Decreasing Cariogenic Bacteria with a Natural, Alternative Prevention Therapy utilizing Phytochemistry (Plant Extracts)

Ramakrishna Y * / Goda H ** / Baliga MS *** / Munshi AK ****

The association between the oral microbiota and oral diseases is well established. Various antimicrobial agents including antibiotics are commercially available against oral pathogenic bacteria. For the reasons of antibiotic resistance, their adverse effects and financial considerations in the developing countries, there is a need for alternate preventive and curative treatment options that are also safe, effective and economical. Traditional medicines have been used since ancient times for the treatment of oral diseases including dental caries, periodontal diseases that affect the majority of the population and can affect a person's overall health. Natural phytochemicals are certain organic components isolated from plants and some of these extracts are considered to be beneficial to health. They serve as antioxidants, enhance immune response, provide protection against oral cancer and other diseases and also repair DNA damage caused by smoking and other toxic exposure, and detoxify carcinogens. The natural products derived from medicinal plants have proven to be an abundant source of biologically active compounds, many of which have been the basis for the development of new lead chemicals for pharmaceuticals.They are considered to be good alternatives to synthetic chemicals. This article presents a review of natural alternatives derived from plants and plant products that can serve as a prevention and treatment option against cariogenic bacteria.

Keywords: *Plant extracts, Phytochemicals, Oral microflora, Antimicrobial efficacy, Phytosomes, Cariogenic bacteria*

J Clin Pediatr Dent 36(1): 55–64, 2011

INTRODUCTION

Oral diseases continue to be a major health problem worldwide. Dental caries and periodontal diseases are among the most important global oral health problems.[1] Despite general advances in the overall health of people living in industrialized countries, including oral health, the prevalence of dental caries in school aged children is close to 90% with the majority of adults also affected.[2] Oral health is integral to general well-being and relates to the quality of life. There is considerable evidence linking poor oral health to chronic conditions and systemic diseases such as cardiovascular diseases, rheumatoid arthritis and osteoporosis.[3] The economic impact of oral diseases is an important consideration with up to 10% of public health expenditure in developed countries related to curative dental care.[4] While there has been a marked improvement in oral health in most developed countries worldwide, populations of dentally disadvantaged individuals exist in these countries, often indigenous child populations and those people of low socio-economic status, where oral health is deteriorating.[5] In most developing countries, expenditure in oral health care is low; access to dental healthcare is limited and is generally restricted to emergency dental care or pain relief.[2]

The link between oral diseases and the activities of microbial species that form part of the microbiota of the oral cavity is well established.[6] Oral diseases, such as dental caries and periodontal disease, should be considered as consequences of ecologically driven imbalances of oral microbial biofilms. Both diseases are caused by micro-organisms belonging to the resident oral microflora rather than by classic microbial pathogens. Thus, most individuals harbour the micro-organisms involved in these diseases.[7] Dental plaque incorporates all of the features of biofilm architecture and microbial community interaction, but it is different in that it

* Ramakrishna Yeluri, MDS, Professor, Dept. of Pedodontics and Preventive Dentistry, K. D. Dental College and Hospital, Mathura, U.P, INDIA.

** Goda Holla, BDS, Postgraduate Student, Dept. of Pedodontics and Preventive Dentistry, K. D. Dental College and Hospital, Mathura, U.P, INDIA.

*** Sudhindra Baliga M, MDS, Professor, Dept. of Pedodontics and Preventive Dentistry, Sharad Pawar Dental College and Hospital, Wardha, Maharashtra, INDIA

**** Autar Krishen Munshi, MDS, Senior Professor and Head, Dept. of Pedodontics and Preventive Dentistry, Dean, Director and Principal, K. D. Dental College and Hospital, Mathura, U.P, INDIA.

Send all correspondence to: Dr. Ramakrishna Yeluri, Professor, Dept. of Pedodontics and Preventive Dentistry, K. D. Dental College and Hospital, Mathura – Delhi N.H #2, Mathura - 281001, Uttar Pradesh, INDIA.

Phone:+919997951558
Fax: 0565-2530764

Email: drramakrishnay@indiatimes.com,
kittypedo@yahoo.com

has more than 700 contributing oral microbial species in the oral cavity and a distinct method of conditioning the tooth.[6,8–10] Only 20 to 50% of the oral environment is tooth surface, and mucosal surfaces are important contributors to periodontal microbial biofilms.[11] Socransky,[12] defined the organisms within the subgingival microbiota; Haffajee[13] with respect to supragingival microbiota placing them in five " complexes" (Purple, Yellow, Green, Orange and Red). The concept emphasized that microorganisms create their own habitat, interact with each other and are implicated in disease severity.[12, 13] They also demonstrated that certain bacterial complexes were associated with either health or disease. The presence of certain complexes such as the "red complex" were associated more commonly with clinical indicators of periodontal diseases and were rarely detected in the absence of bacteria from other complexes.[12, 14]

Donlan and Costerton[15] offered the most salient description of a biofilm. They stated that a biofilm is " a microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription. A defining characteristic of the multispecies dental plaque biofilm, as well as other microbial biofilms, is communication either from cell to cell or from microcommunity to macrocommunity. The dynamic communication, called "quorum sensing," and regulation provide a mechanism for bacteria to monitor each other's presence and to modulate gene expression in response to changes in population density.[16]

