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Systematic Review

Efficacy of *Glycyrrhiza glabra* in the Treatment of Recurrent Aphthous Stomatitis: A Systematic Review of Randomized Controlled Trials

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Abstract: *Glycyrrhiza glabra* (licorice) has been used as an herbal medicine for a long time due to its anti-inflammatory, antioxidant, and antimicrobial properties. Additionally, multiple reports have demonstrated its ability to promote wound healing. Several randomized controlled or clinical trials (RCTs) have demonstrated its potentially therapeutic effects in oral mucosal diseases, especially in recurrent aphthous stomatitis (RAS). This systematic review aims to summarize the evidence for *Glycyrrhiza glabra* in treating RAS. A systematic search was performed across five databases: PubMed (Medline), ScienceDirect, Scopus document, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Library Database of Systematic Reviews. This study was reported following the PRISMA guidelines. RCT study using *Glycyrrhiza glabra* for treating RAS was included in this study with several reported outcomes like changes in ulcer diameter, pain, and healing periods. Seven RCTs were included, which used *Glycyrrhiza glabra* in the form of patches, pastes, mucoadhesive tablets, and mouthwashes for treating RAS. *Glycyrrhiza glabra* treatment in various regimens showed significant improvements in pain, ulcer diameter, and healing time in patients with RAS. This review suggests the potential of *Glycyrrhiza glabra* as an alternative treatment option for RAS.

Keywords: licorice; *Glycyrrhiza glabra*; recurrent aphthous stomatitis; herbal medicine

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1. Introduction

Recurrent aphthous stomatitis (RAS) is common epithelial tissue damage in the oral mucosa with a round or ovoid ulcer, well-defined borders with an erythematous halo, and a yellow or grey base [1]. RAS occurs in about 20% of the general population and ranges from 5% to 50% in certain ethnic or socioeconomic groups [2–5]. RAS is classified into minor, major, and herpetiform, with the minor type being the most common form [6]. Minor RAS presents as a solitary lesion on the nonkeratinized mucosa of the oral cavity with a lesion size of 3 to 10 mm and a healing duration of 7 to 10 days [7]. The quality of life of RAS patients generally decreases because RAS is painful, so it interferes with speech and mastication functions [8].

There is still no cure for or known cause of RAS [9]. This is because the etiology and pathogenesis of RAS are not known. The current management aims to relieve pain and

accelerate healing, which is determined based on the severity of the ulcerated lesion [10–12]. Patients with minor RAS are often prescribed topical medications such as the antiseptic mouthwash chlorhexidine gluconate 0.2% [13]. However, chlorhexidine gluconate has been reported to cause brown staining of the teeth and tongue, changes in taste perception, accumulation of supragingival plaque, and irritation of the oral mucosa [14,15]. Corticosteroids are the mainstay of RAS with higher severity [8,16]. However, long-term use of topical corticosteroids is contraindicated because it can cause mucosal atrophy. In comparison, systemic corticosteroids can cause a severe effect called adrenal suppression [17].

Glycyrrhiza glabra is commonly known as licorice. Licorice is a perennial herb native to Southern Europe and parts of Asia, and its root is used for various culinary and medicinal purposes. *Glycyrrhiza glabra* root has a sweet taste and is used in the production of candies, confections, and herbal medicine [18]. This plant has long been known as herbal medicine and has been designated as Generally Recognized as Safe (GRAS) by the United States Food and Drug Administration (FDA) [19].

The primary parts of *Glycyrrhiza glabra* used are the roots and rhizomes because these parts have several biological activities such as antioxidant, anti-inflammatory and anti-ulcerative [20]. Bioactive compounds have been detected in the extracts, roots, and leaves of *Glycyrrhiza glabra*, such as glycyrrhetic acid, glycyrrhizin, and phenols (including liquiritigenin, liquiritin, isoliquiritigenin, and isoliquiritin) with anti-oxidant and anti-inflammatory effects [21]. In dentistry, *Glycyrrhiza glabra* effectively treats oro-dental diseases, like dental caries, periodontitis, and oral ulceration [22]. However, no summary of the evidence revealed the effect of *Glycyrrhiza glabra* for treating oral ulcerative lesions, especially RAS. This systematic review aims to summarize the evidence of the potential of *Glycyrrhiza glabra* in different dosage forms, durations, and frequencies of treatment for RAS. The outcomes include RAS-related pain intensity, RAS-related ulcer diameter, and RAS-related ulcer healing time. This systematic review can provide evidence-based knowledge regarding the development of science in dentistry, especially in alternative therapies using herbal medicine for treating any ulceration lesion, especially RAS.

