study was conducted on the oral type of *C. officinalis*, and we found significant positive effects on wound healing on days 7 and 14.

Accordingly, most studies in this field have been consistent with the results of our assessment, indicating the effectiveness of this plant in wound healing.

Since the number of samples was limited, doing similar studies on larger sample size is recommended.

Conclusion

Based on the results of this study, *C. officinalis* may have beneficial healing properties and be effective in accelerating the healing of second-degree burn wounds and can be used as a supplement to treat wounds.

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