In the case of dental caries, a low pH environment caused by microbial fermentation of carbohydrates selects a population of acid-tolerant and acid-producing strains like *mutans streptococci* and *lactobacilli*. Mixed anaerobic microorganisms are involved in periodontal disease, which develops when the plaque community equilibrium is altered and inflammation is induced.[7] It is likely that cooperative interactions between *mutans streptococci* and other oral streptococci play important roles in the development of dental caries.[17,18] Oral streptococci are normal inhabitants of the human oral cavity and play a role in resistance to colonization by invading pathogens.[19,20] *Streptococcus salivarius* is one of several oral commensal bacteria and a major constituent of oral biofilms that colonize the buccal epithelium, tongue and dorsal epithelium.[21] This organism can comprise the majority of the total cultivable flora soft tissues of the mouth, and possesses a number of important biological activities for lactose uptake and urease enzymes that are thought to contribute to the stability of oral communities.[22,23] Furthermore, products (arginine deaminase and urease) from *Streptococcus salivarius* may control oral biofilm formation over a considerable distance to integrate the whole oral cavity into a single, interacting ecosystem.[23] Urea secreted into the oral cavity in saliva[24] and crevicular fluid[25] is metabolized by *Streptococcus salivarius* which is a major and well studied oral ureolytic organism to ammonia and carbon dioxide, causing a pH elevation,[26-30] long suspected of having a major impact on the biofilm as well as the oral ecosystem.

Lactobacilli play a significant role in the oral ecosystem and can be linked with oral disease as well as oral health.[31] The possible actions of this probiotic bacterium in the oral environment are competition binding sites, production of antimicrobial substances and activation and regulation of the immune response.[32] Bacterial antagonism may occur when growth of one bacterial species is hampered by components produced by another species. Lactic acid bacteria produce antimicrobial components and some have the ability to produce hydrogen peroxide (H_2O_2) that can be toxic to organisms producing little or no H_2O_2 – scavenging enzymes.[33,34] Since the discovery by Polonskaia[35] that *L. acidophilus* inhibits growth of certain streptococci *in vitro*, clinical studies have confirmed that probiotic lactobacilli can reduce the counts of salivary *mutans streptococci* after ingestion of L. rhamnosus GG[36,37] and L. reuteri.[38] Furthermore, naturally occurring Lactobacilli species may inhibit growth of laboratory strains of *mutans streptococci* as well as subject's autologous *mutans streptococci in vitro*.[39]

The initiation and progression of dental caries is related to a number of interrelated factors. Any preventive measure that interferes with a number of these respective factors would be a useful anticariogenic tool.[40] The development of chemotherapeutic agents capable of inhibiting dental plaque formation has been of great interest to dental researchers and clinical dentists over the past few decades. Various antibacterial agents including antibiotics are commercially available against oral pathogenic bacteria and significant decline was seen in the level of S. mutans after short-term antibiotic therapy.[41] These antibiotics have side effects such as vomiting, diarrhea and can alter oral microflora.[42-47] Other antibacterial agents such as cetylpyridinium chloride, chlorhexidine and amine fluorides are reported to exhibit toxicity, cause staining of teeth or in the case of ethanol (commonly found in mouthwashes) have been linked to oral cancer.[48-51]

The global need for alternative prevention and treatment options and products for oral diseases that are safe, effective and economical comes from the rise in disease incidence (particularly in developing countries) increased resistance by pathogenic bacteria to currently used antibiotics and chemotherapeutics, opportunistic infections in immunocompromised individuals and financial considerations in the developing countries.[52,53] One such strategy would be to verify the enormous value of medicinal plants. There have been numerous reports of the use of traditional plants and plant products for the treatment of oral diseases,[54-56] especially in the People's Republic of China where many herbal remedies have been investigated.[57–66] Many plant – derived medicines used in traditional medicinal systems have been recorded in pharmacopeias as agents used to treat infections. A number of phytochemicals, including antibacterial agents, have been derived from edible plants and demonstrate antibacterial properties against *Streptococcus mutans*.[67-69] The natural phytochemicals obtained from plant extracts used in traditional medicine may be considered as good alternatives to synthetic chemicals. The purpose of this article is to present a review of natural alternatives derived from plants and plant products that has a potential application against cariogenic bacteria.

Antimicrobial effect of various plant extracts against cariogenic bacteria

Wolinsky *et al*[70] investigated the inhibitory effects of aqueous extracts derived from Neem sticks (Azadirachta indica) upon bacterial aggregation, growth, adhesion to hydroxyapatite, and production of insoluble glucan, which may affect in vitro plaque formation. Neem stick extracts were screened for minimal bacterial growth inhibition against a panel of Streptococci species by means of a broth dilution assay. The pre-treatment of *S. sanguis* with the neem stick extract or the gallotannin-enriched extract from Melaphis chinensis (Aphididae) at 250 µg/mL resulted in a significant inhibition of the bacterial adhesion to saliva-conditioned hydroxyapatite. Pre-treatment of saliva conditioned hydroxyapatite with the neem stick or gallotannin-rich extract prior to exposure to bacteria yielded significant reductions in bacterial adhesion. The neem stick extract and the gallotannin-enriched extract from Melaphis chinensis inhibited insoluble glucan synthesis. These data suggest that neem stick extract can reduce the ability of some Streptococci to colonize tooth surfaces.

Tulsi, scientifically known as Ocimum sanctum, is a plant of Indian origin and a time-tested premier medicinal herb. The extract of tulsi is used to treat a variety of illnesses that include diabetes mellitus, arthritis, bronchitis and skin diseases.[71,72] The antimicrobial property of tulsi has been tested against a variety of microorganisms like *Staphylococcus aureus, Klebsiella, Candida albicans, E. coli and Proteus sp.*[73] The antimicrobial activity of tulsi is attributed to its constituents namely ursolic acid and carvacrol. Recently Magesh *et al*[74] have demonstrated significant anticancer properties of Oscimum sanctum. Pooja *et al*[75] in their study demonstrated an antimicrobial potential of tulsi extract at various concentrations against *S. mutans* and achieved maximum antimicrobial potential at 4% concentration level.

