



## Impact of licorice root on the burn healing process: A double-blinded randomized controlled clinical trial

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### ABSTRACT

**Ethnopharmacological relevance:** Due to the known side effects of many synthetic drugs, the use of herbal and natural substances in treating diseases such as burns has been considered. Licorice is a herbal medicine whose stem and underground roots are used in traditional medicine in many countries, including Iran, for anti-inflammatory, stomach ulcer healing, and antimicrobial purposes.

**Aim of the study:** This study investigated the healing effect of hydroalcoholic extract of licorice root on the wound healing process caused by second-degree burns.

**Methods:** The hydroalcoholic extract of licorice was prepared in ethanol solvent, and then the licorice hydrogel product was designed using gelling compounds. Then, in a double-blinded randomized clinical trial, 50 patients with second-degree burns were selected based on inclusion criteria from the patients referred to Yazd Hospital and Isfahan Hospital. Participants were randomly divided into two groups: the control group receiving hydrogel without extract and the intervention group receiving hydrogel containing licorice root hydroalcoholic extract. The intervention lasted for 15 days, and during this period, the wound-healing process was evaluated on days 1, 3, 6, 10, and 15. Data were analyzed using SPSS software with independent T-test and Mann-Whitney U tests with a maximum error of 5 %.

**Results:** The rate of inflammation (From the 3rd day to the 10th day), redness (From the 6th day to the 15th day), pain (on the 3rd day), and burning (From the 3rd day to the 15th day) of the wound in the group that used the hydrogel-containing hydroalcoholic extract of licorice root was significantly lower than in the control group ( $P < 0.05$ ), and the healing process was significantly faster than the control group.

**Conclusion:** Hydroalcoholic extract of licorice root can accelerate the healing process of second-degree burns.

### 1. Introduction

Burns, one of the most common injuries worldwide, are caused by heat, electricity, chemicals, friction, and radioactive materials and cause damage to the skin, muscles, or other tissues.<sup>1</sup> In the United States, more than one million burn victims require medical attention each year, but only 45,000 require hospitalization. There is also a similar situation in the UK, where burns account for 1 % of emergency workload and 0.014 % of hospital admissions, so it is clear that most burns are not severe and

can be managed outside the hospital.<sup>2</sup> Since the second half of the last century, extensive research on medicinal plants has been done in most countries, and then many herbal medicines have been investigated, prepared, and marketed.<sup>3</sup> The degree of burn is determined according to the involvement of different layers of the skin, including the epidermis, dermis, or the lower areas of the skin, including muscles, tendons, and bones. In the 2nd degree burns that were examined in this study, in addition to the epidermis, the dermis is also damaged. Licorice is a herbal medicine whose stem and underground roots are used in

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traditional medicine in many countries, including Iran, for anti-inflammatory, stomach ulcer healing, and antimicrobial purposes.<sup>4-7</sup> Licorice with the scientific name *Glycyrrhiza glabra* L. is a flowering plant of the bean family Fabaceae, and Iran is one of the countries exporting licorice root. The value of licorice root and rhizome is due to the diversity of their chemicals. The most important biologically active substance in licorice root and rhizome is a triterpenoid called glycyrrhizic acid, which is of particular importance in the food and pharmaceutical industries. Due to the various properties of licorice, multiple products such as licorice powder, extract, and juice have long been prepared.<sup>8</sup> In addition, there are several other compounds, including flavonoids, isoflavones, hydroxy coumarin, sterols, and a small amount of essential oil in the roots of this plant.<sup>9</sup> Al-Snafi in traditional uses of Iraqi medicinal plants has recommended the use of this plant in upper respiratory tract congestion and gastric and duodenal ulcers.<sup>10</sup>

Experimental and clinical studies have shown that this plant has various pharmacological effects, including antioxidant, anti-inflammatory, antiviral, antifungal, antibacterial, antiparasitic, and anti-tumor properties; it is an immunomodulator and has protective effects on the liver, stomach, and neurons.<sup>11</sup> The plant's root contains glabridin, which inhibits melanogenesis by inhibiting tyrosinase without affecting DNA synthesis. Therefore, it is known as the safest pigment-lightening agent with the lowest probability of melanoma.<sup>12</sup> Due to the widespread effects of licorice, especially its analgesic, anti-inflammatory, antimicrobial, and lightening effects, it seemed that this plant could be effective in treating burn wounds. Therefore, a hydrogel was prepared from the hydroalcoholic extract of licorice, and its effects on the skin injury caused by second-degree burns were studied.

