

## REVIEW ARTICLE

# DENTAL APPLICATIONS OF LIQUORICE: A MEDICINE OF YORE

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### ABSTRACT

Oral health influences quality of life and general well-being. Oral diseases can be debilitating and are a major health concern worldwide. Considering the emergence of multi-drug resistant pathogens and financial difficulties in developing countries, there is an urgent need for developing new antimicrobial compounds which are safe, efficient and cost effective. Medicinal plants have been used for time untold for treating human diseases. Liquorice is rich in secondary metabolites which are used in traditional and modern medicine. It has well known properties such as anti-ulcerative, anti-viral, anti-inflammatory, glucocorticoid, antioxidant, anti-carcinogenic and many more. Liquorice extracts and bioactive ingredients have shown beneficial effects in preventing and treating oral diseases.

This paper reviews the potential beneficial effects of liquorice as a prevention and treatment modality in oral diseases. Clinical trials, review of literature and case reports evaluating the effect of liquorice on oral diseases and oral microbes are included.

**Key words:** Liquorice, drug resistance, oral diseases.

## INTRODUCTION

Medicinal plants are a source of potential bioactive compounds for the management of various diseases. Because of the resistance and side effects that pathogenic micro-organisms build against the antibiotics, much attention has been paid to extracts and active compounds isolated from plant species used in herbal medicine.<sup>1</sup>

*Glycyrrhiza glabra* Linn., widely known as liquorice or sweet wood, is one such traditional medicinal plant used by different cultures for centuries to relieve coughs, sore throats, and gastric inflammation.<sup>2</sup> The term *Glycyrrhiza* comes from the Greek words; *glycos* meaning sweet and *rhiza* meaning root.<sup>3</sup> In China, it is called “gancao” (meaning “sweet grass”) and has been recorded around 2100 BC in the Shennong’s Classic of Materia Medica.<sup>4</sup> The Food and Drug Administration (FDA) lists liquorice as GRAS (generally regarded as safe) when used as food seasoning and sweetening agent.<sup>5</sup>

*G. glabra* is a perennial shrub. It has compound, alternate leaves. Its fruit is a compressed legume or pod, with reticulous pitting containing 3-5 brown seeds. Its root system is a long taproot with horizontal stolons which are the source of commercial liquorice. Glycyrrhizin consists of 10%-25% of liquorice, which imparts sweetness. It is fifty times sweeter than refined sugar.<sup>3,6</sup> The yellow colour of liquorice is due to the flavonoid content.<sup>6</sup>

Liquorice is abundant in secondary metabolites linked with various health benefits.<sup>7</sup> Recently, the benefits of liquorice in oral diseases has been of interest. Clinical trials have been performed to evaluate the effects of liquorice in preventing and treating oral diseases.<sup>8</sup>

The antimicrobial efficacy of liquorice has been accounted by various researchers. The organoleptic properties of liquorice stimulate salivary flow. Stimulated saliva contains greater concentration of bicarbonate ions having increased buffering capacity.<sup>9</sup> Added to its potential to clear acids and substrates from plaque and its improved pH, stimulated saliva increases the resistance to caries. The antimicrobial activity may be due to tannins, triterpenoid saponins, and flavonoids.<sup>2,10</sup>

## Mode of Delivery

The mode in which liquorice is delivered is a major criterion to effectuate prolonged duration of action. Liquorice candy or chewing gum, would have an extended release in the mouth enhancing its sustained action. It can be used as a suspension or a gel to increase its action. Liquorice roots have been conventionally used as chew twigs and also as teething sticks which exert a numbing effect on infants’ gums. Liquorice can also be incorporated in infant swipes and pacifiers, serving as a non-cariogenic sweet-tasting alternative to honey-dipped pacifier. Liquorice powder also has reduced the metabolism of sucrose, fructose, and glucose. Further, controlled-release devices, mucosal adherent patches, and even as liquorice-containing resorbable fibres which can be inserted into diseased periodontal site and healing sockets. However, when delivered as a rinse, the duration of action was too short to provide optimum contact of the extracts with the oral cavity. Moreover, the sweet taste promotes early swallowing of saliva and consequent washout of the residual drug from the oral cavity.<sup>9</sup>

## Dental caries and Liquorice

Various factors contributing to the risk of the development of caries are consumption of dietary sugars, non-exposure to fluoride, decrease in the salivary flow, and oral hygiene behaviour of individuals.<sup>11</sup> Various preventive measures such as fluoride, xylitol, CPP-ACP etc are available for preventing dental caries are being followed from a very long time. Herbal products such as *Ocimum sanctum*, *Aloe barbadensis*, and Liquorice which have been found to inhibit dental caries.<sup>12</sup>