A review article by Hamilton-Miller[76] suggested that various components in green and black tea (leaves of Camellia sinensis, [Theaceae]), notably simple catechins, have anti-cariogenic activity. These include: a direct bactericidal effect against *S. mutans* and *S. sobrinus*; prevention of bacterial adherence to teeth; inhibition of glucosyl transferase, thus limiting the biosynthesis of sticky glucan; inhibition of human and bacterial amylases. Ferrazzano *et al*[77] concluded that the anti-cariogenic effects against α-haemolytic streptococci by polyphenols from cocoa, coffee, and tea suggest further possible application of these beverages in the prevention of pathogenesis of dental caries.

Xylitol is a natural sweetener found in xylan-rich plants, trees, fruits and vegetables. The discovery of xylitol is attributed to two groups of researchers (1891): Fischer and Stahel[78] isolated from beech chips and Bertrand[79] isolated from processed wheat and oat straw. Xylitol is also present in human metabolism as a normal metabolic intermediate in the glucoronate xylulose cycle. More than a quarter of a century ago, researchers at the University of Turku, Finland, began to study xylitol as a potential anticariogenic dietary sweetener. The consumption of xylitol- containing diet reduced the incidence of dental caries by 90%.[80] Xylitol consumption also reduced the amount of dental plaque formation by 50% during a period of neglected oral hygiene when the effect was compared to that caused by sucrose.[81–86] Several clinical studies have shown that xylitol, a naturally occurring five-carbon sugar alcohol (Polyol), can be used as an effective caries preventive agent.[87-90] The cariostatic and the therapeutic effects [90] of xylitol have been attributed to both microbiologic and physiochemical actions of xylitol.[91,92] The majority of oral bacteria cannot utilize xylitol[93, 94] and no adaptation to use xylitol has been detected in long-term in vivo studies.[95, 96] On the contrary, acid production and growth of most oral streptococci are inhibited by xylitol.[97,98] This inhibition has been attributed to the intracellular formation of xylitol 5-phosphate, which is toxic to the organism, but not to humans.[97,99] It has been found to specifically interfere with the metabolism and the adherence of *S. mutans*[100–103] and possibly of lactobacillus also.[104]

Loesche *et al*[105] concluded that xylitol significantly reduced the salivary *S. mutans* levels compared with fluoride alone or placebo alone, and stated that "plaque levels of *S. mutans* were significantly reduced compared to values obtained by chewing either sorbitol or fructose-sweetened gum". Subsequent clinical trials during the past 25 yrs have demonstrated that systemic usage of xylitol chewing gum and related xylitol-sweetened products have been associated with an impressive reduction of caries incidence both in juvenile and adult populations.[100,106,107] The main source of commercially produced xylitol is beech bark, corn cobs, straw, seed hulls and nut shells. Although underutilized and often overlooked, xylitol use is compatible and complementary to current oral hygiene recommendation. Xylitol is not a panacea, but it is a practical and effective adjunct to a "state of the art" caries prevention program.[108]

Bhattacharya[109] reported the inhibition of *S. mutans* and other oral Streptococci, by the antimicrobially active ingredients of the hop plant (Humulus lupulus [Cannabaceae]). They found that all tested hop constituents inhibited the Streptococci with minimum inhibitory concentration (MIC) at pH 7.5 ranged from 2 to 50 µg/ml. They also suggested that antimicrobial activity of hop constituents was found to be greater than other plant products such as thymol, nerol, cinnamon oil, oil of clove, menthol and eucalyptol. Numerous studies have investigated the ability of cranberry juice (Vaccinium macrocarpon) 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 seconds 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.[110]

Chung *et al*[111] studied the extract (Macelignan) of Myristica fragrans (Nutmeg, [Myristicacea]), widely cultivated for the spice and flavor of foods, and reported that it possessed strong inhibitory activity against *S. mutans*. The MIC of macelignan against *S. mutans* was 3.9 µg/ml. Macelignan also possessed preferential activity against other oral microorganisms such as *S sobrinus, S salivarius, S sanguis, Lactobacillus acidophilus* and *Lactobacillus casei* in the MIC range of 2-31.3µg/ml. In particular, the bactericidal test showed that macelignan, at a concentration of 20 µg/ml, completely inactivated *S. mutans* in 1 minute. The specific activity and fast-effectiveness of macelignan against oral bacteria strongly suggests that it could be employed as a natural antibacterial agent in functional foods or oral care products.

Propolis is a resinous mixture collected by honey bees (Melipona compressipes fasciculate) from trees (Poplars and Conifers), sap flowers (Genera "Clusia" and "Dalechampia") and other botanical sources and used for sealing unwanted open spaces in the bee hive. Several in vitro and in vivo studies on extract of propolis have demonstrated anti-inflammatory and bactericidal activity and its potential use in the treatment of bacterial diseases.[112–116] Silvana *et al*[117] in their study concluded that propolis extract**,** when used as a mouth rinse**,** showed in vivo antimicrobial activity against S. mutans and might be used as an alternative measure to prevent dental caries. Uzel *et al*[118] also investigated the activity of propolis extract against a number of microorganisms, including *S. mutans* and *S. sobrinus.* Ethanol extracts of four samples of propolis collected from different geographical regions in Anatolia (Turkey), exhibited MIC values of 2–64 µg/ ml, with activity likely to be due to the presence of numerous flavonoids. Propolis showed antimicrobial activity similar to chlorhexidine and greater than clove or sage extracts.[119]