## 2. Methods

### 2.1. Preparation of hydroalcoholic extract of licorice root and hydrogel

Licorice roots were purchased from a reputable medicinal plants shop in Yazd province, Iran. After confirming its authenticity by the Pharmacognosy Department of the School of Pharmacy, Yazd University of Medical Sciences, Iran, the herbarium code SSU0074 was assigned to it. The plant's dried roots were pulverized with a mill, and the dry powder was moistened with sufficient solvent (ethanol, 80 %); then, after being kept in a closed container for 4 h, it was placed in a percolator. In such a way, inside the percolator, it was in contact with enough solvent, and the solvent passed through it. At this stage, first, the lower outlet of the percolator was left open until the continuous and regular exit of the droplets, and then it was closed. The contents were kept in the closed percolator for 24 h to soak well, then a sufficient amount of solvent (approximately 75 % of the final required volume) was gradually added, and the extract was allowed to drain from the percolator slowly. Finally, the wet mass was compressed well to obtain the maximum amount of liquid residue. The obtained extract was filtered, purified by the decantation method, and dried. Finally, the dry hydroalcoholic extract was obtained at a ratio of 16% from the used root powder. The resulting powder was used to prepare the desired concentrations.

### 2.2. Standardization of phenolic compounds of licorice hydroalcoholic extract

Licorice extract solution (20 µl) was mixed in a test tube with distilled water (1.160 ml) and Folin-Ciocalteu reagent (100 µl). After 1–8 min, 300 µl of sodium carbonate solution (20 % w/v) was added to the contents of the test tube. After shaking the test tubes, they were placed in a water bath at 40 °C for 30 min, and then a spectrophotometer read their absorption at a wavelength of 760 nm. Then the solutions of gallic acid with concentrations of 10, 20, and 100 µg/ml were prepared, and the absorbance of the samples was read.<sup>13</sup> After plotting the

gallic acid calibration curve, the amount of total phenol in the licorice extract was calculated as 0.676 mg/g by placing the extract absorption amount in the standard curve's linear equation.

### 2.3. Preparation of licorice hydrogel

Methylparaben as a preservative, glycerin as a skin moisturizer, carbomer as a strong gel maker in an aqueous environment, and triethanolamine as an alkalinizing agent to neutralize carboxylic acid groups were used to prepare a hydrogel (all materials were made in Iran).

To prepare the hydrogel, 0.4 g of 940 carbomer was added to 100 ml of distilled water, and then 8–10 drops of triethanolamine, 5 ml of glycerin, and 0.15 g of methylparaben were mixed with it.

A sufficient amount of the obtained hydrogel was kept for use in the control group, and from the rest of it, using an adequate amount of licorice extract, a 5% licorice hydrogel was prepared. Licorice hydrogels and non-licorice hydrogels were stored in coded 50 g tubes in a refrigerator (2–8 °C).

## 3. Clinical trial

### 3.1. Sample size

The G-Power software with a significance level of 0.05 and a test power of 80 was used to calculate the sample size. The sample size of 48 people was calculated for two groups.

