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Liquorice and its Beneficial Effects in Dentistry-A Review

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Abstract

Liquorice the name given to the roots and stolons of Glycyrrhiza species, has been used since ancient times as a traditional herbal remedy. Liquorice also known as yashtimadhu, sweetwood or mulhatti is one such herbal remedy which has shown to have immense potential in treatment of orofacial diseases. Liquorice contains several classes of secondary metabolites with which numerous human health benefits have been associated. Recent research suggests that liquorice and its bioactive ingredients such as glycyrrhizin, glabridin, licochalcone A, licoricidin, and licorisoflavan A possess potential beneficial effects in oral diseases. This paper reviews the effects of liquorice and its constituents on oral dental diseases (dental caries, candidiasis, Gingivitis,and periodontitis). It also summarizes results of clinical trials that investigated the potential beneficial effects of liquorice and its constituents for preventing/treating oral-dental diseases.

Keywords: Liquorice, Dental caries, Candidiasis, Gingivitis, Periodontitis..

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Introduction

In recent times, there is a rise in use of plant extracts in modern medicine. The search for effective, efficient, safe and economical alternatives have led to a rise in use of natural phytochemicals derived from plants in treating diseases of the human body. A large body of evidence exists to substantiate the use of herbs for preventing and treating human diseases. Liquorice root (Radix Glycyrrhizae) is obtained from perennial plants native to Mediterranean countries, central to southern Russia, and certain regions of Asia. The genus name Glycyrrhiza is derived from the ancient Greek words glycos (meaning sweet) and rhiza (meaning root). Glycyrrhiza glabra L. and

Glycyrrhiza uralensis Fisch. (Fam. Leguminosae) roots are the commonest sources of liquorice used in cosmetics, foods, tobacco, and in both traditional and herbal medicine.

Due to its sweet taste, liquorice has been used worldwide as a sweetener and a flavouring agent in food and medicine production and is listed in the USA by the Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS) (Peters ms et al 2010) Liquorice is rich in secondary metabolites which have beenassociated with various health benefits. Secondary metabolites of liquorice roots have shown to have a beneficial effect in the treatment of various diseases such as cancer, tuberculosis, atherosclerosis, gastric ulcers, immunodeficiency, hepatitis and bacterialinfections s (Isbrucker and Burdock, 2006; Shen et al, 2007; Nassiri Asl and Hosseinzadeh, 2008). Recently the benefits of liquorice in oral diseaseshas been of great interest. Clinical trials have been conductedworldwide to evaluate the effects of liquorice and its metabolites inpreventing and treating various oral diseases such as dental caries, candidiasis, Gingivitis, and periodontitis. This manuscript aims to review, summarize and highlight these beneficial effects of liquorice and its derivatives in preventing and treating oral diseases.

Description Of The Plant, Phytochemical Composition, And Safety

Liquorice, also called as gancao which means "sweet herb" in Chinese and popularly known in India as Jeshthamadh (Marathi), Yashtimadhu and Madhuka (Sanskrit), Jethimadhu (Gujarati), Atimadhurum (Tamil) and Jaishbomodhu (Bengali) belongs to the genus Glycyrrhiza and has been used by humans for various purposes for at least 4000 years (Nomura T et al 2002). It has been mentioned in Ayurvedic texts as Atirasa, Madhurasaa, Madhuka, Yastikavha and Madhuyashtyaahvaa. The genus glycyrrhiza contains about 30 species but dried unpeeled roots of Glycyrrhiza glabra Linn. And Glycyrrhiza uralensis Fisch. (Fam. Leguminosae) are the commonest sources of liquorice. Glycyrrhiza glabra is a perennial shrub which grows to a height of 1 m and has a root system composed of taproot and stolons which are sources of commercial liquorice. Glycyrrhiza uralensis Fisch which is found in the Urals, Siberia and parts of East Asia has similar root system to G. glabra. The sweetness of liquorice comes from glycyrrhizin, which constitutes 10e25% of liquorice and is 50 times sweeter than refined sugar.

