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Review Article

Topical Licorice for Aphthous: A Systematic Review of Clinical Trials

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What's Known

- Licorice has been used to treat oral diseases such as aphthous for decades in many cultures.
- Glycyrrhizin, the major component of licorice, has a similar structure to adrenal steroids, which causes its anti-inflammatory effect.

What's New

- The anti-inflammatory effect of licorice is dose-dependent in aphthous.
- Licorice significantly plays a role in aphthous therapyby reducing healing time, pain, and size of the inflammation zone without side effects.
- Licorice efficacy appears in a 4-8 day treatment period.

Abstract

Background: Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease that affects oral mucosa. The coating agents, topical analgesics, and topical steroids are usually used as treatment methods. *Glycyrrhiza glabra* has been used for RAS treatment based on its anti-inflammatory, antioxidant, and immunomodulatory properties. In this study, a systemic review on the therapeutic effect of topical licorice on RAS management was performed.

Methods: Science Direct, Scopus, Cochrane databases, PubMed Google Scholar, and ResearchGate were searched up to September 2021 to find all English randomized clinical trials studying the effect of *G. glabra,* or its compositions on RAS. Meta-analysis was not conducted because of data heterogeneity. Articles were reviewed qualitatively, and only those with a Jadad score ≥3 were included. Animal studies, *in vitro*, review papers, non-English papers, and case reports were excluded.

Results: Six studies with 314 subjects were included after screening. The result showed licorice has significant effects on RAS pain reduction, ulcer size, and healing time. Its effectiveness is related to its dose-dependent anti-inflammatory and antioxidant effects through several mechanisms. It also has antibacterial effects against *Streptococci mutans* and *Porphyromonas gingivalis* as another mechanism of action in RAS treatment. In addition, licorice can elevate the epidermal growth factor (EGF) level compared to the control group, which has an essential role in oral mucosal tissue integrity.

Conclusion: Licorice extract has been used in different dosage forms, including paste, patch, and mouthwash with concentrations of 1% or 5%. The healing time after licorice therapy is expected to be within 4-8 days. Licorice did not show any adverse effect in the intervention groups, indicating its effectiveness and safety in RAS treatment.

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Keywords ● Glycyrrhiza ● Stomatitis ● Aphthous ● Systematic review

Introduction

Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease affecting oral mucosa. RAS may cause difficulty in speaking, eating, and swallowing, thereby decreasing the patient's quality of life.[1] This disease affects people of all ages. Approximately 5-25% of the population are involved.[2] Moreover,

the prevalence can vary from 5 to 60% based on geographical region, genetics, occupational groups, and social situations.[3]

The etiology is unclear, but researchers have reported several risk factors, including trauma, immunological factors, genetic factors, stress, bacterial and viral factors, systemic disease, food allergy, hormonal factors, medications, and vitamin and micronutrient deficiencies.[4]

According to clinical data, the ulcers are small, painful, round, and generally shallow with a necrotic center and erythematous margins.[5] Still, they are classified into three grades including minor recurrent aphthous stomatitis, major recurrent aphthous stomatitis, and herpetiform ulcers. These three types differ in the lesions' kind, number, and size. Minor RAS is the most common type of lesion, which involves 87% of cases.[5, 6]

Diagnosis is often based on history and clinical presentation; it usually does not require laboratory testing. Although, diagnostic tests might be considered in severe cases. It needs differential diagnosis with similar ulcers such as contact dermatitis, oral cancer, *Herpes simplex*, drug-induced lesions, lupus, lichen planus, Sutton's ulcers, Riga-Fede disease, and *Pemphigus vulgaris*.[7, 8]

RAS does not have any definite treatment; all therapies intend to decrease pain, duration, and disease frequency. Most patients have mild RAS and don't need any treatment. However, treatment should be considered for patients who experience severe forms, painful ulcers, or recurrent forms. Topical therapy is the first therapeutic choice, because it is safe, effective, and has minor drug interaction and side effects.[5, 8] Topical therapies include topical anesthetics (e.g., lidocaine), mouthwashes (e.g., chlorhexidine gluconate, tetracycline, and minocycline mouthwash), occlusive agents (e.g., bismuth subsalicylate, sucralfate, 2-octyl cyanoacrylate, and various bio-adherent emollient pastes), topical corticosteroids (e.g., triamcinolone and dexamethasone), intralesional corticosteroids, and 5% amlexanox hydrochloride oral cream. The last one is a systemic therapy. For patients with a severe form of RAS that is refractory to topical treatment, systemic treatment should be added, such as systemic corticosteroids and colchicine because of the anti-inflammatory effect, pentoxifylline as anti-TNF-α, and other systemic drugs including antibiotics. Topical corticosteroids result in rapid healing, but the long-term use of steroids causes candidal infection. Patients may utilize an alternative therapy such as saltwater solution and sodium bicarbonate, hydrogen peroxide solution, milk of magnesium, and antihistamine drugs such as diphenhydramine.[2, 4]

Common treatments such as anti-inflammatory steroids and chlorhexidine mouthwash have adverse effects, such as developing secondary oral candidiasis and teeth discolorization. Thus, alternative treatments are required.[9]

Many studies have reported that medicinal plants have an anti-inflammatory function with fewer side effects, and they have been used for decades in many countries. Therefore, they can be used as an alternative therapy to steroids.[9-11] The most common route of administration of these plants is mouthwash.[10] These plants include *Aloe vera*, *Morus nigra*, *G. glabra*), *Curcuma longa*,[9] Chamomile, *Myrtus communis*, Camelthorn, *Yunnan baiyao*, *Rhizophora mangle* aqueous bark extract (RMABE), and *Satureja khuzistanica*.[10] One of the most effective plants is licorice.

Licorice is the common name of *G. glabra* (figure 1). The genus name *Glycyrrhiza* is derived from the Greek words "*glycos*" meaning sweet, and "rhiza", meaning root. Roots are the primary source of licorice.[12] Licorice is native to southern Europe and parts of Asia.[13]

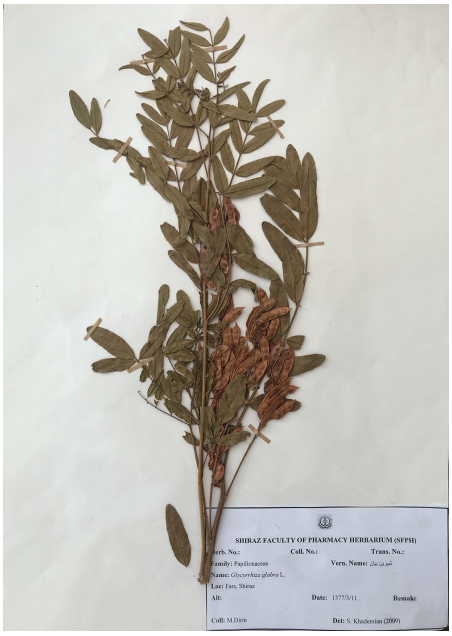

Figure 1: A herbarium sample of *Glycyrrhiza glabra*.

Glycyrrhetic acid is its most potent active metabolite with a corticosteroid-like effect. Due to its anti-inflammatory, antioxidant, and immunomodulatory properties, it has a therapeutic impact on a wide variety of diseases including liver disorders (such as hepatitis B and hepatitis C), gastrointestinal disorders (such as *helicobacter pylori* and peptic ulcer), oral health diseases (including dental caries and xerostomia), sore throats, coughs, disorders

related to energy metabolism (such as fat mass and muscle mass), and skin diseases (such as erythema, atopic dermatitis, vitiligo, and alopecia areata). Glycyrrhetinic acid can prevent cyclooxygenase enzymatic pathway, free oxygen radical production, and cell immigration. It also inhibits 11β-hydroxysteroid dehydrogenase (11β-HSD) and binds to mineralocorticoid receptors. All of these functions result in the anti-inflammatory effect of licorice.[14, 15]

Considering the high prevalence of RAS, lack of a definitive treatment, and considerable effect of licorice on RAS, we decided to perform a systematic review on licorice usage in RAS treatment in human clinical trials. Moreover, licorice effectiveness, mechanisms, and safety will be discussed.

Materials and Methods

Search Strategy and Data Sources

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statements were applied in carrying out this systemic review.[16] Science Direct, Scopus, Cochrane databases, PubMed, Google Scholar, and ResearchGate were searched up to September 2021. In addition, the bibliographies of reviews, and *in vivo*, *in vitro*, and animal studies were scanned for additional relevant papers. The search strategy was as follows in Scopus, but was modified regarding each database or website principle: (Glycyrrhiza glabra OR Licorice OR Liquorice OR Alcacuz) AND (Recurrent Aphthous Stomatitis OR Aphthous OR RAS OR Recurrent aphthous ulceration OR RAU). The screening process was performed as mentioned in the screening and selection technique section.

Two reviewers (FD, and GV) performed database searching and screened the eligibility of studies. Any discrepancies were resolved by discussion through an online meeting (FD, GV, EA). Unresolved challenges were discussed with other researchers. Endnote software (version 20, Clarivate, Philadelphia, PA, USA) was used to organize included articles.

Eligibility Criteria

Inclusion Criteria and Exclusion Criteria

All published clinical trials investigating the effect of licorice topical formulations on RAS in both men and women with a history of RAS independence to any particular disease of any age and any gender were included up to the end of September 2021. We only included articles published in English.

Animal studies, *in vitro*, review papers, non-English papers, case reports, and articles with Jadad score <3 were excluded from the study. Jadad score is a tool to evaluate the methodological quality of clinical trials.[17] But, we searched the references for additional relatable studies.

Screening and Selection Technique

Two investigators (FD, GV) individually screened all relevant paper titles and abstracts to evaluate relatable research regarding inclusion and exclusion criteria. After verifying the suitability of each study by the two mentioned investigators, the Modified Jadad scale was used to assess the quality of the studies. Two researchers (FD, and GV) evaluated each study separately. Through all selected studies, one paper with Jadad scores below three was considered poor quality and excluded. Investigators evaluated all relevant studies to be sure all information was reviewed. During all stages of the research, members consulted and discussed the whole aspects and angles and tried to make the best decision. In case of disagreement, the problem was resolved through discussion, and the main investigator (EA) decided.

Data Collection and Data Item

Two investigators individually assessed the integrity of published papers. After that, needed information, including date of publication, all types of topical formulations and doses in each study, the duration of each survey, studies with placebo groups, double-blinded studies, and the result of each survey, were extracted. The effect of the study was evaluated based on the duration of treatment and reduction of ulcer size and pain in damaged cells.

Data Synthesis

Obtained studies by search strategy were screened, and qualified studies after evaluation with eligibility criteria were included. All related information about *role of G. glabra* in RAS was exploited. Results were divided into demographic and therapeutic indicators. Thus, different studies and their outcomes were compared and evaluated, and finally, the best product and therapeutic regimen were reported. In addition, the mechanism of action is explained based on included articles and other sources such as animal and review studies.

Results

Initial research yielded 128 studies. Fifty-six articles remained after removing duplicates and

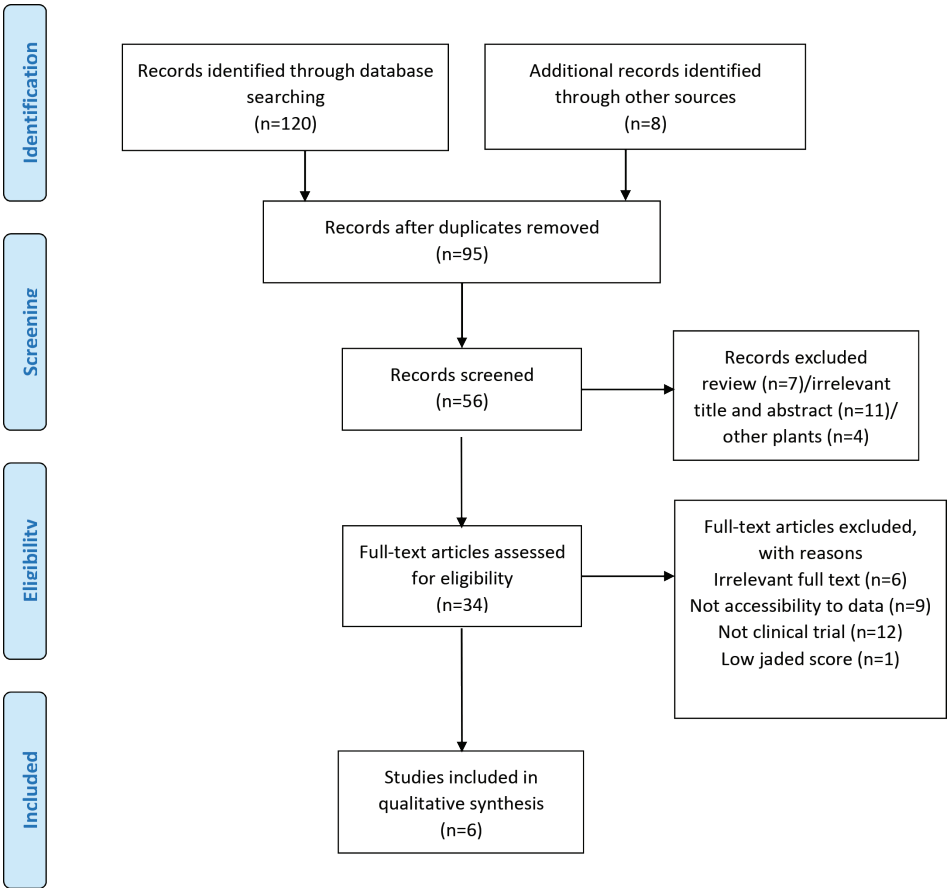

Figure 2: The PRISMA flow chart of the study.

screening records. Twenty-two articles were excluded due to being reviewed, irrelevant titles and abstracts, or being related to other plants. Then, 34 remained papers were assessed for eligibility. Six papers had irrelevant full text, the full text was not accessible for nine studies, twelve articles were not in the field of the clinical trial, and one article had a low Jadad score. Finally, six papers were selected for inclusion in our study (figure 2). The study quality was assessed using the Jadad score (supplementary file 1). Based on the trial randomization, the appropriateness of the randomization process, blinding, the suitability of the blinding process, inclusion/exclusion criteria, side effects, statistical analysis, and withdrawal, the jadad score was determined. Each item was assigned a score of 0 or 1, and the total score ranged from 0 to 8. The mean Jadad score is 5.5. This systematic review defines trials with Jadad scores ≥3 as high-quality trials.

Table 1 provides complete information on the included articles in the systematic review. The inclusion criteria were patients with a history of RAS or at least two confirmed episodes of RAS during a 3-6 months untreated baseline period and currently suffering from aphthous ulcer within the first day of symptoms. The exclusion criteria were the history of licorice allergy, iron deficiency, smoking, and whether the patient received any other treatment in the last four weeks. Besides, in some articles patient exclusion was due to systematic drug therapy during the past three months, using topical treatment before the trial, those with aphthous lesions older than four days, those with a special syndrome such as Bechet's disease, inflammatory RAS as a symptom of bowel disease, diabetes, hypertension, pregnancy, and breastfeeding, which were excluded due to the mineralocorticoid effects of licorice. Moreover, one study excluded patients with major ulcers.[14] The number of subjects consists of 15 to 70 per article. Totally, 314 patients were studied in the included articles. All studies were randomized clinical trials. Four studies[14, 18-20] were double-blind, and two other studies[21, 22] were not blinded. Five studies[14, 18, 20-22] also examined the effect of a placebo, and another one[19] used a group with conventional treatment to compare with the intervention group. The study duration were from five to eight days; the most common duration was five days. In a more detailed form, five studies[14, 19-22] were continued for five days, and another one[18] was continued for eight days.

Table 1: Studies evaluating *G. glabra's* role in RAS management

Authors	Year	Number of partici-pants	Age (years)	Patient population	Therapy and regimen	Groups	Treatment duration	Outcome/Adverse event	Jadad score
Martin and others[18]	2008	69	18	RAU	Licorice patches for 16 hours per day (but not during sleeping)	Licorice patch group/ active placebo patch group/ no-treatment group (each group 23 subjects)	Eight days (visit on days 3, 4, 8 and No-treatment group one more visit on day 10)	By the 8th day, the ulcer size for the active treatment group was significantly lower ($P<0.05$). By the 4th day, the active treatment group reported less pre-stimulus pain ($P<0.01$). At this point, 81% of this group reported no pre-stimulus pain, but 63% of the placebo patch group and 40% of the no-treatment group reported pre-stimulus pain.	6
Moghadamnia and colleagues[20]	2009	15 (5 W, 10 M)	22-35	RAS	Patch containing 1% licorice extract (QID)	The first episode was no-treatment group, the second and third episodes were assigned to bioadhesive without licorice and bioadhesive with licorice, respectively	Five days (visit on days 1, 3, and 5)	Biopatches containing licorice were almost equally effective as patches without licorice.	3.5
Galal and others [22]	2012	40 (13 W, 17 M)	18-35	RAU	Paste containing 1% licorice extract (QID)	Four treatment groups: *Acacia nilotica*, Licorice, acacia&licorice, and control group. (each group has ten subjects)	Five days (visit on days 0, 2, and 5)	Treatment of minor RAS using a mixture of licorice and *Acacia nilotica* extracts revealed more significant pain reduction healing time and potency than each one alone. These results correlated positively with salivary EGF levels measured during the same observational periods.	5
Raeesi and colleagues[14]	2015	60	-	RAS	Paste containing 5% licorice extract (QID)	Three treatment groups: diphenhydramine mouthwash/ paste containing 5% licorice extract/ paste without licorice extract (each group 20 subjects)	Five days (visit in 0, 1, 3, and 5)	A significant reduction in VAS was recorded due to the application of the Licorice Bioadhesive paste 5% on days one, three, and five compared to the control and placebo groups	6
Nasry and others[21]	2016	60 (37 W, 23 M)	19-40	RAS	Pastes containing *Acacia nilotica* & Licorice 1% (QID)	Four treatment groups: adhesive pastes of *Acacia nilotica* & Licorice/ adhesive oral tablets of 2 mg Amlexanox/ diode laser irradiation/ control group received a placebo adhesive tablet (each group 15 subjects)	Five days (visit on days 0, 2, and 5)	All treatment modalities reduced pain and ulcer size compared to the placebo group.	4
Akbari and colleagues[19]	2020	70	18-60	RAS	Diphenhydramine elixir containing 5% licorice extract (QID)	Two-treatment groups: diphenhydramine solution and diphenhydramine-containing *Glycyrrhiza glabra* (Each group 35 subjects)	Five days (visit on days 1, 2, and 5)	Diphenhydramine-containing *G. glabra* was significantly more effective in treating RAS than diphenhydramine solution alone	8

W: Women; M: Men; RAU: Recurrent aphthous ulceration; RAS: Recurrent aphthous stomatitis; QID: Four times a day; EGF: Epidermal growth factor; VAS: Visual analog scale

Clinical trials were carried out on a wide range of ages; the youngest patient was 18, and the oldest was 60 years old. All studies included both men and women. Licorice was used in different doses and dosage forms such as oral patch in two studies[18, 20] (one of them had 1% licorice extract, and the concentration was not mentioned in another one), bioadhesive paste 1% in two studies[21, 22] (also one paste was combined with acacia), bioadhesive paste 5% in one study,[14] and another study[19] used diphenhydramine containing 5% licorice extract. The frequency of use in all studies was four times a day, except one study[19] that used a licorice patch for 16 hours per day. The most frequent dosage form was bioadhesive paste containing 1% licorice four times daily (QID), but based on the results, the patch could be most effective due to its occlusive properties.

No side effects were reported in the included studies. All studies showed significant effects of licorice on reducing ulcer size, and similar results were seen for the pain-relieving effects of licorice. Moreover, another study compared the effect of laser with licorice and observed that the laser was more effective.[21]

Discussion

Licorice has been used to treat RAS for decades. Glycyrrhizin is an active component that has an anti-inflammatory effect. Therefore, it can be used as a treatment for RAS. Many studies carried out on this plant have confirmed its effectiveness. Hence, the parameters related to RAS and the effect of licorice are discussed in the following sections.

Pain

All studies measured pain using a visual analog scale (VAS). Three studies used compound formulations, and three others used single formulations. Five of six demonstrated that the mean pain score showed a statistically significant decrease in the licorice group. The exception was for the study carried out by Nasry and colleagues. In their study, four groups were designed, including *Acacia nilotica* and licorice (acacia&licorice) bioadhesive paste group, oral tablets of 2 mg amlexanox group, diode laser group, and control group. On day five, both amlexanox and laser groups demonstrated a significant decrease in mean pain score compared to the acacia and licorice groups (P<0.001). However, the acacia&licorice group showed better results than the placebo group.[21] Burgess and others reported dissolving an oral patch containing *G. glabra* root extract can be as effective as amlexanox in reducing pain and promoting healing.[23] Galal and colleagues also reported acacia&licorice reduced pain more significantly than each alone.[22] Akbari and others showed that both diphenhydramine solution (DS) and diphenhydramine-containing *G. glabra* (DSG) significantly decreased the mean pain scores (P=0.0001). DSG reduced pain scores more than DS.[19] Moghaddamnia and others used a bioadhesive patch containing 1% licorice extract. They showed that the bio patch with licorice was considerably more effective than the no-treatment group in pain-relieving (P<0.001). Nevertheless, it was equal to the bioadhesive patch without medicine, and they suggested that mechanical mucosal protection has an essential role in reducing pain and healing of RAS.[20] Furthermore, other studies also showed a positive effect of mucosal protection by a patch-like system. Mahdi and colleagues employed a bioadhesive hydrogel patch made of a pharmaceutical-grade cellulose derivative. Patients applied the medication twice a day and reported that the patch could reduce pain and healing time. It might be due to the protective effect of the patch against irritation and secondary infection.[24] Shemer and others reported that the mucoadhesive patch containing citrus oil and magnesium salts was more effective than an oral solution containing benzocaine and compound benzoin tincture in terms of healing time and pain intensity after 12 and 24 hours.[25] Moreover, Daněk and others designed a study with one group was treated with a gel containing choline salicylate and the second treated with the same preparation followed by covering the lesions with a mucoadhesive film. They also reported that covering lesions resulted in a significant pain reduction and duration of patient healing.[26]

It should be noted that the number of subjects in Moghaddamnia's study was limited, and the JADAD score was 3.5, reflecting its low quality. On the other hand, Raeesi and colleagues used a bioadhesive paste containing 5% licorice extract. They reported that the paste and medicine reduced the necrotic zone, erythematous halo, and pain significantly more than the group with diphenhydramine mouthwash and the paste without medication (P=0.0001). They suggested that the difference between their result and Moghaddamnia's study was probably related to the dose-dependent anti-inflammatory effect of licorice.[14] Another study used a licorice gel for atopic dermatitis, and they also reported that 2% topical licorice gel was more effective than 1% in reducing erythema, edema, and itching over two weeks (P<0.05).[27]

Kuriyama and others also reported 1 g topical licorice formulation was more effective than 250 mg and 97 mg in preventing postoperative sore throat.[28] Hassan and colleagues used licorice mouthwash in six patients with mouth ulcers; they reported that ulcer improvement began on the first day in patients with a single ulcer, and complete healing was observed at the end of the third day.[29] We did not include this article in the review due to its low JADAD score. Das and colleagues reported that 15 out of 20 patients who used licorice mouthwash experienced 50-75% improvement within one day, and complete healing was achieved by the third day.[30] Licorice effectiveness may be due to its glycyrrhizic acid, glabridin, and flavonoids that inhibit the enzymatic cyclooxygenase and lipoxygenase pathway. Besides, it has an anti-inflammatory and pain-reducing effect by inhibiting free oxygen radical production and controlling arachidonic acid (AA) metabolism.[19] The mechanism of action will be discussed in the discussion section in detail.

Ulcer Size

Results for size reduction were similar to pain reduction. The size of inflammatory zones was different from less than 1 cm to more than 1 cm based on aphthous type. One study did not analyze the size of lesions, and five studies reported significant mean size reduction compared to the control group. Nasry and colleagues reported that laser, amlexanox, and acacia&licorice groups, all had size reduction compared to the control group. However, the laser and amlexanox groups had the most percentage of mean size reduction.[21] Galal and others revealed that on days two and five, both acacia&licorice and licorice groups showed the smallest mean size, and there was no significant difference between them. Raeesi and others reported a size reduction in the paste with the 5% licorice extract group, which was significantly more than the diphenhydramine mouthwash group and placebo group.[14] In the study of Moghadamnia and colleagues using a one-way ANOVA test showed a significant decrease in ulcer size only on day five ($P<0.001$). They reported that based on previous literature, this reduction in aphthous size could be due to the anti-inflammatory effect of licorice extract.[20] Martin and others study showed the licorice patch treatment group experienced an ulcer size reduction by 90% in the fourth visit (day eight); in contrast, the no-treatment group had an increase in size in comparison to baseline by 13%. They reported active placebo group experienced an ulcer size reduction by 68.5%, which suggests this reduction may be due to the antibiotic effect of powdered star anise fruit added to the placebo patch, which tastes similar to licorice.[18]