### 3.2. Sampling, randomization, and blinding method

This study is a double-blinded, randomized controlled clinical trial. Sampling was done by the easy or accessible method to select the cases from patients with second-degree burns referred to Shohadaye Mehrab Hospital (Yazd, Iran) and Imam Musa Kazem Hospital (Isfahan, Iran). Based on the inclusion criteria, they were randomly selected using the RAND() function of Excel software. The participants were divided into two groups of 25 people, including the group receiving topical licorice hydrogel and the group receiving topical hydrogel (placebo). The two-blinded method was used for blinding. The tubes containing licorice hydrogel or hydrogel were coded, and neither the physician nor the patient knew the contents of the tubes.

### 3.3. Intervention and evaluation

According to the physician's diagnosis, patients who had second-degree burns entered the study after obtaining written and informed consent. The inclusion criteria included patients with second-degree burns, patients aged 16–65 years, burns must have occurred no more than 24 h before the start of the treatment and involved less than 15% of the body surface, the absence of severe systemic diseases such as uncontrolled diabetes mellitus, epilepsy, immune deficiency, skin disease, and lack of a history of allergy to licorice. The exclusion criteria included skin sensitivity to the medication used, pregnancy, and exacerbation of the disease or worsening of the patient.

Demographic information of the patients, including age, sex, weight, underlying diseases, and medications, was recorded. The condition of the lesions was evaluated for pain intensity, burning, inflammation, redness, and general appearance.

The patients in both groups used the medication topically twice a day for 15 days without dressing. The patients were advised to report any problems to their physician immediately.

The burned area was evaluated for pain intensity, burning, redness, and inflammation on days 1, 3, 6, 10, and 15 of the onset of the burn. Redness and inflammation of the wound were scored based on Tables 1–2. Pain and burning were scored based on the VAS scale<sup>14</sup> (Fig. 1).

**Table 1**  
Inflammation scoring scale.

Inflammation	Score
No inflammation	0
Mild	1
Moderate	2
Severe	3

**Table 2**  
Redness scoring scale.

Redness	Score
No Redness	0
Redness less than 25 % of the burn area	1
Redness 25–50 % of the burn area	2
Redness in more than 50 % of the burn area	3

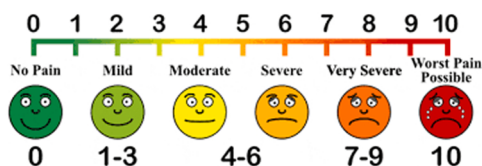


Fig. 1. The Visual Analog Scale (VAS).

3.4. Statistical analysis

The collected data were coded and entered into SPSS statistical software version 20. Descriptive data were reported using mean, standard deviation, frequency, and percentage. Before analyzing the data, the Kolmogorov-Smirnov test examined quantitative variables in terms of normality. Data with normal distribution in the two groups were compared over time using the Repeated Measurement test. The generalized Estimating Equations (G.E.E) test was used to compare the severity of the complication before and after the treatment. If the data were not normal, the non-parametric equivalent tests were used. A significance level of 5 % ( $P < 0.05$ ) was considered for data comparison.

4. Results

4.1. Consort flow diagram

In this study, 82 patients with skin burns were referred to the desired hospitals. Considering the inclusion and exclusion criteria, 28 in the licorice hydrogel group and 26 in the hydrogel group were entered (Fig. 2).

4.2. Demographic data

Patient’s demographic information is summarized in Tables 3–5. The results of the K-square test showed that the observed differences between the two groups in terms of sex, type of burn, burn site, and underlying disease are not statistically significant. As a result, the two groups are identical regarding these variables (Table 3). The normal distribution of three quantitative variables, including age, weight, and percentage of burns, was examined by the Kolmogorov-Smirnov test, and then the appropriate test was selected to compare them. The results showed that the two variables of age and weight have a normal distribution, but the percentage of burns does not have a normal distribution, so to compare it in the two groups, the relevant non-parametric test was used (Table 4).

Due to the homogeneity of age and weight variances in the two groups, the independent t-test was used to compare the mean of these two parameters. This test showed no significant difference between age

and weight in the two groups. Due to the heterogeneity of variance of burn percentage in the two groups, a non-parametric test, the Mann-Whitney U test, was used to compare the burn percentage of burn. This test showed that the two groups with a 95% confidence interval are significantly different in terms of burn percentage (Table 5).