2. Methods

2.1. Study Protocols

The protocol was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol of this study register in PROSPERO with register number CRD420251005074.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria for articles included in this study were as follows:

1. Type of study: randomized controlled/clinical trial (RCT) and double-blind clinical trial study evaluating the topical treatment of *Glycyrrhiza glabra* in RAS;
2. Type of participant (P): patient with RAS lesion (minor, major, or herpetiform type) diagnosed from the subjective and clinical assessments;
3. Type of intervention (I): treatment using *Glycyrrhiza glabra* in any dosage form, frequency, and duration of treatment;
4. Type of comparator (C): control group treated with placebo, antiseptic, or anti-inflammatory agent;
5. Type of outcome measure (O): pain intensity measured with a visual analog scale (VAS), the reduction in ulcerated lesion diameter, and the period of RAS healing.

The exclusion criteria for articles included in this study were as follows:

1. Non-RCTs, reviews, animal studies, and in vitro studies;
2. Patients with underlying diseases, like diabetes mellitus and autoimmune and allergy diseases;
3. The clinical diagnosis of RAS is not defined;
4. Articles not published in English language.

2.3. Search Strategies

The search for articles in this systematic review was carried out from May to December 2023 through five databases, namely: PubMed (Medline), ScienceDirect, Scopus document, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Library Database of Systematic reviews. Relevant keywords containing both the MeSH (medical subject heading) term and entry term were as follows:

1. "licorice" or "*Glycyrrhiza glabra*", AND;
2. "Recurrent aphthous stomatitis" OR "recurrent aphthous ulceration" OR "RAS" OR "aphthous ulcer" OR "oral ulcer" OR "oral wound" OR "oral lesion".

The eligibility of the retrieved studies and any probable pertinent research that was missing was further determined by manually reviewing the reference lists of the included studies.

2.4. Study Selection and Data Extraction

The abstracts and full papers were selected based on this systematic review's inclusion and exclusion criteria. The records retrieved from all databases were imported into Mendeley's desktop and screened based on titles and abstracts after eliminating duplicate records, animal experiments, and reviews. The following information was taken from the source material: the first author's name, publication year, number of samples, interventions and comparisons, and outcomes. Two authors (A.S.I. and M.D.C.S.) independently extracted the data. Disagreements were resolved through comprehensive discussion and examined by a third investigator (D.S.E.).

2.5. Critical Appraisal for Quality if the Study

Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Randomized Controlled Trials was used for critical appraisal. The judgments for potential bias items were categorized as low, unclear, moderate, and high-quality. Disagreements were resolved through comprehensive discussion and examined by a third investigator (D.S.E.).

3. Results

3.1. Study Selection

The systematic search in three databases identified 215 articles. After deduplication, 69 articles was eligible for the screening process. The screening process resulted in 17 articles for retrieval. After the full-text review, only 5 articles met the inclusion criteria and 12 articles were excluded. A citation search during the review process identified two additional relevant articles. In total, seven articles were included for data extraction and synthesis (Figure 1).

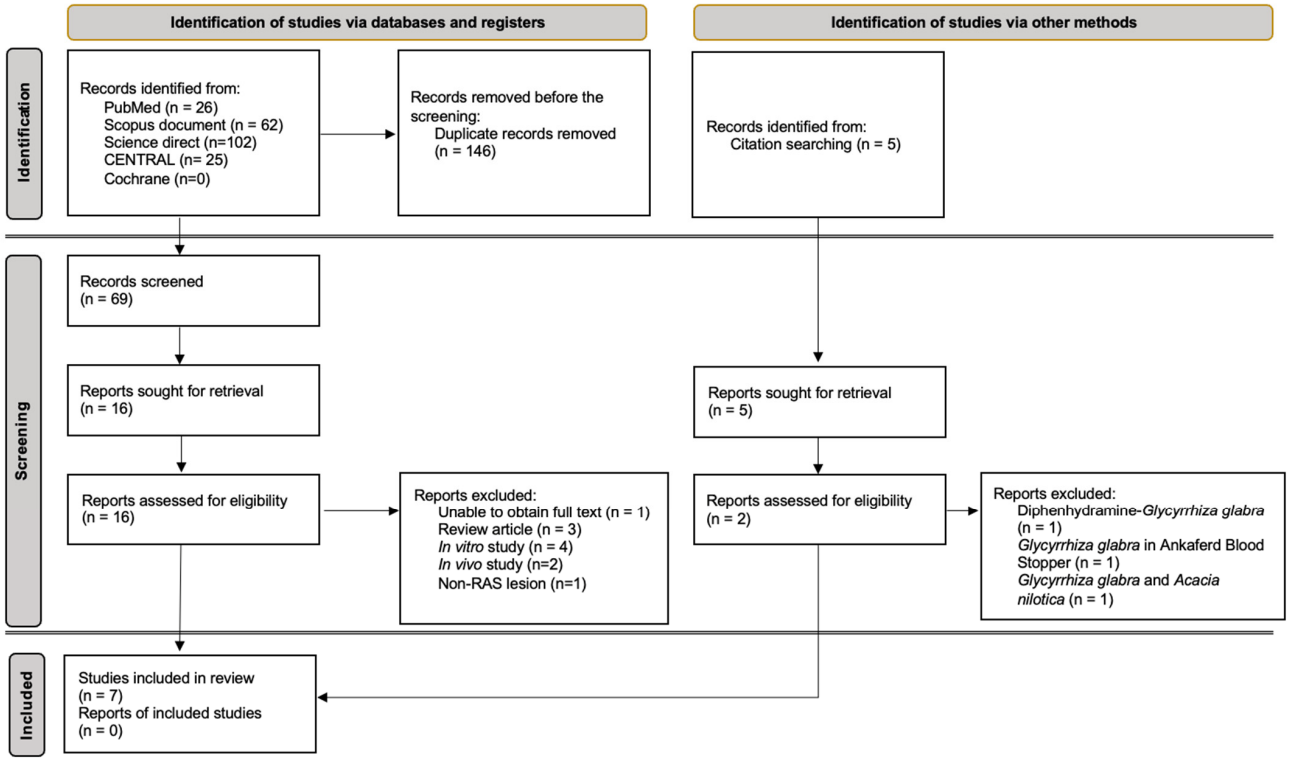


Figure 1. PRISMA flow diagram in this systematic review.

3.2. Characteristics of the Study

There were various RCTs that investigated the efficacy of *Glycyrrhiza glabra* in treating RAS. The studies included a range from randomized controlled trials and randomized clinical trials to double-blind and placebo-controlled trials. The intervention groups received *Glycyrrhiza glabra* in different dosage forms, including patches, pastes, mucoadhesive tablets, and mouthwashes. The trials examined different forms of RAS, including minor, major, and herpetiform types. Control groups across the studies included placebo patches, no treatment, and other active treatments such as vehicle patches and xylitol mouthwash. The frequency of the treatment varied starting once daily up to three or four times daily (Table 1).

Table 1. Summary of RCTs assessing the efficacy of *Glycyrrhiza glabra* in the treatment of RAS.

Type of Study	Type of RAS	Control Group		Intervention Group			Reference
		Subject (*n*)	Dosage From	Subject (*n*)	Dosage Form	Frequency of Treatment	
Placebo-controlled, observer-blind, consecutive-group clinical trial	Minor	-	Vehicle patch	15	Patch	Once daily	[23]
Randomized controlled trial	Minor	7	No treatment	7	Paste	Three times daily	[24]
Randomized controlled trial	NS	10	No treatment	10	Paste	Four times daily	[25]
Randomized controlled double-blind	Minor	20	Placebo patch	20	Paste	Four times daily	[26]
		20	Diphenhydramine mouthwash				
Randomized double-blind, placebo-controlled trial	Minor Major Herpetiform	24	Xylitol mouthwash	30	Mouthwash	Four times daily	[27]
Double-blind clinical trial	Minor	21	Placebo mucoadhesive tablet	21	Mucoadhesive tablet	Three times daily	[28]
Double-blind clinical trial	NR	23	Placebo patch	23	Patch	Once daily	[29]
		23	No treatment				

RAS = recurrent aphthous stomatitis; NR = not reported; NS = not specified.

