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Dental Caries and Medicinal Plants –An Overview

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ABSTRACT

Medicinal plants are useful in many diseases dates back from the history. Plants like *Acacia leucopholea, Albizzia lebback, Bridalia grandis, Drosera peltata, Erthrina variegata* and many other selective plants active against *Streptococcus mutans, Streptococcus sobrinus, Streptococcus oralis and lactobacillus* species has been listed and this review highlight the role of medicinal plants and phytochemicals like flavanoids, polyphenols, terpenes, alkaloids in the treatment of dental caries and infections associated with dental care.

Keywords: Dental plaque: Medicinal plants: Phytochemicals, *Streptococcus mutans* ; *Lactobacillus acidophyllus.*

INTRODUCTION

Dental caries is a multifactorial human disease that has widely affected many populations all over the world. Bacterial plaque plays the primary role in the pathogenesis of the disease. Dental plaque is a general term for the diverse microbial community (predominantly bacteria) found on the tooth surface, embedded in a matrix of polymers of bacterial and salivary origin. Plaque develops naturally on teeth, and forms part of the defence systems of the host by helping to prevent colonisation of enamel by exogenous (and often pathogenic) microorganisms. Plaque is an example of a biofilm showing that the properties of bacteria associated with a surface in a biofilm can be markedly different than those of the same cells growing in liquid broth.

Plaque is found preferentially at protected and stagnant surfaces, and these are at the greatest risk of disease (Scheie, 1994). The attachment, growth, removal and reattachment of bacteria to the tooth surface are a continuous and dynamic process. However, several distinct processes can be recognized: Absorption of salivary proteins and glycoproteins, together with some bacterial molecules, to the tooth surface to form a conditioning film (the acquired pellicle). Long-range (>50nm), non-specific interaction of microbial cell surfaces with the acquired pellicle via van der Waals attractive forces. Shorter-range (10 – 20 nm) interactions, in which the interplay of van der Waals attraction forces and electrostatic repulsion produces a weak area of attraction that can result in reversible adhesion to the surface.

Irreversible adhesion can occur if specific inter-molecular interactions take place between adhesins on the cell surface and receptors in the acquired pellicle. Secondary or late-colonisers attach to primary coloninisers also by specific inter-molecular interactions. Cell division of the attached cells to produce confluent growth, and a bioflim (Freedman, 1974; Houte, 1982). The medicinal plants with their selective activities being reported in Table : 1. The present survey reflects the antimicrobial effects of medicinal plants and phytochemicals like flavanoids, polyphenols, terpenes, alkaloids in the treatment of dental caries and infections associated with dental care.

Symptoms and causes of Dental caries

The list of signs and symptoms mentioned in various sources for Dental caries includes the 8 symptoms listed at Tooth pain, Bad breath , Fever, Chills, Foul taste, Abscess, Cervical adenopathy, Trismus. The most common cause of this disease is the consumption of faulty diet, including soft drinks, cakes, pastries, refined carbohydrates and sugar in all forms. Lack of balance between carbohydrates and proteins and insufficient intake of vitamins and minerals also contribute to this disease. It is commonly prevalent where refined, devitalized, processed and dematerialized foods, grown on soils deficient in minerals, are eaten.

Causative Organisms

The mouth contains a wide variety of oral bacteria, but only a few specific species of bacteria are believed to cause dental caries: *Streptococcus mutans* and *Lactobacilli* among them. *Lactobacillus acidophilus, Actinomyces viscosus, Nocardia spp.*, and Streptococcus

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mutans are most closely associated with caries, particularly root caries. Bacteria collect around the teeth and gums in a sticky, creamy-coloured mass called plaque, which serves as a biofilm. Some sites collect plaque more commonly than others. The grooves on the biting surfaces of molar and premolar teeth provide microscopic retention, as does the point of contact between teeth. Plaque may also collect along the gingiva. ***Streptococcus sobrinus*:** A species of gram-positive, coccoid bacteria isolated from the human tooth surface. Strains have been shown to be cariogenic in experimental animals and may be associated with human dental caries. ***Streptococcus mutans*:** a bacterial species associated with the production of dental caries in humans and in some other animals and with subacute endocarditis.

CATEGORIES OF DENTAL CARIES

The categories of dental caries that are mostly considered by clinicians and researchers are smooth-surface caries, pit and fissure caries, enamel caries, dentinal caries, secondary caries, early childhood caries, and root caries. Mineral is lost through attack by acid generated by bacteria. This is demineralization. If demineralization continues, a cavity eventually occurs in whatever form and in whatever position on the teeth in the mouth. The natural body repair mechanism for dental caries is remineralization related primarily to minerals from saliva diffusing back into the porous

Subsurface region of the caries lesion (Featherstone, 2000). The physical treatment methodologies for restorative dentistry are obviously different, depending on the location, extent, and seriousness of the decay. However, the basic mechanistic principles are the same for all of the above-mentioned categories of dental caries.

