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Original Article

Healing effects of Arnebia euchroma on burn wound in rats: a systematic review

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Abstract

***Background & Aims*:** Nowadays, herbal medicine with antimicrobial and anti-inflammatory activities, such as Arnebia euchroma, has been considered in the treatment of burn wounds. Therefore, this study aimed to determine the healing effect of Arnebia euchroma L on burn wounds in rats by reviewing the results of published studies in this field.

***Materials & Methods*:** The keywords "Arnebia euchroma", "burn", and "rat", and their synonyms were explored in PubMed, Scopus, and ScienceDirect for English articles, and SID, Magiran, and Irandoc for Persian articles without time limitation until May 4, 2021. Inclusion criteria for this study were laboratory research articles focused on the effect of Arnebia euchroma L on wound healing in rats. Finally, the included studies were reviewed and assessed according to the given criteria.

***Results*:** Amongst the seven articles included in this research, four articles studied the healing effect of the medicine on second-degree burn wounds, one article addressed third-degree burn wounds, and two articles generally studied burn wounds. Arnebia euchroma L has been found to be effective in healing burn wounds in approximately 57% of studies, while the rest of the studies have emphasized its ineffectiveness in accelerating burn wound healing.

***Conclusion*:** The literature review demonstrated that Arnebia euchroma is effective in both healing and accelerating the recovery of burn wounds. Since there is an insignificant difference between the number of studies that have found this medicine effective and the number of those that have found it ineffective, further studies are required to determine the effectiveness of this medicine.

***Keywords*:** Arnebia euchroma, Burn, Systematic review, Wound

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Introduction

Cutaneous burns and their complications are among the serious hazards that are life-threatening to humans and result in disability. Burn is considered tissue damage, most commonly caused by hot water and liquids, flammable gases, and building fires, and can systematically or locally affect the skin as the first defensive barrier of the body, ultimately reducing its defensive strength (1, 2).

According to World Health Organization (WHO) counts in 2018, burns and injuries, on average, cause 180,000 deaths every year, with high rates of mortality occurring in poor and less developed countries such as Africa and Southeast Asia (3). According to the available data, burn incidents account for around 6.48% of total accidents in Iran (4). According to the Burn Research Center at the Iran University of Medical Sciences, the prevalence of burn injuries in Iran is eightfold the global statistics (5). The number of people with burn injuries in need of hospital services is approximately 40 per 100,000 population in Iran, and the mortality rate has reached 8.3 in recent years, while in developed countries, it is lower than 5-15 people (6).

Ongoing hospital services are more required in developing countries than in other countries due to their higher rates of burn incidents, as these injuries can lead to disability and even death, as well as irreparable consequences such as depression and isolation (7-9). Moreover, the costs of treatment and health services for burn patients are also high. The average treatment rate for an adult with a burn injury was estimated at more than $73,532 in the United States as a developed country in 2012 (10).

Since burn injuries have physical, socio-economic, and psychological effects on patients and societies, accelerating the treatment of burns has long been considered by physicians and health communities (8). The most commonly administered topical agents in treating burn wounds are silver sulfadiazine, silver nitrate, and mafenide acetate (11). Despite the favorable therapeutic effects of synthetic medications, people are less attracted to them due to their side effects. Instead, they prefer to use herbal medicines more due to their effective compounds, fewer side effects, and economic benefits (12, 13). In fact, more than 80% of people worldwide use herbal medicines in the face of cutaneous problems (14, 15).

Iranian nomadic and rural populations use several medicinal plant species to heal cutaneous lesions (16). The root of Arnebia euchroma (Persian: Abukhalsa or Havachoubeh; from the Boraginaceae family) has been introduced as one of these traditional plants in Iranian traditional and folk medicine literature for the treatment of burn wounds (17). This plant has a herbaceous and hairy appearance (18), and it is laminated, papery long, red, and odorless, which gives off color after exposure to water (12). Arnebia euchroma grows in the Himalayas, western Tibet, and northern Africa and is indigenous to southeastern Iran (19, 20). The compounds such as shikonin, naphthoquinone, and alkannin, which are available in the root of this plant (20), make it a plant with anti-inflammatory, antiseptic, anti-fungal, anti-influenza, anti-HIV, anti-bacterial, and wound healing activities.

