

CLINICAL EFFICACY AND SAFETY OF HERBAL MEDICINE THERAPY IN RECURRENT APHTHOUS STOMATITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Recurrent aphthous stomatitis is the most common oral mucous ulcerative lesion with challenging treatment. Herbal medicine therapy can propose clinical efficacy and safety due to its large biological activities. The objective was to review the clinical efficacy and safety of herbal medicine therapy in terms of ulcer size, pain score, healing duration, and adverse effects in recurrent aphthous stomatitis. A systematic was conducted based on the PRISMA statement. The search was performed using four electronic databases, namely PubMed, Cochrane, Science Direct, and Google Scholar for articles published from 2016 until 2021 using specific keywords. The search was limited to randomized controlled trials (RCTs), in English, full text, and study in humans. The main outcome is expected to be ulcer size, pain score, healing duration, and adverse effects. Quality assessment of selected articles was conducted using the Quality Appraisal of Randomized Trials Checklist (Cochrane Risk of Bias tool). The methodology quality of studies was evaluated using the Cochrane Handbook for Systematic Review of Interventions and Rev Man software. Five articles were eligible for analysis. The population of the sample study ranged from 34-70 patients of 15-65 y old. The herbs used were aloe vera (*Aloe barbadensis* Miller), curcumin (*Curcuma longa*), licorice (*Glycyrrhiza glabra*), tobacco (*Nicotiana tabacum* L.), and pomegranate (*Punica granatum* Linn.). This review showed that there is some evidence of the clinical efficacy and safety of herbal medicine therapy in improved outcomes of recurrent aphthous stomatitis treatment with minimum adverse effects.

Keywords: Herbal medicine, Recurrent aphthous stomatitis, Oral ulcer

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common painful oral mucosal disease characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of systemic disease [1, 2]. RAS is classified according to clinical characteristics, namely minor ulcers, major ulcers, and herpetiform ulcers [3]. The incidence ranges from 20 % to 60 %, depending on the population studied [4]. Prevalence tends to be higher in professional or white-collar, individuals, upper socioeconomic groups, and nonsmokers [3, 4].

There is no specific etiology has been identified, so that the treatment of RAS is non-specific and symptom-based [5]. The goal is to decrease symptoms, reduce ulcer number and size, increase disease-free periods. The best treatment is that which will control ulcers for the longest period with minimal adverse side effects. The treatment approach should be determined by disease severity (pain), the patient's medical history, the frequency of flare-ups, and the patient's ability to tolerate the medication. In all patients with RAS, it is important to rule out predisposing factors and treat any such factors, where possible, before introducing more specific therapy [6, 7].

Treatment for RAS mainly includes localized or general medications [7]. Glucocorticoids, which have proven efficacy and safety, are often among the first choices for localized treatment. However, their long-term use may facilitate oral infection with *Candida albicans*, mucosal atrophy, susceptibility to infection, and gastrointestinal complication [8-10].

Herbal medicine can propose efficacy and safety due to its large biological activities with minimum adverse effects [11]. Indonesia has the second biggest biodiversity in the world, exhibited by a high number of indigenous medicinal plants that can be used as medicine [12, 13]. The Indonesian people, particularly Javanese people, have been using medicinal plants for a long time by drinking herbs derived from medicinal plants. Traditional Indonesian herbal medicine that has been practiced for centuries in Indonesian society is still very popular for maintaining health and treating diseases [13]. Also, approximately 60 % of the world's population put their faith in medicinal herbs [9]. This is due to more believed to be safe from chemical drugs [13].

Li *et al.* conducted a systematic review on the efficacy and safety of topical herbal medicine treatment on recurrent aphthous stomatitis based on the studies published from 1996 to 2015 [14]. Meanwhile, Wahyuni *et al.* conducted a systematic review on the efficacy and safety of plant-based therapy on recurrent aphthous stomatitis and oral mucositis in the past decade [15].

To the best of our knowledge, no systematic review was conducted for randomized controlled trials of intervention regarding clinical efficacy and safety of herbal medicine in RAS for the last five years of studies. Therefore, we conducted this analysis to review the clinical efficacy and safety of herbal medicine therapy in terms of ulcer size, pain score, healing duration, and adverse effects in recurrent aphthous stomatitis.

