Review Article

Herbal Medicine in Treatment of Recurrent Aphthous Stomatitis: A Literature Review

R. Rezvaninejad [1], N. Navabi [2], MR. Khoshroo [3], N. Torabi [4], Z. Atai [5]✉.

[1] Assistant Professor, Department of Oral Medicine, School of Dentistry, Hormozgan University of Medical Sciences, Hormozgan, Iran
[2] Associate Professor, Department of Oral Medicine, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran
[3] Assistant Professor of Physiology, Department of Biology, Kerman Branch, Islamic Azad University, Kerman, Iran
[4] Assistant Professor, Department of Periodontics, Dental Branch, Islamic Azad University, Tehran, Iran
[5] Associate Professor, Kerman Social Determinants on Oral Health Research Center, Department of Oral Medicine, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran

Abstract

Background and Aim: Recurrent aphthous stomatitis (RAS) is the most common oral mucosal lesion in the general population. Different treatments have been used for RAS, including herbal medicine. In this study, the randomized clinical trials (RCTs) on the effect of medicinal plants on RAS were systematically searched and reviewed.

Materials and Methods: The literature from 1985 to 2015 in the PubMed, Scopus, Embase, Cochrane and Medline databases were searched using the relevant keywords. After screening, 15 articles were reviewed.

Results: Herbal medicine has been used in the treatment of RAS for reducing the pain and healing time and promoting ulcer healing. Most herbal products are in the form of mouthwash.

Conclusion: Herbal medicine can be used as an alternative therapy for RAS.

Key Words: Herbal Medicine, Recurrent Aphthous Stomatitis, Literature Review, Randomized Clinical Trial

✉ Corresponding author:
Z. Atai, Associate Professor, Kerman Social Determinants on Oral Health Research Center, Department of Oral Medicine, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran

Z_atai@kmu.ac.ir

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Introduction

Recurrent aphthous stomatitis (RAS) is a common condition characterized by recurring aphthous ulcers [1,2]. The prevalence of RAS in the general population is approximately 20% [2]. The etiology of RAS is unknown, and different factors can cause oral aphthous ulcers including genetic factors, hematologic deficiency, immunologic abnormality and local trauma [3]. Many systemic disorders are correlated with RAS including Behcet's syndrome, vitamin deficiency, Periodic fever adenitis pharyngitis aphthous ulcer (PFAPA), cervical adenopathy and Sweet's syndrome (SS) [4].

RAS is classified according to the clinical presentation of minor ulcers, major ulcers, and herpetiform ulcers [2]. The ulcers of the minor type are the most common ulcers [2,5]. The diameter of minor ulcers is smaller than 1cm and they last for 7 to 14 weeks. The ulcers of the major

type are larger than 1cm and remain in the oral cavity for weeks [2]. The herpetiform type is characterized by multiple (more than 10) small painful ulcers [6].

The diagnosis of RAS is by the exclusion of other diseases [2]. The clinical appearance and medical history help distinguish RAS [3]. Improving the ability of swallowing and speaking are the goal of the treatment of this condition [2]. The management of the disease depends on the severity of the ulcers [2]. Various treatments are available such as antibiotic, anti-inflammatory, topical anesthetic and steroid therapy, and the best treatment for this disease involves the drugs with fewer side effects [3]. Corticosteroid therapy of RAS has many side effects for patients [7].

Nowadays, patients tend to use natural medicine to avoid the side effects of synthetic drugs. For instance, the olive leaf extract contains *oleuropein* antioxidant compounds [8]. Also, it has antiviral and antimicrobial effects [8]. *Ginger* is a native plant and one of the most common medicinal herbs, which contains an anti-inflammatory agent that is used as a sedative and pain regulator [9,10]. *Chamomile tincture* is used for the treatment of RAS, gingivitis, and laryngitis. It has anti-inflammatory, antibacterial, antifungal, and analgesic effects [11].