The majority of studies utilized the maceration technique for processing *Glycyrrhiza glabra*, with the raw materials primarily being roots and rhizomes. The dosage forms administered to subjects included patches, pastes, mucoadhesive tablets, and mouthwashes. The concentration of *Glycyrrhiza glabra* varied across the trials, with two studies using a 1% concentration, while three utilized whole extracts or higher concentrations up to 17.25%. In some cases, specific details such as the concentration and processing techniques were not reported (Table 2).

Table 2. Processing techniques, dosage forms, and concentrations of *Glycyrrhiza glabra* in reported clinical trials.

Glycyrrhiza glabra	Processing Technique	Dosage Form	Concentration	Reference
NR	Maceration	Patch	1%	[23]
Roots and rhizomes	Maceration	Paste	Whole extract	[24]
Roots	Maceration	Paste	1%	[25]
Roots and rhizomes	Maceration	Paste	5%	[26]
NR	NR	Mouthwash	NR	[27]
Roots	Maceration	Mucoadhesive tablet	17.25%	[28]
Roots	NR	Patch	NR	[29]

NR = not reported.

3.3. *Glycyrrhiza glabra* Alleviated RAS-Related Pain Intensity

Different dosage forms of *Glycyrrhiza glabra* were employed in different RCTs with different frequencies, durations, and controls. The duration of treatment varied, with some regimens involving once-daily applications, while others required up to four applications per day. The pain intensity was assessed using the visual analog scale (VAS). Across all studies, significant pain reduction was observed within the first few days of treatment, highlighting the potential effectiveness of *Glycyrrhiza glabra* in alleviating RAS-related pain (Table 3).

Table 3. Treatment duration, pain assessment, and efficacy of *Glycyrrhiza glabra* in clinical trials for RAS.

Dosage form of *Glycyrrhiza glabra*	Control	Duration of Treatment	Pain Assessment	Result	Reference
Patch	Vehicle patch	Once daily	VAS	Significant pain reduction after 1 and 5 days	[23]
Paste	No treatment	Four times daily	VAS	Significant pain reduction after 2 and 5 days	[25]
Paste	Placebo paste	Four times daily	VAS	Significant pain reduction after 3 and 5 days	[26]
Mouthwash	Xylitol mouthwash	Four times daily	VAS	Significant pain reduction after 1 and 2 days	[27]
Mucoadhesive tablet	Diphenhydramine mouthwash / Placebo mucoadhesive tablet	Three times daily	VAS	Significant pain reduction after 1 until 7 days	[28]
Patch	Placebo or patch / No treatment	Once daily	VAS	Significant pain reduction after 1 day	[29]

VAS = visual analog scale.

3.4. *Glycyrrhiza glabra* Accelerating Reduction in RAS Diameter

The treatment durations varied, with some regimens requiring once-daily application and others involving multiple applications per day. Across the studies, significant reductions in ulcer diameter were observed, typically within the first few days of treatment with *Glycyrrhiza glabra*. Five RCTs reported the relationship between decreasing RAS pain intensity and reduction in RAS ulcer diameter. In one study, *Glycyrrhiza glabra* significantly decreased pain intensity after just one day of treatment, while a significant reduction in RAS ulcer diameter was observed after eight days of treatment. The results indicate that *Glycyrrhiza glabra* is effective in accelerating the healing process of ulcers associated with RAS (Table 4).

Table 4. Effect *of Glycyrrhiza glabra* on ulcer diameter reduction in clinical trials for RAS.

Dosage form of *Glycyrrhiza glabra*	Control	Duration of Treatment	Result	Reference
Patch	Vehicle patch	Once daily	Significant ulcer diameter reduction after 5 days	[23]
Paste	No treatment	Three times daily	Significant ulcer diameter reduction after 2 and 3 days	[24]
Paste	No treatment	Four times daily	Significant ulcer diameter reduction after 2 and 5 days	[25]
Paste	Placebo paste / Diphenhydramine mouthwash	Four times daily	Significant ulcer diameter reduction after 3 and 5 days	[26]
Mouthwash	Xylitol mouthwash	Four times daily	Significant ulcer diameter reduction after 1 and 2 days	[27]
Mucoadhesive tablet	Placebo mucoadhesive tablet	Three times daily	Significant ulcer diameter reduction after 3, 5, and 7 days	[28]
Patch	Placebo or no treatment	Once daily	Significant ulcer diameter reduction after 8 days	[29]

3.5. *Glycyrrhiza glabra* Effect on RAS-Related Ulcer Healing Time

Three RCTs investigated the impact of *Glycyrrhiza glabra* on the healing time of RAS. Two of these trials demonstrated a significant effect on healing time and also observed a relationship between improved pain level and reduced ulcer diameter. In contrast, one trial did not show a significant impact on healing time but did report significant improvements in pain intensity and ulcer diameter reduction. Despite the limited data, the findings suggest that *Glycyrrhiza glabra* has a notable effect on accelerating RAS healing time (Table 5).

Table 5. Impact of *Glycyrrhiza glabra* dosage forms on ulcer healing time in clinical trials for RAS.

Dosage form of *Glycyrrhiza glabra*	Control	Duration of Treatment	Result	Reference
Patch	Vehicle patch	Once a day	No significant healing time	[23]
Paste	Placebo paste / Diphenhydramine mouthwash	Four times daily	Significantly faster ulcer healing	[26]
Mouthwash	Diphenhydramine mouthwash	Four times daily	Significantly faster ulcer healing after 1, 3, and 7 days	[29]

3.6. Quality of the Study

Two RCTs showed a high-quality study, while five studies showed a moderate quality. The moderate study lacks a description of the randomization process, blinding treatment procedure, and follow-up rate. The high-quality study has an unclear randomization and follow-up rate (Table 6).

Table 6. The quality assessment of the randomized controlled trials included in this study.

Assessment Criteria	[23]	[24]	[26]	[28]	[29]	[27]	[25]
Selection criteria	√	√	√	√	√	√	√
Randomization	x	X	√	o	o	o	o
Blinding	o	X	√	o	x	√	X
Follow-up rate	X	X	X	X	X	√	X
Intervention detail	√	√	√	√	√	√	√
Outcome measure	√	√	√	√	√	√	√
Statistical analysis	√	√	√	√	√	√	√
Quality	Moderate	Moderate	High	Moderate	Moderate	High	Moderate

√ = Yes; X = No; o = Unclear.

4. Discussion

RAS is characterized by painful, recurring oral ulcers, and its etiopathogenesis involves several key factors [30]. One significant mechanism underlying RAS is the increased production of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α) [31], interleukin 1β (IL-1β) [32], and interleukin 6 (IL-6) [33]. They are released in response to various triggers, leading to an exaggerated inflammatory response in the oral mucosa [34]. This chronic inflammation contributes to the development and persistence of oral ulcers. Additionally, elevated levels of free radicals play a crucial role in the pathogenesis of RAS [35]. Free radicals, including reactive oxygen species (ROS) [36] and nitric oxide (NO) [37], are generated during inflammatory processes and contribute to tissue damage by oxidizing cellular components and disrupting normal cellular functions. The interplay between increased pro-inflammatory cytokines and elevated free radical production exacerbates mucosal damage, impairs healing, and perpetuates the cycle of ulceration seen in RAS.

Glycyrrhiza glabra is a plant native to Asia and Europe. Its roots, which thrive in subtropical and tropical climates, grow well in loose, mineral-rich soil under sunlight [38–40]. The primary parts of the plant used are the roots and rhizomes because these parts were reported to have several medicinal effects such as antioxidant, anti-inflammatory, anti-ulcerative,