4.3. Burn assessment

The wound’s redness, burning, inflammation, pain, and general appearance on days 1, 3, 6, 10, and 15 were evaluated, and the mean scores were calculated and compared between the two groups. Due to the Non-normal distribution of all these variables, a nonparametric test, the Mann-Whitney test, was used to compare the two groups.

4.4. Assessment of redness of the burned area

According to the findings, on the first day, the participants in the placebo group had significantly more redness in the burn area. On the third day, the two groups had no significant difference in redness. From the sixth day onwards, the redness score decreased in both groups, which was significantly higher in the group using the hydrogel-containing licorice extract than in the control group. Hydroalcoholic extract of licorice root significantly reduced the redness of the burn area from the sixth day onwards (Table 6).

4.5. Assessment of burning of the burned area

According to the results, each participant in the intervention and control groups experienced an average of severe burning in the burn area on the first day of the study, which decreased in the following days. The rate of reduction of burning on the third day onwards was significantly higher in the group that used hydrogel-containing licorice extract. The hydrogel containing licorice root hydroalcoholic extract significantly reduced burning (Table 7).

4.6. Assessment of inflammation of the burned area

According to the results, on the first day, moderate inflammation was observed in all participants. On the third day, the inflammation in the licorice group decreased, but the patients in the placebo group continued to experience moderate inflammation as on the first day. The severity of inflammation decreased in the licorice hydrogel group from the third day and the control group from the sixth day, so the reduction was more significant in the licorice group (Table 8).

4.7. Assessment of pain

Burn pain on the first day was similar and severe in both groups. However, from the third day onwards, the pain intensity decreased in both groups but a greater reduction was observed in patients who used the hydrogel-containing licorice extract. From the sixth day onwards, none of the patients reported pain (Table 9).

4.8. Assess the general appearance of the burned area

Findings from the evaluation of the general appearance of the wound show that over time the general appearance of the injury has improved in both groups, while until the tenth day, there is no significant difference between the two groups. But on the 15th day, participants who used the gel containing licorice extract had a significantly improved wound appearance (Table 10).

The sample images of the burned area of the participants and their recovery process are shown in Figs. 3–5.