Ageratina pichinchensis, a wild native plant, is used in Mexico for the treatment of mouth ulcers and for reducing the healing time [12]. The leaves of *Myrtus communis* are used as a mouthwash for the treatment of RAS and oral candidiasis [13]. Different effects have been reported for this herb such as antihyperglycemic, antibacterial, analgesic, and anti-inflammatory effects [13]. *Yunnan baiyao* is a herbal medicine that is widely used for healing the wounds such as RAS [14].

Myrrh is the thorny species of *Commiphora* that is used as an antiseptic, analgesic, and anti-infective agent for wound healing [15]. *Aloe vera* plant has been used for the management of oral lichen planus and RAS. The biologic effects of *Aloe vera* include antifungal, anti-inflammatory, anticancer, and immunomodulatory activities [15]. *Rosa damascena* has been used in traditional medicine and has anti-inflammatory, antioxidative, and antibacterial properties. These properties improve ulcer healing [16].

Camel thorn can endure the most unfavorable environmental conditions and has anti-inflammatory and protective membrane characteristics [17]. It can act as a histidine decarboxylase inhibitor and can prevent the formation of ulcers [17]. *LongoVital* (a herbal-based tablet which contains the recommended daily dose of the most necessary vitamins) is effective in reducing the pain and healing time [18]. *Turmeric* is a dry rhizomatous plant with anti-inflammatory and antioxidative effects that prevents and suppresses the inflammatory process [19].

Rhizophora mangle aqueous bark extract (RMABE) is known as a traditional medicine in different regions [20]. It has been used as an antiseptic and antifungal agent [20] and it reduces the healing time [20]. The leaves and flowers of *Satureja khuzistanica* are used in herbal medicine [24]. The mouthwash made of this plant is considered as an analgesic and wound healer [21]. *Zataria Multiflora Boiss (Shirazi thyme)* is a native plant in Iran. It is useful for pain relieving and wound healing [22]. *Anthemis nobilis* is a remedy for various diseases and has a strong anti-inflammatory and a mild antibacterial effect [22].

Herbal medicine can improve the quality of life and prevent the side effects of chemically synthesized drugs. Therefore, in this study, the randomized clinical trials (RCTs) were searched and reviewed using the keywords related to medicinal plants used in the treatment of RAS. We found which plants and in which forms are effective and can be suggested to clinicians for the treatment of RAS. It seems that patients are more interested in treating wounds with herbal medicine than with synthetic drugs.

Materials and Methods

The literature from 1985 to 2015 in the PubMed, Scopus, Embase, Cochrane, and Medline databases were searched using the relevant keywords. The topical and systemic treatments of RAS were included in this study. The exclusion criteria in this research consisted of aphthous-like ulcers and studies in languages other than English. The searched keywords were as follows:

1-Remedies (MeSH), Herbal Medicine (MeSH), Traditional Medicine (MeSH), Plants (MeSH)

2-Oral Ulcer (MeSH), Recurrent Aphthous Ulcer (MeSH)

First, two researchers independently screened the articles, and then, they compared the search results together according to the MeSH terms in the titles. The researchers imported the articles into the EndNote software program (Clarivate Analytics, Thomson Reuters, USA). Duplicate and irrelevant articles and non-RCTs were excluded. Afterwards, the abstracts and full texts of the remaining articles were studied. Finally, we selected 15 articles for this study. The analyzed data are presented as percentage and frequency with the use of Microsoft Excel (version 2015) software program.

Results

The search of the PubMed, Scopus, Embase, Cochrane, and Medline databases using the relevant MeSH terms revealed 689 articles. We excluded duplicate and irrelevant manuscripts and reviewed the 60 remaining papers. Afterwards, the abstracts and full texts of the papers were studied to examine their eligibility. Finally, 15 studies were selected (Diagram 1). The designs of all the selected studies were triple- and double-blind.

The publication date of the selected articles ranged from 1985 to 2015. Overall, the number of RCTs has followed an ascending trend from 2013 to 2015 (Diagram 2), which prompts journals to publish these types of articles. Most of the studies have reported positive results related to herbal medicine such as decreasing the pain severity and size of the ulcers and reducing the healing time without any adverse effects. Among the reviewed medicinal plants, *Chamomilla*, *Myrtus communis*, *Camel thorn*, *Yunnan baiyao*, *RMABE* and *Satureja khuzistanica* were greatly effective in wound healing and pain relieving.