and anticarcinogenic [21]. The major bioactive components of *Glycyrrhiza glabra* include triterpenes (18α-glycyrrhetinic acid and 18β-glycyrrhetinic acid) and flavonoids (such as licochalcone, isoliquiritigenin, echinatin, glabridin, isoangustone, licoricidin, licorisoflavan A, dehydroglyasperin C and D, and pinocembrin) that are found in the roots and leaves [21,41]. These triterpenes and flavonoids exhibit strong antioxidant and anti-inflammatory effects, which are crucial in the healing of RAS [42]. These bioactive compounds can be obtained with extraction techniques called maceration [23–26,28], a method where the material is immersed in a suitable solvent at room temperature for a specified period. This technique is preferred for its simplicity and ease of use [43–46]. Several studies reported in this systematic review performed maceration to obtain the *Glycyrrhiza glabra* extract [23–26,28], but the presence of a bioactive component was not reported. Four studies reported that the concentration extract used for the treatment was 1% [23,25], 5% [26], and 17.25% [28].

Glycyrrhiza glabra offers promising potential for treating RAS due to its multifaceted therapeutic properties. The primary reason for its efficacy is its rich composition of bioactive compounds [47] (Figure 2). These compounds exhibit strong antioxidant and anti-inflammatory effects, which are crucial in managing RAS. The antioxidant effects of pinocembrin, glabranin, and licoflavanone help decrease NO levels [48], while licochalcone-C modulates key antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase [49]. The reduction in oxidative stress and increase in antioxidants are vital in preventing further mucosal damage, promoting faster healing, and reducing the recurrence of ulcers [24,42]. In terms of anti-inflammatory activity, pinocembrin, glabranin, and licoflavanone inhibit the nuclear translocation of NF-kB; reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1β [50], IL-6 [48], and prostaglandin E2 (PGE2) [51]; and decrease matrix metalloproteinases (MMPs) [42]. Additionally, liquiritigenin promotes Nrf2 translocation, which influences the release of growth factors [52], affects ROS-related gene expression [52], and inhibits the downstream pathways of advanced glycation end-products (AGE)-RAGE signaling [53]. Licochalcone-C further contributes by inhibiting interferon-gamma (IFN-γ) [49]. By altering this factor, *Glycyrrhiza glabra* helps to alleviate the chronic inflammation associated with the condition, thus reducing the severity and frequency of ulceration. Moreover, the muco-protective effects of *Glycyrrhiza glabra* [54] contribute to the formation of a protective barrier over the oral mucosa, which can further help in mitigating the discomfort and pain associated with RAS. The combination of anti-inflammatory, antioxidant, and muco-protective properties makes *Glycyrrhiza glabra* a valuable therapeutic option for managing recurrent aphthous stomatitis. Its ability to address both the inflammatory and oxidative aspects of the disease provides a comprehensive approach to alleviating symptoms and promoting oral mucosal health.

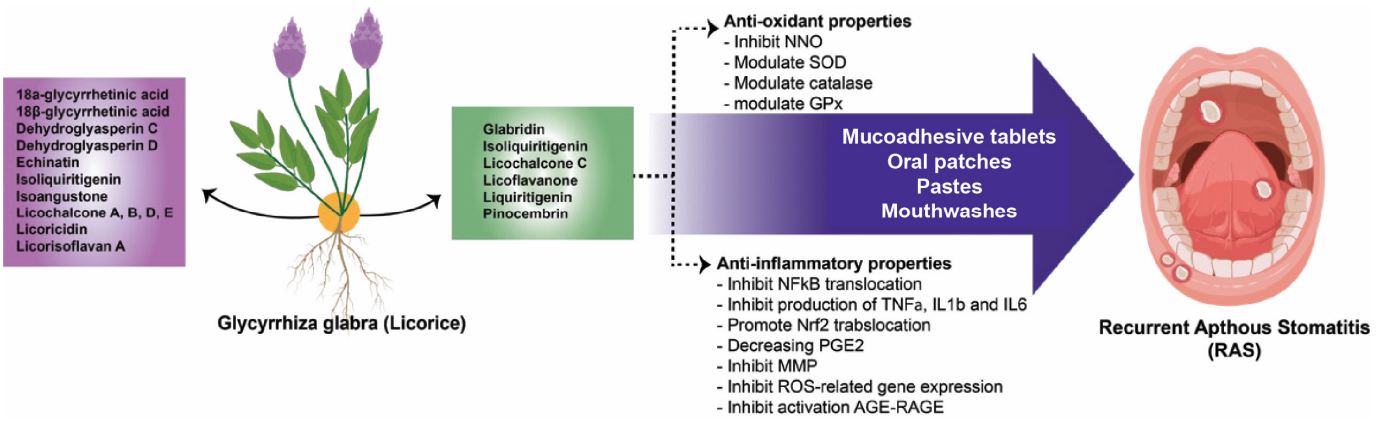


Figure 2. Antioxidant and anti-inflammatory properties of *Glycyrrhiza glabra* for stimulating healing of RAS.