Liquorice has the highest anti-microbial activity against SM when compared to other bacteria.<sup>2,12</sup> Glycyrrhizol A, from the extract of liquorice roots, which employed strong antimicrobial action against cariogenic bacteria.<sup>9</sup> One of its main component, glycyrrhizin, dose-dependently hinders the glucosyltransferase activity, which is necessary for the production of insoluble glucans involved in biofilm formation. Gedalia et al. described that glycyrrhizin, when added to an acidulated phosphate-fluoride solution, increases fluoride uptake

and deposits in the demineralized enamel.<sup>9</sup> Moreover, the presence of alkaloids, tannins and flavonoids prevent the bacterial adherence to the tooth surfaces, inhibit glucan production and have inhibitory effect on amylases. Glabridine is active against both gram-positive strains and gram-negative strains. Glycyrrhetic acid, Glycyrrhizin, flavonoids, isoflavonoids, asparagine and chalcones improves its antiadhesive and antimicrobial properties. Flavonoids isolated from *G. uralensis* have shown to completely inhibit biofilm formation hence recommended in gargling solutions and in dentifrices for prevention of dental caries. Isoflavonoids along with Glycyrrhizol A and B have shown antimicrobial activity against *Streptococcus mutans*. A sugar-free flavoured glycyrrhizol A containing liquorice lollipop when consumed for 10 days twice daily led to a marked reduction in salivary *S. mutans*.<sup>12</sup> Liu et al. reported that glycyrrhizic acid inhibits the multiplication and acid production of *S. mutans* in vitro.

Sugar-free lollipops containing liquorice were given to children twice daily for 3 weeks and the high-risk children had the maximum decrease in *Streptococcus* count. At end of the follow-up period, the SM count which decreased moved the high-risk group down to moderate-risk level. Oznurhan et al. evaluated the effectiveness of a herbal caries-prevention protocol for reducing salivary SM levels in children and found that Liquorice made a significant decrease in the streptococcus count.<sup>12</sup> Söderling et al. reported that liquorice-containing gel inhibits acid production.<sup>13</sup> The use of liquorice extract-containing lollipops can be as a simple and effective way to reduce the risk of dental caries in children. Liquorice extracts can be utilized as a preventive routine in paediatric practice under supervision. The supervision by dentist or parents would limit accidental over consumption by children as high doses of liquorice is associated with respiratory and renal diseases. Moreover, the candies and lollipop way of providing liquorice can be well accepted by the children.<sup>12</sup>

### Gingivitis and liquorice

Gingivitis is characterized by presence of clinical signs of inflammation confined to gingiva. *P. gingivalis* is most strongly associated with the pro-

gression of gingivitis and onset of periodontitis in children. Aqueous extracts of polysaccharides from *G. glabra* have shown anti-adhesive effects against *P. gingivalis*. A supercritical extract of Chinese liquorice along its major isoflavones have shown inhibitory effect on growth, volatile sulfur compounds (VSCs) production and protease activity of *P. gingivalis* therefore controlling halitosis.<sup>14</sup> These studies implicate that liquorice can be used in oral hygiene products to maintain oral and gingival health.

### Periodontitis and liquorice

Periodontitis is an inflammatory disease of the supporting tissues of the teeth resulting in progressive destruction of periodontal ligament and alveolar bone. The treatment of periodontitis involves removal of plaque and calculus and maintenance of good oral hygiene.

The ability of liquorice root polysaccharides to reduce bacterial binding to host cells was observed by Wittschier et al. Polysaccharides from *G. glabra* are potent against bacterial adhesion and can be potential prophylactic tools in alternative treatment regimens against bacterial infection. Bodet et al. found that liquorice extract inhibit the periodontopathogens exhibiting potent anti-inflammatory properties. According to La et al. licorisoiflavan A and licoricidin inhibit matrix metalloproteinases (MMPs) and inflammatory cytokines and can be used in the treatment periodontitis. Licochalcone A inhibits *P. gingivalis* biofilm formation, the key risk microbe for the progression of periodontitis. Recently an in vivo study demonstrated that liquorice extract can prevent the production of MMPs and can be as effective as doxycycline in patients with chronic periodontitis.<sup>8</sup> Pyrano-isoflavans from *G. uralensis* has shown antibacterial activity against *S. mutans* and *P. gingivalis*.<sup>15</sup>

### Oral candidiasis and Liquorice

Oral candidiasis, caused by *Candida albicans* is an opportunistic infection of the oral cavity. *Candida albicans* is an inhabitant of normal flora of the oral cavity and the gastrointestinal tract and causes no

infections in healthy persons.

