

Licorice as a herbal extract in periodontal therapy

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ABSTRACT

Periodontal disease is caused by specific pathogens which results in inflammation of the tooth-supporting structures and subsequently causes the continued breakdown of alveolar bone and periodontal ligament. Licorice (*Glycyrrhiza glabra*) is a perennial herb with substantial medicinal value. Licorice extract is derived from dried, unpeeled stolons and roots of *Glycyrrhiza uralensis* and *G. glabra*. The bioactive ingredients in licorice extract such as glycyrrhizin, licoricidin, glabridin, licochalcone A, and licorisoflavan A have anti-inflammatory, antimicrobial, and anti-adherence effects that are beneficial against periodontal disease. Since periodontal disease has a complex etiology that includes the host response and microorganisms, licorice phytochemicals offer a therapeutic advantage due to their dual functionality. The aim of this review was to enumerate the bioactive compounds present in herbal licorice extract and to elucidate the beneficial effects of licorice and its derivatives in periodontal therapy. Literature review and clinical trials evaluating the effect of licorice on periodontopathogens and periodontal disease are included in this article.

Keywords: Gingivitis, *Glycyrrhiza glabra*, Herbal therapy, Periodontitis

Introduction

Periodontal disease is caused by specific pathogens which results in inflammation of the tooth-supporting structures and subsequently causes the continued breakdown of alveolar bone and periodontal ligament. The pathogenesis of periodontal diseases involves two major causative factors. The first is the microbial factor, that is, the presence of increased levels of periodontopathogenic bacteria in subgingival tissues, which causes periodontal destruction by producing proteinases and toxins (1,2). The pathogens associated with periodontitis are *Porphyromonas gingivalis*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia*. The other factor is the immune response of the host to the periodontal pathogens,

which is the over-production of mediators of inflammation such as cytokines, prostaglandins, and matrix metalloproteinases (MMPs), which regulate the continuance of periodontal disease (3).

Periodontal therapy primarily includes scaling and root planing to eliminate the local factors, that is, plaque and calculus, and to maintain satisfactory oral hygiene. Since periodontal disease is known to be an inflammatory condition with a microbial etiology, the adjunctive use of locally applied or systemic administration of antimicrobials and/or host response-modulating medications has been suggested.

Conventional synthetic agents such as chlorhexidine products which are used therapeutically and prophylactically in dentistry have some disadvantages such as altered taste sensation, tooth staining, and resistance to bacteria, which limit their usage over a long term (4). Therefore, innovative strategies need to be developed against periodontal diseases, such as exploring the extensively available medicinal plants. The active ingredients in medicinal plants restore health, with maximum efficiency and minimal side effects. Herbal extracts incorporated into medications have been found to be safe and efficacious for the treatment of several oral health conditions such as gingival bleeding, dental caries, halitosis, and mouth ulcers. The extracts obtained from aloe vera, green tea plant, neem, tulsi, propolis, rosemary, meswak, turmeric, chamomile, tea tree oil, peppermint oil, cranberry, clove, ginger, etc. have been used commonly for

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the prevention and treatment of different oral diseases. Herbal extracts contain phytochemicals that are responsible for the desired anti-inflammatory and antimicrobial effects (5). Herbal formulations are gaining widespread attention as they do not contain artificial preservatives, alcohol, colors, or flavors, which are commonly found in other drugstore products.

One such herb with medicinal properties is licorice (*Glycyrrhiza glabra*). Licorice, synonym being sweet wood, is found in the Mediterranean region and in a few regions of Asia. Licorice is a perennial herb that holds a sweet taste and has widespread pharmacological effects on human beings. Licorice extract is derived from the dried, unpeeled stolons and roots of *Glycyrrhiza uralensis* and *G. glabra*.

However, limited information is available on the use of this herb in periodontal therapy. The mechanism of action by which licorice works against periodontal diseases has not been elucidated in previous studies. The aim of this review was to enumerate the bioactive compounds present in herbal licorice extract and to elucidate the beneficial effects of licorice and its derivatives in periodontal therapy.

Methodology

The literature search was performed using three databases which included PubMed, Google Scholar, and Cochrane, in addition to searching reference lists of original and review articles. The combination of the following keywords was used to search for relevant articles: "licorice," "Glycyrrhiza glabra," "periodontal therapy," and "periodontal disease." Relevant studies published between 1985 and 2022 were selected. Only articles in English language were considered, and unpublished data were not sought. Two reviewers obtained information on the quality and characteristics of the included studies.