Menezes *et al*[120] investigated the efficacy of a hydroalcoholic extract (HAE) of pomegranate, (Punica granatum [Punicaceae]), in the prevention of dental plaque in a randomized controlled study involving 60 participants who were randomized into three groups: HAE, chlorhexidine and distilled water (control). A significant reduction in bacteria was observed in the HAE and chlorhexidine groups compared to the control group. The authors concluded that pomegranate extract could be useful in the prevention of diseases caused by plaque bacteria. These results are supported by an *in vitro* study of a phytotherapeutic gel containing pomogrenate plant powder, which was able to inhibit the adherence of *S. mutans, S. mitis* and *S. sobrinus* (as well as C. albicans) to the glass surface in the presence of sucrose.[121]

Sofrata *et al*[122] concluded that miswak chewing sticks (Twigs of Salvadora persica) embedded in agar or suspended above the agar plate had strong antibacterial effects against all bacteria tested. The antibacterial effect of suspended miswak sticks suggests the presence of volatile active antibacterial compounds. The inhibitory effect was most pronounced on *P. gingivalis, A. actinomycetemcomitans,* and *H. influenzae*, less on *S. mutans,* and least on *L. acidophilus*. Suspended miswak had comparable or stronger effects than miswak embedded in agar. The antibacterial effect of miswak is attributed to its tannin, saponin and flavanoid content.

Akihiro *et al*[123] in their study found 17 out of 81 edible plants exhibited antibacterial properties against *S. mutans*. They also investigated the stability of the active ingredients against heat treatment or storage at 4°C for one week in these 17 edible plants and concluded that the inhibitory properties of garlic and balsam pear were lost when compared to other samples (clove, nutmeg, thyme, ginger, Japanese ginger, and cinnamon)

Wu[124] reported that raisins contain polyphenols, flavonoids and iron that may benefit human health. However, their oral health benefits are less well understood. Through antimicrobial assay-guided fractionation and purification, compounds identified with growth inhibition against oral pathogens were oleanolic acid, oleanolic aldehyde, linoleic acid, linolenic acid, betulin, betulinic acid, 5-(hydroxymethyl)-2-furfural, rutin, beta-sitosterol, and beta-sitosterol glucoside. Oleanolic acid suppressed *in vitro* adherence of cariogenic *S. mutans* biofilm. When the effect of raisins and raisin-containing bran cereal on *in vivo* plaque acidogenicity was examined in 7 to 11 years old children, it was found that raisins did not allow the plaque to decline below pH '-6-' over the 30-min test period. Grape seed extract, high in proanthocyanidins, positively affected the *in vitro* demineralization and/or remineralization processes of artificial root caries lesions, suggesting its potential as a promising natural agent for non-invasive root caries therapy. Raisins represent a healthy alternative to the commonly consumed sugary snack foods.

Table 1. Various Other Plants with Antimicrobial Activity against *S. Mutans*

Plant Extract	*MIC*	
Drosera peltata (shield sundew or pale sundew)	15.6 – 31.3µg/ml	Didry L *et al* 1998[125]
Coptidis Rhizoma (golden thread rhizome)	31.0 – 250µg/ml	Hu JP *et al* 2000[126]
Morus alba (White mulberry) (Moraceae)	1µg/ml	Park KM 2003 [127]
Helichrysum italicum (curry plant)	31.3 – 62.5µg/ml	Nostro A *et al* 2004[128]
Eucalyptus leaves (Eucalyptus globulus)	0.5-1 µg/ml	Nagata H 2006[129]
Pistacia lentiscus (mastic gum)	>1mg/ml	Sterer N 2006 [130]
Psidium guajava (Guava, Myrtaceae)	2-4mg/ml	Prabu GR 2006 [131]
Mikania (Exotic weed, Asteraceae)	12.5-100µg/ml	Song JH 2006 [132]
Piper cubeba (Java pepper)	90 – 200µg/ml	Silva ML *et al* 2007[133]
Red grape	500 µg/ml	Smullen J 2007 [134]
Naringin flavonoid in citrus fruits	9.8-125mg/ml	Tsui VW 2008 [135]

Essential oils and Essential oil components

Essential oils are odorous, volatile products of plant secondary metabolism, found in many leaves and stems. They have been formulated into several over-the-counter oral hygiene products, and the efficacy of mouth rinses containing essential oils has been reported since the 1890's, and, concerning oral micro-organisms, they proved to be beneficial and safe with daily health routines.[136,137] The essential oil of Melaleuca alternifolia (Myrtaceae), known as tea tree oil (TTO), has been used medicinally for many years. TTO has antimicrobial properties and is used in the superficial treatment of skin infections. The activity of TTO against an extensive collection of oral bacterial isolates was investigated by Hammer *et al*[138] who determined that the MIC and MBC values were in the range of 0.003-2.0% (v/v).

At present a variety of such components has been identified, some of which have made their way into commercial products and Shapiro *et al*[139] in their study described a survey of antimicrobial properties of some commercially available essential oils and essential oil components, singly and in dyadic combination, towards a large number of laboratory strains of oral bacteria that have been implicated in the development and / or progression of dental diseases. They concluded that Australian tea-tree oil, peppermint oil and sage oil proved to be the most potent essential oils, whereas thymol and eugenol were potent essential oil components.

