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Original Article

Dentistry Section

Effect of Liquorice Extract on Oral Health: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Oral diseases continue to be a significant global public health challenge. Chlorhexidine (CHX) is widely regarded as the gold standard for chemical plaque control; however, its prolonged use is linked to adverse effects. Herbal alternatives such as *Glycyrrhiza glabra* (liquorice) have gained attention due to their antimicrobial and anti-inflammatory properties.

Aim: To systematically evaluate the clinical effectiveness of liquorice extract on dental caries, plaque, gingivitis, Recurrent Aphthous Stomatitis (RAS), and oral mucositis through systematic review and meta-analysis.

Materials and Methods: This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Metanalyses (PRISMA) guidelines and registered in International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023476073). Electronic databases, including PubMed, EMBASE, Web of Science, Cochrane, and Google Scholar, were searched from 2017 to 2023. Only RCTs published in English were included. Two independent reviewers screened studies, extracted data, and assessed risk of bias using the Cochrane Collaboration tool. Meta-analysis was performed using Review Manager (RevMan) version 5.4.1 software.

Results: Out of 1,677 records identified, seven RCTs met the inclusion criteria for qualitative synthesis, and six were included in quantitative meta-analysis. Liquorice extract demonstrated significant reduction in *Streptococcus mutans* levels, DMFT scores, pain scores in RAS, and mucositis severity compared with placebo/control. However, in plaque and gingivitis reduction, chlorhexidine showed greater clinical improvement than liquorice. Substantial heterogeneity was observed in pooled analyses (I^2=98%).

Conclusion: Liquorice extract exhibits promising antimicrobial and anti-inflammatory properties in the management of dental caries, aphthous ulcers, and mucositis. However, current evidence does not conclusively support its superiority over chlorhexidine for plaque and gingivitis control. High-quality, adequately powered RCTs with standardised concentrations and longer follow-up are required before recommending liquorice as a definitive alternative to chlorhexidine.

Keywords: Glycyrrhiza glabra, Dental caries, Gingivitis, Oral mucositis, Aphthous ulcer

INTRODUCTION

Oral diseases are a significant public health issue globally, affecting nearly 3.5 billion people worldwide [1]. The World Health Organisation (WHO) states that around 44.5% of the world's population is affected by oral diseases, out of which 53.8% corresponds to dental caries, 19% belong to periodontal diseases, and 27.2% include other conditions such as oral ulcers, lesions, and inflammation [2]. The oral cavity must be maintained clean and hygienic, as any infection there can result in bacteraemia, which will affect the general health [3]. Dental caries is one of the most common problems experienced by almost every individual once in a lifetime and is the costliest treatment, which consumes 5% of total health services [4]. Any initial lesion on the tooth surface left untreated will lead to caries and involvement of the pulp overtime. Gingivitis, which has a direct association with dental plaque, affects the oral health of 70%-100% of the population across the world [5]. Recurrent Aphthous Stomatitis (RAS) is the most frequent oral ulceration, affecting about 25% of the population and with an incidence rate of 5-50% [6]. It causes solitary or many painful ulcers in the oral mucosa. Considering the significance of oral disease prevalence and its direct impact on overall health, preventive and control measures are required. On the other hand, mechanical removal of dental plaque by toothbrushing, flossing, and using interdental brushes are common method to maintain oral hygiene. However, this mechanical approach by most individuals is often not sufficiently effective, suggesting that chemical plaque control by mouthwashes could be beneficial as a supplement to daily oral care. Chlorhexidine cationic biguanide [CHX] is a long-established classical substance and is the gold standard for its broad-spectrum antiseptic action proven by many in-vitro and in-vivo studies [7-10]. Undesirable side effects, including cytotoxicity, antimicrobial resistance, and staining, impede the long-term effectiveness and patient acceptability of CHX mouthwashes. Thus, the pursuit of alternatives continues, with a trend towards biogenic agents [8]. Herbal mouthwashes may offer an advantage over chlorhexidine mouthwash, especially for prolonged use, because of fewer adverse effects and superior anti-inflammatory characteristics [9]. Thus, on probing, all herbal extracts have the latent potential to establish a healthy oral cavity, replacing the chemical solutions that may cause adverse effects. One such discovery paved the way for the flourishing of liquorice and its benefits in oral diseases and conditions. Recent research suggests that liquorice extracts have potential beneficial effects on oral diseases [10]. These effects have been associated with the anti-adherence, anti-microbial, and anti-inflammatory properties of the compounds.