Components in licorice extract

Licorice is a potential source of natural anti-inflammatory agents. Its major active component is glycyrrhetic acid (GA) that is derived from licorice root extract. Major phytochemicals found in licorice are shown in Table I (Fig. 1) (6).

Safe usage of licorice

The Food and Drug Administration (FDA) has labeled licorice as "Generally Recognized as Safe." It has been suggested to be safe when used in minimal quantities by people who are not allergic to glycyrrhizin (7,8). Intake of excessive quantity, that is, over 200 mg, of licorice may cause hypertension, hypokalemia, rhabdomyolysis, respiratory impairment, muscle paralysis, hyperparathyroidism, acute renal failure, and encephalopathy (9). According to the World Health Organization (WHO), 100 mg/day of licorice can be used safely without adverse effects. A potential risk of excessive bleeding may be seen in patients using medications for anti-clotting for cerebrovascular or cardiovascular diseases in conjunction with licorice-containing herbal medications due to its antiplatelet and anticoagulant effects (10).

TABLE I - Important phytochemicals in licorice root

Group	Bioactive compounds
Aurones	Licoagroaurone
Benzofurans	Licocoumarone
Chalcones	Isoliquiritigenin, licochalcone A
Coumarins	Glycerol, glabrocoumarone, glycocoumarin, licofuranocoumarin, glabrocoumarin
Flavonoids	Glabrol, liquiritigenin
Isoflavonoids	Glabridin, glabrone, licoricidin, licoisoflavones A and B, licorisoflavan A
Pterocarpenes	Glycyrrhizol A
Saponins	Glycyrrhizin, glycyrrhizic acid, 18 β -glycyrrhetic acid, liquiritic acid, glabrolide
Stilbenes	Gancaonin G

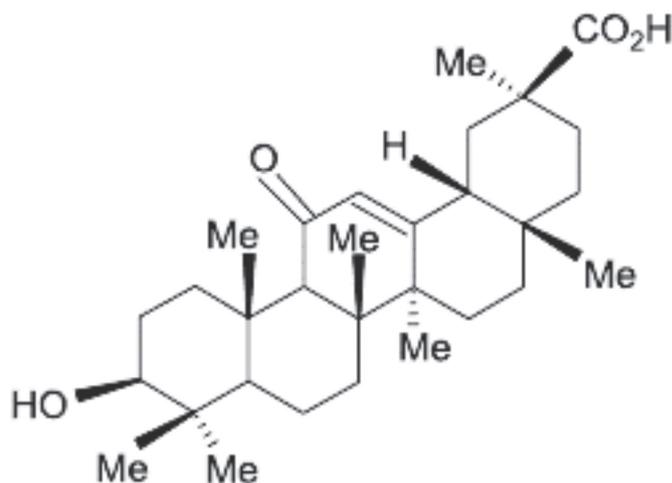


Fig. 1 - Chemical structure of glycyrrhetic acid.

Effects of licorice

Licorice constituents have shown antimicrobial (11), antiviral (12), anti-inflammatory (13), antidiabetic, antitumor, immunoregulatory (14), sedative (15), antidepressive (16), estrogenic (17,18), antioxidant (19), hepatoprotective (20), neuroprotective activities (21), and skin effects (22). The active constituents of licorice extract have a potential role on the oral microorganisms as well as the host response involved in orodental diseases like periodontitis, dental caries, recurrent aphthous ulcers, and candidiasis.

Antiviral effects – Licorice extracts inhibit the growth of viruses such as herpes simplex, influenza virus, and vesicular stomatitis virus. Glycyrrhizin prevents the replication of viruses and interferes with viral binding (12).

Antidiabetic activity – Glycycomarin, glycerin, etc., present in *G. glabra* extracts lower blood glucose level by binding to peroxisome proliferator-activated receptor (PPAR) gamma. Glabridin helps in efficient glucose utilization and prevents glucose intolerance by translocation of GLUT-4 (14).

Antitumor activity – 18- β -GA and glycyrrhizic acids induce mitochondrial permeability transition causing tumor cell apoptosis (14).

Immunoregulatory effect – Glycyrrhiza extracts stimulate the immune system by production of macrophages and lymphocytes, and increasing the phagocytic capacity of neutrophils. It prevented the accumulation of immune complexes involved in autoimmune diseases such as systemic lupus erythematosus (14).