The medicinal plants have been most commonly used as a mouthwash for the treatment of oral ulcers (Diagram 3), and usually, the leaves of the plants, applied three or four times a day, have been used for this purpose (Table 1).

Discussion

The majority of the evaluated studies have reported favorable results related to herbal medicine such as decreasing the pain and size of the ulcers and reducing the healing time without any adverse effects. Currently, people tend to change their lifestyle and use herbal medicine due to the safety of medicinal plants.

The effective agents in *Chamomilla* are *Camazolene* and *Azulene* distillates and flavonoids. *Azulene* and *Camazolene* have anti-inflammatory and analgesic characteristics [11]. Also, the flavonoids are known to have anti-inflammatory effects [11]. The efficacy of *Camel thorn* is due to flavanone glycosides (*Alhagitin* and *Alhagidin*) that are similar to *naringenin* [17]. *Anthemis nobilis* contains *Azulene* compounds that have anti-inflammatory effects in the oral cavity when used as a mouthwash [22]. The active ingredients of *Zataria multiflora*, which induce antimicrobial effects, are *carvacrol* and flavonoids [22].

It appears that the olive leaf extract has a phenolic component (*oleuropein*) that can treat RAS [8]. It is applied as an antioxidant, antiviral, and antimicrobial agent [8]. *Ginger* has three main active ingredients with unique properties [10]. These chemical constituents are *gingerol*, *shogaol*, and *zingerone* that may have anticancer, anti-inflammatory, and antioxidative effects [10].

The major antioxidant and anti-inflammatory substance in *turmeric* is *curcumin* (yellow pigment) [19]. Inhibiting the production of reactive oxygen and preventing inflammatory reactions have been related to the decreasing rate of release and metabolism of arachidonic acid [19]. *Ageratina pichinchensis* contains galectin-7, a chemical compound responsible for the wound healing activity, which can induce cellular proliferation [12]. *Myrtus communis* is used as the *amlexanox* oral paste and helps in reducing the healing time with the active ingredients of benzyl alcohol, galectin, glycerol monostearate, mineral oil, pectin, petrolatum and sodium carboxymethyl-cellulose [13,22]. The *Aloe vera* mucoadhesive gel contains an active ingredient at a 5% concentration with antiulcer activity [15]. The Myrrh-based oral mucoadhesive gel containing furanoeudesma-1,3-diene, which is an anti-inflammatory agent, is considered to have mucous membrane protection activity [15]. *Rosa damascena* mouthwash contains tannic acid as the active ingredient and induces wound healing and ulcer protection [16].