Licochalcone A, liquiritigenin and glabridin have shown to be effective in preventing biofilm formation, growth and yeast-hyphal transition of *C. albicans*.<sup>16</sup> Motseiet al. reported the antifungal effect of aqueous extract of *G. glabra* on *C. albicans*. Glabridin also showed resistance modifying activity against drug resistant mutants of *C. albicans*. Animal studies conducted by Lee et al. concluded that Liquiritigenin can protect mice against disseminated candidiasis by the CD4+ Th1 immune response. These compounds can act with nystatin against *C. Albicans*. Thus, liquorice can be a useful alternative for the management of oral candidiasis.<sup>8</sup>

### Recurrent aphthous ulcer and liquorice

Recurrent aphthous ulcers are the most common oral mucosal disease seen in children and adults . Burgess et al. documented that commercially available Canker Melts GX patches containing liquorice decrease the lesion size, duration and pain thereby improvising healing.<sup>17</sup> Martin et al. observed an improvement in pain using an oral patch impregnated with liquorice extract when used for up to 8 days. An in vivo study demonstrated the effectiveness of liquorice bio adhesive in the pain control and the inflammatory halo and necrotic centre of aphthous ulcers.<sup>8</sup> All of these investigations emphasize on the therapeutic benefits of liquorice on aphthous ulcers.

### Oral cancer and liquorice

Liquorice has been investigated as a chemotherapeutic agent for its role in treatment of oral carcinomas. Isoliquiritigenin, isolated from liquorice is a novel inhibitor of tumor angiogenesis and possesses great remedial potential for Adenoid cystic carcinoma and oral squamous cell carcinoma.<sup>8,10</sup>

Licochalcone A induces apoptotic cell death of oral squamous cell carcinoma cells. Kim et al. proposed that Licochalcone A decreases the number of viable oral cancer cells. Shen et al. advocated that licochalcone A significantly inhibited the cellinvasion capacities of SCC-25 cells.

Water-soluble polysaccharide from the roots of *Glycyrrhiza inflata* specifically decreased cell viability of human oral cancer SCC-25 cells via the induction of apoptosis . All the above studies show that liquorice has the potential to be a safe chemotherapeutic agent in the management of oral cancer.<sup>8</sup>

### Root canal irrigant, medicament and Liquorice

Intracanal irrigants have been used for cleaning and shaping to bring down bacterial load in the root canal. *Enterococcus faecalis* is the chief micro-organism recovered from root canals of the teeth where previous endodontic therapy has failed and is the paramount cause of failure of root canal therapy. Studies have focused on finding herbal alternatives which are effective against *E. faecalis*.<sup>2,18</sup>

Badret al. estimated the antibacterial and cytotoxic effects of liquorice as a root canal medicament and compared its action to calcium hydroxide  $\text{Ca}(\text{OH})_2$ . Liquorice extract either by itself or in conjunction with  $\text{Ca}(\text{OH})_2$  had superior inhibitory effect against *E. faecalis* compared to  $\text{Ca}(\text{OH})_2$  alone.<sup>19</sup>

### Role of Liquoricein Radiotherapy Induced Mucositis

Oral mucositis is the main adverse effect of radiotherapy of the head and neck region, which is painful. The mode of action of *Glycyrrhiza* extract on mucositis may be mediated through inhibition of activated macrophages leading to hindrance in the prostaglandin E2 production, and formation of superoxide and hydroperoxide in macrophages. The anti-inflammatory effects of glycyrrhizin are mediated by its ability to decrease generation of reactive oxygen species, and direct scavenging of free radicals.

In a double-blind, randomized prospective trial, liquorice mucoadhesive films were effective in the management of oral mucositis. Also, lyophilized liquorice extract containing mouth wash before and immediately after each session of radiotherapy have shown reduction in mucositis.<sup>20</sup>

## CONCLUSION

The focus for the using natural alternatives are cost viability, accessibility, low harmfulness, expanded time span of usability and absence of microbial protection reported up until this point. Ayurvedic medicinal plants are good candidates for development of novel medicines in future. The present review provides a direction for future investigators to carry out research on the various phytochemicals of *G. glabra* so that its constituents can be added in dental products making it beneficial to oral care. The studies should be directed to explore, evaluate and test the therapeutic benefits of *G. glabra* in dentistry.

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