Sedative effect – Glabridin shows sedative and hypotonic effects by positively modulating the gamma-aminobutyric acid (GABA) receptors (15).

Antidepressive effect – Licorice shows antidepressive effects by inhibition of monoamine oxidase and increasing epinephrine and dopamine levels in the brain (16).

Estrogenic effect – Licorice extracts show estrogenic activity through uterine retention and vaginal opening. Isoflavones present in licorice can influence sexual development, impair estrus cycling, and alter the proper functioning of the ovarian, hypothalamus, and pituitary glands. Glabridin can be used as a treatment for menopausal symptoms (17,18).

Hepatoprotective activities – Glycyrrhizin has shown improved liver histology and reduced serum aminotransferases. It shows hepatoprotective effect against CCl₄-induced oxidative stress, prevents oxidative and hepatic damage caused due to aflatoxin, and improves liver function (20).

Neuroprotective activities – Licorice has an antioxidant activity that can reduce brain damage by eliminating or utilizing the free radicals and improving neural function and memory (21).

Skin effects – Licorice is popular in treating dermatitis, pruritus, cysts, and eczema. It is also used for cosmetic formulation as a depigmenting agent to inhibit the tyrosinase enzyme (22).

Mechanism of action

The beneficial effects of licorice can be due to various mechanisms.

Antimicrobial activity

Microbial growth is selectively inhibited by the isoprenoid phenols present in *G. glabra*. The presence of secondary metabolites, such as alkaloids, saponins, flavonoids, and alkaloids, is responsible for the antibacterial activity (23,24). The reduction in bacterial gene expression, decrease in growth of bacteria, and inhibition of production of bacterial toxins are suggested as the mechanism behind this (24,25).

Licorice extract showed antimicrobial effects against *P. gingivalis* with minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 25 and 62.5 μ g/mL, respectively (26). Glycyrrhizol A showed a strong antibacterial effect against *Streptococcus mutans* with MIC of 1 μ g/mL. GA at an appropriate concentration has good efficacy against isolated periodontopathogenic and capnophilic bacteria (27). The MICs of GA were 8, 16, and 8 mg/L for *A. actinomycetemcomitans*, *Eikenella corrodens*, and *Capnocytophaga*, respectively, and the MBC was 16 mg/L for all species (28).

Antioxidant activity

Licorice phytochemicals exhibit significant antioxidant activity. Licorice hinders the synthesis of reactive oxygen species (ROS) by neutrophils at the site of inflammation. *G. glabra* contains licochalcones B and D, which show powerful scavenging activity on DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) radical and also have the ability to prevent the peroxidation of microsomal lipids (29,30).

Anti-inflammatory activity

GA activates signaling of glucocorticoid receptors since its chemical structure resembles the glucocorticoids, and it also inhibits the classical complement pathway, both of which are responsible for its anti-inflammatory properties.

Preclinical studies have also shown that licorice inhibits synthesis of prostaglandins and cyclooxygenase activity, and also indirectly inhibits aggregation of platelets as well as the components of the inflammatory cascade (31). Licorice extract prevents the phosphorylation of proteins involved in intracellular signaling of macrophages, such as the transcription factors, nuclear factor-kappa B, and activator protein (AP) 1, which play an important role in the pathways of inflammatory signaling (32).

Licorice in periodontal disease

The bioactive ingredients in licorice like glycyrrhizin, glabridin, licorisoflavan A, licochalcone A, and licoricidin are effective against periodontal disease. Table II summarizes the studies which suggest the potential use of licorice in periodontal therapy.

These ingredients exhibit antimicrobial, anti-inflammatory, and anti-adherence effects (Fig. 2). Since the etiology of periodontal diseases is complex involving the periodontal pathogens and host immune response, dual functionality compounds such as the phytochemicals in licorice offer therapeutic superiority. Phytochemicals are structurally distinct from the conventional microbial-derived antibiotics, and so are advantageous as antimicrobials. The phytochemicals act against different bacterial strains by inhibiting the efflux pumps, inhibiting the cell wall biosynthesis by interacting with the cell membrane, and by inhibition of enzymes such as dihydrofolate reductase, urease, and sortase A (51). Thus, their mechanisms of action are different from classic substances and against which microbial resistance does not develop.

The ability of licorice to inhibit the formation of dental plaque enhances its significance in the treatment of periodontal disease. At high concentrations of licorice extract (5%-10%), there was a slight reduction in bacterial growth and formation of plaque was completely inhibited. No effect was seen on either adherence or growth with lower concentrations. At high concentrations (0.5%-1%) of its pure active component, that is, glycyrrhizin, there was a complete inhibition in the adherence, whereas partial inhibition was observed at lower concentrations. The surface activity of glycyrrhizin could be responsible for its inhibitory effect, as



TABLE II - List of studies suggesting the potential use of licorice in periodontal therapy

Authors	Study design	Findings
Sharma et al 2022 (33)	Randomized controlled trial	Both licorice and chlorhexidine mouthwash inhibited the accumulation of plaque and inflammation of the gingiva. The herbal mouthwash was shown to be effective as a self-care treatment since chemical formulations are associated with adverse effects with long-term usage.
Madan et al 2019 (34)	Randomized clinical trial	Bleeding of the gingiva, probing pocket depth, and attachment loss were significantly decreased in patients using <i>Glycyrrhiza glabra</i> gum paint in 10% concentration. It can be used for longer periods to prevent and treat periodontal disease as they do not have any side effects, and thus, it is also effective as an alternative for synthetic agents.
Takamori et al 2018 (35)	Animal study	Loss of attachment, immune complex formation, and inflammatory cell infiltration were greater in the lipopolysaccharide (LPS) group than in the control, and were completely reduced in the glycyrrhetic acid (GA) groups. Increased alveolar bone destruction was seen in the LPS group than in the GA or control groups. Hence, in the experimentally induced periodontitis model in rats, GA had the ability to reduce periodontal destruction.
Suwannakul and Chaibenjawong 2017 (26)	In vitro study	Licorice extract showed antimicrobial effects against <i>Porphyromonas gingivalis</i> with MBC and MIC of 25 and 62.5 µg/mL respectively. It also reduced the quantity of biofilm and the activities of Arg- and Kgp-proteases.
Salehi et al 2017 (36)	Double-blind clinical trial	Mucoadhesive tablets containing licorice extract can relieve pain, decrease the diameter of the ulcer and the inflammation around it, and improve the recovery in aphthous stomatitis.
Jain et al 2017 (37)	Randomized clinical trial	Licorice mouthwash reduced the accumulation of plaque and inflammation of gingiva, without any tooth discoloration or unpleasant taste sensation.
Shivprasad et al 2017 (38)	Randomized controlled trial	Subgingivally delivered licorice as an adjunctive treatment modality to scaling and root planing showed clinical and microbiological benefits in periodontal therapy, with a reduction in the prevalence of <i>P. gingivalis</i> .
Ali and Mohammed 2016 (39)	Comparative human study	Licorice extract based mouthwash inhibits plaque formation and inflammation of gingiva without any adverse effects. Therefore, it can be used as an adjunctive to scaling and root planing in periodontal treatment.
Hamdon et al 2014 (40)	Human study	Licorice extract showed antibacterial effects against <i>Aggregatibacter actinomycetemcomitans</i> , based on antimicrobial sensitivity tests. The antibacterial effect was greater against planktonic cells as compared to the cells within the biofilm. It produced an inhibition zone similar to tetracyclines with a concentration of 250 µg.
Kim et al 2013 (41)	In vitro study	18α-GA is effective in the treatment of vascular diseases caused by <i>P. gingivalis</i> . It reduces vascular permeability induced by LPS by inhibiting IL-8 production from the endothelium.
Farhad et al 2013 (42)	Experimental human study	A significant reduction of MMP-8 concentration was seen in both licorice and doxycycline groups than in the placebo group. The licorice group showed better reduction of MMP-8 concentration than doxycycline group, which was not statistically significant. Hence, licorice extract can be as potent as antibiotics such as doxycycline to treat periodontal diseases by preventing the MMP production by host cells.
Kim et al 2012 (43)	In vitro study	Glabridin inhibits activation of signaling molecules induced by RANKL and other transcription factors of osteoclast precursors, and so it can be used to inhibit osteoclastogenesis.
Zhu et al 2012 (44)	Animal study	Isoliquiritigenin (ISL) inhibits osteoclastogenesis induced by RANKL and bone loss by various signaling pathways. Hence, it has the potential to be used as a therapeutic or preventive agent for the treatment of lytic bone diseases.
Feldman et al 2012 (45)	In vitro study	Licochalcone A inhibits the two primary causative factors of periodontitis, i.e., formation of biofilm with <i>P. gingivalis</i> and the immune response of the host.
La et al 2011 (46)	In vitro study	Licoricidin (LC) and licorisoflavan A (LIA) inhibited the production of IL-6, MMP-7, -8, and -9 in macrophages. They can be used to treat MMP and cytokine-mediated conditions such as periodontal disease, and are potent host-modulating agents.
Bodet et al 2008 (32)	In vitro study	Licorice extract showed anti-inflammatory effects by reducing the IL-1b, -6, -8 and TNF-α responses of macrophages induced by LPS. It is a potential therapeutic agent to prevent or treat the tissue destruction caused due to periodontal disease.
Wittschier et al 2006 (47)	In vitro study	The polysaccharides in <i>G. glabra</i> inhibit bacterial adhesion and thus can be potential therapeutic agents against bacterial infection.
He et al 2006 (27)	In vitro study	Glycyrrhizol B and gancaonin G showed moderate antibacterial effect against <i>Streptococcus mutans</i> , while Glycyrrhizol A showed strong antibacterial effect with MIC of 1 µg/mL. Hence, the roots of <i>Glycyrrhiza uralensis</i> contain isoflavones which exhibit antibacterial effects.

Authors	Study design	Findings
Choi 2005 (48)	Animal study	Glabridin, an estrogenic plant product, stimulates the in vitro formation of bone in cultured osteoblasts. Thus, glabridin can be a potent agent in the management of osteoporosis.
Salari et al 2003 (49)	Human study	Enoxolone with the mentioned concentrations is effective against isolated periodontopathogenic and capnophilic bacteria. Its MICs were 8 µg/mL for <i>A. actinomycetemcomitans</i> and <i>Capnocytophaga</i> species, and 16 µg/mL for <i>Eikenella corrodens</i> . The MBC was also 16 µg/mL for all the microorganisms.
Salari and Kadkhoda 2003 (28)	In vitro study	GA at an appropriate concentration has good efficacy against isolated periodontopathogenic and capnophilic bacteria. The MICs of GA were 8, 16, and 8 mg/L for <i>A. actinomycetemcomitans</i> , <i>Eikenella corrodens</i> and <i>Capnocytophaga</i> , respectively, and the MBC was 16 mg/L for all species.
Saeedi et al 2003 (50)	Randomized, controlled trial	Edema, erythema, and itching were more effectively reduced with 2% licorice topical gel than with 1% gel in 2 weeks.

IL = interleukin; MBC = minimum inhibitory concentration; MIC = minimum bactericidal concentration; MMP = matrix metalloproteinase; TNF = tumor necrosis factor.

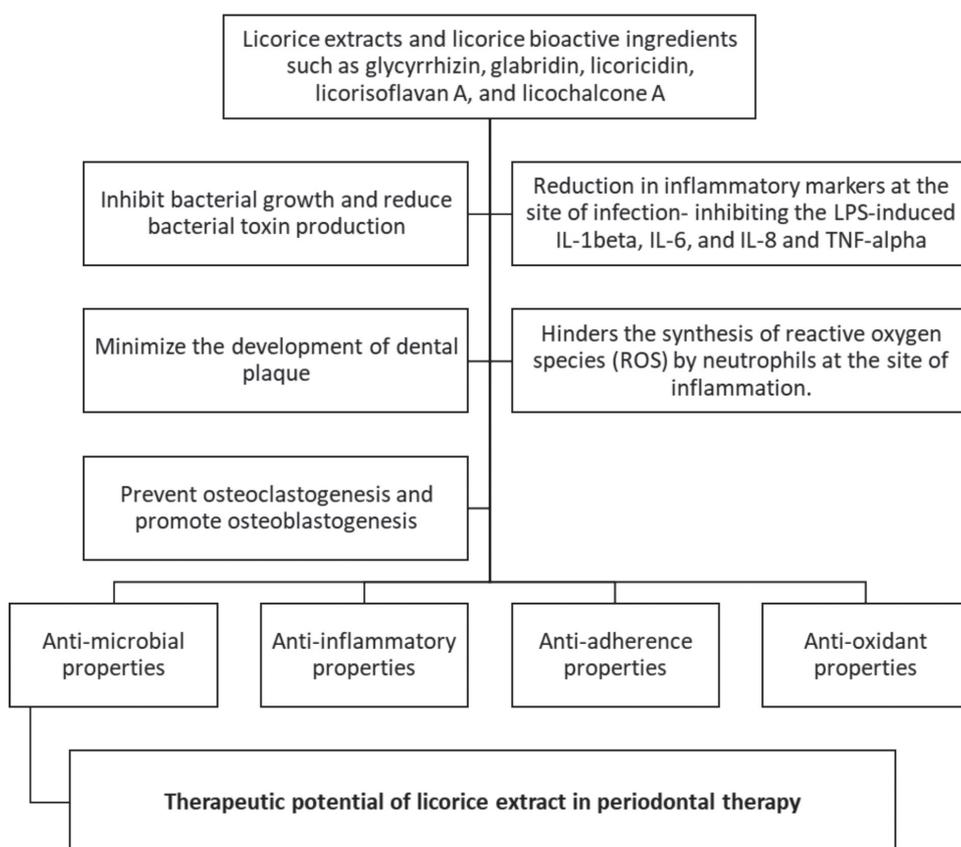


Fig. 2 - Mechanism of action of licorice in periodontal therapy.

bacterial adherence and growth are known to be affected by surfactants. Bacterial adherence can also be inhibited by the adsorption of glycyrrhizin onto smooth surfaces. Licorice extract shows minimal antibacterial activity along with its effect on inhibition of plaque. Glycyrrhizin as a vehicle can be effective for topical agents used orally due to its sweetness, good dispersing properties, and the ability to remain stable in the form of aqueous gels. This suggests that the balance of the oral microbial flora will not be affected on using glycyrrhizin as an oral medication (52).

Phytochemicals of *G. glabra* reduce bacterial growth and inhibit the mediators of inflammation at the infection site.

It also inhibits the activity of osteoclasts responsible for destruction of alveolar bone in periodontal disease and promotes the formation of bone by stimulating osteoblastogenesis. High amounts of inflammatory markers like interleukin (IL)-1 β , IL-2, IL-6, IL-8, tumor necrosis factor (TNF)- α , and RANKL are present in patients with periodontal disease. Licorice extract showed potent anti-inflammatory properties by inhibiting these proinflammatory mediators stimulated by lipopolysaccharide (LPS) from *A. actinomycetemcomitans* and *P. gingivalis* (32).

Resorption of alveolar bone is an important feature of periodontitis. The differentiation, activation, and survival of

osteoclasts are regulated by RANKL leading to bone resorption. Glabridin can be used to inhibit osteoclastogenesis by preventing the activation of signaling molecules induced by RANKL and subsequent transcription factors for osteoclast precursors, suggesting its therapeutic potential (34).

Recommendations for future research

Though the use of herbals for medicinal purpose is traced back to several centuries, it is only in recent evidence-based era that methodical and systematic approaches to study their properties have been reinstated. This has sparked a wide interest for their application in all healthcare specialties including periodontal therapy. The beneficial phytochemicals in licorice must be studied so as to incorporate these herbal extracts in oral care products that may be useful in dental therapy.

In vitro studies have shown the capability of licorice and its bioactive components in periodontal therapy; however, most of the clinical studies have limitations pertaining to the design of the study and the number of participants included in the study, which makes them statistically insignificant. Thus, further clinical studies need to be carried out to investigate the oral care products containing licorice extracts, in the forms of toothpaste, mouthwash chewing gum, and gel to be able to validate its beneficial effects. The local application of these bioactive compounds would be more suitable. For example, the local application of a licorice-based gel into sites with periodontal disease permits the bioactive ingredients to be released slowly, which will act locally on the periodontal pathogens and the host immune response, the two contributory factors in the destruction of periodontal tissues.

Further research focusing on the in vivo anti-inflammatory/antimicrobial effects of licorice is required on larger sample sizes to better understand its specific role in the management of periodontitis. Clinical trials evaluating the effect of licorice extract on periodontopathogens and inflammatory cytokines would be recommended.

Conclusion

The usage of herbal agents for the treatment of periodontal disease is considered as an intriguing alternative to conventional antibiotics due to their lesser negative effects and to overcome drug resistance during treatment. Licorice extracts exhibit a wide range of biological effects such as anti-inflammatory, antioxidant, and antimicrobial activities. It has the ability to prevent the release of proinflammatory mediators and MMPs from host cells, and hence it is a potent agent for periodontal therapy. The bioactive ingredients present in this herb help in reducing loss of alveolar bone, which is commonly associated with periodontal disease. It should also be emphasized that no adverse effects have been seen with the use of licorice extracts. Hence, local application of licorice-containing agents into the diseased periodontal sites can be beneficial, which would act locally on periodontopathogens and the host inflammatory response.

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