Safety issues related to plant extracts

The clinical studies reviewed in this article have generally assessed the efficacy of plant extracts against cariogenic bacteria. However, the safety and possible side-effects of such products must also be considered. Groppo *et al*[140] have concluded that 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 such products and the need for more clinical studies is recommended. In addition, caution should be used whenever attempts are made to alter the oral biofilm due to the "law of unforeseen consequences" i.e. the anti-microbial nature of some of these products may adversely affect the probiotic population of the host resulting with a net negative health situation.

The role of Phytosome Technology and Phytopharmacology

Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytoconstituents, despite having excellent bioactivity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting with poor absorption and poor bioavailability.[141] Phytosome technology markedly enhances the bioavailability of phytomedicines. Phytosomes are advanced forms of herbal formulations that are better absorbed (pharmacokinetic), and as a result, produce better bioavailability (pharmacodynamic) and therefore more effective than the conventional herbal extracts.[142,143] Phytosomes are produced by a patented process whereby the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. This phyto-phospholipid complex, phytosome resembles a little cell. The term "phyto" means plant while "some" means cell-like.

Phytosome technology has effectively enhanced the bioavailability of many popular herbal extracts including milk thistle (Silybin Phytosome TM [Silybum marianum]), Ginkgo biloba (Ginkgo Phytosome TM), Grape seed (Grape seed Phytosome TM [Vitis vinefera]), Green tea (Green Tea Phytosome TM [Thea sinensis]), Hawthorn (Hawthorn Phytosome TM [Crataegus sp]), Ginseng (Ginseng Phytosome TM [Panax ginseng]) and can be developed for various therapeutic uses or dietary supplements.[143-147] A thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties.[141] Several excellent phytoconstituents have been successfully delivered through phytosome technology in the field of medicine and exhibiting remarkable therapeutic efficacy in animal as well as in human model.[146,148] These extracts can be standardized accordingly and may be formulated as phytosomes against cariogenic bacteria so that they can be delivered in the form of mouthwashes, toothpastes, chewing gums, candies and varnishes.

Phytosomes have the following advantages[144,145,149]

1. They enhance the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route with better bioavailability, hence significantly greater therapeutic benefit.
2. As the absorption of active constituent(s) is improved, its dose requirement is also reduced.
3. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
4. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show a better stability profile.
5. Added nutritional benefit of phospholipids.

CONCLUSIONS

A range of chemical agents have been used in the prevention and treatment of dental caries, although concerns about the safety of some of these methods have increased consumer demand for alternative methods. Hence, there has been recent interest in testing natural products, including plant-derived compounds, for anti-cariogenic properties. The documented antimicrobial effects of plant extracts against cariogenic bacteria provides considerable evidence that plant extracts, essential oils and purified phytochemicals have the potential to be developed into agents that can be used as preventive or treatment therapies for oral diseases.

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, to reduce the overall burden of oral diseases worldwide. In particular, clinical studies that address issues such as adequate statistical power, blinding, standardization of extracts or purified compounds, and quality control will be required. In addition there are a lot of challenges to overcome, especially because of lack of good scientific evidence concerning the cost effectiveness of these preparations. The phytosome technology may not be economical at this point of time, but with the advancement of dental research this natural-based therapy could prove both useful and cost effective.