Consequently, it is used in traditional medicine through smoking or ointment (12). The oil of this plant is also known to be useful for healing burn injuries (21). In addition, the literature in this field suggests that even the root of this plant can be used as an analgesic for earaches and toothaches (22). The alkaloids in the root of this plant (alkannin and shikonin) reduce the compound contents such as malondialdehyde, carbonyl, and reactive oxygen species (ROS) , ultimately preventing oxidative stress and resulting in its anti-inflammatory and wound healing activities (12, 23, 24).

In recent decades, several studies have addressed the effect of Arnebia euchroma on the treatment of burn wounds. Saghafi et al. (8) found that Arnebia euchroma ointment can reduce the wound size to some extent and has a better effect on superficial burns than other wound dressings. Hoseini-Tahmasbi et al. (12), in a study entitled "Effect of Arnebia euchroma root extract on burn wound healing in Balb/c mice," concluded that the Arnebia euchroma root has an insignificant healing effect on second-degree burns.

Nikzad et al. (11) also concluded that the Arnebia euchroma plant has no significant effect on the healing process of burns. Since several studies have addressed the effect of the Arnebia euchroma plant with different findings and there is no review article in this field, the present study aims to systematically review the studies on the healing effect of the Arnebia euchroma plant on burn wounds.

Materials & Methods

The present systematic review aimed to determine the healing effect of Arnebia euchroma on burn wounds in rats by reviewing the results of published studies in this field. For this purpose, PubMed, Scopus, and ScienceDirect databases were explored for retrieving English articles, and SID, Magiran, and Irandoc databases were used for retrieving Persian articles. The literature search in the above-mentioned scientific databases, based on the search strategy presented in Table 1, was performed independently by two researchers and was referred to a third person in case of any discrepancies. Keywords were searched in all sections of the articles, including title, abstract, text, and keywords. Literature searches were conducted without time limitations until May 4, 2021. The criteria for inclusion and exclusion are stated in Table 2.

Table 1. Resource search strategy in scientific databases

Time limitation	**Till 04 May 2021**
Language limitation	English and Persian
Database	PubMed, Scopus, ScienceDirect, Magiran, SID, Irandoc
#1	"Arnebia euchroma"
#2	"Burn wound " OR "burns"
#3	"Wound Healing"OR "Healing, Wound" OR "Healings, Wound" OR "wounds Healings"
Search	#1 AND #2 AND #3

Table 2. PICOs, inclusion criteria and exclusion criteria applied to database search

PICOS	**Inclusion criteria**	**Exclusion criteria**
Population	Rats	Other animals and humans
Intervention	Arnebia euchroma ointment	Other materials
Comparison	Does not exist	Does not exist
Outcome	Burn wound healing	Other results (examining surgical wound healing and laser wound healing)
Study design	Laboratory studies	All brief reports, letters to the editor, conference abstracts, observational studies, review articles

In order to evaluate the quality of the studies, three authors independently checked the quality of the articles using the evaluation tool for laboratory studies (SciRAP) (25). This tool contains 16 questions. If an item was not applicable to the essay, it was not scored (not applicable (N.A.)). The final score was calculated using the following equation:

$$\text{SciRAP score} = F + (PF*0.5)\ T * 100 / T \quad (1)$$

Equation 1 shows the calculation of the SciRAP score, where F is the number of “fulfilled” criteria, PF

is the number of “partially fulfilled” criteria, and T is the total number of criteria, excluding criteria that have been removed. The calculation of the score takes into account the weight attributed to individual criteria, i.e., each criterion is multiplied by its weight. The final score is between 0 and 100. The articles with the score of 0 to 49 were categorized in "low quality" branch and removed. Studies with scores of 50 to 80 were considered as "moderate quality" cases and were retained cautiously. Finally, articles with scores higher than 80 were remained and put in the category of "high quality" studies.