MATERIALS AND METHODS

Protocol and eligibility criteria

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The PICO items were population or patient or problem (recurrent aphthous stomatitis and human patients), intervention (herbal medicine therapy), comparison (placebo or chemical drugs), and outcome (clinical efficacy and safety).

The inclusion criteria were studies published from 2016 to 2021 with full text available, English-language, a study in humans, randomized controlled trials (RCTs) that evaluated the efficacy and safety of herbal medicine therapy in RAS, and no restrictions on age, sex, or race. We decided to collect studies from 2016 to 2021 because there were no systematic reviews conducted on articles from the past five years. Articles were excluded for duplication and irrelevant with the topic, including non-herbal, animal-based, and non-recurrent aphthous stomatitis.

Information sources and search

The electronic literature search was performed using PubMed, Cochrane, Science Direct, and Google Scholar for articles published from 2016 until 2021 (date of search: May 24–30, 2021). The keywords used were "herbal medicine" [MeSH terms] OR "medicinal

herbs" [MeSH terms] OR "medicinal plants" [MeSH terms] OR "plant extracts" [MeSH terms] AND "oral ulcer" [MeSH terms] OR stomatitis [MeSH terms] OR "stomatitis, aphthous" [MeSH terms] OR "oral lesions" [Text Word] OR "oral mucosa" [MeSH terms]. The PRISMA flow diagram showed below (fig. 1).

Study selection, data collection, and data items

The article selection process was conducted by one independent reviewer (N. T. H.). The following data for each study were extracted from full-text articles using a data extraction form and stored in 2020 Microsoft Excel file format: references, study design, setting, scientific name, part or extract, age range, sample size or the number of patients, drug formula, drug preparation and usage, treatment duration, outcome, and biological actions (table 1). The main outcome of the study was ulcer size, pain score, healing duration, and adverse effects.

Risk of bias in the individual studies and across studies

The quality of the enrolled publications was assessed according to the Cochrane Handbook for Systematic Review of Interventions and Rev Man 5.4 software [16]. The assessment of the risk of bias was done by one independent reviewer (N. T. H.). The assessment criteria were random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. There is no scoring system in Cochrane Risk of Bias. Review authors' judgment involves answering a specific question for each entry. In all cases, an answer 'Yes' indicates a low risk of bias, an answer 'No' indicates a high risk of bias, and an answer 'Unclear' indicates insufficient information [16].

Table 1: Characteristics of enrolled studies

References	Study design	Setting	Scientific name	Part/extract	Age range, a sample of size	Form-ula	Preparation and usage		Treatment duration	Outcome	Biological actions
							Treatment group	Control group			
[10]	RCT	Birja, Iran	Licorice (<i>Glycyrrhiza glabra</i>)	Hydro-ethanolic extract of licorice root	18-60 y old patients	Solution	Intervention DSG (n=35): diphenhydramine containing <i>Glycyrrhiza glabra</i> (DSG), swish 3 ml of solution around their mouth for about 3 min 4 times a day	Intervention DS (n=35): diphenhydramine solution (DS), swish 3 ml of solution around their mouth for about 3 min 4 times a day	5 d and until complete healing	The severity of pain and pain score (VAS): DSG reduced pain scores more than DS (statistically different) Duration of wound healing: A significant difference in the average duration of wound healing between the two groups, as it was decreased by 1.5 d in DSG group Adverse effects: No adverse effect	Anti-inflammatory and antimicrobial
[17]	RCT	Kermanshah, Iran	Pomegranate (<i>Punica granatum</i> Linn.)	Pomegranate peel extract (PPE)	19-42 y old patients	Gel	Study group (n=28): apply PPE 10% gel, twice daily	Control group (n=28): apply placebo gel, twice daily	1 w	Ulcer size: The PPE group showed marked reduction in ulcer size at days 3 (p = 0.001), 5 (p<0.001), and 7 (p = 0.01) when compared to the placebo group The pain of ulcer region (VAS): On day 7, no patients in PPE group had any pain (p = 0.01) Healing duration of ulcers: Statistically significant (p<0.001) Adverse effects: No adverse effect	Antioxidant anti-inflammatory, antibacterial, and antifungal