Healing Time

Three studies reported significant differences in healing time between groups. Raeesi and colleagues reported healing time as nine days for the diphenhydramine mouthwash group, four days for bioadhesive paste containing 5% of licorice extract, and seven days for the placebo group.[14] Akbari and others reported two healing times with 1.5 days difference (6 days for DS and 4.5 days for DSG).[19] Moghadamnia and others reported that despite differences in healing time (9.53±1.8 for the no-treatment, 8.6±1.68 for bio patch without licorice, and 8.46±1.55 for licorice bio patch groups), the ANOVA test result did not show a significant difference.[20]

Epidermal Growth Factor (EGF) Level

EGF is a polypeptide found in different biological fluids, including saliva. EGF stimulates cell proliferation in various tissue.[31] Binding to EGF receptors stimulates gene regulation,[31] DNA synthesis, stimulation of protein synthesis, cytoprotection, and ulcer healing.[32] The salivary levels of EGF have an essential role in oral mucosal tissue integrity.[32] In different types of oral mucosal disease, low salivary EGF levels have been reported.[22] Galal and colleagues tried to determine the correlation between pain and ulcer size reduction and the EGF level. They reported the dramatically lowest mean EGF level in the control group. This reduction in EGF occurs when the disease is active and weakens the protective effect of saliva on the oral epithelium. On the other hand, they reported that both acacia&licorice and licorice groups showed the highest level of EGF. The higher EGF in the acacia&licorice group than in the acacia and control groups might be due to the combined antimicrobial and anti-inflammatory effect of acacia and licorice. This combination results in enhancing EGF recovery and promotes aphthous healing. Besides, the anti-inflammatory effect of licorice individually or mixed has a greater effect on the healing process and pain reduction.[22]

Mechanism of Action

It is well known that eicosanoids, prostaglandin E_2 (PGE_2), and thromboxane A_2 (TXA_2) participate in the inflammatory process.[33] Cyclooxygenase-2 (COX-2) catalyzes AA's conversion into PGE_2 and TXA_2. The balance of COX derivate influences different processes in the body such as inflammation.[34] The active metabolite in

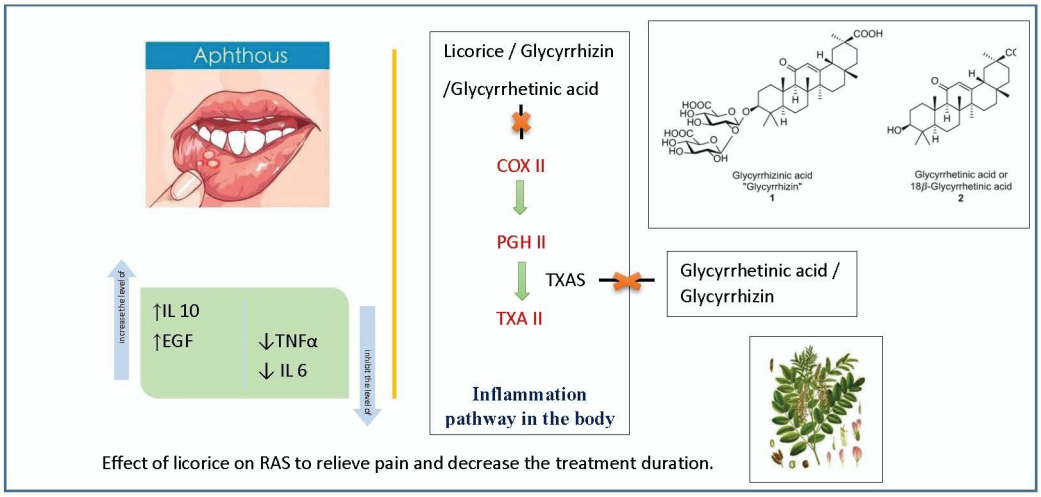

Figure 3: The mechanism of licorice in aphthous management is shown.