Liquorice is produced from the unpeeled, dried roots and stolons of G. glabra and G. uralensis. Phytochemically, both plants are among those

well studied and contain several classes of secondary metabolites, the most abundant being saponins, flavonoids, isoflavonoids, chalcones, and coumarins as well as minoramounts of aurones, benzofurans, phenols, pterocarpans, and stilbenes(Wang et al, 2000; Kondo et al, 2007)Ayurvedic texts like Charaka and Sushrutahave mentioned the role of liquorice in Dantaroga (diseases of teeth) and Dantmamsaroga (diseases of gums). Liquorice has also shown great potential in treatment of oral diseases.Liquorice constituents are known as generally recognized as safe for use in foods and over-the-counter drugs by the United States Food and Drug Administration((Isbrucker and Burdock, 2006). It is assumed that these products do not pose a health hazard, provided that they are not consumed in excess or by individuals who are sensitive to low levels of glycyrrhizin. Liqcorice root is available under various forms (candies, capsules, tablets, liquid extracts, etc.). Solid extract (250–500 mg) consumed three times daily has been suggested for medicinal purposes. Large amounts of liquorice, more particularly glycyrrhizin, may cause severe hypertension, hypokalemia, and hypermineralocorticoid-like effects through inhibition of 11b-hydroxysteroid dehydrogenase, which is responsible for the renal conversion of cortisol into cortisone. This inhibition results in elevated levels of cortisol in the collecting duct of kidney, and potassium is excreted while sodium is retained, leading to hypertension. A linear dose-dependent rise in blood pressure has been reported for liquorice consumption (20–200 g daily for 2–4 weeks) corresponding to a daily intake of 75– 540 mg glycyrretinic acid (Sigurjonsdottir et al, 2001). These effects, which are reversible upon withdrawal of liqcorice or glycyrrhizin, may be more important for individuals using glucocorticoids on a regular basis. Several other adverse effects, including headache, premature birth, muscle weakness, and paralysis, have also been reported. In addition, liquorice has been shown to be a potent inhibitor of cytochrome CYP3A4 activity Because this liver enzyme is responsible for metabolism of a wide range of drug molecules, a prolonged intake of high doses of liquorice may affect the metabolism of coadministrated drugs, such as warfarin, hydrocortisone, and acetaminophen (Nassiri Asl and Hosseinzadeh, 2008)

Dental Caries and Liquorice

Dental caries is an infectious microbial disease that results in localized dissolution and destruction of calcified tissues of teeth. Mutans group of streptococci, Streptococcus sanguis, Lactobacillus spp. and Actinomyces spp. are implicated in the pathogenesis of tooth decay.

Streptococcus mutans help in the pathogenesis of dental caries by forming the extracellular polymeric substances including exopolysaccharides (EPS), eDNA and lipoteichoic acid (LTA). EPS produced by S. mutans forms a matrixwhich helps in the accumulation of microbes on the teeth, protects them and creates an acidic microenvironment which helps in the formation and progression of dental caries . These bacteria ferment sugars in diet and produce lactic acid as a by-product which leads to the dissolution and destruction of tooth structure(Takahashi N et al 2008).

Although the anti-cariogenic properties of liquorice have been discussed for many years, few studies have been published evaluating its role as an anticariogenic agent. Recently, liquorice has been studied extensively for its anticaries properties. He et al. extracted pterocarpenes namely glycyrrhizol A and glycyrrhizol B along with four known isoflavonoids, 5-O-methylglycryol, isoglycyrol, 6,8-diisoprenyl-5,7,40-trihydroxyisoflavone and gancaonin G from theroots of Glycyrrhiza uralensis and concluded that all these metabolites show activity against S. mutans whereas glycyrrhizol A andn 6,8-diisopreny l-5,7,40 -trihydroxyisoflavone had highest antimicrobial activity against these bacteria(He J, Chen L et al 2006). Based on the above observations, Hu et al. developed a sugar-free orange flavoured liquorice lollipop containing glycyrrhizol A for caries prevention. They found that liquorice lollipops are safe and effective against S. mutans when consumed for 10 days (twice daily) and lead to a marked reduction in salivary S. mutans . The results of an in vitro study conducted by Liu et al. reported that glycyrrhizic acid inhibits the multiplication and acid producing of S. mutans and can inhibit the growth of these bacteria in vitro . A clinical study evaluated the potential of liquorice lollipops for caries control in pre-school children. In this study, the study subjects consumed liquorice lollipops twice a day for a period of 3 weeks and interestingly it was noted that there was a steep decline in the number of S. mutans. The numbers were reduced for a period 22 days after the last lollipop and then began to rebound . Study conducted by Mentes on liquorice lollipops et al. observed that there was a reduction of S. mutans with consumption of two liquorice lollipops for a period of 21 days period (Mentes JC et al 2012). Even though liquorice lollipops show promise further double blinded, randomized longitudinal studies using more human subjects are required before the liquorice lollipops can be used as anti caries products for caries prevention in high risk children and adults. Ayurveda recommends

chewing on liquorice herbal sticks, twelve angulas (9 inches) long and thickness of one's little finger to reduce dental caries and plaque. There is considerable amount of data which states that liquorice is effective as an anticaries agent, however there is a need for more randomised clinical trials before liquorice can be safely incorporated used in oral hygiene products.

Oral Candidiasis and Liquorice

Oral candidiasis (candidosis or thrush) is caused by a yeast like fungus called Candida albicans and is an opportunistic infection of the oral cavity . Candida albicans is an inhabitant of normal flora of the mouth and the gastrointestinal tract and causes no infections in healthy individuals. Predisposing factors for oral candidial infections include medications like antibiotics and corticosteroids, systemic diseases like diabetes mellitus and hypothyroidism, nutritional deficiencies like iron and B12 deficiencies, xerostomia, immunosuppressive diseases and therapy (Zunt SL et al 2000). Pseudomembranous candidiasis also called as thrush, is one of the most common forms of oral candidiasis. It is a white pseudomembrane consisting of desquamated epithelial cells, necrotic debris, fibrin and fungal hyphae. It occurs most frequently on the surface of the buccal mucosa and tongue but is also seen on hard and soft palate, tongue, periodontal tissue and oropharynx. Erythematous candidiasis is associated with burning mouth secondary to antibiotic therapy, corticosteroids or diseases which suppress the immune system. Asymptomatic form of erythematous candidiasis, also called as Denture stomatitis is characterized by diffuse erythema and edema of the palatal mucosa that is in contact with the denture. Denture stomatitis can be localized or generalized . Virulence factors of *C. albicans* such as adhesion, proteinases secretion, yeastehyphal transition and phenotypic switching are responsible for host damage. The treatment for oral candidiasis is topical or systemic use of antifungal drugs, management of predisposing factors, oral hygiene and disinfection of prosthetic appliances. Antimicrobial drug resistance has led to the need for development of alternative drugs. Several studies have investigated the effects of liquorice on C. albicans. Utsunomiya et al. noticed that compared to normal mice, MAIDS mice (mice infected with LPBM5 murine leukemia virus) are 100 times more susceptible to infection with *C. albicans* and administration of glycyrrhizin improved the resistance of MAIDS mice to *C. albicans* infection (Utsunomiya T et al 2000).

Another in vitro study conducted by Motsei et al. screened liquorice extracts against C.

albicans and reported the antifungal effect of fresh water extract of *G. glabra* on *C. Albicans*. Interestingly, Glabridin from the roots of *G. glabra* showed resistance modifying activity against drug resistant mutants of *C. albicans* at a minimum inhibitory concentration of 31.25e250 mg/ mL. Animal studies conducted by Lee et al. concluded that Liquiritigenin (LG) found in liquorice can protect mice against disseminated candidiasis by the CD4þ Th1 immune response (Lee JY et al 2009). A more recent study evaluated the effects of Glabridin and Licochalcone A on growth, biofilm formation and yeastehyphal transition of C. albicans. Results showed that Licochalcone A has a significant effect on biofilm formation, while both licochalcone A and glabridin prevented yeastehyphal transition in C. albicans. They also stated that both these compounds can act synergistically with nystatin against *C. Albicans*. Furthermore, research shows that 18b-glycyrrhetinic acid can be beneficial in the treatment of Th1-disordered diseases due to *C. Albicans*. Although more in vitro and in vivo studies are required to explore the beneficial effects of liquorice on oral candidiasis, the findings of these studies suggest that liquorice can be a useful therapeutic alternative for the treatment of oral candidacies.

Gingivitis and Liquorice

Gingivitis is characterized by presence of clinical signs of inflammation that are confined to gingiva. Porphyromonas gingivalis does not initially colonize clean tooth surfaces and adheres to bacteria already present in plaque mass and plays a potential role in the etiology of childhood gingivitis. The presence of P. gingivalis is most strongly associated with the progression of gingivitis and onset of periodontitis in healthy children (Newman MG et al2009). Few studies have investigated the effect of liquorice on P. gingivalis. Aqueous extracts of raw polysaccharides from G. glabra have shown to have strong anti adhesive effects against P. gingivalis.

Interestingly, a supercritical extract of Chinese liquorice (Glycyrrhiza uralensis), and its major isoflavans, Licoricidin and Licorisoflavan A showed to have an inhibitory effect on growth, volatile sulfur compounds (VSCs) production and protease activity of P. gingivalis therefore controlling halitosis (Tanabe S et al 2012). These studies implicate that liquorice can be used in oral hygiene products to maintain gingival and oral health.

Periodontitis and Liquorice

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms resulting in progressive destruction of periodontal ligament

and alveolar bone. Periodontitis is characterised by attachment loss, increased probing depth or recession, bleeding on probing, changes in bone height and density, mobility and loss of teeth in advanced cases . The etiological factors of this destructive process involves both tissue damage from bacteria and bacterial products in plaque and indirect damage through bacterial induction of the host immune and inflammatory responses by the over production of inflammatory mediators and matrix metalloproteinases (MMPs) leading to the progression and severity of periodontitis . The pathogens detected in high levels in chronic form of periodontitis include P. gingivalis, Tannerella forsythia, Prevotella intermedia, Treponema denticola, Spirochetes and Aggregatibacter actinomycetemcomitans. The treatment of periodontitis involves removal of plaque and calculus through scaling and root planning and maintenance of good oral hygiene. This non-surgical pocket therapy helps in reduction of pocket depth, tissue inflammation, increases clinical attachment level and improves the condition of the periodontium . Administration of low dose doxycycline has been reported to provide additional benefits(Preshaw PMet al 2004).

Clinical trials aiming to find natural resources for treatment of periodontitis have looked into the phytochemicals of Liquorice to prevent and treat periodontitis. The ability of liquorice root polysaccharides to reduce bacterial binding to host cells was observed after pre-treatment of P. gingivalis by Wittschier et al. The data suggested that polysaccharides from G. glabra are a potent agent against bacterial adhesion and are able to block the initial step of an infection and thus can be potential prophylactic tools in alternative treatment regimens against bacterial infection . Patients with periodontal inflammation have high concentration of proinflammatory mediators such as interleukin (IL)-1beta, IL-2, IL -6, IL-8 receptor activator of nuclear factor kappa-B ligand (RANKL) and tumour necrosis factor e alpha in macrophages of inflamed gingival tissues . Bodet et al. investigated the response of liquorice on periodontopathogen-induced inflammatory response and found that liquorice extract exhibited potent anti-inflammatory properties by inhibiting the periodontopathogen LPS-induced IL-1beta, IL6, and IL-8 and TNF-alpha responses of macrophages stimulated with A. actinomycetemcomitans and P. gingivalis lipopolysaccharide (LPS). According to La et al. licoricidin and licorisoflavan Aeffectively inhibit inflammatory cytokines and matrix metalloproteinases (MMPs) and can be used in the treatment of cytokine and/or MMP-mediated disorders such as periodontitis .

Licochalcone A inhibits P. gingivalis biofilm formation and the host immune response, the two principal etiological factors of periodontitis.18 alpha-glycyrrhetinic acid appears to significantly reduces P. gingivalis LPS-induced vascular permeability by repressing NF-kB-dependent endothelial IL-8 production, suggesting its therapeutic potential in P. gingivalis-related vascular diseases .Recently an in vivo study demonstrated that liquorice extract can prevent the production of MMPs by host cell and can be as effective as doxycycline in patients with chronic periodontitis .One of the prominent features of periodontitis is resorption of the alveolar bone. Receptor activator of nuclear factor kappa-B ligand RANKL is an important factor in bone resorption as it is involved inosteoclast differentiation, activation and survival.

Therapeutic potential of liquorice on RANKL has been evaluated. 18b-Glycyrrhetinic acid administered in interleukin-10-deficient mice which are highly disease susceptible, resulted in a dramatic reduction of in interleukin-10-deficient mice . Zhu et al. noted that administration of isoliquiritigen prevented inflammatory bone loss in mice by attenuating osteoclast activity (Zhu L et l 2012).It has been suggested that glabridin can be used in preventing osteoclastogenesis by inhibiting RANKL-induced activation of signalling molecules and subsequenttranscription factors in osteoclast precursors(Kim HS et al 2012).

Conclusion

Recent research suggests that liquorice extracts bioactive ingredients such as glabridin, licoricidin, licorisoflavan A, licochalcone A, and glycyrrhizin have beneficial effects in oral diseases like dental caries, candidiasis, Gingivitis and periodontitis. These effects have been associated with the anti-adherence, anti-microbial, and anti-inflammatory properties of the compounds. Further in vivo studies should be directed to explore and evaluate the therapeutic benefits of liquorice in dentistry

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