Following the literature selection based on the study inclusion and exclusion criteria, data were collected using a data extraction form according to the study objectives. A table was designed to extract data from the included studies. The table consisted of the author's name, year of publication, study location, study type, sample size, intervention group, control group, side effects, study objectives, and results. Data extraction was done independently by two members of the research team. In case of disagreement, they were referred to a third person. We conducted the data analysis through the content analysis method. The content analysis method uses quantitative techniques that convert data quantitatively (percentage and count).

Results

A total of 1,916 articles were found for the present review research, 123 of which were eliminated due to duplication. After removing 1,786 irrelevant articles and one article with no available full text, six articles remained for review in the present study. Another related article was also included in this study after reviewing the sources of six selected articles. Also, studies achieved enough score in the quality assessment step and remained for further investigations. The inclusion and exclusion process of articles is shown in a PRISMA diagram in Figure 1 (26).

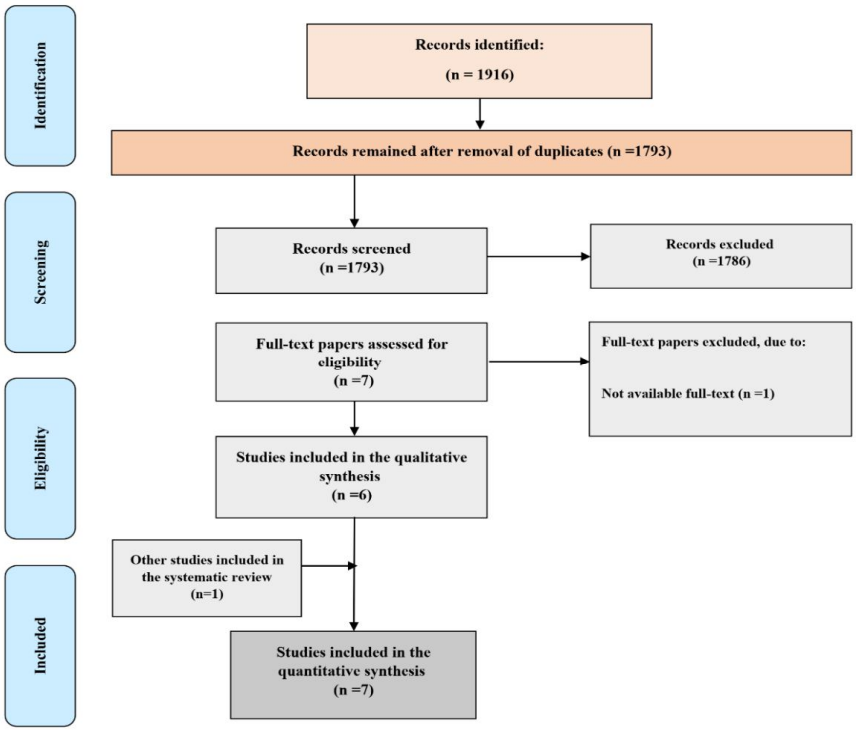

Fig. 1. PRISMA diagram for searching resources

Among the seven articles, three were in Persian, four were in English, and all the reviewed articles were laboratory studies. Approximately 71% of the studies (n = 5) used Arnebia euchroma L to assess its healing effect on burn wounds. One article (14.28%) used the root of Arnebia euchroma L, and the other article (14.28%) employed the leaves of Arnebia euchroma L plant.

Approximately 57% of the articles (n = 4) studied the effect of the medicine on second-degree burn wounds, while one article assessed the effect of the medicine on third-degree burn wounds, and the other two articles analyzed the effect of the medicine on burn wounds in general.

Around 86% of the articles (n = 6) used sulfadiazine in the control group and compared it with Arnebia euchroma L for its effect on burn wound healing. Furthermore, the base ointment, normal saline, vaseline, honey wax-based herbal medicine, cold cream, and goat lipid were among the other medications used in the control group to be compared with Arnebia euchroma L.