REFERENCES

1. Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century – The approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol, 31(Suppl. 1): 3–24, 2003.
2. Petersen PE, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. Bull World Health Organ, 83(9): 661–9, 2005.
3. Rautemaa R, Lauhio A, Cullinan MP, Seymour GJ. Oral infections and systemic disease- an emerging problem in medicine. Clin Microbiol Infect, 13(11): 1041–7, 2007.
4. Peterson PE. The burden of oral disease: challenges to improving oral health in the 21st century. Bull World Health Organ, 83(1): 3, 2005.
5. Jamieson LM, Parker EJ, Armfield JM. Indigenous child oral health at a regional and state level. J Paediatr Child Health, 43(3): 117–21, 2007.
6. Jenkinson HF, Lamont RJ. Oral microbial communities in sickness and in health. Trends Microbiol, 13(12): 589–95, 2005.
7. Marsh PD. Microbial ecology of dental plaque and its significance in health and disease. Adv Dent Res, 8(2): 263–271, 1994.
8. Kroes I, Leep PW, Relman DA. Bacterial diversity within the human subgingival crevice. Proc Natl Acad Sci USA, 96(25): 14547–14552, 1999.
9. Aas JA, Paster BJ, Stokes LN, Oslen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. J Clin Microbiol, 43(11): 5721–5732, 2005.
10. Tencate JM. Biofilms, a new approach to the microbiology of dental plaque. Odontol, 94(1): 1–9, 2006.
11. Kerr WJS, Geddes DAM. The areas of various surfaces in the human mouth from nine years to adulthood. J Dent Res, 70(12): 1528–30, 1991.
12. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol, 25(2): 134–44, 1998.
13. Haffajee AD, Socransky SS, Patel MR, Song X. Microbial complexes in supragingival plaque. Oral Microbiol Immunol, 23(3): 196–205, 2008.
14. Socransky SS, Haffajee AD. Dental biofilms: difficult therapeutic targets. Periodontol 2000, 28: 12–55, 2002.
15. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev, 15(2): 167–93, 2002.
16. Camilli A, Bassler BL. Bacterial small-molecule signaling pathways. Science, 311 (5764): 1113–6, 2006.
17. Kolenbrander PE, London J. Adhere today, here tomorrow: oral bacterial adherence. J Bacteriol, 175(11): 3247–52, 1993.
18. Kreth J, Merritt J, Shi W, Qi F. Competition and coexistence between Streptococcus mutans and Streptococcus sanguinis in the dental biofilm. J Bacteriol, 187(21): 7193–203, 2005.
19. Tsuda H, Yamashita Y, Shibata Y, Nakano Y, Koga T. Genes involved in Bacitracin resistance in Streptococcus mutans. Antimicrob Agents Chemother, 46(12): 3756–64, 2002.
20. Tada A, Senpuku H, Motozawa Y, Yoshihara A, Hanada N, Tanzawa H. Association between commensal bacteria and opportunistic pathogens in the dental plaque of elderly individuals. Clin Microbiol Infect, 12: 776–81, 2006.
21. Bowden GHW, Ellwood DC, Hamilton IR. Microbial ecology of the oral cavity. In: Advances in microbial ecology, Alexander M, Ed., New York: Plenum. Press, 3: 135–217, 1979.
22. Chen YY, Clancy KA, Burne RA. Streptococcus salivarius urease: genetic and biochemical characterization and expression in a dental plaque Streptococcus. Infect Immun, 64(2): 585–92, 1996.
23. Sissons CH, Yakub S. Supression of urease levels in Streptococcus salivarius by cysteine, related compounds and by sulfide. Oral Microbiol Immunol, 15: 317–24, 2000.
24. Kopstein J, Wrong OM. The origin and fate of salivary urea and ammonia in man. Clin Sci Mol Med, 52(1): 9–17, 1977.
25. Golub LM, Borden SM, Kleinberg I. Urea content of gingival crevicular fluid and its relation to periodontal disease in humans. J Periodontal Res, 6: 243–51, 1971.
26. Kleinberg I. Effect of urea concentration on human plaque pH levels in situ. Arch Oral Biol, 12: 1475–84, 1967.
27. Sissons CH, Cutress TW, Pearce EIF. Kinetics and product stoichiometry of ureolysis by human salivary bacteria and artificial mouth plaques. Arch Oral Biol, 30: 781–90, 1985.
28. Sissons CH, Cutress TW. In vitro urea dependent pH changes by human salivary bacteria and dispersed artificial mouth bacterial plaques. Arch Oral Biol, 32: 181–9, 1987.
29. Sissons CH, Perinpanayagam HER, Hancock EM, Cutress TW. pH regulation of urease levels in Streptococcus salivarius. J Dent Res, 69(5): 1131–7, 1990.
30. Sissons CH, Perinpanayagam HER, Hancock EM. Processes involved in the regulation of urease levels in Streptococcus salivarius by pH. Oral Microbiol Immunol, 7: 159–64, 1992.
31. Badet C, Thebaud NB. Ecology of Lactobacilli in the oral cavity: A Review of literature. The Open Microbial J, 2: 38–48, 2008.
32. Meurman JH. Probiotics: do they have a role in oral medicine and dentistry? Eur J Oral Sci, 113: 188–96, 2005.
33. Quwehand AC. Antimicrobial components from lactic acid bacteria. In Lactic acid bacteria: microbiology and functional aspects 2nd ed., Salminen S, von Wright A, Ed., New York: Dekker Inc: 139: 160, 1998.
34. Allaker RP, Douglas CW. Novel anti-microbial therapies for dental plaque- related diseases. Int J Antimicrob Agents, 33(1): 8–13, 2009.
35. Polonskaia MS. Antibiotic substances in acidophil bacteria. Mikrobiologiia, 21: 303–10, 1952.
36. Nase L, Hatakka K, Savilahti E, Saxelin M, Ponka A, Poussa T, Korpela R, Meurman JH. Effect of long term consumption of a probiotic bacterium, Lactobacillus Rhamnosus GG in milk on dental caries and caries risk in children. Caries Res, 35 (5): 412–20, 2001.
37. Ahola AJ, Yli Knuuttila H, Suomalainen T, Poussa T, Ahlstrom A, Meurman JH, Korpela R. Short term consumption of probiotic- containing cheese and its effect on dental caries risk factors. Arch Oral Biol, 47(11): 799–804, 2002.
38. Nikawa H, Makihira S, Fukushima H, Nishimura H, Ozaki Y, Ishida K, Darmawan S, Hamada T, Hara K, Matwumoto A, Aimi R. Lactobacillus Reuteri in bovine milk fermented decreases the oral carriage of mutans streptococci. Int J Food Microbiol, 95(2): 219–23, 2004.
39. Simark-Mattsson C, Emilson CG, Hakansson EG, Jacobsson C, Roos K, Halm S. Lactobacillus-mediated interference of mutans streptococci in caries-free vs. caries-active subjects. Eur J Oral Sci, 115: 308–14, 2007.
40. Drucker DB, Green RM. The relative cariogenicity of different streptococci in the gnotobiotic WAG/RIJ rat. Arch Oral Biol, 26(7): 599–606, 1981.
41. John R, Prabhu NT, Munshi AK. Effect of short-term antibiotic therapy on salivary S. mutans levels in children. J Ind Soc Pedod Preven Dent, 14(4): 123–7, 1996.

