

NATURAL THERAPEUTIC AGENTS IN THE TREATMENT OF RECURRENT APHTHOUS ULCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Recurrent aphthous ulcer is a painful oral mucosa ulcer that affects about 20% of the population. Researchers have recently presented new therapeutic options, including herbal pharmaceuticals. We wanted to see how different herbal therapeutic agents affected the size of the aphthous ulcer, pain intensity, and healing time in this systematic review and meta-analysis. A systematic search was performed to extract articles from the Saudi Dental Library, Google Scholar, Science direct, SciELO, Directory of Open Access Journals, Cochrane Library, and PubMed. We included 9 articles with a total of 844 patients (441 cases and 403 controls). The ulcer size progression was significantly reduced on the 3rd (SMD -0.70; 95 percent confidence interval (CI) [-1.23, -0.17], P=0.010) and 5th days (SMD -0.92; 95 percent CI [-1.66, -0.18], P=0.003) days. However, this reduction was not significant on the 7th day (SMD -0.41; 95% CI [-0.97, -0.15], P=0.15). There was a significant decrease in the pain intensity within the 3rd (SMD -2.14; 95% CI [-3.64, -0.63], P=0.005), 5th (SMD -1.88; 95% CI [-3.17, -0.58], P=0.005), and 7th days (SMD -1.87; 95% CI [-3.19, -0.54], P=0.006). Ulcer healing duration was significantly decreased post-treatment (SMD -0.96; 95% CI [-1.81, -0.10], P=0.03). All herbal medicines effectively reduce ulcer size and pain intensity, limiting ulcer healing duration. Aloe vera gel, hydroalcoholic extract of *Punica granatum* (PG), and camel thorn distillate were most effective in decreasing the ulcer size. Moreover, PG extract displayed the best prognosis in reducing pain intensity and minimizing the healing duration.

Key words: Herbal medicine, Recurrent aphthous ulcer, Meta-analysis, Systematic review, Dentistry.

Introduction

The most common oral mucosal disease is recurrent aphthous stomatitis (RAS). The fundamental etiology and pathology, however, remain unknown [1]. Every medical professional, particularly dentists, should understand the integrating clinical, histological, and molecular concepts of RAS during the initial examination. There are three major types of aphthae according to distinct RAS appearances as follows: (i) major (MaRAS or Sutton's disease)—larger and deeper RAS that heal slowly and often cause scarring, (ii) minor (MiRAS or Mikulicz's aphthae)—containing >80% of all RAS cases and measuring up to 1 cm in diameter, and (iii) herpetiform (HeRAS)—manifesting as multiple recurrent clusters of small ulcers (<4 mm in diameter) [2, 3].

The lesion exhibits self-healing within 7–10 days, without leaving a scar [4, 5]. Some patients with severe pain and difficulty in eating do not require treatment and should be treated using palliative care [6, 7]. RAS is prevalent across all ages in developed countries [7, 8]. The incidence is high in women, non-smokers, the white race, and those with high socioeconomic status [9, 10].

The largest study on recurrent aphthous ulcer (RAU) comprised 10,000 young adults from 21 different countries and demonstrated that 38.7% and 49.7% of men and women suffered from RAU in their lives [11]. RAS treatment aims to relieve pain, prevent secondary infection, and promote healing. However, topical anti-inflammatory and anti-allergic medicines play an important role in the treatment of mild aphthous ulcers [12].

There are reports on several treatment options. Amlexanox 5%, for example, speeds healing and reduces pain, erythema, and lesion size [13, 14]; laser treatment is an alternative remedy for oral disorders characterized by pain and inflammatory reactions, as well as those requiring tissue regeneration. By reducing edema and pain and promoting cellular bio-stimulation, this therapy aids anti-inflammatory responses [15].

For decades, natural herbal medications have been widely used as an alternative therapy for RAS in various countries. They have been shown to lower the severity of pain and the duration of ulcers. One of these therapeutic alternatives to sesame is a natural phenolic component and a significant lignan extracted from sesame seeds (*Sesamum indicum*) and sesame oil [16].

Sesamol's anti-cancer therapeutic potential has been studied in several investigations. It has antioxidant, antimutagenic, anti-hepatotoxic, anti-inflammatory, anti-aging, and chemopreventive qualities, as well as acting as a metabolic regulator [17, 18]. However, to the authors' knowledge, no previous studies have comprehensively investigated herbal medicine efficacy in RAS treatment. As a result, the purpose of this study was to look into the usage of herbal medicine and its usefulness in the treatment of RAS.