RMABE contains a biologically active complex

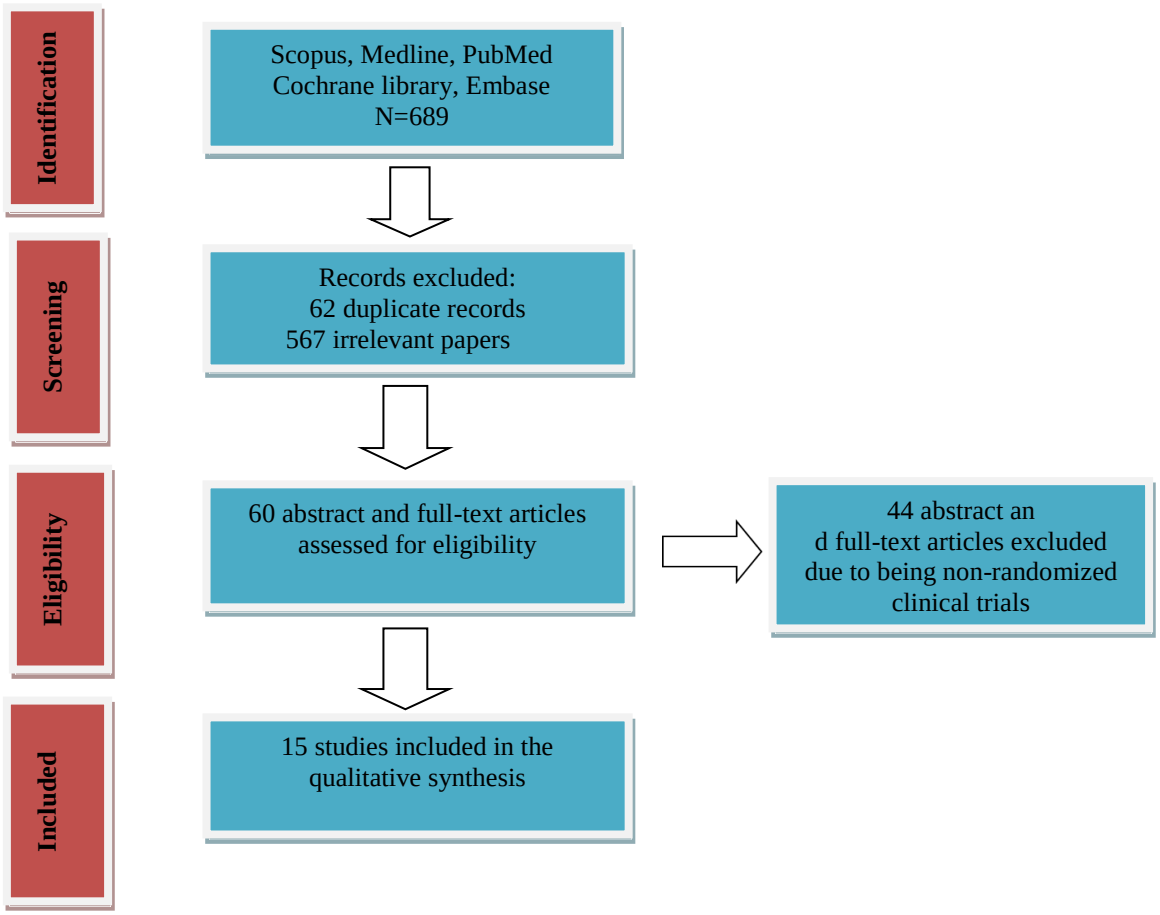

Diagram 1. Systematic review searching

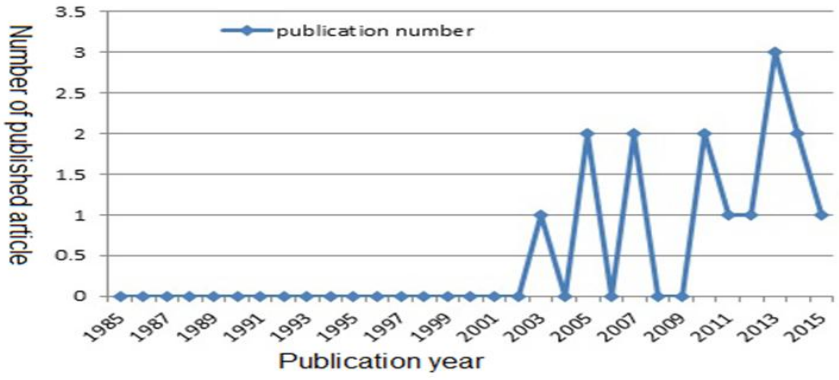

Diagram 2. Number of published randomized clinical trials (RCTs) on herbal medicine used for the treatment of recurrent aphthous stomatitis (RAS)