CARIES MECHANISM

Dental caries is a simple process in concept: In outline the caries mechanism can be described as follows (Featherstone, 2000):

1. Acidogenic (acid-producing) oral plaque bacteria ferment carbohydrates that are taken into the mouth, thereby producing organic acids, including lactic, formic, acetic, and propionic.
2. These acids diffuse into the enamel (Featherstone, 1983), dentin, or cementum, partially dissolving the mineral crystals (LeGeros, 1991) as they travel.
3. Mineral (calcium and phosphate) diffuses out of the tooth, leading eventually to cavitation if the process continues.
4. Demineralization can be reversed by calcium and phosphate, together with fluoride, diffusing into the tooth and depositing a new veneer on the crystal remnants in the non-cavitated lesion.
5. The new mineral crystal surface is much more resistant to acid as compared with the original carbonated hydroxyapatite mineral.
6. The process of demineralization and remineralization generally occurs numerous times daily, leading either to cavitation, to repair and reversal, or to maintenance of the *status quo*.

In root caries, the same mechanism occurs as outlined above, initially causing demineralization and exposure of the collagen fibrils (Wefel *et al.*, 1985). Once the collagen is exposed, it is open to breakdown by bacterially derived enzymes, leading to rapid cavitation and breakdown of the dentin in the tooth root (Clarkson *et al.*, 1986; Kawasaki and Featherstone, 1997).

The bacteria that produce the acids fall into the category of acidogenic bacteria and are also aciduric, which means that they can live preferentially under acid conditions (Loesche, 1986). In normal dental plaque, these acidogenic bacteria occupy less than 1% of the total flora. As caries becomes progressive and more aggressive, the environment in the plaque becomes more frequently acidic, and these aciduric bacteria survive at the expense of the other benign bacteria. The most important aspect for the current discussion is that all acids produced by the bacteria—including lactic, acetic, formic, and propionic acids—can readily dissolve tooth mineral (Featherstone and Rodgers, 1981). Two major groups of bacteria produce such acids, namely, the mutans streptococci (including *Streptococcus mutans* and *Streptococcus sobrinus*) and the lactobacilli species (Loesche, 1986; Leverett *et al.*, 1993). There are undoubtedly other acidogenic organisms involved in dental caries. Until fairly recently, it was considered that early childhood caries, a particularly rampant form of caries manifested in young children, had a different etiology. However, it is now obvious that the same bacteria are involved, but the reasons for the rapid progression of the disease in these children are still uncertain (Alaluusua *et al.*, 1987; Caufield *et al.*, 1993). Pit and fissure caries now occupies much of the caries seen in Western countries, since it appears that common therapeutic measures such as fluoride in the drinking water and in fluoride products is not as effective in these surfaces.

Wherever bacteria have niches in which to live, these acidogenic/aciduric bacteria preferentially survive well. Therefore, orthodontic subjects who have brackets or bands are at high risk of caries, because the bacteria live well in the surrounding edges of these appliances (O'Reilly and Featherstone, 1987). The same applies to restorations with poor margins and pits and fissures.

THE CARIES BALANCE

Remineralization has been demonstrated in the laboratory for all types of caries listed above, but of course, the deeper the caries lesion, the harder it is for remineralization to be effective (ten Cate and Featherstone, 1991). Whether a lesion will progress, stay the same, or reverse is determined by the balance between protective factors and pathological factors (Featherstone, 2000). This balance is illustrated in If the pathological factors predominate, then caries progresses. If the protective factors predominate, then caries is halted or reversed. In simple terms, the pathological factors are cariogenic bacteria, salivary dysfunction, and frequency of ingestion of fermentable carbohydrates. Once established in a particular person's mouth, these cariogenic bacteria are very difficult to manage. Protective factors include most of the components in saliva (such as calcium), phosphate, fluoride, protective proteins that form the pellicle, proteins that maintain supersaturation of the mineral in saliva and plaque, and antibacterial substances naturally in saliva but also supplied extrinsically (*e.g.*, chlorhexidine), salivary fluoride, fluoride from external sources, and substances (*e.g.*, chewing gum) that stimulate salivary function.Fig.1.conceptually summarizes the dynamic process of dental caries as being a balance, or imbalance, between demineralization and remineralization that occurs numerous times daily in the mouths of most humans.

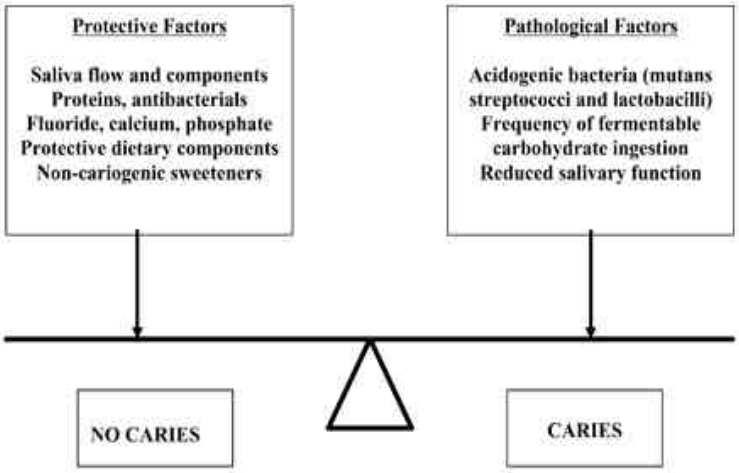

Figure 1. Schematic diagram of the balance between pathological factors and protective factors in the dental caries process. (Featherstone ,1999)

Table : 1 Medicinal plants in the treatment of Dental caries

S. No	Botanical Name	Part used	Inhibition Organisms
1.	*Acacia leucophloea*	Bark	*S.mutans*
2.	*Albizia lebbeck*	Bark	*S.mutans*
3.	*Abies canadensis*	Whole plant	*S.mutans*
4.	*Aristolochia cymbifera*	Whole plant	*S.mutans*
5.	*Annona senegalensis*	Whole plant	*S.mutans*
6.	*Albizia julibrissin*	Whole plant	*S.mutans*
7.	*Allium Sativum*	Bulbs	*S.mutans*
8.	*Anacyclus pyrethrum*	Root	*S.mutans*
9.	*Areca catechu*	Nuts	*S.mutans*
10.	*Breynia nivosus*	Whole plant	*S. mutans*
14.	*Citrus medica*	Roots	*S.mutans*
15.	*Coptidis rhizoma*	Whole plant	*S.mutans*
16.	*Caesalpinia martius*	Fruits	*S.mutans, S.oralis, L. casei*
17.	*Cocos nucifera*	Whole plant	*S.mutans*
18.	*Caesalpinia pyramidalis*	Whole plant	*S.mutans*
19.	*Chelidonium majus*	Whole plant	*S.mutans*
20.	*Drosera peltata*	Whole plant	*S. mutans S. sobrinus*
21.	*Embelia ribes*	Fruit	*S.mutans*
22.	*Erythrina variegata*	Root	*S.mutans, S.Sanguis*
23.	*Euclea natalensis*	Whole plant	*S.mutans*
24.	*Fiscus microcarpa*	Aerial part	*S.mutans*
25.	*Gymnema Sylvester*	Leaves,Roots	*S.mutans*
27.	*Glycyrrhiza glabra*	Root	*S.mutans*
28.	*Hamamelis virginiana*	Leaves	*Preveotella spp. Actinomyces odontolitycus*
29.	*Harungana madagascariensis*	Leaves	*Actinomyces Fusobacterium, Lactobacillus, Prevotella, Propioni bacterium Streptococcus sps*
30.	*Helichrysum italicum*	Whole plant	*S. mutans, S. sanguis S. sobrinus*
31.	*Ginkgo biloba*	Whole plant	*S.mutans*
32.	*Juniperus virginiana*	Whole plant	*S.mutans*
33.	*Kaemperia pandurata*	Dried rhizomes, root	*S.mutans*
34.	*Legenaria sicerania*	Leaves	*S.mutans*
35.	*Mentha arvensis*	Leaves	*S.mutans*
36.	*Mikania lavigata*	Aerial parts	*S.mutans S.sobrinus*
37.	*Mikania glomerata*	Whole plant	*S.cricetus*
38.	*Melissa officinalis*	Whole plant	*S.mutans, S.sanguis*
39.	*Magnolia grandiflora*	Whole plant	*S.mutans S.sganguis*
40.	*Melissa officinalis*	Whole plant	S.mutans, S.sanguis
41.	*Magnolia grandiflora*	Whole plant	S.mutans, S.sanguis
42.	*Nicotiana tabacum*	leaves	*S.mutans*
43.	*Physalis angulata*	Flower	*S.mutans*
44.	*Pinus virginiana*	Whole plant	*S.mutans*
45.	*Pistacia lentiscus*	mastic gum	*P. gingivalis*
46.	*Pistacia vera*	Whole plant	*oral streptococci*
47.	*Piper cubeba*	Whole plant	*periodontal pathogens*
48.	*Polygonum cuspidatum*	Root	*S.mutans, S.sobrinus*
49.	*Rheedia brasiliensis*	Fruit	*S.mutans*
50.	*Rhus corriaria*	Whole plant	*S.mutans S.sanguis*
51.	*R.corriaria*	Whole plant	*S.mutans, S.sanguis*
52.	*Rosmarinus officinalis*	Whole plant	*S.mutans*
53.	*Quercus infectoria*	Gall	*S.mutans*
54.	*Rhus corriaria*	Whole plant	*S.mutans, S. sanguis*
55.	*Syzygium cumini*	Bark	*S.mutans*
56.	*Sassafras albidum*	Whole plant	*S.mutans*
57.	*Solanum xathaocarpum*	Whole plant	*S.mutans*
58.	*Syzygium aromaticum*	Dried flower	*S.aureus*
59.	*Thymus vulgaris*	Whole plant	*S.mutans, S.sanguis*
60.	*Tanacetum vulgare*	Whole plant	*S.aureus*
61.	*Thuja plicata*	Whole plant	*S.aureas*
62.	*Ziziphus joazeiro*	Whole plant	*S.aureus*

Phytochemicals and Dental caries

Phytochemicals that have been shown to be active against oral pathogens.

Flavonoids and Polyphenols

Two active isoprenylflavones, artocarpin and artocarpesin, were isolated from *Artocarpus heterophyllus* (Moraceae). These inhibited the growth of numerous cariogenic and oral bacteria, including mutans and other oral streptococci, actinomyces and lactobacilli. Flavonone phytoalexins from *Sophora exigua* (Leguminosae) have been shown to inhibit the growth of numerous cariogenic bacteria, with 5,7,2',4'-tetrahydroxy-8-lavandulylflavanone being the most active (Tsuchiya H et al 1994). *Erythrina variegata* (Leguminosae) is used in folk medicine in tropical and subtropical regions and displays a number of biological properties, including antibacterial activity. Seven isoflavonoids isolated from the roots of this plant were tested for their ability to inhibit the growth of cariogenic oral bacteria. In addition, erycristagallin completely suppressed the incorporation of radio la-

beled thymidine and glucose in *S. mutans*, suggesting that the compound interferes with bacterial uptake of metabolites (Sato M *et al* 2002).

The root bark of *Morus alba* (Moraceae) has been used as a traditional medicine in Asian countries and exhibits antibacterial activity against food poisoning micro-organisms. Using activity against *S. mutans* in bioassay-guided fractionation of a methanol extract of dried root bark, and organic solvent fractions of this extract, the active antibacterial constituent was identified as kuwanon G. The compound displayed an MIC of 8 µg ml^{-1} against *S. mutans*, which was comparable to chlorhexidine and vancomycin (1 µg ml^{-1}). Time-kill assays indicated that *S. mutans* was completely inactivated by 20 µg ml^{-1} kuwanon G within 1 min, while testing against other bacteria suggested that the compound displayed preferential antimicrobial activity against cariogenic bacteria. Electron microscopic examination of *S. mutans* cells treated with kuwanon G indicated that the mode of antibacterial action was inhibition or blocking of cell growth, as treated cells showed a disintegrated surface and an unclear cell margin. A similar mode of antibacterial action has been reported for the compound isopanduratin A isolated from *Kaempferia pandurate* (Zingiberaceae) (Hwang JK et al 2004),

A number of components of tea, *Camelia sinensis* (Theaceae), exhibit anticariogenic effects through various modes of action, including bactericidal effects on oral bacteria, prevention of adherence of bacteria to tooth surfaces, inhibition of glucan production and inhibition of amylases. Monomeric polyphenols, in particular simple catechins such as epicatechin, epicatechin gallate, and epigallocatechin gallate are believed to be responsible for these biological effects. (Sasaki H *et al* 2004)

The paste of tender leaves of *Psidium guajava* (Myrtaceae) has been used traditionally to maintain oral hygiene, while other parts of the plant have various bioactive properties. (Prabu GR *et al* 2006).

A methanol extract of *P. guajava* leaves was shown to exhibit inhibitory activity against two strains of *S. mutans*. Fractionation guided by bioautography yielded the active compound, quercetin-3-*O*-α–L-arabinopyranoside or guaijaverin, which had MIC values of 2–4 mg ml^{-1}. At sub-MIC values, guaijaverin was also able to inhibit acid production of the test bacteria, decrease the hydrophobicity of one of the bacteria and inhibit the adherence of both bacteria to glass. The anti-adherent properties of this plant were supported by the reduction of cell-surface hydrophobicity observed in 'early settler' plaque bacteria (*S. mitis*, *S. sanguinis* and *Actinomyces*) exposed to 1 mg ml^{-1} *P. guajava* extract. Recently, a proteomics approach was used to show that treatment of *S. mutans* with a low concentration (1.6%, v/v) of a *Psidium cattleianum* water extract resulted in the down regulation of genes involved in lactic acid production, general metabolism and glycolysis . (Brighenti FL *et al* 2008), at higher concentrations (25–100%, v/v), the extract was able to inhibit *S. mutans* biofilms.

Malvidin-3,5-diglucoside (malvin) was identified as the active constituent of an ethanol extract of *Alcea longipedicellata* (Malvaceae) responsible for activity against oral streptococci, with . The compound macelignan was isolated from *Myristica fragrans* (Myristicaceae) and shown to exert antimicrobial activity against *S. mutans* comparable to chlorhexidine and superior to other natural anticariogenic agents (sanguinarine, eucalyptol, thymol, menthol and methyl salicylate). Macelignan (20 µg ml^{-1}) displayed rapid antibacterial activity and completely eliminated viable *S. mutans* within 1 min. It also showed preferential activity against other cariogenic bacteria. Macelignan also displayed antibiofilm activity against *S. mutans*, *S. sanguis* and *A. viscosus* (Rukayadi Y et al 2008).

A plant compound, (–)-cubebin, a naturally found derivative and three semi-synthetic derivatives were evaluated against a number of Gram-positive oral bacteria and the yeast *Candida albicans*. While bacteriostatic and/or fungicidal activity was observed with all test compounds (although at levels well above those of chlorhexidine), no information concerning the activity against Gram-negative pathogens was provided.

Naringin, a polymethoxylated flavonoid commonly found in citrus fruit and an FDA-approved health supplement, was shown to inhibit the growth of periodontal pathogens and other common oral microorganisms. Using time–kill assays, naringin was shown to be particularly effective against *Actinobacillus actinomycetemcomitans* and *P. gingivalis* with significant growth inhibition within 3 h and greater inhibition with increasing incubation time and naringin concentration.

Terpenes

Bakuchiol isolated from the Chinese medicinal plant, *Psoralea corylifolia* (Fabaceae), has shown activity against numerous Gram-positive and Gram-negative oral pathogens. It was able to inhibit the growth of *S. mutans* under a range of sucrose concentrations, pH values and in the presence of organic acids in a temperature-dependent manner and also inhibited the growth of cells adhered to a glass surface .

(Liu *et al* 2006) purified seven new *ent*-rosane diterpenoids and a new labdane diterpene from the Chinese medicinal plant, *Sagittaria sagittifolia* (Alismaceae). Four of these compounds (sagittine A–D) exhibited antibacterial activity against *S. mutans* and *Actinomyces naeslundii* while another (Sagittine E) was only active against *A. naeslundii* (MIC = 62.5 µg ml^{-1}). Recently, the same group identified five new diterpenoids from *Sagittaria pygmaea*. None of these displayed activity against *A. actinomycetemcomitans*, while four of the others were active against *A. viscosus* and three were active against *S. mutans*, of which 18-ß-D-3',6'-diacetoxyglucopyranosyl-*ent*-kaur-16-ene was the most active .

Curcuma xanthorrhiza (Zingiberaceae) has traditionally been used to treat a number of disorders. Xanthorrhizol, isolated from a methanol extract of the plant roots, was shown to have high levels of antibacterial activity against oral pathogens.

Alkaloids

The alkaloid berberine isolated from *C. rhizoma* (Ranunculacea) showed bactericidal activity against oral bacteria, with greatest activity against *A. actinomycetemcomitans* and *P. gingivalis* although much less activity was observed against *Lactobacillus* and *Streptococcus* species. Berberine also inhibited the collagenase activity of *A. actinomycetemcomitans* and *P. gingivalis*.(Hu JP *et al*2000).

Sugar Alcohols

Xylitol is a sugar alcohol naturally found in plants that is used as an artificial sweetener in many foods. Its anticariogenic properties were investigated by adding 0.78–50% xylitol to broth cultures of *S. mutans*, *S. saliviarius* and *S. sanguis*, incubating at 37°C for 18 h and deter-

mining the optical density of the cultures. *Streptococcus mutans* was the only bacterium significantly inhibited by xylitol at 1.56%, while all bacteria showed statistically significant inhibition at levels above 1.56%. Studies exhibited the anticariogenic effects by inhibiting the growth of *S. mutans* while not affecting other streptococci that are part of the normal oral flora. (Sahni PS et al 2002)

Other Phytochemicals

Several constituents found in hops, *Humulus lupulus* (Cannabaceae), have been found to display antibacterial activity against *S. mutans*, *S. saliviarius* and *S. sanguis* in disc diffusion assays. (Bhattacharya S *et al* 2003) The MICs of beta acid, xanthohumol (a flavonoid), tetra iso-α acid , iso-α -acid and thymol (a terpene) against *S. mutans* were determined as 2.0, 12.5, 12.5, 50 and 150 µg ml^{-1}, respectively. These antibacterial activities were enhanced in the presence of ascorbic acid or when pH was lowered, suggesting that this effect was the result of the acidic nature of ascorbic acid. Furthermore, the antibacterial activity of 20% ethanol was found to increase in the presence of beta acid or thymol.

The antimicrobial properties of a number of commercially available dentifrices containing herbal products have been evaluated against oral pathogens. The antimicrobial effectiveness of the products varied greatly; 10 of the 14 products showed activity against all test bacteria (*S. mutans, S. sanguis* and *A. viscosus*), but only 6 of these were able to inhibit the yeast *C. albicans*. The observations that some of the dentifrices exhibited no antimicrobial activity and that some appear to have been contaminated by other microorganisms were of particular concern.

Thirty-nine natural products were tested for their antibacterial properties against four strains of *S. mutans* and their ability to prevent adherence of the bacteria. (Badria FA *et al* 2004) Catechol was the most active and inhibited both the growth and adherence of all test bacteria, while emetine hydrochloride and quinidine sulfate inhibited three of the bacterial strains, but not always to the same extent as catechol.

Plant Extracts and Phytochemicals which Inhibit the Adhesion of Oral Bacteria

As a part of some of the studies described above, plants extracts and phytochemicals were investigated for their ability to prevent adhesion of cariogenic bacteria to surfaces. In the following section, studies which have investigated this activity as a major objective are discussed, even though antibacterial properties may have also been investigated.

Anti-adhesion Activity of Crude or Total Plant Extracts

Cranberry, *Vaccinium macrocarpon* (Ericaceae), has been recognized for its beneficial effects on human health, including the prevention urinary tract infections by interfering with adhesion of *Escherichia coli* to cells and preventing adhesion of *Helicobactor pylori* to gastric mucosa.(Johnson-White B et al 2006) Numerous studies have investigated the ability of cranberry juice or cranberry constituents to prevent adhesion of oral pathogens to surfaces and related phenomena, such as the production of glucans and fructans, and the formation of biofilms. Exposure of oral streptococci to 25% cranberry juice for as little as 10 s has been shown to inhibit adsorption of cells to saliva-coated hydroxyapatite beads by between 61.8% and 95.1%, with the exception of *S. sobrinus* for which reduced adsorption was seen after 10 min. In addition, cell surface hydrophobicity of some of the bacteria was reduced and a preparation of high molecular weight cranberry juice constituents inhibited biofilm formation. These data indicated that cranberry juice could prevent dental plaque development by inhibiting the initial phase of biofilm formation. A preparation of high molecular weight cranberry material was also shown to reduce the activity of fructosyltransferase and glucosyltransferase and promote the desorption of *S. sobrinus* biofilms, especially those formed by nonsucrose-dependent adhesion in the absence of polysaccharides. Bacteria pre-exposed to high molecular weight cranberry material produced thinner biofilms with reduced bacterial density. Similar results were obtained with *P. gingivalis*, in that a high molecular weight cranberry fraction inhibited biofilm formation while not affecting growth and viability of bacteria. At concentrations of 62.5 µg ml^{-1} and higher, the fraction significantly inhibited biofilm formation, yet no effect on bacterial growth or biofilm viability was apparent with concentrations up to 250 µg ml^{-1}. However, this treatment did not result in biofilm desorption. The specific inhibitory effect of cranberry juice on *S. mutans* biofilm formation has been suggested to be related to the inhibition of glucan-related processes (inhibition of glucosyltransferase, blocking of bacterial adhesion mediated by surface glucans and reduction of insoluble glucan content). Recently, the cranberry juice constituents active against *S. mutans* biofilms have been identified as polyphenols, specifically proanthocyanidins and flavonols. (Duarte S, et al 2006)

In vitro experiments showed that cacao bean husk extract markedly reduced the growth rate and inhibited insoluble glucan synthesis of *S. mutans* and sucrose-dependent adhesion of *S. mutans* and *S. sobrinus* to a glass surface. (Song JH *et al* 2006) In addition, *in vivo* experiments in pathogen-free rats infected with these bacteria indicated that the extract exhibited significant cariostatic activity.

Two methods, adherence to glass and adherence to saliva-coated hydroxyapatite (S-HA), were used to assess the effect of ethanol extracts of six plants on the adherence of *S. mutans*.(Limsong J *et a l*) Extracts of *Andrographis paniculata* (Acanthaceae), *Cassia alata* (Leguminosae), *Camellia sinensis*, *Psidium guava* and *Harrisonia perforata* (Simaroubaceae) were able to inhibit one or both strains of *S. mutans* tested using both methods, although relatively high concentrations were required . Overall, the active extracts were less effective in inhibiting adhesion to S-HA than to glass, suggesting that salivary glycoproteins are important in bacteria–surface interactions, leading to stronger adherence to S-HA. *Camellia sinensis* extract exhibited the greatest inhibition of glucosyltransferase activity while *Andrographis paniculata* extract showed greatest inhibition of glucan-binding lectin activity of both strains.

As mentioned above an ethanol extract of *Helichrysum italicum* (Compositae) powdered flowering tops was found to exert antimicrobial activity against *S. mutans*, *S. sanguis* and *S. sobrinus* . The extracts were able to reduce cell surface hydrophobicity, adherence to glass and cellular aggregation of *S. mutans* in the presence of dextran. Plants of the genus *Mikania* (Asteraceae) are used medicinally in Brazil because of their numerous pharmacological properties. Extracts and fractions of the aerial parts of *Mikania laevigata* and *M. glomerata* have been shown to inhibit the growth of mutans streptococci and sucrose-dependent adherence of cells to a glass surface.

(Yatsuda R *et al* 2005)Analysis of the hexane fraction of the extracts, which displayed the most potent activities, indicated that the active components have nonpolar characteristics.

Methanol extracts of the roots of *Polygonum cuspidatum* (Polygonaceae), traditionally used in Korea to maintain oral health, were shown to reduce the viability of *S. mutans* and *S. sobrinus* as well as inhibit sucrose-dependent adherence, water-*insoluble glucan formation, glycolytic acid production and acid tolerance. (Song JH et* al 2006) The authors suggested that inhibitory effects may be mediated by the presence of alkaloids, phenolics and sterol/terpenes in the extract.

Aqueous and methanol extracts of cloves from *Syzygium aromaticum* (Myrtceae) were shown to affect the cariogenic properties of *S. mutans*, as exhibited by the ability of the extracts to inhibit adhesion of the bacteria to glass, reduce cell surface hydrophobicity and inhibit the production of glucosyltransferase . While some differences in the activities of the aqueous and solvent extracts were observed, overall this study showed that the two extracts were equally effective.

Crude aqueous extracts of *Piper betle*, a plant used traditionally in the control of dental and oral diseases in South East Asia, have been shown to inhibit the growth, adherence and glucan production of *S. mutans*. Further studies showed that acid production was also inhibited, while microscopic examination of bacterial cells exposed to extract showed cells with 'nucleoid material coagulated into thick electron-dense filaments and destruction of the plasma cell membrane and inner cell wall' which was more apparent with higher extract concentrations. Bioautography identified one major phenolic constituent as the antimicrobial component of the extract. (Nalina T et al 2007)

Anti-adhesion Activity of Purified Phytochemicals

An investigation of the effects of macrocarpals (phloroglucinol-sesquiterpene-coupled compounds) extracted from eucalyptus leaves on periodontopathic bacteria demonstrated that these compounds were able to inhibit the growth of the majority of bacterial strains tested (Nagata H *et al* 2006). *Porphyromonas gingivalis* was the most sensitive bacterium with an MIC of 1 μg ml^{-1} for macrocarpals A and B, and 0.5 μg ml^{-1} for macrocarpal C. In addition, all three compounds inhibit the expression of *P. gingivalis* proteases and the binding of cells to S-HA by 70–80% at a concentration of 10 μg ml^{-1}.

As mentioned above, xanthorrhizol has been shown to inhibit the growth of oral pathogens. The ability of xanthorrhizol to inhibit bioflims of *S. mutans* has also been investigated. Using 4-, 12-, 20- and 24-h old bioflims, the greatest level of inhibition was observed at the adherent (4 h) stage (complete inhibition at concentrations of 5, 10 and 50 μmol l^{-1}). In older biofilms, 76% inhibition was achieved with 50 μmol l^{-1} and an exposure time of 60 min.

The activities of plant extracts and phytochemicals detailed in the sections above do not necessarily indicate that all of these products will have clinical value. In fact, many of the products are effective only at relatively high concentrations. (Cos *et al*, 2006*)* suggested that strict criteria should be used to assess the potential application of natural products. In the context of anti-infective agents, MIC levels of <100 μg ml^{-1} are indicative of useful bioactivity for natural product extracts. Numerous studies have compared active compounds to currently used antibacterial compounds used in dentistry, such as chlorhexidine and triclosan, as a way of determining relative effectiveness. The MIC of chlorhexidine is 1 μg ml^{-1} while triclosan has an MIC of 0.1–20 μg ml^{-1} .Using the above criteria, extracts with MIC values of ⩽100 μg $ml^{-1}$and isolated phytochemicals with MIC values of ⩽20 μg ml^{-1} may be considered useful for the development as products for application against oral infections.

Safety Issues Related to Phytomedicines Used in Dentistry

The clinical studies reviewed above have generally assessed the efficacy of products containing plant-derived products. However, the safety and possible side-effects of such products must also be considered. Indeed, these issues have recently been reviewed by Groppo *et al* 2008. In relation to natural products used in dentistry. In agreement with other studies of the clinical use of natural products, there is limited information available about the quality, safety and efficacy of herbal products used in dentistry. Given the possibility of adverse interactions between herbal formulations with conventional drugs, caution should be exercised when using herbal medicines and the need for more clinical studies is recommended. This review also considered the use of herbal products in other aspects of dentistry, including as endodontic irrigants, anti-inflammatory agents and those with sedative and anxiolytic activities.

As demonstrated by the examples included in this review, there is considerable evidence that plants plant extracts, essential oils and purified phytochemicals have the potential to be developed into agents that can be used as preventative or treatment therapies for oral diseases of dental caries. While it is encouraging to see a number of clinical trials of such products, further studies of the safety and efficacy of these agents will be important to establish whether they offer therapeutic benefits, either alone or in combination with conventional therapies, that can help to reduce the overall burden of oral diseases of dental caries worldwide. In particular, studies that address issues such as adequate statistical power, blinding, standardization of extracts or purified compounds, and quality control would be of great value.

REFERENCES:

1. Clarkson BH, Hall D, Heilman JR, Wefel JS (1986). Effect of proteolytic enzymes on caries lesion formation in vitro. *J Oral Pathol* 15:423–429.
2. Featherstone JD (1983). Diffusion phenomena and enamel caries development. In: Cariology today. Int. Congr., 1984. Zürich: Karger.
3. Featherstone JD (1999). Prevention and reversal of dental caries: role of low level fluoride. *Community Dent Oral Epidemiol* 27:31–40.
4. Featherstone JD (2000). The science and practice of caries prevention. J Am Dent Assoc 131:887–899.
5. Featherstone JD, Nelson DG, McLean JD (1981). An electron microscope study of modifications to defect regions in dental enamel and synthetic apatites. *Caries Res* 15:278–288.
6. Freedman ML, Tanzer JM (1974). Dissociation of Plaque Formation from Glucan- Induced Agglutination in Mutants of *Streptococcus mutans*. Infect Immun. 10(1): 189–196.
7. Groppo FC, Bergamaschi Cde C, Cogo K, Franz-Montan M, Motta RH, de Andrade ED. (2008;) Use of phytotherapy in dentistry. Phytother Res 22:: 993-8.
8. Hu JP, Takahashi N, Yamada T. (2000;) *Coptidis rhizoma* inhibits growth and proteases of oral bacteria. Oral Dis 6:: 297-302.
9. Hwang JK, Chung JY, Baek NI, Park JH. (2004;) Isopanduratin A from *Kaempferia pandurata* as an active antibacterial agent against cariogenic *Streptococcus mutans.* Int J Antimicrob Agents 23:: 377?81.

10. Johnson-White B, Buquo L, Zeinali M, Ligler FS. (2006;) Prevention of nonspecific bacterial cell adhesion in immunoassays by use of cranberry juice. Anal Chem 78:: 853-
11. 7.
12. Kawasaki K, Featherstone JD (1997). Effects of collagenase on root demineralization. *J Dent Res* 76:588–595. Krasse B (1988). Biological factors as indicators of future caries. *Int Dent J* 38:219–225.
13. Kawasaki K, Featherstone JD (1997). Effects of collagenase on root demineralization. *J Dent Res* 76:588–595. Krasse B (1988). Biological factors as indicators of future caries. *Int Dent J* 38:219–225.
14. LeGeros RZ (1991). Calcium phosphates in oral biology and medicine. Basel: Karger.
15. Leverett DH, Proskin HM, Featherstone JD, Adair SM, Eisenberg AD, Mundorff-Shrestha SA, (1993). Caries risk assessment in a longitudinal discrimination study. *J Dent Res* 72:538–543.
16. Limsong J, Benjavongkulchai E, Kuvatanasuchati J. (2004) Inhibitory effect of some herbal extracts on adherence of *Streptococcus mutans*. J Ethnopharmacol 92: 281-9.
17. Liu XT, Pan Q, Shi Y, Williams ID, Sung HH, Zhang Q, et al. entrosane and labdane diterpenoids from *Sagittaria sagittifolia* and their antibacterial activity against three oral pathogens. J Nat Prod (2006 ;) 69: 255-60.
18. Loesche WJ (1986). Role of *Streptococcus mutans* in human dental decay. *Microbiol Rev* 50:353–380.
19. .Nagata H, Inagaki Y, Yamamoto Y, Maeda K, Kataoka K, Osawa K, (2006) Inhibitory effects of macrocarpals on the biological activity of *Porphyromonas gingivalis* and other periodontopathic bacteria. Oral Microbiol Immunol 21:: 159-63.
20. Nalina T, Rahim ZHA. The crude aqueous extract of *Piper betle* L. and its antibacterial effect towards Streptococcus mutans. Am J Biochem Biotechnol (2007;) 3:: 10-5.
21. O'Reilly MM, Featherstone JD (1987). De- and remineralization around orthodontic appliances: an *in vivo* study. *Am J Orthod* 92:33–40.
22. Prabu GR, Gnanamani A, Sadulla S. Guaijaverin (2006) - a plant flavonoid as potential antiplaque agent against *Streptococcus mutans.* J Appl Microbiol 101:: 487-95.
23. Rukayadi Y, Kim KH, Hwang JK. (2008) *In vitro* anti-biofilm activity of macelignan isolated from *Myristica fragrans* Houtt. against oral primary colonizer bacteria. Phytother Res 22: 308-12.
24. Sahni PS, Gillespie MJ, Botto RW, Otsuka AS. (2002) *In vitro* testing of xylitol as an anticariogenic agent. Gen Dent 50: 340-3.
25. Sasaki H, Matsumoto M, Tanaka T, Maeda M, Nakai M, Hamada S, (2004) Antibacterial activity of polyphenol components in oolong tea extract against *Streptococcus mutans*. Caries Res 38: 2-8.
26. Sato M, Tanaka H, Fujiwara S, Hirata M, Yamaguchi R, Etoh H, et al. (2002) Antibacterial property of isoflavonoids isolated from *Erythrina variegata* against cariogenic oral bacteria. Phytomedicine 9: 427-33.
27. Scheie AAA (1994). Mechanisms of dental plaque formation. Adv. Dent. Res. 8(2):246-253.
28. Song JH, Kim SK, Chang KW, Han SK, Yi HK, Jeon JG. (2006) *In vitro* inhibitory effects of *Polygonum cuspidatum* on bacterial viability and virulence factors of *Streptococcus mutans* and *Streptococcus sobrinus*. Arch Oral Bill 51: 1131-40.
29. Song JH, Kim SK, Chang KW, Han SK, Yi HK, Jeon JG. (2006) *In vitro* inhibitory effects of *Polygonum cuspidatum* on bacterial viability and virulence factors of *Streptococcus mutans* and *Streptococcus sobrinus*. Arch Oral Biol 51: 1131-40.
30. Ten Cate JM, Featherstone JD (1991). Mechanistic aspects of the interactions between fluoride and dental enamel. *CRC Crit Rev Oral Biol Med* 2:283–296.
31. Tsuchiya H, Sato M, Iinuma M, Yokoyama J, Ohyama M, Tanaka T, (1994) Inhibition of the growth of cariogenic bacteria in vitro by plant flavanones. Experientia 50:: 846-9.
32. Wefel JS, Clarkson BH, Heilman JR (1985). Natural root caries: a histo logic and microradiographic evaluation. *J Oral Pathol* 14:615–623.

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