The statistical population in one of the articles (14.28%) consisted of diabetic rats, while lab mice and rats were studied in other articles. The study results showed that approximately 57% of the articles (n = 4) considered Arnebia euchroma L effective in healing burn wounds, and 43% of the articles (n = 3) stated that this medicine has no significant effect on accelerating the recovery of burn wounds. Although 57% of the studies confirmed the effectiveness of this medicine, it still can't be concluded that Arnebia euchroma L is an effective medicine in accelerating the healing and recovery of burn wounds and needs more examination in this subject to fully prove its effectiveness. Table 3 presents the full characteristics of the reviewed studies.

Table 3. Results of the literature review included in the study.

First author' s name/publication year	Study location	Study type	Study objective	Sample size	Intervention group	Control group	Side effects	Main result	Score	Quality
Nasiri et al.(27) /(2015)	Mazandaran	Clinical trial	Determination of the healing effect of topical treatment with Arnebia euchroma on second-degree burn wounds in rat	Fifty rats were divided into five groups of 10 rats.	Groups 4 and 5: 5% and 10% Arnebia euchroma were wound dressed daily for 30 days.	Group 1: The wound was washed and wound dressed with normal saline only once a day for 30 days. Group 2: A base ointment was used once a day for 30 days. Group 3 was treated with 1% sulfadiazine ointment daily for 30 days.	No side effects and toxicity	Arnebia euchroma ointment was an effective treatment for burn wounds compared to SSD and could be considered as an alternative topical treatment for burn wounds.	92.8%	High quality

Pirbalouti et al. (30)/(2009)	Pirbalouti et al. (29)/(2011)	Ashkani-Esfahani et al. (28)/(2012)	**First author' s name/publication year**
Shahrekord	Shahrekord	Shiraz	**Study location**
Clinical trial	Clinical trial	Clinical trial	**Study type**
Evaluation of burn healing properties of Arnebia euchroma and Malva sylvestris	Evaluation of the burn healing properties of Arnebia euchroma ointment in diabetic rats	Study of the healing effect of Arnebia euchroma ointment in comparison with sulfadiazine in third-degree burn wounds	**Study objective**
Fifty-four rats were divided into six groups of 9 rats.	Thirty-six rats were divided into four groups of 9 rats.	48 rats were divided into four groups of 12 rats	**Sample size**
Group 4 was treated with goat lipid ointment containing Arnebia euchroma extract.	Group 3: Diabetic rats treated with Arnebia euchroma ointment	Two groups received 10% and 20% Arnebia euchroma every 24 h for 28 days.	**Intervention group**
Group 1 was treated with cold ointment. Groups 2 & 3 were treated with cold cream containing two extracts. Group 5 was treated with goat lipid. Group 6 was treated with silver sulfadiazine ointment.	Group 1: Normal rats with base ointment. Group 2: Diabetic rats with base ointment. Group 4: Diabetic rats treated with silver sulfadiazine ointment	With no intervention. Sulfadiazine group was wound dressed every 24 h for 28 days.	**Control group**
Nothing reported.	Nothing reported.	Nothing reported.	**Side effects**
Wound shrinkage was significantly faster and higher in goat lipid-treated animals containing Arnebia euchroma root extract and cold ointment containing Malva sylvestris extract. The epithelialization period was shorter in animals treated with goat lipid containing Arnebia euchroma. The results showed that Arnebia euchroma ointment effectively accelerated the healing of burn wounds in rats.	Animals treated with Arnebia euchroma significantly reduced burn wound size and higher healing compared to other groups (p<0.05).	Arnebia euchroma is more effective than sulfadiazine in treating second-degree burn wounds, and 10% Arnebia euchroma is more effective.	**Main result**
86.66%	50%	75%	**Score**
High quality	Moderate quality	Moderate quality	**Quality**