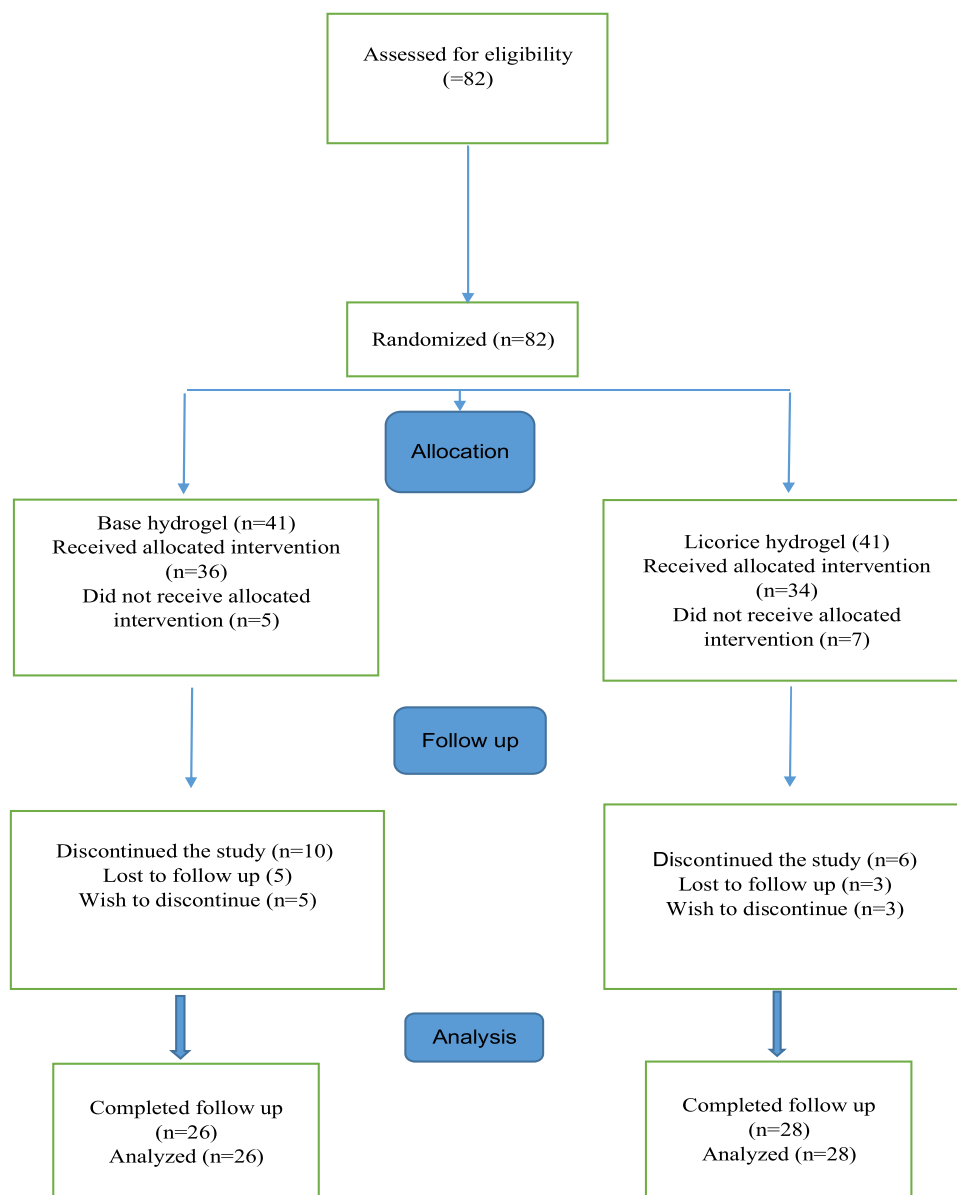


Fig. 2. Consort flow diagram.

**Table 3**  
Frequency and comparison of demographic variables in the two groups.

Variable	Classification	Licorice hydrogel group	Base hydrogel group	P value
Sex	Male	18 (72 %)	19 (76 %)	0.747
	Female	7 (28 %)	6 (24 %)	
type of burn	Hot liquid	17 (68 %)	18 (72 %)	0.989
	Fire	6 (24 %)	5 (20 %)	
	Electricity	1 (4.2 %)	1 (4.2 %)	
	Hot material	1 (4.2 %)	1 (4.2 %)	
burn site	Hand	12 (50 %)	16 (64 %)	0.314
	Foot	9 (37.5 %)	9 (37.5 %)	
	head, and chest	0 (0 %)	0 (0 %)	
	abdomen	2 (8.3 %)	0 (0 %)	
		1 (4.2 %)	0 (0 %)	
underlying disease	Yes	2 (8.3 %)	4 (16.6 %)	0.384
	No	23 (92 %)	21 (84 %)	

**Table 4**  
The Kolmogorov-Smirnov test results to investigate the distribution of quantitative demographic variables.

Variable	z-score	P value	Distribution	Test type	Test
Sex	0.555	0.917	Normal	Parametric	The independent t-test
Weight	0.645	0.800	Normal	Parametric	The independent t-test
Percentage of burns	1.412	0.037	Non-Normal	Non-Parametric	The Mann-Whitney U test

**5. Discussion**

Many people suffer from burns every year, which lead to complications such as disability, the spread of infection, and death, and the patient may suffer cosmetic and psychological disorders. Second-degree burns are a wide range of burns that destroy the epidermis and damage the dermis. In recent years, special attention has been paid to traditional

**Table 5**

Mean and standard deviation of age, weight, and percentage of burns in the two groups.