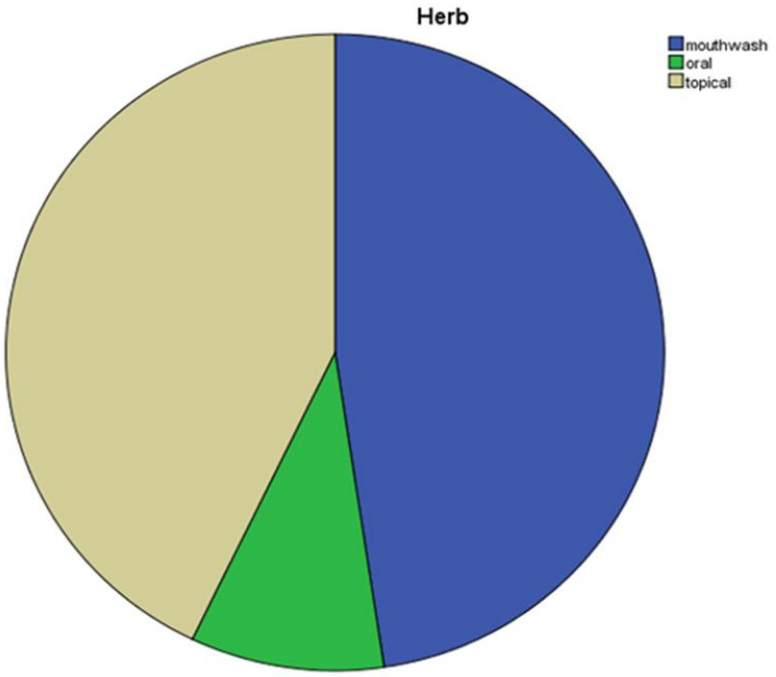

Diagram 3. The therapeutic form of the plants used for the treatment of oral ulcers

with an antimicrobial effect that includes tannins (as the main active component), free carbohydrates, saturated long-chain fatty acids, essential oil and phytosterols [20]. The extract and essential oil of *Satureja khuzistanica* contain *carvacrol*, the main constituent of this plan, which is used as an antimicrobial and analgesic substance for wound healing [21].

Conclusion

The majority of the reviewed studies have reported satisfactory results related to herbal medicine such as decreasing the pain and size of the ulcers and reducing the healing time without any side effects. Among the studied medicinal plants, *Chamomilla*, *Myrtus communis*, *Camel thorn*, *Yunnan baiyao*, *RMABE* and *Satureja khuzistanica* have been greatly effective in wound healing and pain relieving. We recommend traditional medicine as an alternative approach for the treatment of minor RAS.

Table 1. The name, portion, form, and dosage of the herbs

Herb	Portion	Form	Dosage
Chamomilla tincture	Leaves	Mouthwash	10 drops, each time for 3 minutes, TID
Ageratina pichinchensis	Aerial parts	Paste	Topical application, TID
Myrtus communis	Leaves	Paste	Topical application, QID
Yunnan baiyao	Roots	Toothpaste	1g, regular tooth brushing for 3 minutes, BID
Aloe vera	Leaves	Oral mucoadhesive gel	Topical application, QID
Myrrh	Leaves	Oral mucoadhesive gel	Topical application, QID
Rosa damascena	Flowers	Mouthwash	5ml, each time for 30 seconds, QID
Purslane	Leaves	Capsule	235mg, BID
Ginger	Dried rhizome	Oral mucoadhesive gel	Topical application, QID
LongoVital	Leaves, flowers, seeds	Vitamin tablets	TID
Camel thorn	Upper portion, roots, flowers	Mouthwash	Each time for 1 minute, QID
Turmeric	Dried rhizome	Powder	Topical application, BID
Rhizophora mangle aqueous bark extract (RMABE)	Bark	Paste	Topical application, QD
Satureja khuzistanica	Flowers	Mouthwash	5 drops, each time for 1 minute, QID
Essential oil of Satureja khuzistanica	Leaves	Mouthwash	5 drops, each time for 1 minute, QID
Zataria multiflora	Leaves	Mouthwash	10 drops, each time for 1 minute, 5X a day
Anthemis nobilis	Leaves	Mouthwash	10 drops, each time for 1 minute, 5X a day
Myrtus communis	Leaves	Mouthwash	10 drops, each time for 1 minute, 5X a day
Olive	Leaves	Mouthwash	10 drops, each time for 2 minutes, QID
Zataria multiflora+ Anthemis nobilis	Leaves	Mouthwash	10 drops, each time for 1 minute, 5X a day

QD=once a day, BID= two times a day, TID= three times a day, QID=four times a day, 5X=five times

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