Hoseini-Tahmasbi et al. (12)/(2013)	Saghafi et al. (8)/(2018)	**First author' s name/publication year**
Shahrekord	Tehran	**Study location**
Clinical trial	Clinical trial	**Study type**
Effect of Arnebia euchroma on second-degree burn wound healing in Balb/c mice	Study of the effect of Arnebia euchroma ointment on the healing of deep second-degree burn wound in rats	**Study objective**
One hundred five mice were divided into five groups of 20 mice and one group of five mice.	24 rats (12 rats in the intervention group and 12 rats in the control group)	**Sample size**
Intervention groups 1 and 2, which included 1% and 10% of Arnebia euchroma root, were used twice daily for 21 days.	Arnebia euchroma ointment (daily wound dressing until complete recovery)	**Intervention group**
Control group. Control group (negative) on which the intervention was not performed. The control group received 1 g of Vaseline ointment twice a day for 21 days. The control group (positive) received silver sulfadiazine ointment twice daily for 21 days.	Vaseline wound dressing (daily wound dressing until complete recovery)	**Control group**
Nothing reported.	Nothing reported.	**Side effects**
The highest recovery was observed in the groups of silver sulfadiazine, without intervention, vaseline, 1% Arnebia euchroma, and 10% Arnebia euchroma, respectively. The silver sulfadiazine group showed the highest effect among the study groups, so the Arnebia euchroma root could not effectively heal second-degree burn wounds in mice.	An herbal medicine containing Arnebia euchroma extract has no significant effect on the healing process of deep second-degree burn wounds in rats compared to the control group (vaseline). There was no significant difference in the amount of collagen and inflammatory cells between the two groups. The wound size in the intervention group was more significant than the control group in all three days (5, 15, 25), which indicates that the wound in the control group had better healing (P=0.040).	**Main result**
75%	72.72%	**Score**
Moderate quality	Moderate quality	**Quality**

First author' s name/publication year	Study location	Study type	Study objective	Sample size	Intervention group	Control group	Side effects	Main result	Score	Quality
Nikzad et al. (11)/(2010)	Kashan	Clinical trial	Study of the healing effect of Arnebia euchroma leaves on second-degree burn wounds in adult rats.	Forty rats were divided into four groups of 10 rats.	Honey wax-based herbal medicine and containing Arnebia euchroma leaves (daily wound dressing for 30 days)	Group: 1. Normal saline group. 2. Treated with silver sulfadiazine. 3. Honey wax-based herbal medicine without Arnebia euchroma leaves (daily wound dressing for 30 days).	Nothing reported.	Arnebia euchroma leaf has no significant effect on the healing process of second-degree burns in rats and can even delay healing. In contrast, the herbal medicine without Arnebia euchroma leaves based on honey wax had a significant effect on healing second-degree burns.	85.71%	High quality

Discussion

The present study aimed to assess the healing effect of Arnebia euchroma on burn wounds through a literature review. This review revealed that Arnebia euchroma is effective in healing and accelerating the recovery of burn wounds. Although multiple efforts have been made in medicine to find an effective medication to accelerate the healing of burn wounds, studies are still ongoing as no definitive medication has been introduced to accelerate the wound healing process (31). Nowadays, the application of plant-based medications with antimicrobial and anti-inflammatory activities has been considered significant. Therefore, research on these sources paves the way to develop new medications (32). Arnebia euchroma is one of the medications, the effectiveness of which in wound healing has been proven in some studies. Rafiei et al. (2020) studied the effect of Arnebia euchroma ointment on the healing process of surgical wounds, and its effect on wound healing was confirmed, showing a significant difference in the wound healing rate of the intervention group compared to the control group (18). Biochemical studies have also suggested that Arnebia euchroma root ointment, with its chemical compounds such as shikonin and alkannin and its extensive medicinal and biological activities, has wound healing, anti-bacterial, anti-fungal, antiviral, anti-inflammatory, anti-tumor, and anti-cancer activities, and it is used in East Asia to treat burnt skin and wounds (33, 34). Haghbeen et al. (35) also conducted a study to investigate the antimicrobial activity of Arnebia euchroma. Moreover, the chemical analysis of this study indicated that the dried roots of this plant contain approximately 8.5% shikakai pigment, and after optimizing the results, it was proved that these pigments were ineffective against some fungi and gram-negative and gram-positive bacteria; however, they had a significant effect against Micrococcus luteus (35). Aliasl et al. (2015) studied the healing effect of Arnebia euchroma ointment on

wounds induced by fractional CO_2 laser in rats. Their results indicated less erythema and crusting in the group using Arnebia euchroma ointment compared to other groups (36) and confirmed the healing effect of Arnebia euchroma on wounds.