Variable	Licorice hydrogel group		Base hydrogel group		P value
	Mean	S.D	Mean	S.D	
Age (year)	32.33	12.869	38.69	13.383	0.994
Weight (kg)	72.67	15.863	75.27	11.252	0.504
Burn percentage (%)	5.5	2.992	3.6	2.98	0.005

medicine. In this regard, plants such as *Aloe vera* L., Sesame, Abukhalsa (*Arnebia euchroma* L.), walnut, and hemp (*Cannabis*) have been studied for burns. In this research, according to the properties mentioned for licorice in traditional medicine texts, a hydrogel was prepared from the hydroalcoholic extract of licorice root, and its effects on wound healing caused by second-degree burns were investigated. The findings show that compared to the control gel, the hydroalcoholic extract of licorice root reduces the redness of the burn area from the sixth day and the burning, inflammation, and pain from the third day. Also, the general

**Table 6**

Evaluation of the effect of licorice extract gel on redness caused by burns.

	1st day		3rd day		6th day		10th day		15th day	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
<b>Licorice hydrogel</b>	2.4	0.764	2.72	0.614	1.4	0.645	0.76	0.436	0.12	0.332
<b>Hydrogel</b>	2.8	0.645	2.68	0.690	1.92	0.640	1.12	0.600	0.60	0.500
<b>P value</b>	0.030		0.934		0.007		0.023		0.000	

**Table 7**

Evaluation of the effect of licorice extract gel on burning caused by burns.

	1st day		3rd day		6th day		10th day		15th day	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
<b>Licorice hydrogel</b>	3.16	0.554	1.12	0.332	0.88	0.526	0.20	0.408	0.04	0.200
<b>Hydrogel</b>	3.00	0.707	2.72	0.678	1.88	0.600	1.08	0.640	0.44	0.507
<b>P value</b>	0.400		0.000		0.000		0.000		0.001	

**Table 8**

Evaluation of the effect of licorice extract gel on inflammation caused by burns.

	1st day		3rd day		6th day		10th day		15th day	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
<b>Licorice hydrogel</b>	2.00	0.500	1.32	0.476	0.84	0.374	0.48	0.510	0.12	0.332
<b>Hydrogel</b>	2.08	0.400	2.08	0.909	1.44	0.651	0.84	0.473	0.32	0.748
<b>P value</b>	0.394		0.015		0.000		0.001		0.540	

**Table 9**

Evaluation of the effect of licorice extract gel on pain caused by burns.

	1st day		3rd day		6th day		10th day		15th day	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
<b>Licorice hydrogel</b>	3.24	0.523	1.44	0.507	0.00	0.000	0.00	0.000	0.00	0.000
<b>Hydrogel</b>	3.24	0.663	2.72	0.614	0.00	0.000	0.00	0.000	0.00	0.000
<b>P value</b>	0.787		0.000							

**Table 10**

Evaluation of the effect of licorice extract gel on the general appearance of the wound caused by burns.

	1st day		3rd day		6th day		10th day		15th day	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
<b>Licorice hydrogel</b>	2.52	0.586	1.80	0.408	1.24	0.436	0.88	0.332	0.36	0.490
<b>Hydrogel</b>	2.44	0.712	1.92	0.572	1.36	0.569	1.00	0.289	0.64	0.490
<b>P value</b>	0.626		0.447		0.341		0.179		0.050	

appearance of the wound was more favorable on the 15th day in the group of patients who used hydrogels containing hydroalcoholic extract of licorice root. In this regard, the findings of Oloumi et al. showed that ethanolic extract of licorice reduces xylene-induced ear edema and carrageenan-induced foot edema in rats.<sup>15</sup> Another study found that the aqueous extract of licorice root causes a significant increase in fibroblasts, capillary growth, hydroxyproline content, and tensile strength of wounds. Also, after the intervention, the wound area in the group that used this extract was significantly less than the placebo group.<sup>16</sup>