42. Goodson JM, Tanner A. Antibiotic resistance of the subgingival microbiota following local tetracycline therapy. Oral Microbiol Immunol, 7(2): 113–7, 1992.
43. Davies J. Inactivation of antibiotics and the dissemination of resistance genes. Science, 264: 375–82, 1994.
44. Preus HR, Lassen J, Aass AM et al. Bacterial resistance following subgingival and systemic administration of minocycline. J Clin Periodontol, 22: 380–4, 1995.
45. Gilbert P, Das J, Foley I. Biofilm susceptibility to antimicrobials. Adv Dent Res, 11: 160–7, 1997.
46. Tenover FC. Development and spread of bacterial resistance to antimicrobial agents: an overview. Clin Infect Dis, 33: 108–15, 2001.
47. Roberts MC. Antibiotic toxicity, interactions and resistance development. Periodontal 2000, 28: 280–97, 2002.
48. Knoll-Kohler E, Stiebel J. Amine fluoride gel affects the viability and the generation of superoxide anions in human polymorphonuclear leukocytes: an in vitro study. Eur J Oral Sci, 110: 296–301, 2002.
49. Lachenmeier DW. Safety evaluation of topical applications of ethanol on the skin and inside the oral cavity. J Occup Med Toxicol, 3: 26, 2008.
50. McCullough MJ, Farah CS. The role of alcohol in oral carcinogenesis with particular reference to alcohol-containing mouthwashes. Aust Dent J, 53(4): 302–5, 2008.
51. Neumegen RA, Fernandez-Alba AR, Chisti Y. Toxicities of triclosan, phenol, and copper sulfate in activated sludge. Environ Toxicol, 20(2): 160–4, 2005.
52. Tichy J, Novak J. Extraction, assay and analysis of antimicrobials from plants with activity against dental pathogens (Streptococcus sp.). J Altern Complement Med, 4(1): 39–45, 1998.
53. Badria FA, Zidan OA. Natural products for dental caries prevention. J Med Food, 7(3): 381–4, 2004.
54. Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev, 12(4): 564–82, 1999.
55. Kalemba D, Kunicka A. Antibacterial and antifungal properties of essential oils. Curr Med Chem, 10(10): 813–29, 2003.
56. Kim HS. Do not put too much value on conventional medicines. J Ethnopharmacol, 100(1-2): 37–9, 2005.
57. Tsao TF, Newnan MG, Kwok YY, Horikoshi AK. Effetc of Chinese and western antimicrobial agents on selected oral bacteria. J Dent Res, 61(9): 1103–6, 1982.
58. Hwang JK, Shim JS, Pyun YR. Antibacterial activity of xanthorrhizol from Curcuma xanthorrhiza against oral pathogens. Fitoterapia, 71(3); 321–3, 2000.
59. Hu JP, Takahashin N, Yamada T. Coptidis rhizome inhibits growth and proteases of oral bacteria. Oral Dis, 6(5): 297–302, 2000.
60. Kastura H, Tsukiyama RI, Suzuki A, Kobayashi M. In vitro antimicrobial activities of bakuchiol against oral microorganisms. Antimicrob Agents Chemother, 45(11): 3009–13, 2001.
61. Hwang JK, Chung JY, Baek NI, Park JH. Isopanduratin A from Kaempferia pandurata as an active antibacterial agent against cariogenic Streptococcus mutancs. Int J Antimicrob Agents, 23(4): 377–81, 2004.
62. Xiao J, Liu Y, Zuo YL, Li JY, Ye L, Zhou XD. Effects of Nidus Vespae extract and chemical fractions on the growth and acidogenicity of oral microorganisms. Arch Oral Biol, 51(9): 804–13, 2006.
63. Song JH, Kim SK, Chang KW, Han SK, Yi HK, Jeon JG. In vitro inhibitory effects of Polygonum cuspidatum on bacterial viability and virulence factors of Streptococcus mutans and Streptococcus sobrinus. Arch Oral Biol, 51(12): 1131–40, 2006.
64. Liu XT, Pan Q, Shi Y, Williams ID, Sung HH, Zhang Q et al. ent-rosane and labdane diterpenoids from Sagittaria sagittifolia and their antibacterial activity against three oral pathogens. J Nat Prod, 69(2): 255–60, 2006.
65. Liu XT, Shi Y, Yu B, Williams ID, Sung HH, Zhang Q et al. Antibacterial diterpenoids from Sagittaria pygmaea. Planta Med, 73(1): 84–90, 2007.
66. Wong RWK, Haqq U, Samaranayake L, Yuen MKZ, Seneviratne CJ, Kao R. Antimicrobial activity of Chinese medicine herbs against common bacteria in oral biofilm. A Pilot study. Int J Oral Maxillo Surg, 39: 599–605, 2010.
67. Hirasawa M, Shouji, N, Neta T, Fukushima K, Takeda K. Three kinds of antibacterial components from Lentinus edodes (Berk.). Int J Antimicrob Agents, 11(2): 151–7, 1999.
68. Yamada Y, Yamamoto A, Yoneda N, Nakatani N. Identification of kaempferol from the leaves of Diospyros kaki and its antimicrobial activity against Streptococcus mutans. Biocontrol Sci, 4: 97–100, 1999.
69. Jayaprakasha, Selve GK, Sakariah K. Antibacterial and antioxidant activities of grape (Vitis vinifera) seed extracts. Food Research International, 36(2): 117–22, 2003.
70. Wolinsky LE, Mania S, Nachnani S, Ling S. The inhibiting effect of aqueous.Azadirachta indica (Neem) extract upon bacterial properties influencing in vitro plaque formation. J Dent Res, 75(2): 816–22, 1996.
71. Prakash P, Gupta N. Therapeutic uses of Ocimum sanctum linn (Tulsi) with a note on eugenol and its pharmacological actions. A short review. Indian J Physiol Pharmacol, 49(2): 125–31, 2005.
72. Viyoch J, Pisutthanan N, Faikreua A, Nupangta K, Wangtorpol K, Ngokkuen J. Evaluation of invitro antimicrobial activity of thai basil oils and their micro-emulsion formulae against Propionibacterium acnes. Int J Cosmet Sci, 28(2): 125–33, 2006.
73. Geeta, Vasudevan DM, Kedlaya R, Deepa S, Ballal M. Activity of Ocimum sanctum (the traditional Indian medicinal plant) against enteric pathogens. Ind J Med Sci, 55(8): 434–8, 472, 2001.
74. Magesh V, Lee JC, Ahn KS, Lee HJ, Lee EO, Shim BS et al. Ocimum sanctum induces apoptosis in A549 lung cancer cells and suppresses the in vivo growth of Lewis lung cancer cells. Phytother Res, 23(10): 1385–91, 2009.
75. Pooja A, Nagesh L, Murlikrishnan. Evaluation of the antimicrobial activity of various concentrations of Tulsi (Ocimum sanctum) extract against Streptococcus mutans: An in vitro study. Ind J Dent Res, 21(3): 357–9, 2010.
76. Hamilton-Miller J.M.T. Anti-cariogenic properties of tea (Camellia sinensis). J Med Microbiol, 50(4): 299–302, 2001.
77. Gianmaria F. Ferrazzano, Ivana Amato, Aniello Ingenito, Antonino De Natale, Antonino Pollio. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). Fitoterapia, 80(5): 255–62, 2009.
78. Fischer E, Stahel R. Zur Kenntniss der Xylose. Ber Dtsch Chem Ges, 24: 528–39, 1891.
79. Bertrand MG. Recherches zur quelques dérivés du xylose. Bull Soc Chim. Paris, 5: 554–7, 1891.
80. Scheinin A, Mäkinen KK, Ylitalo K. Turku sugar studies: I. An intermediate report on the effect of sucrose, fructose and xylitol diets on the caries incidence in man. Acta Odontol Sand, 32(6): 383–412, 1974.
81. Scheinin A, Mäkinen KK. The effect of various sugars on the formation and chemical composition of dental plaque. Int Dent J, 21: 302–21, 1971.
82. Scheinin A, Mäkinen KK. Effect of sugars and sugar mixtures on dental plaque. Acta Odontol Scand, 30(2): 235–57, 1972.
83. Mäkinen KK, Scheinin A. Turku sugar studies: II. Preliminary biochemical and general findings. Acta Odontol Scand, 32(6): 413–21, 1974.
84. Mouton C, Scheinin A, Mäkinen KK. Effect of plaque on a xylitol containing chewing gum: A pilot study. Acta Odontol Scand, 33(1): 27–31, 1975.
85. Mouton C, Scheinin A, Mäkinen KK. Effect of plaque on a xylitol containing chewing gum: A clinical and biochemical study. Acta Odontol Scand, 33(1): 33–40, 1975.
86. Mouton C, Scheinin A, Mäkinen KK. Effect of a xylitol chewing gum on plaque quantity and quality. Acta Odontol Scand, 33(5): 251–7, 1975.
87. Scheinin A, Mäkinen KK. Eds. Turku sugar studies. Acta Odontol Scand, 33(Suppl 70): 1–30, 1975.
88. Scheinin A, Bánóczy J. Xylitol and caries: the collaborative WHO oral disease preventive programme in Hungary. Int Dent J, 35(1): 50–7, 1985.