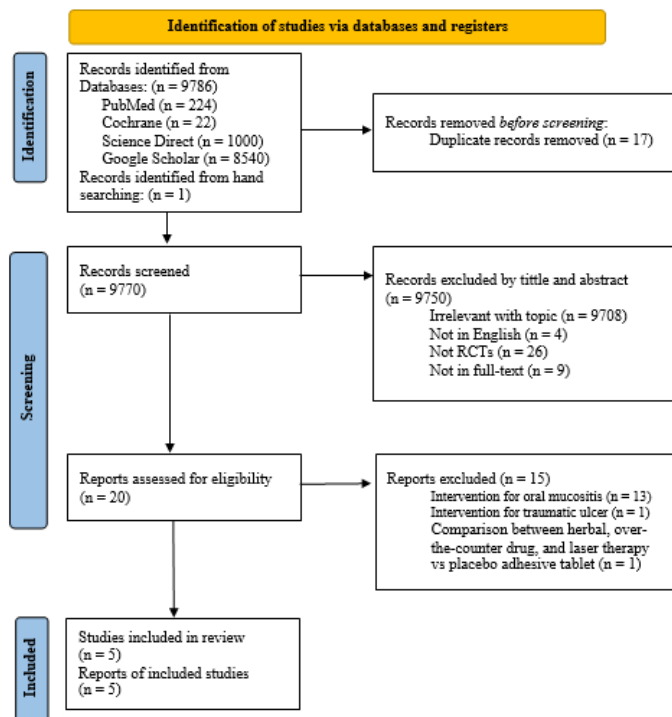


Fig. 1: PRISMA flow diagram

Table 1: Characteristics of enrolled studies (continued #1)

References	Study design	Setting	Scientific name	Part/extract	Age range, sample of size	Form-ula	Preparation and usage		Treatment duration	Outcome	Biological actions
							Reatment group	Control group			
[18]	RCT	India	<i>Aloe barbadensis</i> Miller, <i>Aloe aborescens</i>	Leaves	20-50 y old 34 patients	Gel	Group A (n=17): topical aloe vera gel (Forever Bright Aloe vera Gel) 3 times a day for 7 d or until the ulcer heals completely	Group B (n=17): topical triamcinolone acetonide 0.1% (Kenacort oral paste) 3 times a day for 7 d or until the ulcer heals completely	7 d or until the ulcer heals completely	Size of ulcer: Not statistically significant Pain (VAS) and burning sensation: Statistically significant (*p<0.05) at visit 2 (0-3 d) on aloe vera group compared to kenacort group Adverse effects: No adverse effect	Antibacterial, antifungal, anti-inflammatory, antioxidant, antitumor, and immune boosting
[19]	RCT	Rasht, Iran	<i>Curcuma longa</i>	Turmeric extract	Not mentioned 58 patients	Orabase	Group A (n=29): 5% of curcumin orabase, 3 times a day	Group B (n=29): 0.1% of triamcinolone acetonide orabase, three times a day	10 d	Diameter of lesions, pain and inflammation (VAS): Not statistically significant Adverse effects: No adverse effect	Anti-inflammatory, analgesic, antimicrobial, antitumor
[20]	RCT	Kerman-shah, Iran	<i>Nicotiana tabacum</i> (L.)	Dried leaves of <i>Nicotiana tabacum</i>	15-65 y old 54 patients	Mouth-wash	Group of tobacco treatment (n=27): 3000 ml of filtrated decoction was mixed with 3 grams of a mixture of methylparaben and propylparaben (9:1), apply 10 ml of mouthwash, 3 times a day	Group of placebo (n=27): apply 10 ml of mouthwash, 3 times a day	5 d	Size and number of ulcers and pain (VAS): Statistically significant (**p<0.01) Adverse effects: No adverse effect	Anti-inflammatory

RESULTS

The search strategy performed a total of 9786 articles from electronic databases and one article from hand searching. The 17 articles were excluded for duplication. According to the exclusion criteria, screening of the titles and abstracts resulted from the removal of 9750 articles. A full-text review of the remaining 20 articles indicated that 5 studies met the inclusion criteria and they were enrolled into the final analysis. The flow chart displayed in fig. 1 shows the detailed selection process.

The characteristics of the 5 studies are summarized in table 1. The sample size ranged from 34-70 patients of 15-65 y old. Five different types of herbal medicine, in the form of gel, orabase, solution, and mouthwash, were used. The experimental period of these trials ranged from 5 to 10 d [10, 17-20].

The risk of bias and quality assessment of each study can be seen below. Table 2 showed risk of bias in each component, fig. 2 showed risk of bias graph across all included studies and fig. 3 showed the risk of bias summary about each risk of bias item for each included study.

Table 2: Risk of bias

Authors, year, and references	Risk of Bias						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other bias
Akbari <i>et al.</i> , 2020 [10]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear
Darakhshan <i>et al.</i> , 2019 [17]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Giroh <i>et al.</i> , 2019 [18]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Kia <i>et al.</i> , 2020 [19]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	High risk
Vaziri <i>et al.</i> , 2016 [20]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear

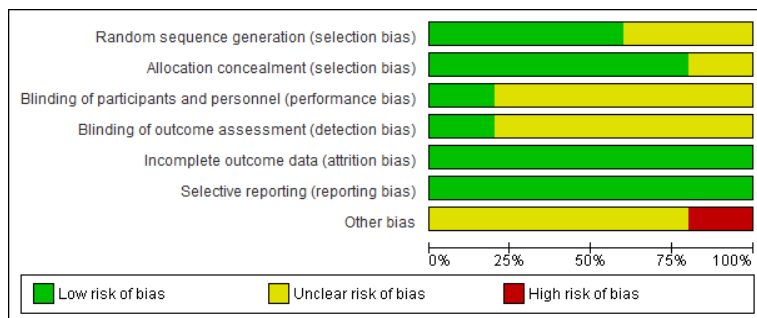


Fig. 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

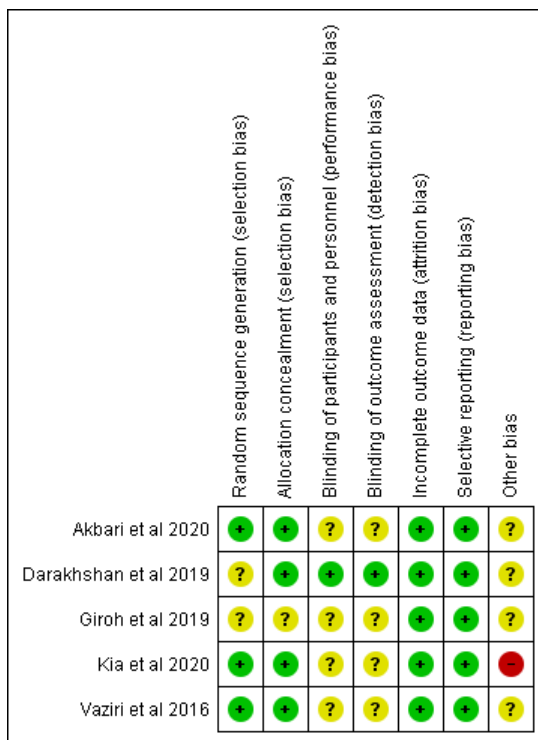


Fig. 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study

The heterogeneity was assessed subjectively by N. T. H and W. H. without measurement of I^2 . Those were the intervention, dosage, drugs formula, treatment duration, application method, and sample size. Due to the heterogeneity of the enrolled studies, only descriptive analysis was conducted in this study.

The main outcome measures assessed in this study were ulcer size, pain score, healing duration, and adverse effects. Four of five studies reported a change in ulcer size which was measured by different methods but in the same unit (millimeter). Vaziri *et al.* evaluated the ulcer measurement by the distance between two opposites outside edges of the white border in terms of a millimeter. Two measurements approximately 90 degrees from each other were determined, the largest distance was used as one measurement. The two measurements were then multiplied to represent the cross-sectional areas of the aphthous [20]. Giroh *et al.* and Darakhshan *et al.* determined the ulcer size using a calibrated dental probe in millimeters [17, 18]. While Kia *et al.* determined the ulcer size using a caliper in millimeters [19].

Two studies reported by Darakhshan *et al.* and Vaziri *et al.* showed statistical significance in reducing ulcer size [17, 20]. Darakhshan *et al.* reported ulcer size reduction by using pomegranate at day 3 ($p = 0.001$), day 5 ($p < 0.001$), and day 7 ($p = 0.01$) when compared to placebo [17]. While Vaziri *et al.* reported *Nicotiana tabacum* showed ulcer size reduction at day 3 (** $p < 0.01$) and day 5 (** $p < 0.01$) when compared to placebo [20].

On the other hand, Giroh *et al.* and Kia *et al.* reported no statistical significance in reducing ulcer size [18,19]. Giroh *et al.* reported that aloe vera compared to kenacort was not statistically significant in reducing ulcer size [18]. Kia *et al.* reported that curcumin is not statistically significant in reducing ulcer size compared to triamcinolone [19].

Pain scores were determined by the Visual Analog Scale (VAS) in all studies. Four studies showed that herbal medicine was statistically significant in reducing pain scores. In contrast, Kia *et al.* reported no statistically significant difference between the two groups (curcumin and triamcinolone) [19].

Darakhshan *et al.* reported that pomegranate significantly reducing pain at day 3 ($p < 0.001$), day 5 ($p < 0.001$), and day 7 ($p = 0.01$) compared to the placebo group [17]. Akbari *et al.* reported that licorice (diphenhydramine-containing glycyrrhiza glabra or DSG) significantly reducing pain scores more than the diphenhydramine solution (DS) group on day 1 ($p = 0.0001$), day 3 ($p = 0.003$), and day 5 ($p = 0.0001$) [10]. Vaziri *et al.* reported that *Nicotiana tabacum* significantly reduced pain scores on days 3 (** $p < 0.01$) and day 5 (** $p < 0.01$) [20]. Giroh *et al.* reported that aloe vera significantly reducing pain score at visit 2 (0-3 d) when compared to kenacort (* $p < 0.05$) [18].

Akbari *et al.* and Darakhshan *et al.* reported statistically significant healing duration [10,17]. Akbari *et al.* reported that licorice need 7 d to heal with mean \pm SD (4.5 \pm 1.19) and $p = 0.0001$ [10]. Darakhshan *et al.* also reported that pomegranate needs 7 d to heal with mean \pm SD (4.91 \pm 1.16) and $p < 0.001$ [17]. All studies reported no adverse effects [10, 17-20].

DISCUSSION

A total of 70 subjects in 5 clinical trials were analyzed in the present analysis. Compared with controls, most herbal medicine can greatly improve the patients' symptoms by reducing ulcer size, relieving pain, and shortening healing duration without adverse effects. The homogeneity of the studies was quite poor, with variables such as the various type of intervention, dosage, drug formula, application method, sample size, and experiment duration. Therefore, a meta-analysis could not be conducted based on the current data.

In the studies included in this review, the treatment duration ranged from 5-10 d. Akbari *et al.* studied licorice for 5 d (until complete healing), Darakhshan *et al.* studied pomegranate for 7 d, Giroh *et al.* studied aloe vera for 7 d, Kia *et al.* studied curcumin for 10 d, and Vaziri *et al.* studied *Nicotiana tabacum* for 5 d [10, 17-20]. The outcome measurement in those studies was the size of the ulcer (diameter of lesions), pain (burning sensation), duration of wound healing, and adverse effects [10, 17-20].

The drug formula was diverse in these five included studies. Akbari *et al.* used solution, Darakhshan *et al.* and Giroh *et al.* used gel, Kia *et al.* used orabase, while Vaziri *et al.* used mouthwash [10, 17-20]. Because of the drug's formula heterogeneity, we could not compare it. However, the gel form of the same medication has better efficacy in comparison with mouthwash because of more time exposure. Nevertheless, it depends strongly on its bioadhesive properties, bioavailability, solubility, and external factors such as mechanical stress and the washing effect of saliva [21].

Nicotiana tabacum, when compared to placebo can significantly reduce ulcer size and pain score without any adverse effects [20]. This is in line with a study conducted by Zakaria *et al.* They reported the nicotine group showed a lower mean with a significant difference after 6 d in comparison with the placebo group regarding pain and erythema scores. A lower mean of ulcer size was recorded in the nicotine group, with a significant difference after 4 and 6 d [22].

Nicotiana tabacum has anti-inflammatory effects. Combustible products of smoking are known to stimulate increased keratinization of the oral mucosa and therefore resist the formation of aphthous ulcers and reduce trauma or bacterial penetration of the mucous membrane in smokers compared to non-smokers. This composition may be attributed to the presence of the main alkaloid of *Nicotiana tabacum*, nicotine, which showed a remarkable protective effect in aphthous ulcers and Bechet syndrome by using oral nicotine replacement therapy [20].

Nicotine and its metabolites exhibited immunosuppressive activity and lead to a reduction in inflammatory condition by different known mechanisms, including antibody-forming cell response, suppression of neutrophil-mediated inflammatory action, inhibition of endothelial cell release of IL-8, inhibition IL-1 β , IL-2, IL-10, TNF- α , IFN- γ release, decrease the level of immune globulins, impairment of antigen-mediated signaling T-cells, and inducing T-cell allergy as well as attenuation of IFN signaling [20].

Pomegranate peel extract (PPE) 10 % gel was significantly effective in reducing ulcer size and pain score without any adverse effects when compared to placebo. The healing duration in pomegranate was 4.91 \pm 1.16, which was faster than placebo [17]. It showed antioxidant, anti-microbial, and anti-inflammatory effects. Pomegranate enhances or maintains the free radical scavenging activity of the hepatic enzymes, namely superoxide dismutase (SOD), catalase, and peroxidase. Antimicrobial activity by controlling adhesion potential of *Streptococcus mutans* and *Streptococcus sanguis* to the oral cavity surface. Pomegranate also decreases the level of SOD (a salivary defense system) to promote anti-inflammatory effects [17]. Polyphenolic compounds in the pomegranate, including anthocyanins, have an anti-inflammatory effect and prevent the adhesion of leukocytes to endothelial cells, and it decreases the level of IL-2, IFN- γ , and TNF- α . Reducing these inflammatory factors is effective in treating RAS and diabetes. The pomegranate is also against oxidative stress by inhibiting free radicals and having antioxidant properties [23].

Ghalayani *et al.* studied *Punica granatum* (PG) in the management of RAS. The findings of this study revealed that PG extract in the form of oral gel (10%) may be beneficial in reducing RAS pain and has a positive effect in reducing the overall period of complete healing. It was concluded that PG is an effective herbal medicine for the management of RAS [24]. In line with Tavangar *et al.* showed that *Punica granatum* gel has a successful effect in controlling and treating RAS [23].

Licorice in DSG group promotes 1.5 d faster-wound healing compared to DS group. Licorice also statistically significantly reduces pain score compared to DS group [10]. In line with the study conducted by Martin *et al.* examining the effect of a patch containing glycyrrhiza root extract on aphthous ulcers. They reported that the patch was more effective than the placebo in reducing the healing duration of RAS [25].

Licorice (*Glycyrrhiza glabra*) is one of the oldest medicinal plants. The main ingredient of licorice is glycyrrhizic acid and glabridin. It has anti-inflammatory and antimicrobial effects. These effects might be due to the glycyrrhizic acid, glabridin, and flavonoid in licorice, which inhibit the

enzymatic pathways of cyclooxygenase (COX) and lipoxygenase. Licorice and its active components inhibit the production of free oxygen radicals as well as cell migration, and thus control arachidonic acid metabolism, vascular permeability, and allergy, thereby reducing inflammatory reactions and the severity of pain [10].

Giroh *et al.* reported the size of ulcers in the treatment of aloe vera and kenacort were not statistically significant [18]. Bhalang *et al.* who evaluate the effectiveness of acemannan (extract of aloe vera) in RAS, also found that 0.1% of triamcinolone acetonide was inferior to aloe vera in reducing ulcer size [26]. While Giroh *et al.* reported that aloe vera was statistically significant in reducing pain and burning sensation without adverse effects [18].

Aloe vera has anti-inflammatory and wound-healing effects. The mechanism of the wound healing effect was to increase epithelial cell migration and the synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of the wound. In addition, aloe vera increases the wound closure rate and tensile strength of the wound. Aloe vera gel forms a protective coating on the affected areas and helps in healing wounds, fastens the healing rate, and relieves pain. Aloe vera and its components inhibit the COX pathway and prostaglandin E2, leukocyte adhesion, and pro-inflammatory cytokines, which reduce inflammation [18].

Kia *et al.* showed that there were no statistical differences in pain severity and lesion size between 5% of curcumin and 0.1% of triamcinolone acetonide [19]. In contrast to a study conducted by Manifar *et al.*, showed 2% of curcumin gel significantly reduces pain severity and size of ulcer compared to placebo [27]. Curcumin has an anti-inflammatory and antioxidant effect. The mechanism of the anti-inflammatory effect was to inhibit the phospholipase, lipids, COX-2, and reduction of IL-1, IL-6, and TNF- α . Moreover, curcumin stimulates cortisol secretion which generates a reduction of IL-1, IL-6, and TNF- α . One of the probable mechanisms in the description of aphthous healing by curcumin may be related to its antioxidant effects [19]. All of these herbs in included studies had no adverse effects [10, 17-20]. The mechanism of included herbal medicine can be seen on fig. 4.

Most of these included studies showed a low risk of bias. This means that plausible bias is unlikely to seriously alter the results [16]. The limitation of this review was the heterogeneity of included studies that were assessed subjectively. In summary, the current data show favorable benefits of herbal medicine in treating RAS. So, there is some evidence to suggest that herbal medicine therapy is an effective and safe alternative option for RAS treatment. Moreover, this review can be implemented as a reference for the development of further research for herbal medicine therapy in recurrent aphthous stomatitis treatment.

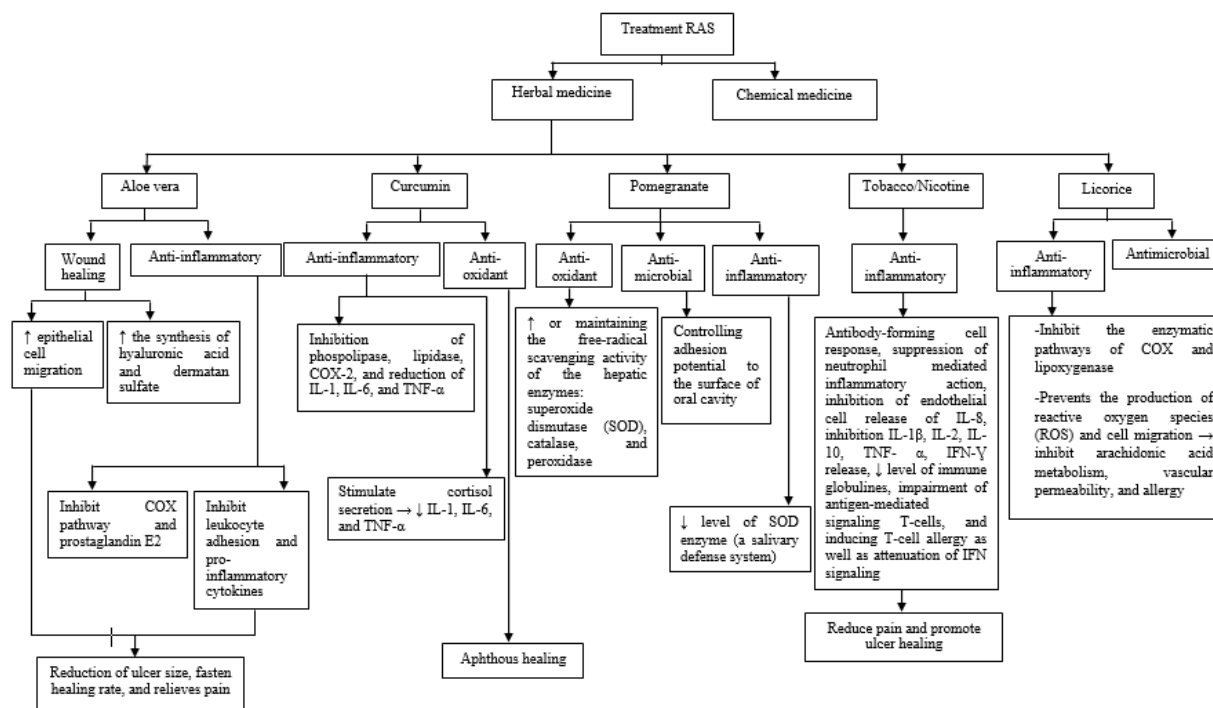


Fig. 4: Mechanism of included herbal medicine [10, 17-20]

CONCLUSION

This review showed that there is some evidence of the clinical efficacy and safety of herbal medicine therapy in improved outcomes of recurrent aphthous stomatitis treatment with minimum adverse effects.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

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