The review of the seven RCTs on *Glycyrrhiza glabra* for treating RAS indicates that *Glycyrrhiza glabra* shows promise in managing this condition. The trials demonstrate that *Glycyrrhiza glabra*, administered in various dosage forms (patches, pastes, mucoadhesive tablets, and mouthwashes), is effective in reducing RAS-related pain and accelerating ulcer healing. Most studies observed significant pain reduction and a decrease in ulcer diameter within the initial days of treatment. Patches and mucoadhesive tablets appear to offer superior benefits over pastes and mouthwashes, likely due to their ability to provide prolonged contact with the lesion, ensuring sustained drug release and better adherence to the ulcer site. Several studies showed that patches or films can accelerate ulcer healing [55–57]. However, variations in the concentration and extraction process of *Glycyrrhiza glabra*, as well as differences in treatment regimens, highlight the need for standardized protocols.

In reviewing the seven RCTs included in this analysis, two studies demonstrated a high quality, while the remaining five were classified as moderate quality. Studies deemed moderate lacked details in several critical areas: the randomization process, blinding of treatment, and follow-up rates. These limitations introduce a potential risk of bias, as inadequate randomization and blinding could lead to biased results, particularly if patient expectations or clinician assessments influenced the outcomes. Furthermore, insufficient follow-up data can weaken the internal validity of findings, as loss to follow-up might affect the generalizability of results to all RAS patients.

Even the high-quality studies were not without flaws, notably lacking clarity on randomization methods and follow-up completeness. Such gaps could lead to overestimation or underestimation of *Glycyrrhiza glabra*'s effect size in reducing pain and accelerating ulcer healing. Although the overall trend across the studies indicates beneficial outcomes, these methodological limitations underscore the need for cautious interpretation of the results. Further high-quality, rigorously designed trials with standardized protocols for dosing and application methods are necessary to confirm *Glycyrrhiza glabra*'s efficacy in managing RAS and to establish reliable treatment recommendations.

Future research should focus on the standardization of dosage and formulation of *Glycyrrhiza glabra* to determine the most effective and consistent treatment regimen. Investigations into the long-term efficacy and safety of *Glycyrrhiza glabra* for RAS are needed to establish sustained benefits and potential side effects. Research should explore the underlying mechanisms by which *Glycyrrhiza glabra* alleviates RAS symptoms, focusing on its anti-inflammatory and antioxidant properties. In clinical practice, *Glycyrrhiza glabra* could be considered as a complementary treatment option for patients with RAS. Its application in various dosage forms, such as patches and pastes, offers flexibility in treatment options. Clinicians should evaluate the specific formulation and concentration that best suit individual patient needs based on the latest research findings. Personalized treatment plans may improve patient outcomes and enhance the management of RAS symptoms.

The limitations of this systematic review lie in that the studies varied in their dosage forms, concentrations, and treatment regimens, which complicates the comparison and generalization of results. The second limitation is limited data on bioactive components and chemical composition of *Glycyrrhiza glabra* extracts, leaving gaps in understanding how different components contribute to its efficacy. Addressing these limitations through more uniform and comprehensive research will help refine the application of *Glycyrrhiza glabra* in treating RAS and contribute to a more robust understanding of its therapeutic potential.

5. Conclusions

This study demonstrated the therapeutic efficacy of *Glycyrrhiza glabra* in treating RAS. Its effectiveness is due to its bioactive compounds, which have strong anti-inflammatory

and antioxidant properties, which help reduce pain, accelerate ulcer healing, and alleviate the symptoms associated with RAS. Future research should focus on refining treatment regimens, understanding the long-term efficacy and safety, and exploring the specific mechanisms through which *Glycyrrhiza glabra* operates to better inform its use as a complementary treatment for RAS.

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