Materials and Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were used to report this systematic study.

Search strategy

From 2010 to 2020, we conducted a comprehensive electronic search in numerous well-known databases, including Saudi Dental Library, Google Scholar, Science direct, SciELO, Directory of Open Access Journals, Cochrane Library, and PubMed, with time and language constraints.

Eligibility criteria and study selection

The inclusion criteria were as follows:

- Research was conducted from January 1, 2010, to December 30, 2020.
- Randomized clinical trials.
- Double-blinded studies.
- Triple-blinded clinical trials.
- Patients without systemic diseases.
- English publications.
- No restrictions on age, sex, and race.
- Only patients diagnosed with RAS.
- Herbal medicine as the therapeutic agent (natural products).

The exclusion criteria were as follows:

- Studies with no access to availability.
- Animal studies.
- Duplication publications.
- Cases or trials without a control group.
- Reviews.
- Books.
- Research reports without relevant or adequate information.
- Published in any foreign language.
- Published before 2010.
- Chemical products as the therapeutic agent.

Data analysis

For the interest analysis, we used Review Manager 5.4 to conduct the qualitative data synthesis. Several known databases were systematically searched, including the Saudi Dental Library, Google Scholar, Science direct, SciELO, Directory of Open Access Journals, Cochrane Library, and PubMed. We combined the search terms and limited the study to the English language. According to the PRISMA checklist, all articles were screened based on their title, abstract, and full text. The collected data were subsequently analyzed using a forest plot design.

Study selection

The electronic search approach yielded 69 papers, which were reduced to 61 when duplicate publications were removed. Among the 61 articles considered eligible for further evaluation, 50 were excluded after the title and abstract screening for irrelevant outcomes or incorrect target population. Moreover, we excluded two articles for inappropriate analysis after performing a full-text assessment. The qualitative synthesis of the present review eventually contained 9 papers (**Figure 1**).

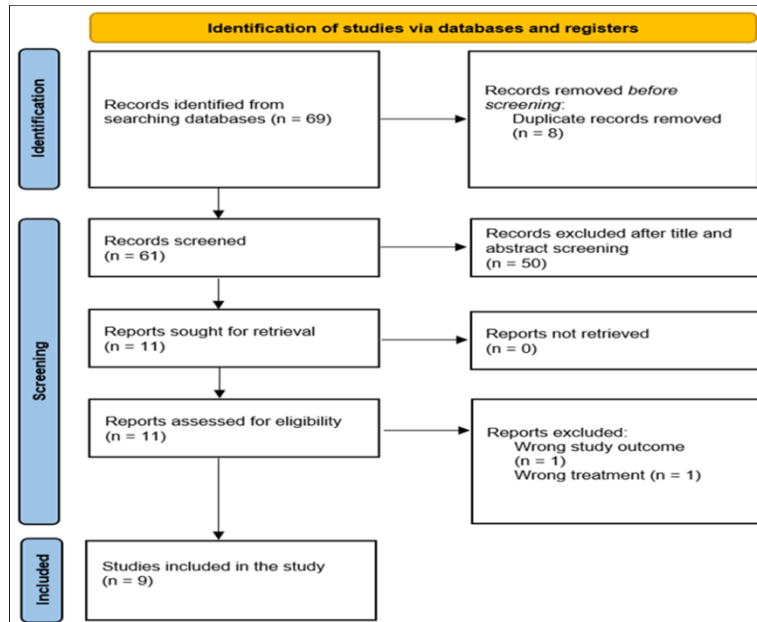


Figure 1. PRISMA flow chart

Results and Discussion

The general characteristics of the nine studies selected for this review are summarized in **Table 1**. Among these, two studies were conducted in China [19, 20], five in Iran [21-25], one in Saudi Arabia [26], and one in Belgium [27]. All studies were published as journal articles and/or

dissertations in English from 2010 until 2020. Moreover, all studies were conducted as *in vivo* human trials. However, there was no difference in the research aim; all studies evaluated the efficacy and safety of different herbal medicines for RAS.

Table 1. Study characteristics, including interventions

Authors	Country	Techniques	Vivo (Human)	Aims of study
Ghalayani <i>et al.</i> , (2013) [21]	Iran	A randomized, double-blind, and placebo-controlled study	<i>In vivo</i> (Human)	To assess the efficacy of <i>Punica granatum</i> extract on the clinical management of RAS.
Liu <i>et al.</i> , (2012) [19]	China	A randomized, double-blind, placebo-controlled investigation conducted across three stomatology clinical centers	<i>In vivo</i> (Human)	To assess the efficacy of Yunnan Baiyao herbal extract formulated in toothpaste as an alternative therapy for minor RAS.
Darakhshan <i>et al.</i> , (2019) [22]	Iran	This study was divided into two segments: (i) laboratory procedures that involved the preparation of palmar-plantar erythrodysesthesia topical gel; (ii) a clinical trial that assessed its effects on RAS	<i>In vivo</i> (Human)	To determine the effects of native pomegranate from western Iran and not the central regions, on RAS lesions.
Shi <i>et al.</i> , (2020) [20]	China	A clinical trial	<i>In vivo</i> (Human)	To develop and test the efficacy of aloe vera fermentation gel in reducing healing time and restoring microbial diversity in the oral cavity of patients with RAS.
Babae <i>et al.</i> , (2015) [23]	Iran	A triple-blind clinical trial study	<i>In vivo</i> (Human)	To assess the therapeutic effects of <i>Zataria multiflora</i> in treating oral aphthous lesions.
Hoseinpour <i>et al.</i> , (2011) [24]	Iran	A randomized, double-blind, placebo-controlled investigation	<i>In vivo</i> (Human)	Mouthwash containing <i>Rosa damascena</i> extract was more effective than the placebo in the treatment of recurrent aphthous stomatitis.

Mansour <i>et al.</i> , (2014) [26]	Saudi Arabia	A randomized, double-blind, and placebo-controlled study	<i>In vivo</i> (Human)	To assess the clinical efficacy and safety of novel customized natural oral mucoadhesive gels, containing aloe vera or myrrh as the active ingredients in treating MiRAS.
Deshmukh & Bagewadi, (2014) [27]	Belgium	A randomized clinical trial	<i>In vivo</i> (Human)	To assess and compare the efficacy of Curcumin with triamcinolone acetone gel in treating MiRAS.
Pourahmad <i>et al.</i> , (2010) [25]	Iran	A randomized, double-blind, and placebo-controlled clinical trial.	<i>In vivo</i> (Human)	To assess the effects of camel thorn distillate on RAS.

Description of the assessed publications

From the databases indicated above, we chose 61 abstracts that were published in English. Following screening the titles and abstracts, 50 papers were deleted, and two articles were removed after the full-text review, based on the exclusion criteria. The final analysis includes a full-text assessment of the extant 9 papers that matched the inclusion criteria.

The characteristics of the 9 articles are summarised in **Tables 1 and 2**. A total of 844 RAS patients were included in this study. Each study included a sample size ranging from 28 to 227 patients.

Characteristics of the included studies

Table 2. Treatment, duration, main outcomes, and side effects

Author/Year	Treatment course	Outcomes (size, pain, and healing rate)	Side effects
Ghalayani <i>et al.</i> , (2013) [21]	7 days	Pain using the Visual Analog Scale (VAS), ulcer size, and healing rate	Minimal side effects
Liu <i>et al.</i> , (2012) [19]	5 days	Pain, ulcer size, and healing rate	No side effect
Darakhshan <i>et al.</i> , (2019) [22]	7 days	Pain using the VAS and healing rate	No side effect
Shi <i>et al.</i> , (2020) [20]	10 days	Pain and healing rate	No side effect
Babae <i>et al.</i> , (2015) [23]	10 days	Pain intensity and healing rate	No side effect
Hoseinpour <i>et al.</i> , (2011) [24]	14 days	Pain and ulcer size	No side effect
Mansour <i>et al.</i> , (2014) [26]	6 days	Pain using the VAS and ulcer size	No side effect
Deshmukh & Bagewadi, (2014) [27]	6 months	Pain using the VAS, ulcer size, and healing rate	No side effect
Pourahmad <i>et al.</i> , (2010) [25]	2 weeks	Pain using the numeric rating scale and ulcer size	No side effect

Thirteen types of herbal medicine were used in gargles, membranes, mucoadhesive patches, toothpaste, and gelatin preparations. One was a traditional Chinese medicine, and another was an Iranian herbal medication. The experimental period ranged from 5 days to 6 months.

Qualitative data synthesis

The ulcer size, lesion duration, and pain remission were the main result measures examined in this review (**Table 3**).

Table 3. Summary of research outcomes

Authors/year	Article source	Study type	Sample size (treatment/control)	Medications/formula
Ghalayani <i>et al.</i> , (2013) [21]	J Res Pharm Pract. 2013 Apr-Jun; 2(2): 88–92	RCT	40	Punica granatum gel
Liu <i>et al.</i> , (2012) [19]	Evid Based Complement Alternat Med. 2012; 2012: 284620	RCT	227	Toothpaste comprising Yunnan Baiyao
Darakhshan <i>et al.</i> , (2019) [22]	Curr. Issues Pharm. Med. Sci., Vol. 32, No. 3, Pages 115-120	RCT	56	Pomegranate peel gel
Shi <i>et al.</i> , (2020) [20]	Canadian Journal of Infectious Diseases and Medical Microbiology Volume 2020,	RCT	35	Aloe vera gel

Babae <i>et al.</i> , (2015) [23]	Dent Res J (Isfahan). 2015 Sep-Oct; 12(5): 456–460.	A triple-blind clinical trial study	28	Zataria multiflora essential oil
Pourahmad <i>et al.</i> , (2010) [25]	JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2010 May;8(5):348-52.	RCT	93	Camelthorn distillate
Hoseinpour <i>et al.</i> , (2011) [24]	Quintessence Int. 2011 Jun;42(6):483-91.	RCT	50	Rosa damascene mouthwash
Mansour <i>et al.</i> , (2014) [26]	J Oral Pathol Med (2014) 43: 405–409	RCT	90	Novel aloe vera and myrrh-based oral mucoadhesive gel
Deshmukh & Bagewadi, (2014) [27]	Int J Pharm Investig . 2014 Jul;4(3):138-41	RCT	60	Curcumin with triamcinolone acetone gel
Gavanji <i>et al.</i> , (2014) [28]	Integr Med Res 2014 Jun;3(2):83-90.	Double-blind	210	Alcoholic and water fragments of Punica granatum var. passiflora, P. granatum var. Sweet Alak, and P. granatum var. Saveh Black w

Size of ulcers

In their research, Deshmukh *et al.* and Mansour *et al.* measured the ulcer's maximal diameter and discovered that ulcer diameters varied. At the end of the treatment, they reported a statistically significant reduction in ulcer size [26, 27]. Hoseinpour *et al.*, on the other hand, found no statistically significant difference in ulcer size [24]. Liu *et al.*, on the other hand, measured the ulcer's maximal diameter and vertical diameter [19].

Pain reduction

Pain reduction was the major outcome index in all included trials. Ten of the 9 studies used the visual analog scale (VAS) to estimate the pain level. Only Pourahmad *et al.* used the numeric rating scale to assess the pain level [25]. The VAS scores in the herbal medicine groups were considerably lower than the control groups in all of the studies analyzed.

Side effects

Ten studies reported no side effects, whereas one study reported minimal side effects. Ghalayani *et al.* reported minimal side effects with the topical application of a hydroalcoholic extract of *Punica granatum* (PG) [21]; however, the report did not contain any detailed information.

Duration of ulcers

The duration of the ulcer was documented in six trials. The average healing time for aloe vera fermentation gel and chitosan gel, according to Shi *et al.*, was 7.40 ± 1.85 days and 7.93 ± 1.84 days, respectively [20]. According to Halayani *et al.*, there was a significant difference in mean

healing time between 8.6 ± 0.99 days of placebo therapy and 5.3 ± 0.81 days of PG extract treatment ($P < 0.001$) [21].

Deshmukh *et al.* demonstrated a statistical significance in the ulcer duration in both groups from day 0 to day 7 [27]. However, there was no statistical significance in the duration of ulcers between group I (Curcumin gel) and group II (triamcinolone acetone gel).

Quantitative data synthesis

Main outcomes

The major findings of the meta-analysis were the differences in the improvement in ulcer size and pain intensity within the 3rd, 5th, and 7th days post-treatment. The secondary outcomes included the mean duration of ulcer healing. All results were reported using the random effect models.

There was significant reduction in ulcer size progression within the 3rd (standardized mean difference, [SMD] -0.70; 95% confidence interval [CI] [-1.23, -0.17], $P=0.010$) and 5th days (SMD -0.92; 95% CI [-1.66, -0.18], $P=0.01$) However, this reduction in ulcer size was not significant on the 7th day (SMD -0.41; 95% CI [-0.97, -0.15], $P=0.15$) (**Figure 2**).

There was a significant decrease in the pain intensity within the 3rd (SMD -2.14; 95% CI [-3.64, -0.63], $P=0.005$), 5th (SMD -1.88; 95% CI [-3.17, -0.58], $P=0.005$), and 7th days (SMD -1.87; 95% CI [-3.19, -0.54], $P=0.006$) (**Figure 3**). Ulcer healing duration significantly decreased after initiating the treatment (SMD -0.96; 95% CI [-1.81, -0.10], $P=0.03$) (**Figure 4**).

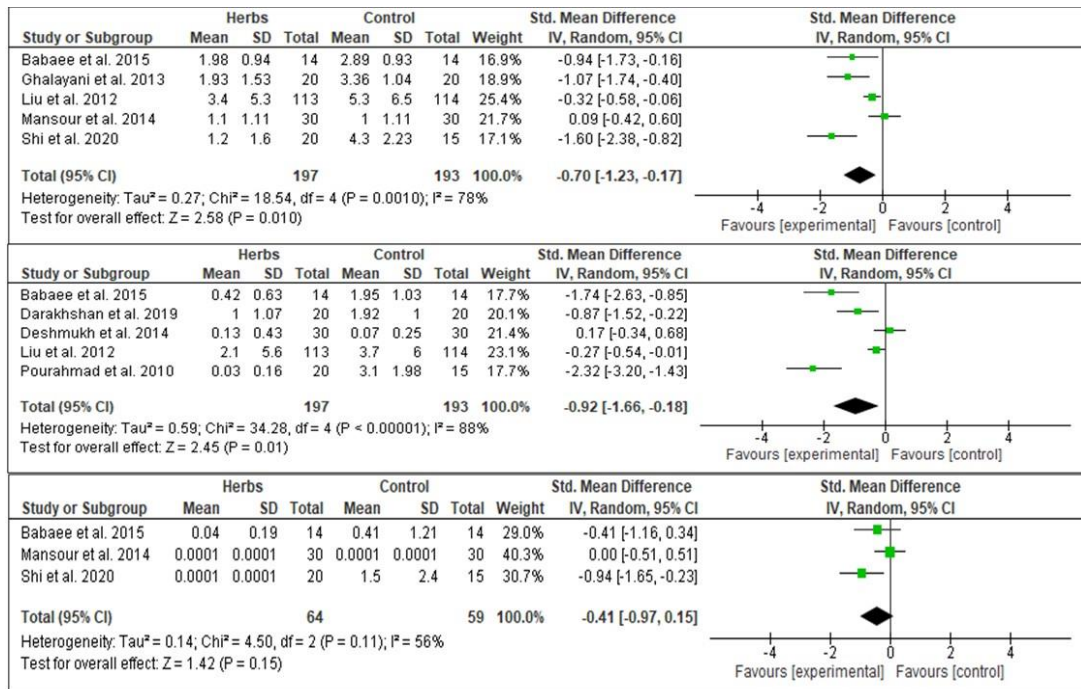


Figure 2. Post-treatment progression of the ulcer size after 3,5, and 7 days

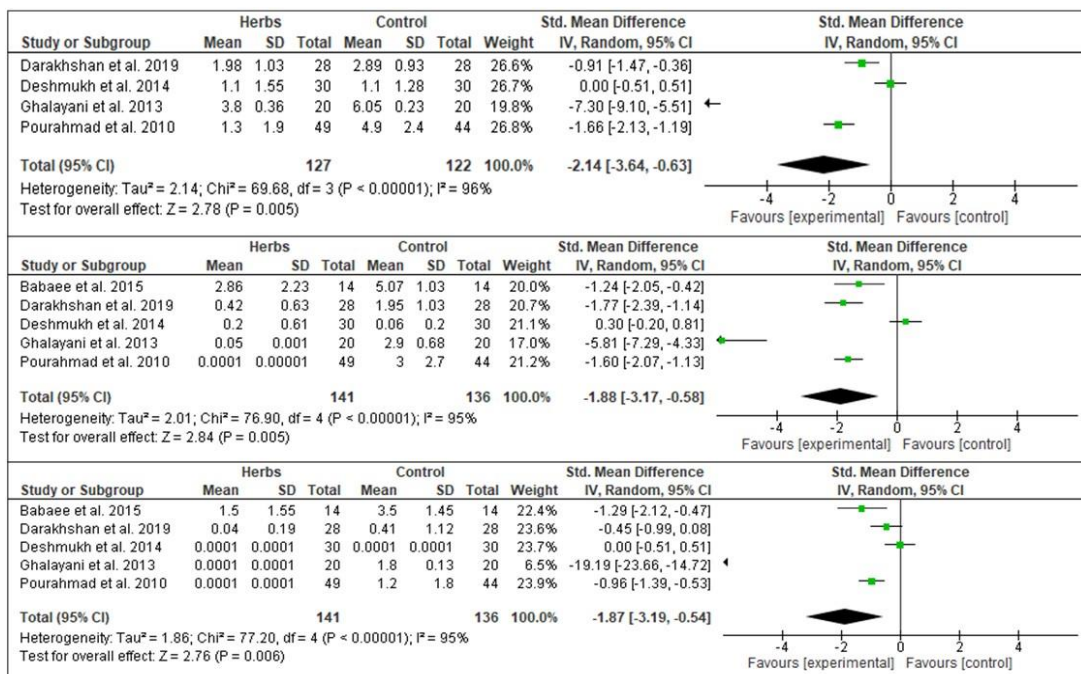


Figure 3. The pain intensity on 3rd, 5th and 7th day

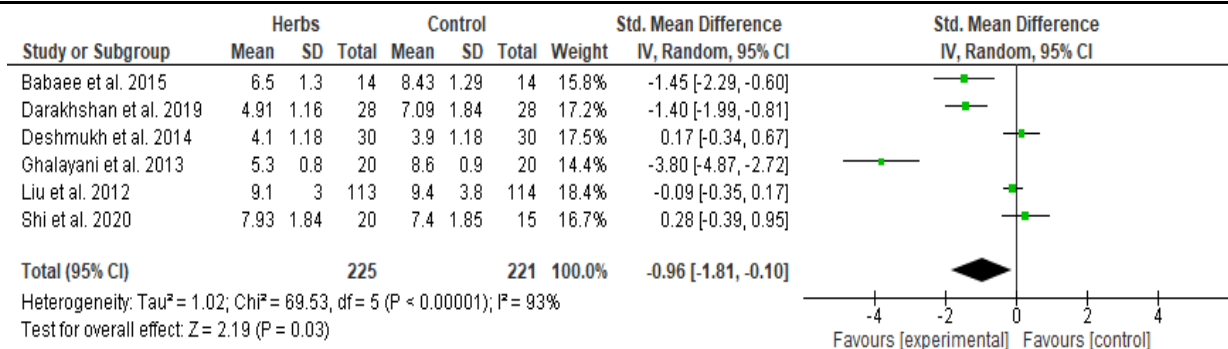


Figure 4. Ulcer healing duration

Heterogeneity and publication bias

The almost symmetrical distribution of data acquired from all experiments was revealed by visual inspection of the funnel plots. However, significant heterogeneity was observed in all analyses conducted on the ulcer size, pain intensity, and healing duration.

We evaluated the effects of natural and experimental treatments on the size of RAS, pain intensity, and ulcer healing length in this systematic review and meta-analysis. Different treatment modalities were introduced to improve RAS. The pooled analysis showed that the included herbs effectively reduced the ulcer size and pain intensity, lowering the healing duration. The findings regarding the ulcer size were consistent with those by Heydarpour *et al.*, who assessed non-pharmaceutical interventions for treating RAS [29]. Compared with the control group, topical herbal medications or natural derivatives considerably relieved RAS symptoms by reducing the pain, ulcer size, and healing duration without serious side effects [29].

