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Systematic Review

The efficacy of Licorice (*Glycyrrhiza glabra*) in reducing pain, as compared to other pharmacological interventions, including placebo, in recurrent aphthous stomatitis, oral lichen planus and radiation-induced oral mucositis: a systematic review

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ABSTRACT

Licorice (*Glycyrrhiza glabra*) is one of the oldest medicinal herbs, also reported by Avicenna, with several therapeutic advantages such as wound healing, improvement of asthma, urinary infections and stomach ulcers, as well as pain-relieving characteristics. The review aims to assess the efficacy of licorice (*Glycyrrhiza glabra*) in reducing pain compared to other pharmacological interventions, including placebo, in recurrent aphthous stomatitis, oral lichen planus and radiation-induced oral mucositis. Four electronic databases, registries of current studies and a manual search were used to find randomized controlled trials (RCTs) that evaluated the effectiveness of licorice (*Glycyrrhiza glabra*) in reducing pain compared to other pharmacological interventions, including placebo, in recurrent aphthous stomatitis, oral lichen planus and radiation-induced oral mucositis patients up to December 2022. The primary outcomes were pain reduction and secondary outcomes included reduction in size of the lesion. Seven RCTs with a total of 326 patients were included. Our analysis indicated that Licorice is as effective as other pharmacological and placebo therapies in treating recurrent aphthous ulcer, oral lichen planus and oral mucositis. All of the RCTs that are included here showed a substantial decrease in visual analogue scale scores, demonstrating the efficacy of liquorice in comparison to other pharmaceutical therapies with negligible adverse effects. Thus, Licorice is a potential pain reducing herbal medicine and can be effectively used in oral lesions like RAS, OLP, radiation induced mucositis for relieving pain.

Keywords: Analgesic effects, *Glycyrrhiza glabra*, Licorice, Oral lichen planus, Pain reduction, Recurrent aphthous stomatitis, Radiation-induced oral mucositis

INTRODUCTION

The frequent oral condition known as recurrent aphthous stomatitis (RAS) is characterized by a number of tiny, round or oval mucosal ulcers with defined edges, erythematous halos, and gray or yellow floors.[1] Because the etiology is unknown, therapy remains symptomatic. When topical treatment fails, systemic drugs are utilized which may lead to several adverse effects.[2] Oral Lichen Planus (OLP) is autoimmune illness characterized by "Wickham striae".[3] It causes discomfort, burning sensations and has the potential to become cancerous if not addressed. It has no definitive treatment.[4] Mucositis is a major issue in patients undergoing head and neck radiation, resulting in a poor quality of life, decreased nutrition and mouth discomfort. Until now, several strategies have been developed to prevent and treat mucositis, but none of these has been able to completely

eradicate mucositis.[5] Liqorice has traditionally been used as a medicinal herb. A with the given statements below -

“In traditional Chinese, Ayurvedic, and herbal medicine, licorice has long been utilized. With glycyrrhizin serving as the primary active ingredient, the licorice plant is home to a variety of bioactive chemicals such as flavonoids, triterpenes, and secondary metabolites. The anti-inflammatory, antioxidant, antiviral, anticancer, hepatoprotective, and neuroprotective qualities of licorice components have been discovered.[6] They seem to have impacts on morphine tolerance and antidepressant properties as well. Using a variety of mechanisms, including gap junction blockade, α2A-adrenoceptor antagonism, and inhibition of the high mobility group box 1 protein (HMGB1), glycyrrhizin and its metabolite glycyrrhetic (glycyrrhetinic) acid, as well as other licorice-derived compounds like isoflavonoids, elicit strong anti-inflammatory effects”.[6]

Glycyrrhetic acid inhibits 11b-hydroxysteroid dehydrogenase (11bHSD), which stops the production of pro-inflammatory cytokines and chemokines that are essential for inflammatory processes, more effectively than corticosteroids.[7]

By inhibiting the nuclear factor kappa B pathway, the liqorice flavonoids isoliquiritigenin and liquiditinin have anti-inflammatory properties and can lessen pain.[8] Additionally, carbenoxolone, a glycyrrhetic acid derivative, can help cure oral mucosal ulcers by acting as a mucosal protective agent.[7]

METHODS

Study design

All studies included in the review were Randomized controlled trial studies.

Study place

Study locations include Iran, Taiwan and India. Most of the studies were from Iran.

Study duration

Studies were searched up to September 2022.

Participants

Studies were searched up to September 2022.

Protocol and registration

Following the PRISMA (2020) standards, the protocol for this systematic review was created and registered in the International Prospective Register of Systematic Reviews or PROSPERO.[8] (registration ID - CRD42023466926).

Search strategy

The following mesh pattern was used to search the Pubmed database for articles up until September 2022. ("Licorice" OR "*Glycyrrhiza glabra*") AND ("Pain reduction" OR "analgesic effects" OR "pain relief") AND ("Recurrent aphthous stomatitis" OR "RAS" OR "oral lichen planus" OR "OLP" OR "radiation-induced oral mucositis").

The initial search identified 128 studies. After the elimination of duplicates and the initial screening of records, 56 articles were retained. Further screening excluded 22 articles due to reasons such as being reviews, having irrelevant titles and abstracts or focusing on plants other than the subject of interest.

This left 34 papers for detailed eligibility assessment. Of these, six were excluded because of irrelevant content, nine were inaccessible in full text, twelve did not pertain to clinical trials and one was dismissed due to a low Jadad score. Ultimately, seven papers met all criteria and were included in our analysis.

Software used

Patients suffering from recurrent aphthous stomatitis (RAS), oral lichen planus (OLP) and radiation-induced oral mucositis.

Overview of intervention type

There were some common trends across the studies. All studies compared outcomes related to the use of natural ingredients like liquorice, Aloe Vera and sesame oil in treating oral mucosal diseases by measuring pain.

Exclusion of the studies

In the final screening of the review, studies were excluded because they did not meet the eligibility criteria or did not fulfil the PICO question of the study. Any articles written in a language other than English were also excluded, as well as grey literature, letters to the editor, case reports and conference proceedings. Although many of the excluded studies contained useful contextual and intervention-related information, their study designs did not allow for an unbiased assessment of the intervention's effectiveness. (give reference to studies included).

PICO of the study

Population

Patients suffering from recurrent aphthous stomatitis (RAS), oral lichen planus (OLP) and radiation-induced oral mucositis.

Intervention

Bioadhesive paste containing 5% liquorice extract.

Comparison

Routine management and bioadhesive paste without liquorice (placebo).

Outcome

Reduction in pain as measured by the visual analog scale (VAS), reduction in the necrotic zone area and time to complete healing of ulcers.

RESULTS

In all the seven included randomized controlled trials licorice was used in one or the other form to check for pain reduction in patients with radiation induced oral mucositis, oral lichen planus and recurrent aphthous ulcer. Four studies evaluated the recurrent aphthous stomatitis patients, two studies checked the pain score for mucositis caused due to radiation therapy and one study was done on oral lichen planus patients. Study characteristics, outcome variables, pain sensation using VAS score of included studies are as given in table 1. All the lesions treated with licorice for reducing pain gave statistically significant outcome.

Risk of bias

Risk of bias was done using ROB 2.0 using robvis software.

The traffic light system is used to show the risk of bias in different domains across several studies, with red indicating a high risk of bias, yellow some concerns and green low risk.

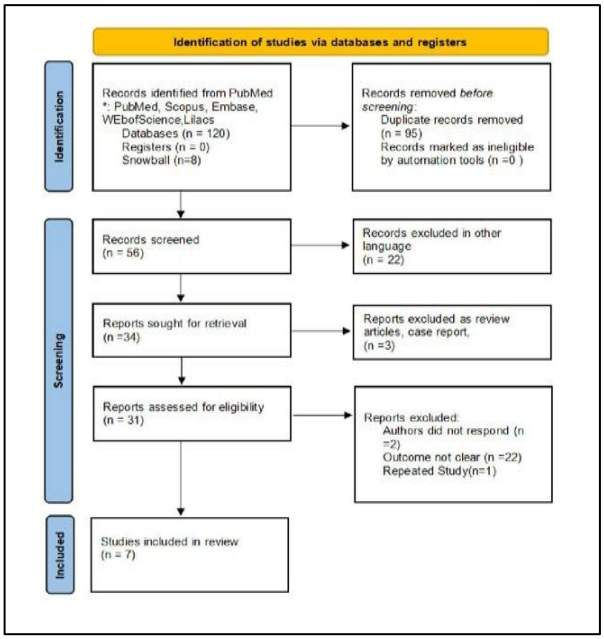

Figure 1: Prisma flowchart of selection of studies.

Overall, it communicates a summary of each study's reliability and methodological quality, which is critical when synthesizing evidence in systematic reviews or meta-analyses. The color-coded key aids in quick visual interpretation: green for low risk, red for high risk and yellow for some concerns.

Table 1: Study characteristics of included studies.

S. no.	Study	Age group (in years)	Gender	Sample size	Lesion	Duration of study
1.	Moghadamnia et al[17]	22–35	Male-10 Female-5	15	RAS	3 episodes for 5 days
2.	Ghalyani et al[16]	Over 18	Male-37 Female-23	60	Mucositis	4 weeks
3.	Inamdar et al[18]	20-70	Equal	30	OLP	6 weeks
4.	Raeesi et al[19]	Average 25	Male-13 Female-47	60	RAS	5 days
5.	Akbari et al[20]	18 to 60	Male-22 Female-48	70	RAS	5 days
6.	Liu et al[21]	Older than 20	Male-24 Female-30	54	RAS	3 days
7.	Najafi et al[22]	Upto 60	Male-24 Female-13	37	Mucositis	14 days

Table 2: Outcome variables or measures, pain sensation using vas score of included studies.

Study	Study group	Control group	Pain sensation using VAS score	P value	Outcome	Adverse effect
Moghadamnia et al[17]	Bio adhesive with licorice	Bio adhesive without licorice	Patches without licorice - 5.8 Patches with licorice - 5.4	0.0001	significant	Not any

Continued.

Study	Study group	Control group	Pain sensation using VAS score	P value	Outcome	Adverse effect
Ghalyani et al[16]	Licorice group	Triamcinolone	Triamcinolone group- 4: 2.20±2.02 Licorice group - 2.08±1.90	0	Significant	Not any
Inamdar et al[18]	AV and licorice and sesame oil mouthwash group	Placebo	AV, licorice and sesame oil mouthwash group p<0.0001	<0.0001	Significant	Not any
Raeesi et al[19]	5% Licorice bioadhesive paste	Bioadhesive paste without Licorice	Pain reduction in group A was more as compared to group B and group C.	<0.001	significant	Not any
Akbari et al[20]	diphenhydramine-containing *Glycyrrhiza glabra* (DSG)	diphenhydramine solution (DS)	DS- 1.71±1.69 DSG- 0.54±1.31)	0.0001	Significant	Not any
Liu et al[21]	Licorice	Placebo	Licorice-1.07 (0.69) Placebo- 4.08 (2.02)	0.0001	Significant	Not any
Najafi et al[22]	Glycyrrhiza aqueous extract	Placebo	Glycyrrhiza aqueous extract-5.26 Placebo-5.22	<0.001	Significant	Not any

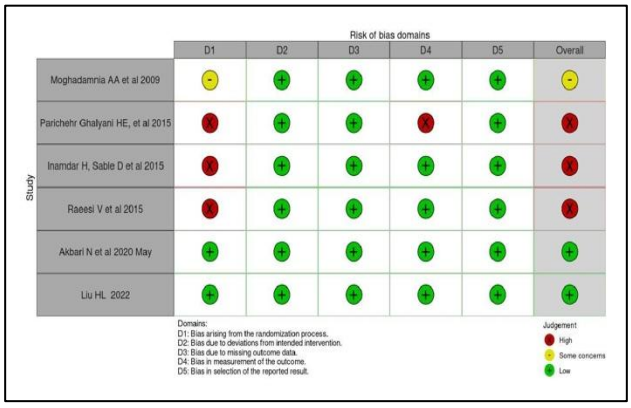

Figure 2: Risk of bias for individual studies.

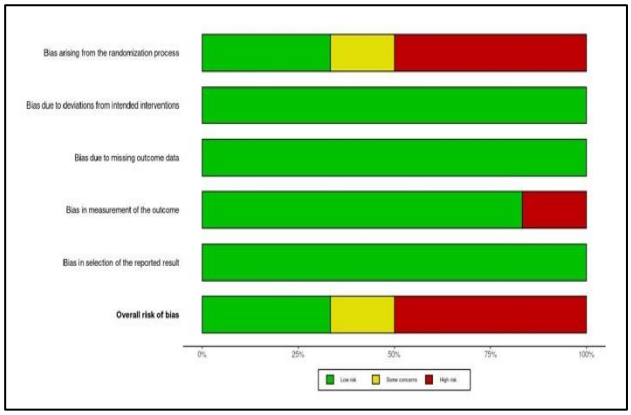

Figure 3: Risk of bias for overall.

DISCUSSION

Worldwide demand for pharmaceuticals derived from natural sources has surged because of the growing expense and adverse effects of allopathic medications. Ayurvedic medicine has traditionally made use of medicinal herbs, thus providing a solid foundation for future selection and application of medicinal plants in the creation of new medications. It has been established that G. glabra has pharmacological and therapeutic value.

The current review offers the efficacy of licorice in reducing pain of oral lesions so future researchers can look forward to studying, investigate, assess and evaluate G. glabra's potential therapeutic effects for dentistry and might incorporate them to dental products and improve oral health.[9]

RAS is characterized by repeated erosions and ulcers that are painful. This pain may worsen with food consumption causing extreme discomfort that interferes with the patient's ability to communicate and eat.[10] In order to ease discomfort, encourage healing and stop secondary infection, palliative treatment is given for recurring aphthous ulcers. In 1989, Das et al, conducted a very preliminary investigation with 20 patients and found that using mouthwash whose content is extract of deglycerolized licorice for two weeks tended to relieve pain and speeds up healing process of ulcers.[11] On the other hand, Martin et al found that the use of oral patch that is self-dissolving and contains licorice extract applied for 8 days showed improvement in size of ulcer

and pain when compared with placebo patch in RCT study with 23 participants.[12]

Lichen planus (LP) is an inflammatory disease that initially affected the skin, hair, eyes, mucous membranes and nails. Oral lichen planus (OLP) is the term for lesions observed in the mouth cavity. In total 53.6% of individuals with cutaneous LP also have OLP.[13] In a study conducted by Najaf et al, out of 22 patients, 12 patients were randomly assigned in the triamcinolone acetonide group and 10 in *Glycyrrhizia glabra* (1%) orabase group. The study concluded that topical *Glycyrrhiza glabra* is a promising alternative in the treatment of OLP.[14]

Oral cancers make up 10 percent from all malignancies in men and 4 percentage in women. Inflammation of mucosa, also known as oral mucositis-a common and severe consequence of radiation therapy for regions involving head and neck. It typically occurs during the early stages of treatment. The condition worsens with ongoing therapy. The severity of this issue may lead individuals to discontinue therapy. It is classified into four grades ranging from 0 to 4 based on clinical examination. Mucositis (Grade 3-4) can cause taste loss, hemorrhage, decreased food and fluid intake, ulcers, pain, as well as low quality of life.[15] Ghalayani et al, found that licorice adhesive films effectively treated oral mucositis in patients undergoing postoperative adjuvant or final radiotherapy. Friedman's test revealed substantial improvement in the mean pain score and mucositis scale after four weeks.[16]

All things considered, Glycyrrhiza extract's anti-inflammatory properties may be the mechanism of action for mucositis. This is because it inhibits active macrophages, which in turn inhibits the generation of prostaglandin E2 and the creation of superoxide and hydroperoxide by macrophages. It has been demonstrated that an extract of *G. uralensis* coupled with its main isoflavans, licoricidin and licorisoflavan A, inhibits *Porphyromonas gingivalis* growth, the formation of volatile sulphur compounds and its protease activity.

These outcomes have shown promise in the treatment of foetor oris. One crucial component, glaciridine, exhibits activity against both gram-positive and gram-negative bacteria. Glycyrrhizin, glycyrrhetinic acid, flavonoids, asparagine, isoflavonoids and chalcones also enhance its antibacterial and antiadhesive qualities.[9]

Gargling solutions and dentrifices are advised for the prevention of dental caries because the flavonoids 1, methoxyficifolinol, licorisoflavan A and 6,8-diprenylgenistein, which were extracted from *Glycyrrhiza uralensis,* have been proven to totally suppress the formation of biofilm. The flavonoid isoliquiritigenin (ISL), which was extracted from liquorice, is a new inhibitor of tumour angiogenesis. It has a lot of therapeutic potential for Adenoid cystic carcinoma and may even be used as a cancer chemotherapeutic agent. Licochalcone A can be utilised to treat human oral squamous cell carcinoma since studies have demonstrated that it causes apoptotic cell death of oral squamous cell carcinoma cells by downregulating Sp1 expression.

By causing apoptosis, a water-soluble polysaccharide (GIP1) derived from Glycyrrhiza inflata roots reduced the viability of human oral cancer cells.[9] Thus, the pharmacological and therapeutic benefits of licorice create a solid foundation for future medicinal plant selection and utilisation in the formulation of new medications.

The sample size taken should be of a higher number for statistical measurements and the studies undertaken for evaluating the pain reducing effect of licorice are very few in number to give a strong statement about the result. To verify its efficacy, investigate its complete therapeutic potential and create standardized treatment regimens, further clinical trials and research are required.

CONCLUSION

Research has examined the use of licorice's and it's all bioactive constituent's potential for treatment and avoidance of many oral health conditions. Whenever it is used in mouthwash and as bioadhesive patches, licorice has demonstrated anti-inflammatory properties, as well as the capacity to lessen pain and encourage healing in some oral disorders. All things considered, licorice is a powerful, promising, economical natural medicinal agent for a range of oral illnesses and it can also be used for reducing pain for oral lesion patients with causing minimal to no adverse effects.

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Ethical approval: Not required

REFERENCES

1. Manfredini M, Guida S, Giovani M, Lippolis N, Spinas E, Farnetani F, et al. Recurrent aphthous stomatitis: treatment and management. Dermatol Pract Conceptual. 2021;11(4):76.
2. Savadori P, Rai PM, Tadakamadla S, Khijmatgar S, Inchingolo F, Greco C, et al. Minor recurrent aphthous ulcer management with hyaluronic acid gel in an italian cohort: a double-blind randomized clinical trial. BioMed Res Int 2022;2(1):7202831.
3. Moayeri H, Rajabi A, Mohammadi M, Moghaddam SB. Effects of Curcumin on the treatment of oral lichen planus symptoms: a systematic review and meta-analysis study. BMC Oral Health. 2024;24(1):104.
4. Kalaskar AR, Bhowate RR, Kalaskar RR, Walde SR, Ramteke RD, Banode PP. Efficacy of herbal interventions in oral lichen planus: A systematic review. Contemporary Clin Dent. 2020;11(4):311.

5. Ramezani V, Ghadirian S, Shabani M, Boroumand MA, Daneshvar R, Saghafi F. Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: a preliminary randomized controlled clinical trial. BMC Cancer. 2023;23(1):354.
6. Bell RF, Moreira VM, Kalso EA, Yli-Kauhaluoma J. Liquorice for pain. Therapeutic advances in psychopharmacol. 2021;11:20451253211024873.
7. Kwon YJ, Son DH, Chung TH, Lee YJ. A review of the pharmacological efficacy and safety of licorice root from corroborative clinical trial findings. J Medicinal Foof. 2020;23(1):12-20.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:71.
9. Hambire C, Hambire U. *Glycyrrhiza glabra*: Its role in dentistry. SRM J Res Dental Sci. 2020;11(2):106-9.
10. Wang Z, Cao H, Xiong J, Lu Y, Deng Y, Nan H, et al. Recent advances in the aetiology of recurrent aphthous stomatitis (RAS). Postgrad Med J. 2022;98(1155):57-66.
11. Das SK, Das V, Gulati AK, Singh VP. Deglycyrrhizinated liquorice in aphthous ulcers. The J Assoc Physicians India 1989;37(10):647.
12. Martin MD, Sherman J, Van Der Ven P, Burgess J. A controlled trial of a dissolving oral patch containing glycyrrhiza (licorice) herbal extract for the treatment of aphthous ulcers. Gen Dent 2008;56:206-10.
13. Elenbaas A, Enciso R, Al-Eryani K. Oral lichen planus: a review of clinical features, etiologies and treatments. Dentistry Review 2022;2(1):100007.
14. Najaf S, Beytolahi JM, Aleboye N, Gholizadeh N, Sadegi T. Comparison of *Glycyrrhiza glabra* inorabase with triamcinolone acetonide orabase in the treatment of oral lichen planus. Avicenna J Dental Res. 2016;8(3):5.
15. Rotaru DI, Sofineti D, Bolboacă SD, Bulboacă AE. Diagnostic criteria of oral lichen planus: A narrative review. Acta Clinica Croatica. 2020;59(3):513.
16. Ghalayani P, Emami H, Pakravan F, Nasr Isfahani M. Comparison of triamcinolone acetonide mucoadhesive film with licorice mucoadhesive film on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial. Asia-Pacific J Clin Oncol. 2017;13(2):48-56.
17. Moghadamnia AA, Motallebnejad M, Khanian M. The efficacy of the bioadhesive patches containing licorice extract in the management of recurrent aphthous stomatitis. Phytother Res. 2009;23(2):246-50.
18. Inamdar H, Sable D, Subramaniam AV, Subramaniam T, Choudhery A. Evaluation of efficacy of indigenously prepared formulation of aloe vera, licorice and sesame oil in treatment of oral lichen planus: An in vivo study. J Adv Clin Res Insights. 2015;2:237-41.
19. Raeesi V, Arbabi-Kalati F, Akbari N, Hamishekar H. Comparison effectiveness of the bioadhesive paste containing licorice 5% with bioadhesive paste without drug in the management of recurrent aphthous stomatitis. Population. 2015;1(2).
20. Akbari N, Asadimehr N, Kiani Z. The effects of licorice containing diphenhydramine solution on recurrent aphthous stomatitis: A double-blind, randomized clinical trial. Complement Ther Med. 2020;50:102401.
21. Liu HL, Hsu PY, Chung YC, Lin CH, Lin KY. Effective licorice gargle juice for aphthous ulcer pain relief: A randomized double-blind placebo-controlled trial. Pakistan J Pharm Sci. 2022;35(5):1321-6.
22. Najafi S, Koujan SE, Manifar S, Kharazifard MJ, Kidi S, Hajheidary S. Preventive effect of Glycyrrhiza glabra extract on oral mucositis in patients under head and neck radiotherapy: A randomized clinical trial. J Dentist (Tehran, Iran). 2017;14(5):267.

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