Some studies examined the effectiveness of Arnebia euchroma in treating burn wounds in other populations. According to Ogurtan et al. (37), the healing effect of the Arnebia euchroma plant on burn wounds in rabbits was assessed, through which complete healing was achieved as a result of using this medicine, except in cases of severe burns. This result could be evidence of the pervasive effect of Arnebia euchroma in the treatment of burn wounds.

However, the form of medication can also significantly affect its effectiveness and the extent to which the medication heals burn wounds or other wounds, which has been cited as an important issue in other studies involving medications that affect burns. As in the study of Tehrani et al. (38) on the healing effect of sesame oil ointment on burn wounds in rats and the investigation conducted by Afshari et al. (39) on the healing effect of lavender essential oil with sesame oil and silver sulfadiazine on wounds in Mus musculus mouse, the results showed a positive effect of sesame oil on burn wound healing. It was also stated that the difference between the results of the studies of Tehrani et al. (38) and Afshari et al. (39) could be due to the consumption of sesame oil ointment in comparison with its liquid form. The above results indicate the effect of the medicine form on the medicine's effectiveness, and the same can be depicted for Arnebia euchroma.

According to a study conducted by Mohsenikia et al. (40) entitled "Wound healing effect of Arnebia euchroma gel on excisional wounds in rats," the positive effect of this medication was confirmed on reducing inflammation, increasing the rate of epithelialization, and rapidly shrinking the wound (40). Ilkhani et al. (41) also used Arnebia euchroma ointment in different combinations to heal wounds. They finally reported the healing effect of combining Arnebia euchroma ointment with pistachio oil (Pistacia atlantica) and animal oil in nine days, Arnebia euchroma ointment with eucerin base in 11 days, and honey in 11 days (41). Furthermore, Boström et al. (42) and Al-Dujaili et al. (43) demonstrated that Arnebia euchroma root oil has optimal effects in accelerating the healing process of cutaneous wounds in rabbits. According to the results, most studies have used the ointment form of Arnebia euchroma, and other forms of this herbal medicine, such as gels, may lead to alterations in the study results. Therefore, further studies are required to determine the effect of Arnebia euchroma medicine on its effectiveness in wound healing.

Other noteworthy points in the studies are the lack of side effects reported in most studies and the slight difference between the number of studies that have confirmed the effectiveness of Arnebia euchroma and the number of studies that have considered it ineffective in healing burn wounds, which also necessitates further studies on a broader and more homogeneous population, more research on the Arnebia euchroma leaf and root, and its various medicinal forms.

We were informed about the limitations of the present study. The most important one is that there was a low number of related articles with minor differences in their results. Therefore, it was hard to conclude whether Arnebia euchroma L is an effective medicine in accelerating the healing and recovery of burn wounds or not. We suggest that more examinations in this subject must be conducted to prove its effectiveness. Another limitation of this study was the inaccessibility of the full text of some articles. In addition, since the included articles were limited to articles in Persian and English, related studies written in other languages were not involved in the present study, which may have affected the results.

Conclusions

Cutaneous burns and their complications are considered serious hazards, which are life-threatening and associated with disability. Herbal-based medicines, such as Arnebia euchroma, are considered in the

treatment of burn wounds. Several studies have addressed the effect of the Arnebia euchroma plant with different findings. Therefore, reviewing the healing effect of Arnebia euchroma L on burn wounds, based on the results of published articles, can be an effective way to determine its real effect on the mentioned wounds. Reviewing the results of studies showed that there is no significant difference between the number of studies that have found this medicine effective and the number of those that have found it ineffective. Therefore, further studies are suggested to determine the effectiveness of this medicine.

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Conflict of interest

The authors report no conflict of interest.

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Ethical statement

The current study is a systematic review and does not have a code of ethics.

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