Licorice root contains several compounds of the family of triterpenes, saponins, flavonoids, isoflavones, hydroxycoumarin, sterols, and, to a lesser extent, essential oils. The most crucial active ingredient is glycyrrhizin, a glycyrrhizic acid in the form of sodium and potassium salts.<sup>17</sup> This phenolic substance has antioxidant activity and can inhibit inflammatory factors. such as protein kinase C, phospholipase A, phosphodiesterase, prostaglandin, and histamine.<sup>9</sup> The phenolic compounds in licorice root have also been shown to reduce free radicals in the cellular space and the inflammatory process by regulating the expression of cyclooxygenase, nitric oxide synthase, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ),



Fig. 3. Hot oil burn on the right foot (Participant code: 11) and its healing process with a hydrogel containing hydroalcoholic extract of licorice root.



Fig. 4. Second-degree burns caused by boiling water in the patient's right hand (Participant code: 16) and its healing process using hydrogel containing hydroalcoholic extract of licorice root.

and interleukin 6 (IL6) as anti-inflammatory agents.<sup>18</sup> Licorice root also has antimicrobial effects, which in turn heals wounds faster. Al-Snafi's review reported that ethanolic, methanolic, and chloroform extracts of licorice root have an inhibitory effect on *Escherichia coli*, *Salmonella*, and *Staphylococcus aureus*.<sup>19</sup> Rodino et al. also reported that licorice ethanolic extract impacts *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mutans*, *Streptococcus sanguinis*, *Enterococcus faecalis*, and *Actinomyces viscosus*.<sup>20</sup> It has been found that licuroside and glycyram in licorice hydroalcoholic extract can inhibit the growth of some microorganisms including *Staphylococcus aureus* and *Candida albicans*.<sup>21</sup> Inhibition of gram-positive microorganisms can be particularly valuable in preventing burn infections.

Although no previous study directly points to the role of licorice root hydroalcoholic extract in healing wound burns, the present study's findings and previous findings confirm its anti-inflammatory, antimicrobial, anti-inflammatory effects, and analgesic effects.

In this study, no side effects were observed with the topical application of licorice, while the oral use of licorice can cause complications such as edema, high blood pressure, hypokalemia, and arrhythmia.<sup>22</sup>

## 6. Conclusion

Based on the present research findings, the hydroalcoholic extract of licorice root can accelerate the healing process of wounds caused by second-degree burns and can be considered a complementary treatment

for mild and moderate burns.

## Study limitations

In this study, the intervention and control groups were not identical in burn percentage, so the group using the hydrogel containing hydroalcoholic extract of licorice root had a higher burn percentage. However, given that the burn wound healing process was significantly more desirable in the intervention with licorice, this does not affect the results and may even indicate that the actual effect is better than the effect obtained.

## Declarations

none.

## Ethical approval

Before conducting the study, the code of ethics was obtained from the ethics committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1398.179). With the approval of the research by the Iranian registry of clinical trials (IRCT), the code IRCT20191106045356N5 was obtained. All patients consciously signed the consent form. During the study, they were under the supervision of a physician. In case of exacerbation of the disease, they were excluded



**Fig. 5.** Second-degree burns caused by gasoline fire in the patient's chest and neck (Participant code: 17) and its healing process with a hydrogel containing hydroalcoholic extract of licorice root.

from the study and treated appropriately.

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### CRediT authorship contribution statement

M.Z. and A.R. conceived of the presented idea and supervised the implementation and findings of this work. M.E. developed the theory and performed the computations. B.H and F.M and A.R performed the work. All authors discussed the results and contributed to the final manuscript.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Consent to participate

All of the participants in this research have been explained: the research may not be of direct benefit to me. my participation is completely voluntary. my right to withdraw from the study at any time without any implications to me.

### Consent to publish

All of the authors give consent for the publication of identifiable details, which can include photographs, tables, and details within the text to be published in the above Journal and Article.

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