Clinical trials have been conducted worldwide to evaluate the effects of liquorice and its metabolites in preventing and treating various oral diseases, such as dental caries, periodontal diseases, candidiasis, aphthous ulcers, and debilitating diseases like oral cancer [8-11]. The results of existing literature are inconsistent, and the scarcity of meta-analytical evidence highlights the clinical effects of liquorice on dental caries, gingivitis, aphthous ulcer and mucositis. Therefore, the present study aimed to conduct an evidence based research through a systematic review and a meta-analysis of liquorice extract on dental caries, plaque, gingivitis, RAS, and oral mucositis.

MATERIALS AND METHODS

This systematic review and meta-analysis are based on the guidelines of PRISMA [12] and registered in PROSPERO (CRD42023476073).

Question of Interest

According to the PICO (Population, Intervention, Comparison, Outcome) principle, the following research question was framed. "Does liquorice have an effect on dental caries, gingivitis, oral ulcers, and mucositis on comparing with chlorhexidine or saline?"

PICO Analysis

Population: Only randomised controlled studies that had recruited participants aged between 3 and 55 years with high caries risk, moderate gingivitis, and patients with recurrent aphthous stomatitis and mucositis were included in this review.

Intervention: The following interventions in various forms were considered:1%, 2%, 1.6% and 20% of liquorice mouthwash, liquorice lozenges, lollipops containing liquorice extracts, and liquorice containing diphenhydramine solution.

Comparison: Chlorhexidine mouthwash (0.2%), saline (0.9%), and a control group receiving counselling on maintaining oral health were taken as comparison groups to assess the effect of the intervention.

Outcome: Effect of liquorice on dental caries, gingivitis, aphthous ulcer healing, and mucosal inflammation.

Inclusion criteria: This systematic review included all published English articles (between 2017 and 2023) on randomised controlled trials that investigated the effect of liquorice extract on both men and women aged 3-55 years with a history of high dental caries, initial enamel lesions, moderate gingivitis, aphthous ulcers, and mucositis. The studies comprised the intervention group(s) that contains licorice extract(s) and were included for the systematic review. The randomised control studies included either 0.2% chlorhexidine, saline [0.9%], or a control.

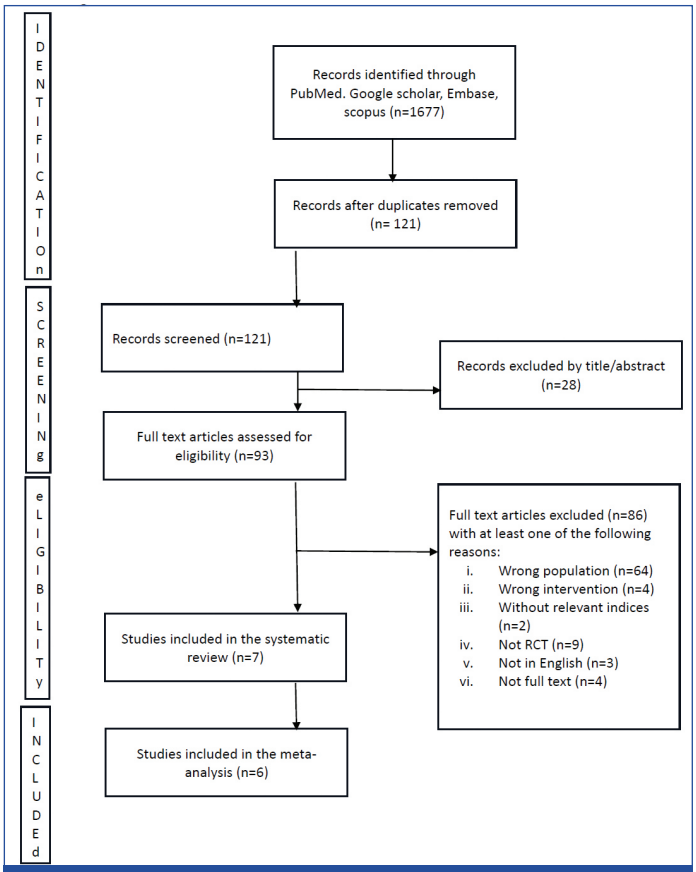
Exclusion criteria: Animal studies, in-vitro studies, review papers, case reports, and non English articles are not considered in this study. Studies that had participants who were undertaking orthodontic treatment, and studies that included participants with systemic illness, were excluded.

Data Source and Search Strategy

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. An electronic search was done in PubMed, EMBASE, Web of Science, and Google Scholar, Cochrane Central Register of Controlled Trials to select the published articles between the years 2017 and 2023. To search databases, stringsof search (MeSH) terms, consisting of relevant text wordsand Boolean links, were constructed : (("glycyrrhiza"[MeSH Terms] OR "glycyrrhiza"[All Fields] OR "licorices"[All Fields] OR "liquorices"[All Fields] OR "liquorice"[All Fields] OR "glycyrrhiza glabra extract"[Supplementary Concept] OR "glycyrrhiza glabra extract"[All Fields] OR "licorice"[All Fields]) AND ("dental caries"[MeSH Terms] OR ("dental"[All Fields] AND "caries"[All Fields]) OR "dental caries"[All Fields]))"gingiva"[MeSH Terms] OR "gingiva"[All Fields] OR "gingival"[All Fields] OR "gingivally"[All Fields] OR "gingivals"[All Fields] OR "gingivitis"[MeSH Terms] OR "gingivitis"[All Fields] OR "gingivitides"[All Fields]"mucositis"[MeSH Terms] OR "mucositis"[All Fields] OR "mucositides"[All Fields] OR "mucous membrane"[MeSH Terms] OR ("mucous"[All Fields] AND "membrane"[All Fields]) OR "mucous membrane"[All Fields].The PRISMA statements were applied in carrying out this systematic review. Subsequently, a manual search was carried out based on the reference lists of selected trials and related reviews.

Study Selection

Following the search process, the titles of the initially retrieved papers were independently checked by two reviewers (KT and IK). Once duplicates and irrelevant publications were eliminated, abstracts that satisfied the eligibility criteria were evaluated. Full-text copies were retrieved for those articles that lacked sufficient data in the title or in the abstract to arrive at a clear decision. All the full-text papers were reviewed, and any disagreement that persisted regarding the eligibility criteria was solved through discussion or if necessary, third-party help was obtained, or the article was excluded from the study. All the selected articles were read and evaluated for final eligibility independently by both reviewers. 1677 articles were identified from the search through PubMed, EMBASE, Google scholar and Web of Science. A total of 121 articles were retrieved after the removal of duplicates (n=1556). Abstracts of 93 articles were reviewed independently after the exclusion of 28 articles after reading the abstract, as they did not meet the inclusion criteria. Finally, seven studies were selected for systematic review, and 6 studies were taken for future evaluation of meta-analysis [Table/Fig-1].



[Table/Fig-1]: PRISMA flowchart.

Data Extraction

Study details were entered into the characteristics of the included studies table [13-20] [Table/Fig-2]. A standard data extraction sheet was developed a priori, and the data were extracted and cross-checked for accuracy by two independent reviewers regarding Title and author, Year of publication, Participants with age, sample size, and gender, Intervention with the mode of delivery, concentration if the intervention used, and duration, Comparison, Outcome.

Assessment of Methodological Quality

The risk of bias was independently graded by two reviewers (KT and IK) using the Cochrane Collaboration's tool for assessing the risk of bias described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) [14] [Table/Fig-3].

Summary Measures

The streptococcus colony-forming count, caries activity test, Gingival Index (GI), Plaque Index (PI), visual analogue scale, duration of wound healing for aphthous ulcers, and mucositis grading were the main parameters used for evaluating the microbial, clinical, and patient-reported outcomes. For the additional meta-analysis, means, Standard Deviation (SD), and other significant data were

Parameters assessed	Title and author name	Year of publication	Population with age and sample size	Intervention	Comparison	Outcome
1) Dental Caries	A randomised, double-blinded, placebo-controlled trial of a mouthwash containing *Glycyrrhiza uralensis* extract for preventing DC. (Kim YR and Nam SH) [14]	2022	60 volunteers with minimal enamel caries. 30 patients in the intervention group and 30 patients in the control group.	15 mL mouthwash containing 1mg/mL of *Glycyrrhiza* extract	Control group – saline [0.9%] 15 mL	There was a significant decrease in the caries activity test in the group containing *Glycyrrhiza uralensis* mouthwash. Mean value of carieview score after 5 days was 45.54 in the test group and 60.22 in the control group.
2) Dental caries	Effect of liquorice candies on remineralisation of initial enamel carious lesion (Pooja HR et al.,) [15]	2023	6 patients (6-12 years) extracting sound tooth and requiring ortho denture	Lozenges	Demineralised enamel blocks	Formation of remineralising layer in the enamel blocks of patients.
3) Dental caries	Lollipop containing *Glycyrrhiza uralensis* extract reduces s.mutans colonisation and maintains oral microbial diversity in Chinese preschool children. (Chen Y et al.,) [16]	2023	37 children with high caries risk (average of 4 years) 23 children were included in the test group and 14 children in control group.	Lollipop	Placebo – counselling on control group	Exposure of 25 microgram/mL decreases 98.8% bacteria, 50 microgram/mL reduces 99.5% bacteria after 5 minutes and 99.9% bacteria is killed after 3 hours.
4) Dental caries	Efficacy of liquorice on salivary s.mutans levels vs chlorhexidine mouthwash in high caries risk patients: A RCT (Helmy N et al.,) [17]	2021	52 participants (18-55 years) With high caries risk. 26 participants were allocated in treatment group and the other 26 participants in control group.	Mouthwash containing 1.6 gm/100 mL of liquorice extraction	Chlorhexidine mouthwash 10 mL	There was no significant difference between the two groups. Mean value of Streptococcus mutans count was 69.11 in test group and 67.64 in the control group. Liquorice-raises salivary PH and reduces the level of Streptococcus mutans and hence can be used as a suitable alternative.
5) Plaque and gingivitis	Effect of liquorice (root extract) mouth rinse on dental plaque and gingivitis –A RCT (Sharma S et al.,) [18]	2022	44 subjects (18-30 years) with moderate gingivitis. 22 participants received liquorice extract and other 22 received chlorhexidine mouthwash.	20% of liquorice root extract Mouth-rinse	0.2% chlorhexidine	There was a statistically significant reduction in both groups, but the magnitude of reduction is greater in the CHX group for PI and GI scores, with a mean difference of 0.32 and 0.65, respectively, after 15 days.
6) Oral ulcer	The effect of liquorice-containing diphenhydramine solution on recurrent aphthous stomatitis: A double blind, randomised clinical trial. (Akbari N et al.,) [19]	2020	70 patients (18-60 years) suffering from RAS. 35 participants in one group received treatment, and the other 35 participants were allocated in control group.	5% liquorice extract mouthwash	Control group	There was a significant reduction in pain with an average pain score of 1.71 in the control group and 0.54 in the test group, and a significant reduction in the wound healing duration by 1.5 days as compared to the control group.
7) Mucositis and radiotherapy	Preventive effect of Glycyrrhiza glabra on oral mucositis in patients under head and neck radiotherapy (Najafi S et al.,)[20]	2017	37 patients with head and neck cancer (>18 years) who receive radiotherapy. 19 patients received glycyrrhiza extract, and 18 patients were used as controls.	Topical application of 100cc of 50% Glycyrrhiza extract	Control group	There was a significant reduction in wound size after 2 weeks, with a mean value of 4.34 mm in the test group and 5.22 mm in the control group. The mean score of mucosal irritation was 5.26 and 6.33 in the test and control group respectively.

[Table/Fig-2]: Data extraction of included studies [14-20].

Study	Randomisation	Allocation concealment	Assessor blinded	Dropouts described	Risk Of Bias
1. A randomised, double blinded, placebo-controlled trial of a mouthwash containing *Glycyrrhiza uralensis* extract for preventing DC. (Kim YR, and Nam SH) [14]	Yes	Yes	Yes	Yes	Low
2. Effect of liquorice candies on remineralisation of initial enamel carious lesion (Pooja HR et al.,) [15]	No	No	No	No	High
3. Lollipop containing *Glycyrrhiza uralensis* extract reduces s.mutans colonisation and maintains oral microbial diversity in chinese preschool children (Chen Y et al.,) [16]	No	Yes	No	No	High
4. Efficacy of licorice on salivary s.mutans levels vs chlorhexidine mouthwash in high caries risk patients: A RCT (Helmy N et al.,) [17]	No	No	No	No	High
5. Effect of liquorice (root extract) mouth rinse on dental plaque and gingivitis – A RCT (Sharma S et al.,) [18]	Yes	Yes	Yes	Yes	Low
6. The effect of licorice containing diphenhydramine solution on recurrent aphthous stomatitis: A double blind, randomised clinical trial (Akbari N et al.,) [19]	No	Yes	Yes	No	Moderate
7. Preventive effect of Glycyrrhiza glabra on oral mucositis in patients under head and neck radiotherapy (Najafi S et al.,) [20]	Yes	Yes	Yes	No	Low

[Table/Fig-3]: Quality assessment table [14-20].

also gathered, including standard error, medians, percentages, and interquartile ranges.

STATISTICAL ANALYSIS

The meta-analysis was performed using RevMan software [Review Manager (RevMan) (Computer program) version 5.4.1, The Cochrane Collaboration, 2020]. Given the heterogeneity of the studies, a random-effect model was used; the Mean Difference (MD) and Standard Deviation (SD) were used to evaluate the continuous variable with a 95% Confidence Interval (CI). Statistical heterogeneity of between-study variability was assessed using the *Q* statistic and the I^2 test. Finally, a Forest plot of all the studies with the final estimates was generated

RESULTS

Study Selection

The initial search identified 1677 studies, of which 7 studies [13-20] were based on independent reviews that met the inclusion criteria and were selected for systematic review. Of these, 6 studies were included in the meta-analyses due to unclear quantitative data, poor quality of the study and inconsistent outcome measurements.

Characteristics of the Trial Setting

Out of seven studies, 2 studies were carried out in Iran [19,20], two studies were conducted in India [18,15], one study in Los Angeles [16], another study in Egypt [17], and the geographic location of the one study [13] was not mentioned in the article.

Characteristics of the Participants

The assessment of the age group of the participants revealed that 4 [13,17-19] out of 7 studies included participants between the ages of 18 and 55 years. One study [15] recruited participants aged 6-12 years, another [16] with an average of 4 years, and one [20] included participants with an average age of 45 years. Of the 7 studies included, 4 studies [13,18-20] were double-blinded. All studies excluded patients with a habit of smoking, who take antibiotics, are pregnant, have hypertension, evidence of parafunctional habits, TMJ disorders, severe periodontal disease, or severe medical complications. Two studies [16,17] recruited participants with high caries status with *Streptococcus mutans* count >$5*10^5$. Kim YR and Nam SH [13] utilised the carieview score to assess caries activity in their study, and one study [15] assessed the remineralisation as an outcome. Sharma S et al., [18] included participants with moderate gingivitis, and it was evaluated using the Gingival Index (GI), and dental plaque was evaluated using the Turesky modification of the Quigley Hein Plaque Index (PI). One study [19] included participants suffering from RAS and assessed mucositis for those who have a definite diagnosis of Head and Neck cancer who are going to undergo Radiation Therapy of at least 50 Gy, but not the patients who have already received any type of radiation therapy [20].

Characteristics of the Intervention

Out of 7 studies, 4 studies [13,17-19] used in the intervention, 1 study [15] as lozenges, 1 [16] as a lollipop, and one in the form of a topical extract [20]. Out of 7 studies, 5 [13,17-20] have mentioned the percentage of liquorice used, which varied from 100cc of 50%, 1%,1.6%, 5%, and 20%. Except for one study [13], assessments of participants' compliance and usage of the intervention were clearly described.

- 100 ccs of 50% aqueous extract of Glycyrrhiza to be used two times a day for 14 days after radiotherapy [20].
- Diphenhydramine solution with 5% hydroethanolic extract of liquorice [19].
- 20%, i.e. 2 gm of liquorice extract in 10 mL of distilled water. 10 mL of this extract is to be rinsed daily for 60 sec for 23 days [18].
- 1.6% of liquorice extract. 10 mL of mouthwash for 1 minute for 7 days [17].
- Lozenges and lollipops to be chewed once daily [16,15].

Characteristics of the Outcome

Dental caries: In one study, at the end of 1 week, the mean Streptococcal mutans count decreased from 257.83±117.63 to 78.26±35.12 in the 1.6% liquorice group and from 280.87±94.05 to 86.30±27.64 in the 2% CHX group, with no statistically significant difference between groups [17]. Another study reported enamel remineralisation was observed in the confocal microscope following 7 days of liquorice lozenge use [15]. Additionally, caries activity (Carieview score) decreased from 54.89 to 45.54 after 5 days of 1% liquorice mouthwash [13]. A study using liquorice-containing lollipops demonstrated a significant reduction in salivary *S. mutans* levels, with near-complete suppression after 3 weeks, while the control group showed a 25% increase [16].

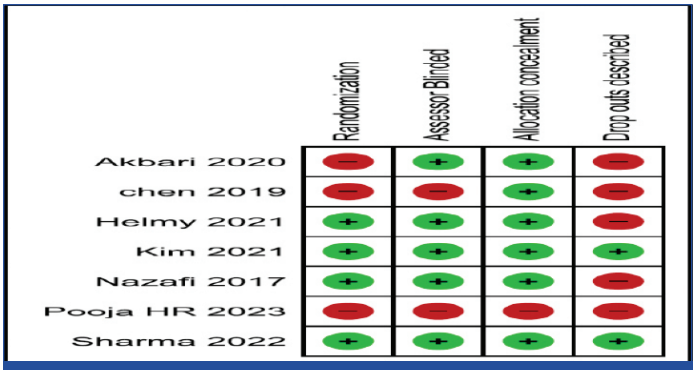
Gingivitis and plaque: After 15 days of usage of 0.2% CHX mouthwash, GI was reduced from 1.95 to 0.74 and PI from 2.6 to 0.47. By using 20% licorice mouthwash, GI was reduced from 1.85 to 1.40 and PI from 0.79 to 0.47.The results of the present study demonstrated that both liquorice and CHX mouth rinses reduced PI and GI scores in participants, but the reduction was considerable in the CHX group as compared to the liquorice group, and their differences were statistically significant ($p<0.001$) for both groups after 15 days. The liquorice extract reduces plaque formation and thus can alter the course of gingival inflammation [18].

Recurrent aphthous stomatitis: One study evaluating RAS utilised a combination of liquorice extract and diphenhydramine, which may have influenced pain reduction outcomes independently. Liquorice revealed a positive reduction in the average pain score from 7 to 1.71 after the intervention for 5 days. There was a significant difference between the two groups in terms of the average pain scores on the first (7±1.28versus 5.31±1.28), third (4.02±1.8 vs. 2.86±1.56), and fifth days (1.71±1.69 vs. 0.54±1.31) of the intervention. Indeed, liquorice significantly reduced the average wound healing duration by 1.5 days, as compared to the control group ($p=0.0001$) [19].

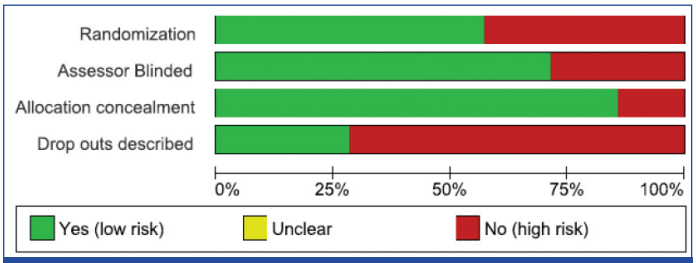
Oral mucositis: One study evaluating recurrent aphthous stomatitis utilised a combination of liquorice extract and diphenhydramine, which may have influenced pain reduction outcomes independently. Topical application of 100cc of 50% *Glycyrrhiza glabra* (liquorice) solution for 14 days brought a significant reduction in the irritation and wound size (by 0.88mm). The mean score of oral mucosal irritation was 5.26 (liquorice) and 6.33 (placebo). The mean and SD for oral mucosal wound size were 4.34±1.23 in the intervention group and 5.22±1.37 in the placebo group, respectively, and there were statistically significant differences between the two groups. The liquorice significantly decreased oral mucositis, wound size, and irritation [20].

Quality and Risk of Bias

Quality assessment and risk of bias were calculated using the Revman software Cochrane Collaboration tool. Four studies [13,17-20] have been categorised as low risk of bias, of which two studies [18,13] have met all criteria of Randomisation, assessor-blinded, Allocation concealment, and description of dropout rates. Two studies [20,17] have failed to describe the dropout rates in their methodology. Akbari N et al., [19] have been categorised under moderate risk and met two out of four criteria [Randomisation, assessor blinded]. Two studies [17,15] have been categorised as high risk. A study by Pooja et al., [15] did not meet any of the criteria and resulted in plausible bias that seriously weakened confidence in the results and could not derive an evidence-based conclusion. Hence, this study was eliminated to include in the further meta-analysis [Table/Fig-4,5].



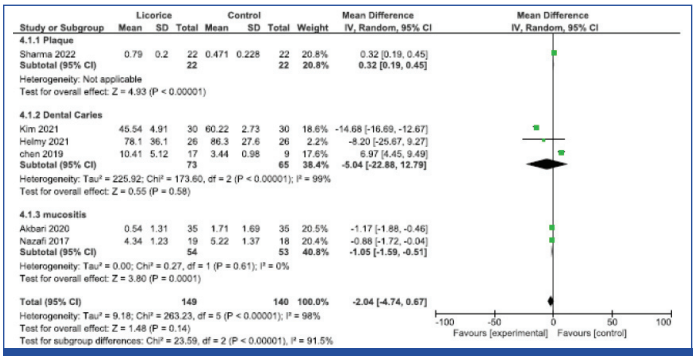
[Table/Fig-4]: Summary of risk of bias of the included study.



[Table/Fig-5]: Quality assessment of the selected studies (the RevMan software). Green represents a low risk of bias, yellow represents some concerns, and red represents a high risk of bias.

Quantitative Synthesis [Meta-Analysis]

When liquorice and chlorhexidine/saline/Control were compared by meta-analysis [Forest plot analysis], four studies were included for dental caries [13-17], one each for plaque control [18], aphthous ulcer [19], and mucositis [20]. Significant differences were observed in two studies [13,15] in favour of liquorice rather than control, and a study was done by Chen Y et al., [16], who concluded that the result was in favour of the control group. The mean plaque index score at the endpoint of follow-up was significantly lower after the use of liquorice (liquorice to placebo: liquorice: control 0.32, 95% CI (0.19, 0.452), (p=0.000), and the results favour the CHX in plaque control. As to the effect on the healing of aphthous ulcers and mucositis, liquorice showed significant results compared to the control group. [aphthous ulcer: liquorice versus control group mean difference: -1.17 (CI: -1.88, -0.46); mucositis: liquorice versus control group mean difference: -0.88 (CI: -1.72, -0.04). Substantial heterogeneity was observed in those meta-analyses [tau^2=9.18; x^2=263.32; I^2=98%] [Table/Fig-6].



[Table/Fig-6]: Forest plot analysis for the included studies.

DISCUSSION

A wide range of oral hygiene methods is being opted for worldwide to reduce the risk of oral diseases. A variety of studies have been conducted in the past 30 years to demonstrate the effect of mouthwashes against dental caries, halitosis, and other oral conditions. Chlorhexidine-containing mouthwashes are the gold standard in providing antibacterial activity and plaque control. However, certain adverse effects of utilising chlorhexidine mouthwash are observed, such as staining, loss of taste sensation, allergic reaction, and development of resistance [21].

On long-term exposure to mouth rinses containing chlorhexidine, localised staining of teeth due to interaction with the chromogens in food particles is noticed [22]. There are plenty of randomised clinical trials explaining the mouthwashes containing extracts of herbal plants such as Camellia sinensis (green tea) and Azadirachta indica (neem), and essential oils in plaque control and reducing gingivitis [23]. Adding to the discoveries, liquorice has multiple optimistic influences on oral health. The possible mechanism behind the pathophysiology of liquorice in improving oral health status can probably be that the natural compounds, such as catechins, tannins, sterols, and oils, may inhibit the growth and adhesion of oral microorganisms. This, in turn, will suppress the inflammatory mediators such as interleukin, cytokines, and tumour necrosis factor [24]. The primary objective of this review was to determine the effect of liquorice in reducing oral diseases, but its limitations include only a few articles comparing the effect of chlorhexidine vs liquorice extract, and the characteristics of the population taken are heterogeneous.

The strength or the concentration of the intervention used is an important criterion for clinical trials, and certain articles failed to mention the percentage of liquorice mouthwash [15,16] used. A range of 1 mg/mL – 16 mg/mL concentration of liquorice was used for preventing dental caries in two clinical trials [13,17]. The liquorice-containing lollipops 2x/day, levels of *S. mutans* decreased dramatically (>80% reduction in bacterial count) over the course of the study [16]. The reduction in the count of *Streptococcus mutans* and remineralisation of enamel was strongly evident using liquorice extract [15].

About 20% (w/v) liquorice root extract mouth rinse was given to the participants in the study [18] to assess the effectiveness of liquorice (root extract) mouth rinse against dental plaque and gingivitis. The reduction was considerable in the CHX group as compared to the liquorice group, and the clinical outcome stated that no significant effect existed in comparison with chlorhexidine in reducing the gingivitis [18].

The review found that 100 cc of 50% aqueous extract of Glycyrrhiza was used in the case of mucositis, which brought a significant reduction in mucosal irritation and mucosal wound size and helped in the healing of the specific oral condition. The study came out with a reason that Glycyrrhiza extract on mucositis may be mediated by its anti-inflammatory effects through inhibition of activated macrophages, leading to inhibition of the prostaglandin E2 production, and formation of superoxide and hydroperoxide in macrophages [20].

Five studies [13,17-20] used liquorice in the form of the extract [mouthwash/mouth rinse] while two studies reported that lollypop has been used in the form of lollypops and candies [15,16]. According to the dropout evaluation included in the review, two studies [13,18] noted dropouts and explained how the dropouts were managed using statistical methods, while five out of seven studies did not describe dropouts in their investigations. A crucial component of any clinical research is the loss to follow-up, as the incomplete follow-up in RCTs may affect the validity of data and exacerbate bias [25]. The follow-up time of studies also varied from five days to 3 weeks. Long-term follow-up determines the long-term effect of liquorice extract in the oral cavity. Hence, more articles with long-term follow-up are essential in the future to arrive at a strong conclusion.

A few studies failed to mention their process of randomisation [15-19], allocation concealment [15,17], blinding [15-17], sample justification [15,19], baseline comparison [15], and inclusion and exclusion criteria [15,16]. Hence, quality assessment among the seven studies showed that 4 studies [13,17,18,20] were of low risk of bias, two studies [15,16] exhibited high risk, and one study [19] exhibited moderate risk of bias. The inclusion of diphenhydramine in combination with liquorice extract in one study represents a potential confounding factor, as diphenhydramine itself possesses analgesic and anti-inflammatory properties. This limits the ability to attribute

observed effects solely to liquorice [19]. Nonetheless, variations existed in the liquorice concentration, active ingredients in herbal mouthwashes, administration forms, intervention measurement techniques, outcome evaluations, follow-up duration, randomisation, and blinded methods, all of which can have an impact on the trial's outcomes and contribute to the high heterogeneity.

Limitation(s)

Although the current review provided some clinical evidence regarding the effectiveness of chlorhexidine and liquorice extract against dental caries, gingivitis, mucositis, and aphthous ulcers, more proper randomised controlled trials are needed to weigh the clinical outcomes with more evidence. Most clinical trials were rated as having high-quality evidence (low risk); therefore, the results described should be carefully analysed and generalised. The present meta-analysis demonstrated a very high level of heterogeneity among the included studies (I^2=98%) when the fixed-effect model was applied. Such substantial heterogeneity suggests considerable variability in study design, sample characteristics, intervention protocols, and outcome assessment across the included studies. Future research should focus on conducting well-designed, adequately powered, and standardised RCTs to minimise heterogeneity and provide stronger, more conclusive evidence.

CONCLUSION(S)

Evidence derived from this systematic review states that liquorice extract has a potential effect on lowering dental caries, gingivitis, mucositis, and aphthous ulcers and can effectively replace chlorhexidine mouth rinses. While the selected trial did not find any difference in plaque control between herbal and Chlorhexidine mouthwashes, more high-quality RCTs are required to provide more evidence to support therapeutic decision-making. Additionally, the use of herbal products in the treatment of oral diseases is thought to be promising, and it warrants further research to seek more effective herbal mouthwashes with either traditional medicine formulations or new herbal preparations.

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