89. Kandelman D, Gagnon G. Clinical results after 12 months from a study of the incidence and progression of dental caries in relation to consumption of chewing gum containing xylitol in school preventive programs. J Dent Res, 66(8): 1407–11, 1987.
90. Isokangas P, Alanen P, Tiekso J, Mäkinen KK. Xylitol chewing gum in caries prevention: a field study in children at caries-active ages. J Am Dent Assoc, 117(2): 315–20, 1988.
91. Mäkinen KK. New biochemical aspects of sweetners. Int Dent J, 35: 23–35, 1985.
92. Mäkinen KK, Isokangas P. Relationship between carbohydrate sweetners and oral diseases. Prog Food Nut Sci, 12: 73–109, 1988.
93. Edwardsson S, Berkhed D, Mejare B. Acid production from lycasin, maltitol, sorbitol and xylitol by oral streptococci and lactobacilli. Acta Odontol Scand, 35(5): 257–63, 1977.
94. Havenaar R, Huis In't Veld JHJ, Backer Dirke O, de Stoppelaar JD. Some bacteriological aspects of sugar substitutes. In: Guggenheim, Ed., Health and sugar substitutes. Basel: Karger, 192–8, 1979.
95. Mäkinen KK, Virtanen KK. Effect of 4.5 year use of xylitol and sorbitol on plaque. J Dent Res, 57(3): 441–6, 1978.
96. Mäkinen KK, Söderling E, Hämäläinen K, Antonen P. Effect of long term use of xylitol on dental plaque. Proc Finn Dent Soc, 81(1): 28–35, 1985.
97. Assev S, Vegarud G, Rölla G. Growth inhibition of streptococcus mutans strain OZM 176 by xylitol. Acta Pathol Microbiol Immunol Scand Sect B, 88: 61–3, 1980.
98. Vadeboncoeur C, Trahan L, Mouton C, Mayrand D. Effect of xylitol on the growth and glycolysis of acidogenic oral bacteria. J Dent Res, 62(8): 882–4, 1983.
99. Trahan L, Bareil M, Gauther L, Vadeboncoeur C. Transport and phosphorylation of xylitol by a fructose phosphotransferace system in streptococcus mutans. Caries Res, 19(1): 53–63, 1985.
100. Mäkinen KK. Latest dental studies on xylitol and mechanisms of action of xylitol in caries limitation; In Grenby TH (Ed): Progress in sweeteners, London, Elsevier, 331–62, 1989.
101. Trahan L. Xylitol: a review of its action on mutans streptococci and dental plaque – its clinical significance. Int Dent J, 45 (1 Suppl 1): 77–92, 1995.
102. