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Herbs in dentistry

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Abstract
Rising cost of drugs, emerging antibiotic resistance and perceived safety of herbal medicine has led to its popularity among consumers, medical practitioners and researchers alike. The increase in awareness had lead to studies being conducted addressing its properties, mode of action, efficacy and toxicity of herbs in hopes of improving the safety and efficacy of herb derived alternative medicine. Plants are widely used as antibacterial agents because they produce a wide array of bioactive components, most of which probably function as chemical defense against predation or infection and have attracted researchers to exploit these bioactive components for application in the dentistry field. Despite its effectiveness in treating a diseases with a less side effects in comparison with the traditional medicines, side- effects do occur. This article will discuss some of herbs used in dentistry, which will covers its application, research findings, toxicology profiles and side effects. The plants include Miswak (*Salvadora persica*), Bloodroot plant (*Sanguinarine*), Licorice root (*Glycyrrhiza* root), Chicory (*Cichorium Intybus Linn*), Neem (*Azadirachta indica*), Garlic (*Allium sativum*), Betel (*Piper betel*), Clove (*Syzygium aromaticum*), and Triphala (*T. chebula*).

Keywords: *Salvadora persica*, *Sanguinarine*, *Glycyrrhiza* root, *Cichorium Intybus* Linn, *Azadirachta indica*, *Allium sativum*, *Piper betel*, *Syzygium aromaticum*, *T. chebula*.

Introduction
Herbal products have been used since ancient times by traditional healers in folk medicine. The late 20th century saw the gain in popularity of herbal-based product among consumers due to the perceived safety with reduced side effects and the rising cost of conventional medicine. The growing use of herbal products stimulated research and development dedicated to herbal medicine. In the field of medicine, many plants have established their importance in treating illness all around the world. Herbs have been widely studied because of their chemical constituents or phytochemicals presents in various parts of the plants. Although originally they are produced as part of plant's protective and preventive mechanisms, it is now scientifically proven that these chemical constituents can be used to protect humans against human diseases. Plant herbs are highly effective as antibacterial agents because of their ability to penetrate and cause damage to the walls of both gram positive and gram negative bacteria. This finally, will lead to the destruction of the bacteria cells (Seyyednejad *et al.,* 2010) [52].
In the field of dentistry, many research focus on the use of herbs to treat chronic diseases such as dental caries, gingivitis and periodontal diseases. The specialty requires more information through well-conducted research in order to establish the safe practice of incorporating herbal derived products as part of an evidenced based treatment of patients. This paper will review some herbaceous plants which have been studied to treat these oral diseases.

Salvadora persica
The *Salvadora persica* tree or also known as Darakht-e-Miswak or toothbrush tree in Persian is an evergreen shrub that belongs to the Salvadoraceae family. The plant is also commonly known as Miswak tree. Their importance in dentistry has been well established way back from 5,000 BC. The twigs from this plant were originally used by the Babylonians as a chewing sticks and the trend rapidly travelled throughout the Greek and Roman empires. Other nations followed suit and the use of these chewing spread widely among the Egyptians, Jews, and the Muslim worlds. In fact the practice of brushing with Miswak may still be seen right to this very day (Lewis *et al.,* 1977) [33].
The plant contains many chemical components of medical importance. Among such components are sodium chloride, calcium oxalate, silica, fluoride, sulfated compounds,

vitamin C and tannic acid. In addition, the plant also contains saponins, flavonoids, and an alkaloid known as salvadorine, trimethylamine, beta- sit- o sterol and benzyl isothiocyanate. The compound benzyl- isothiocyanate, which is largely found in the plant root oil, exhibited broad- spectrum bactericidal activity and been shown to inhibits the growth as well as acid production of *Streptococcus mutans*. Many of the *Salvadora persica*'s constituents cited above, have been reported to help in preventing decay and thus promotes the preservation of human dentition with proper utilizations. The plant can act as an antibacterial agent and also can be use to strengthen the gingival due to the presence of sulfur and the alkaloids (salvadorine). Eventhough tannins in high levels may cause staining of the teeth, the compound together with resins able to provide protection against caries by forming a layer over the enamel. Chloride on the other hand act as an anti plaque agent that inhibit calculus formation and regular use of the chewing stick over an extended period will reduced calculus deposits. Besides the woods, the leaves, fruits and seeds of this plant have also been used in traditional medicine to stimulate appetite, as a mild laxative, diuretic and anti-fungal medication in as well as in the African countries (Akhtar *et al.,* 1981, Al Sadhan *et al.,* 1999, Almas *et al.,* 2004, Almas *et al.,* 1999, Darmani *et al.,* 2006, Darout *et al.,* 2002, Ezmirly *et al.,* 1981 and Al-Otaibi *et al.,* 2003) [1, 7, 2, 3, 14, 18, 21, 8].

In the recent years, among the properties of Miswak that have been widely studied by the researchers are the antimicrobial effects, especially their efficacy towards some of the known dental pathogens. Khalessi *et al* in 2004 [28] compared the oral health efficacy of *Persica* mouthwashes with that of a placebo, in which the results shows that the use of *Persica* mouthwash improves gingival health and lead to a low carriage rate of cariogenic bacteria when compared with pretreatment values. Al-Lafi and Ababneh in 1995 [4] conducted *in vitro* study on the effect of the extract of Miswak (chewing sticks) used in Jordan and the Middle East on oral bacteria. The results showed that among the common oral bacteria, *Streptococcus* microorganisms, including mutans *streptococci* are the most vulnerable towards the action of *S. persica* extract. A clinical study by Almas and Al-Zeid in 2004, [2] on the effect of Miswak extract, toothbrush, and normal saline on salivary *mutans* and *lactobacilli* also revealed a similar results where they concluded that the Miswak has an immediate antimicrobial effect against *Streptococcus mutants*. The greatest reduction in the microorganisms was observed when using Miswak in comparison with toothbrushes. However, there was no significant reduction in *lactobacilli*. It was concluded that Miswak possesses an immediate antimicrobial effect. Kaur *et al* in 2004 evaluated the immediate term effect of chewing commercially available Meswak (*Salvadora persica*) on levels of calcium, chloride, phosphate and thiocyanate in whole saliva concluded that the use of Miswak as a chewing stick or in any other forms of oral medication is safe. It was also observed that the Miswak mouthwash significantly lowers the gingival index and bleeding index.

In order to establish an effective role of an ideal antimicrobial agent, cytotoxicity test are required to be conducted to determine its ability to kill microbes while causing minimal toxicity to host cells (minimum collateral damage). In 1983, Mohammad and Turner, tested the cytotoxic potential of the *S. persica* miswak and its diffusible components on oral tissues using the tissue culture agar overlay method. The results reported that there are no cytotoxic effects of freshly cut *S. persica* chewing stick on oral tissues. However, Darmani *et al.,* (2003) [15] demonstrated that direct administration of high doses of *S. persica* miswak extract to mice results in minor side effects on male and female reproductive system and fertility. A recent comparative study by Almas *et al.,* (2012), on the cytotoxicity of *S. persica* aqueous extract and chlorhexidine gluconate on L929 mouse fibroblasts showed that the cell viability of miswak extract was as high as 95% in original strength (50%) dilutions, while the cell viability of CHX is 3%, in the corresponding concentrations. They concluded that Miswak extract had significantly less cytotoxicity than CHX in the original and 1/2, 1/4 dilutions ($p=0.05$).

The track record of their use and the available evidence have showed that the plant is not harmful to human consumption, however further research is required to assess the comparative cytotoxic effects of miswak extract on various cell lines for example macrophages, epithelial cells, fibroblasts and osteoblasts. This will provide the researchers with a clearer picture on the toxicology profile of the plant and in future allow the extension of its application for periodontal or oral surgery procedures.

Sanguinarine canadensis

Sanguinarine canadensis is a herbaceous perennial that is known with several names such as bloodroot plant, Indian paint, redroot, pauson, or tetterwort, is a member of the Papaveraceae (poppy family) and can be largely found throughout most of North America east of the Rocky Mountains. The rhizomes of *Sanguinaria canadensis* produce an extract in benzophenanthridine alkaloids, in particular, sanguinarine. It also contain the chemically reactive iminiumions which was postulated to contribute to its medical effects (Caballero George *et al.,* 2002). Several clinical studies have been carried out to determine its efficacy in eliminating oral bacteria. The plant shows antimicrobial effects whereby short term studies have shown variable but significant plaque inhibitory effects. However, the effects of the plant on gingivitis appear to be ambiguous. It has also been shown, the use of Sanguinarine and zinc act synergistically in suppressing the growth of various oral strains of *streptococci* (Eisenberg *et al.,* 1991) [19].

In vitro cytotoxic tests of chloride's using cell lines and primary cells from oral human tissues showed mixed results whereby similar potencies among the established cell lines, S-G gingival epithelial cells and to KB carcinoma cells, whereas HGF-1 gingival fibroblasts were more tolerant. It is also curious to see that for gingival primary cell culture, appeared to be more sensitive to sanguinarine chloride than were the established cell lines (Babich *et al* in 1996) [10] showing vacuolization and multinucleation of cells and a lag in growth kinetics. However, the cytotoxicity of sanguinarine chloride to the S-G cells was observed to be lessened in the presence of hepatic microsomal fractions which may be reflective of their tolerance by the human body. There are not much up to date research conducted on the cytotoxicity effects of Sanguinarine on oral cells lines. The plant was also considered unsafe for use in children and pregnant or lactating women, as long-term use may lead to nausea and vomiting, glaucoma, edema, heart disease, miscarriage, diarrhea, stomach pain, visual changes, and paralysis. Further research on its cytotoxicity effects on the oral cell lines will provide clearer toxicology profile and prove the long term safety of this plant when incorporated into dental products such as dentifrice and mouthrinse.

Licorice root

Licorice root refers to the roots and stolons of *Glycyrrhiza* species. They contain glycyrrhizol A, a compound that has strong antimicrobial activity against cariogenic bacteria. The

Licorice root has been widely used as herbal medicine dating back to at least 500 BC. Its traditional applications as both a demulcent and an anti-inflammatory, are known across diverse cultures and the plant is often used to sooth respiratory or gastrointestinal (GI) symptoms (Shibata, 2000) [53].

There have not been any human clinical trials to prove its licorice effectiveness in relation to dentistry. However there are several *in vitro* studies that have been carried out to bring light the evidence that licorice and its bioactive components may provide a new natural therapy to treat or prevent periodontitis. The crude extract from *G. uralensis* was reported by Bergeron *et al* in 2008 to inhibit both the growth and biofilm formation of *Porphyromonas gingivalis* which is one of the main chronic periodontitis causing bacteria. Licorice root extract have been observed to have an antifungal effect on *Candida albicans* which is one of the organisms implicated in oral candidiasis. Glabridin, glycyrrhetinic acid and licochalcone found in the licorice are some of the bioactive components in the licorice which showed promising effects in the inhibition of biofilm formation, growth and killing of *Candida albicans* (Martins *et al.,* 2014) [34].

Sakagami *et al* in 2000, have studied the cytotoxicity activity of licorice root phenolics compounds, involving glyasperin A, gancaonin P, licochalcone B, topazolin, gancaonin O and gancaonin R against human oral tumors cells lines. The results postulated that these compounds display specific cytotoxic activity against cancer cell lines rather than normal cells. However, it is a single research that have been conducted and a further systematic studies must be done involving many normal and tumor cells to confirm this point. Large intake of compound glycyrrhizin can cause high blood pressure, salt and water retention, and low potassium levels and may lead to heart problems. Therefore, the incorporation of licorice roots as part of a dental solution must be preceded with caution, intensive research and clinical trials to avoid any dangerous circumstances.

Chicory

Cichorium Intybus Linn (Chicory), is an ancient ayurvedic herb in the Asteraceae family that has been widely applied in Ayurvedic medicine for the treatment of acne, ophthalmic conditions and inflammation of throat. Traditional practitioners also believed that the plant can be used to purify and enrich blood, reduce inflammation of soft tissues and prevent pain in the joints. Signoretto *et al* in 2011 has investigated the effects of chicory extracts on *Prevotella intermedia*, a periodontopathogenic bacterium and the results revealed that the chicory extracts have a moderate bactericidal effect on the bacterium. The effectiveness of the extract is due to the similar mode of action of the extract as antibiotics such as quinolones or β-lactams causing inhibition of bacterial DNA and the increase in cell mass. These findings supported the fact that the extract can be advantageously used as an oral hygiene formulation products such as mouthwashes and toothpastes.

Schmidt *et al.,* (2007) [51] evaluated the toxicology profile of sesquiterpene lactones, chemical components found in chicory root extract and the results revealed that the compound was non-toxic and non- mutagenic when tested on Sprague–Dawley rats. There were no previous study that in which can support this research on the toxicity of sesquiterpene, however there were several animal studies that have been performed using aqueous and ethanolic extracts without report of possible toxicity (Gadgoli and Mishra, 1997, Kim, 2000, Roberfroid, 2000, Kim *et al.,* 2002) [24, 30, 29].

Eventhough the toxicology profile on rats have shown a good outcome, this result has to be replicated in more than one study. Moreover, there are no up to date research on the toxicology of the chicory root extract on oral cell lines and therefore the information on its safetyness on oral administration are unknown.

Azadirachta indica

Azadirachta indica or more commonly known, as neem is a type of evergreen tree with well-known medical properties. The plant has been used in the Ayurveda, Unani and Homoeopathic medicine. The plant contains numerous bioactive components from in parts of the tree which contribute to its effectiveness as natural medicine. The plants demonstrated to have immunomodulatory, anti-inflammatory, anti-hyperglycaemic, anti-ulcer, anti-malarial, anti-fungal, anti-bacterial, anti-viral, antioxidant, anti-mutagenic and anti-carcinogenic properties (Nataranjan *et al.,* 2003) [39].

Neem also has established its medical efficacy as an antimicrobial drug in treating oral diseases caused by oral microbes. It was reported that the neem stick can reduce the adherence of *streptococci*. Aqueous extract of neem also have been studied for its anti-microbial effectiveness against some dental caries pathogens including *Streptococcus mutans*, *Streptococcus salivarius*, Streptococcus mitis and *Streptococcus sanguis* and again the effectiveness in the inhibition of *S. mutans* can be seen (Prashant *et al.,* 2007) [43].

The inhibitory effect of different extract of *Azadirachta indica* consist against dental caries pathogens, *Streptococcus mutans*, *Streptococcus salivarius* and *Fusobacterium nucleatum* showed that the petroleum ether and chloroform extract of the neem possessed the highest antimicrobial activity (Lakshmi *et al.,* 2012) [32]. However the study did not include any cytotoxicity test and thus it is difficult to prove that the antibacterial property was due to the plant rather than the solvent used.

Verma *et al* in 2011 compared the cytotoxicity of chlorhexidine (CHX) and neem extract on cultured human gingival fibroblasts (hGF). The results showed that the cytotoxicity of CHX is seen at the initiating concentration of 1% (43.10%cell death). When compared with neem extract, the plant did not show any cytotoxicity and maintained the level of cell death of about 31% even at 100% concentration which clearly suggested that Neem extract is more reliable and safe even in higher concentration compared to CHX.

Allium sativum

Allium sativum, garlic, is well-known to possess antibacterial, antifungal and antiviral effects. Studies have been done to investigate its antibacterial effects against oral pathogens. Bakri and Dowglas in 2005, [12] concluded that the garlic extract able to inhibit the growth of oral pathogens and portrays therapeutic value for periodontal infection (Bakri *et al.,* 2005) [12]. The plant also showed promising antibacterial effects against wide range of Gram- positive as well as Gram-negative bacteria and fungi (Ankri *et al.,* 1999) [6]. Garlic is also capable of inhibiting the multidrug- resistant enterotoxic genetic strain of *Escherichia coli*. Garlic juices were concluded to have great antibacterial effects against *Streptococcus mutans*, isolated from human carious teeth that are resistant towards antibiotics such as penicillin, amoxicillin, tetracycline and erythromycin (Fani *et al.,* 2007, Xavier *et al.,* 2007) [22, 59]. The usage of garlic juices may produce unpleasant smell and tasteto the consumer, however, the efficacy of garlic juices in reducing the amount of oral bacteria was higher than chlorhexidine and may be used as an effective mouthwash (Groppo *et al.,* 2007) [26]. This is proven by an

earlier study that showed mouthwash containing 10% garlic in quarter Ringer solution produced a drastic reduction of number of oral bacteria (Elmina *et al.,* 1983) [20]. In a study comparing the antibacterial effect of eucalyptus (*Globuluslabill*) and garlic (*Allium sativum*) extracts against oral cariogenic bacteria, the results showed that the garlic extract is more promising antibacterial agent compared to eucalyptus (Motamayel *et al.,* 2013) [36].

Islam *et al.,* (2011) [27], determined the cytotoxicity and cancer (HeLa) cell killing efficacy of aqueous garlic (*Allium sativum*) at various concentrations. Results revealed a dose-dependant inhibition of cancer cells with greater inhibition at higher concentration of aqueous garlic. There are also some reports which indicate the use of garlic may cause allergic reactions such as contact dermatitis and asthmatic attacks, increased bacterial attachment to orthodontic wires. However there are inadequate research conducted to address these concerns (Taheri *et al.,* 2011) [58].

Piper betel linn

Piper betel linn is the leaf of a vine that belonging to the Piperaceae family. It has been proven to have antimicrobial as well as antileshmian properties (Sarkar *et al.,* 2008) [50]. The crude extract of the plant has been seen to reduce the growth, adhering ability, glucosyltransferase activity against *Streptococcus mutans*. It was suggested that the suppression of the growth of the bacteria may render the process of plaque formation incomplete and thus minimize the accumulation of plaque on the tooth surface (Nalina *et al.,* 2007) [38]. The exposure of bacteria towards the *Piper betel* extracts also showed profound ultra- structural changes to their morphology. It is accepted that presence of betel in a mouth rinse formulation was useful in oral plaque control. The effect of combination of neem and betel leaf against oral bacteria has been investigated by a group of researchers (Salam *et al.,* 2014) [49]. Result from this study was promising and antimicrobial activity was seen against the isolated bacteria from saliva samples of 50 patients suffering experiencing dental caries and gingivitis. The methanol and aqueous extract of both plants showed antimicrobial activity against the isolated bacteria, in which the methanol showed the highest activity even with lower concentrations.

Roy *et al* in 2013, also reported results on cytotoxicity towards both normal and tumor cell lines, however it was displayed that the plant showed toxicity effects on tumor cells and non for the normal cells. Results also indicate that *Piper betel* extract portrays a dose-dependent and time-dependent cell killing, whereby the increase in the cell death rate is proportional to the increase of the concentration of the extract irrespective of the cell type.

Syzygium aromaticum

Syzygium aromaticum, commonly known as clove, have widely been used as a spice in cuisines all over the world. The oil produced from cloves have often been used to relief toothache. Clove oil is usually applied in an undiluted form using a plug of cotton wool and applied into the cavity of the tooth. The methanolic extract of the clove has been reported to be effective against gram-negative anaerobic periodontal pathogens (Cai *et al.,* 1996) [17]. The clove and clove bud's oil were reported to have potential antimicrobial activity against five dental caries causing microorganisms, *Streptococcus mutans*, *Staphylococcus aureus*, *Lactobacillus acidophilus*, *Candida albicans*, and *Saccharomyces cerevisiae*. The phytochemical analysis of ethanol extract of *Syzygium aromaticum* revealed the presence of alkaloids, flavonoids, glycosides, tannins, saponins, reducing sugar and steroids. The plant also showed very strong antimicrobial activity against several oral bacteria, *Streptococcus mutans*, *Enterococcus faecalis*, *Lactobacillus acidophilus*, *Candida albicans* and *Candida tropicalis*. The study also revealed that *Syzygium aromaticum* was more affective antimicrobial agent compared to *Aloe barbadensis*, *Cinnamumzeylanicum*, *Tinospora coridfolia*, *Centella asiatica*, *Zingiber officinale*, *Allium sativum*, *Curcuma longa*, *Curcuma longa*, *Glycyrrhiza glabra*, *Ocimum sanctum* and *Piper nigrum*.

According to Prashar *et al.,* (2006) [44], the essential oil extracted from clove contains eugenol and β-caryophyllene. They are generally recognized as 'safe', but *in-vitro* study demonstrated that clove oil was found to be highly cytotoxic at concentration as low as 0.03% (v/v) with up to 73% of this effect attributable to eugenol for human fibroblasts and endothelial cells. β-caryophyllene did not exhibit any cytotoxic activity, indicating that other cytotoxic components may also exist within the parent oil. To prove this point, more research must be conducted on its cytotoxicity and must includes the crude extract form of the clove that might not be as cytotoxic as the crude oil.

Triphala

Triphala or the scientific name is *T. chebula* is a medical plant known as Kadukka in Tamil. The plant contains hydrolysable tannins (13%) such as gallic acid, chebulagic acid and corilagin. The plant proven to be antibacterial friendly against cariogenic bacteria. The components present in the plants also aids in the removal of smear layer thereby acting as chelating agent and have been suggested as an alternative for sodium hypochlorite for root canal irrigation (Prabhakar *et al.,* 2010) [42]. Low concentrations of triphala have been shown to successfully inhibit the growth of *Streptococcus mutans* and *Lactobacillus* (Srinagesh *et al.,* 2011, Bajaj *et al.,* 2011, Hegde *et al.,* 2011) [56, 11, 31].

There were not many researchs that can be found on the cytotoxicity of the plant against cancerous or normal cells or even on oral cell lines. Therefore, the absence of these tests cause difficulties in determining the toxicology profile and whether it is safe and relevant for oral healthcare.

Conclusion

Based on the discussion, we see the potential of incorporating herbs-derived antimicrobial agents for the treatment of chronic diseases of the gums and supporting tissues of the teeth. Herbal active compounds may also be incorporated into dental products such as dentifrices and mouthrinses for preventing caries and their associated problems. Therefore, more *in vivo* and *in vitro* investigations in a standardized manner are needed to fill the gap in the information that we have regarding the potential use of herbal-based products in Dentistry.

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