licorice extract is glycyrrhizin, which is converted to glycyrrhetinic acid by intestinal microflora.[15] Licorice and its active metabolites have an anti-inflammatory effect by blocking the COX-2/ TxA_2 pathway[35] (figure 3). The glycyrrhetinic acid is a potent metabolite with corticosteroid-like effects [15] by inhibiting 11β-hydroxysteroid dehydrogenase, which stops the conversion of active cortisol into inactive cortisone.[15, 36] Besides, other studies showed licorice increased the concentration of corticosteroids, such as prednisone and prednisolone, and endogenous corticosteroid levels by inhibiting their metabolism. The major glycyrrhizin cortisol-like effect is due to phospholipase A_2 inhibition.[35] This enzyme breaks down biomembrane to librate AA, a precursor of eicosanoids such as prostaglandins.[37] Licorice has an antioxidant activity that improves wound healing.[38] It also inhibits the production of proinflammatory cytokines and CD14, reduces plasma levels of tumor necrosis factor and interleukin-6 (IL-6), and increases IL-10 production.[38] On the other hand, some studies reported licorice has antibacterial activity against *Streptococci mutans* and *porphyromonas gingivalis*, which can effectively prevent and treat dental decay and oral infection.[15, 39] The anti-inflammatory effects of licorice through different mechanisms and its antibacterial effects provides evidence for the therapeutic potential of licorice in RAS healing.

Outcome and Safety

The oral high dose licorice induced hyper mineralocorticoidism and subsequently, sodium retention, hypokalemia, systolic and diastolic blood pressure elevation, and the depression of the renin-angiotensin-aldosterone system.[19, 40] A study reported that a regular intake of 100 mg glycyrrhizic acid per day equal to 50 g licorice could develop adverse but minor side effects. In contrast, most subjects who intake 400 mg glycyrrhizic acid daily developed adverse effects.[40] A daily intake of 1–10 mg glycyrrhizic acid is suggested to be safe for healthy adults.[40] Another study also suggested a daily intake of 50 g of licorice (equivalent to 75 mg glycyrrhetinic acid) for two weeks could result in hypertension. After two weeks, the maximal effect on blood pressure subsequent to the daily intake of licorice was observed.[41] Despite these side effects, none of the studies reported any side effects, showing that topical application and short-duration licorice usage would be safe.

Limitations and Future Perspective

Since the anti-inflammatory effect of licorice is dose-dependent, a higher concentration formulation is to be evaluated. The use of medicinal plants to reduce pain and healing time of aphthous have gained attention due to less side effects and drug-resistance. Licorice in combination with other plants with anti-inflammatory or antimicrobial properties could increase its effectiveness. Therefore, it is recommended to study a new combined formulation. Patch, paste, gel, and mouth wash have been studied in different articles; we suggest new dosage forms such as fast dissolving tablet, fast dissolving film, and oral spray to be evaluated in the future studies. Since diabetic and hypertension patients were excluded in clinical trials, and studies have not reported side effects in topical and short-duration use of licorice, we recommend performing a clinical trial on these groups. It could be helpful to study mucosal absorption, and the main mechanism of action of licorice and its main ingredients in topical use due to the lack of data on this topic. As aphthous stomatitis is recurrent, a survey of

higher number of subjects for a more extended time might be helpful.

As the language of the included studies was limited, non-English papers were missed. Moreover, the accessibility to all needed research data limited our data synthesis. Moreover, the research team did not perform an exact meta-analysis due to the heterogeneity of data.

Conclusion

In conclusion, licorice significantly promotes healing, pain reduction, healing time, and size of the inflammation zone without side effects. The pain reduction begins on the first day. The total healing time depends on the type of aphthous and its severity and is expected to take four to eight days based on the studies. The protective role of patches is effective in healing and pain reduction.

Authors' Contribution

F.D, G.V, and E.A performed the Prisma and Jadad steps. E.A, M.Z, M.R, and A.B were involved in planning and supervising the work. F.D, G.V, W,Y, and A.B extracted data from included studies. All authors contributed to drafting the manuscript. All authors critically revised the manuscript. All authors discussed the results and commented on the manuscript. All authors approved the final version of the manuscript for publication.

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