This review reported that aloe vera fermentation gel and hydroalcoholic extract of PG were most effective in reducing the ulcer size (SMD -1.60; 95% CI [-2.38, -0.82]) and (SMD -1.07; 95% CI [-1.74, -0.40]), respectively, within the 3rd day. Aloe vera fermentation gel improved healing and restored RAS microbiota abnormalities, according to Shi *et al.* [20]. It has the potential to reduce the number of dangerous oral bacteria like Actinomyces and Granulicatella, signifying a better prognosis. As a result, it may improve the quality of life for RAS patients [20]. For RAS patients, wound healing and anti-inflammation are crucial. Aloe vera is a cactus-like plant that is widely used in medicine to treat burn injuries, cutaneous lesions, and mouth ulcers, making it an ideal RAS treatment option [23].

There are limited data on the effects of PG in treating RAS; however, Ghalayani *et al.* reported that the topical application of PG hydroalcoholic extract might be an effective treatment for MiRAS. The benefits of using PG in RAS treatment include clinical improvements such as pain reduction and improved RAS healing time, patient compliance, convenience of usage, and minimal side effects [21].

Camelthorn distillate also revealed a good prognosis for the ulcer size on the 5th day of initiating treatment (SMD -2.32; 95% CI [-3.20, -1.43]). Pourahmad *et al.* reported that camel thorn distillate displays similar efficacy as other medications used to treat oral aphthous ulcers. Its medicinal activity could be attributed to the flavanones (albagitin and alhagidin) found in this plant [25].

Aloe vera and myrrh did not significantly decrease the ulcer size within the 3rd (SMD 0.09; 95% CI [-0.42, 0.60]) and (SMD 0.00; 95% CI [-0.51, 0.51]) 7th day of treatment, compared with the medicines in other included studies. However, Mansour *et al.* suggested that herbal medicines could provide an alternate therapy for MiRAS. The short-term topical treatment of aloe vera and myrrh has proven beneficial in RAS management. Although aloe vera is more effective in reducing ulcer size, erythema, and exudation, myrrh was more effective in reducing pain. In addition, the absence of side effects with any of the three mucoadhesive gels credences these medication formulations' safety [26].

Aloe vera's wound-healing qualities have been linked to numerous mechanisms, including keeping the wound moist, encouraging epithelial cell migration, accelerating collagen maturation, enhancing collagen cross-linking, and increasing blood flow [30-34].

PG hydroalcoholic extract demonstrated the best prognosis in decreasing pain intensity within the 3rd (SMD -7.30; 95% CI [-9.10, -5.51]), 5th (SMD -5.81; 95% CI [-7.29, -4.33]), and 7th days (SMD -19.19; 95% CI [-23.66, -14.72]). Furthermore, it was most effective in minimizing the healing duration (SMD -3.80; 95% CI [-4.87, -2.72]).

Ghalayani *et al.* reported a decrease in pain elimination by 3.4 days, compared with the control group (5.7 days) [21]. The antioxidant activity of PG neutralizes oxygen free radicals, which are vital in the inflammatory process and the development of aphthous ulcers. This, in turn, may promote the healing process [35]. Considering its ability to prevent enterotoxin production, Braga *et al.* proposed PG extract as a promising antibacterial therapeutic agent. The effectiveness of PG products can be attributed to their anti-irritant and anti-inflammatory properties [36].

This review has a few limitations. The included trials displayed poor homogeneity with several factors such as different types of treatment, sample size, dosage, application strategy, test measure, and treatment period. In addition, the details regarding the measurement of outcomes were not mentioned. The key outcome indicators, according to current data, are ulcer size, lesion duration, and pain intensity. However, the researchers did not follow the standard method to assess them, particularly the ulcer size. The ulcer size could have been underestimated based on the maximum diameter measurement. Only Liu *et al.* used the greatest diameter and vertical diameter to determine the ulcer size [19].

Conclusion

The pooled results suggested that all included herbs effectively reduced the ulcer size and pain intensity, besides limiting the healing duration within the 3rd, 5th, and 7th days after initiating the treatment. Aloe vera gel, PG hydroalcoholic extract, and camel thorn distillate were most effective in decreasing the ulcer size. PG extract resulted in the best prognosis in reducing the pain intensity and minimizing the healing duration of the ulcer. The formula, dosage, therapy duration, and application procedures of the herbal medication, as well as the control intervention, should be included in future investigations.

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Conflict of interest: None

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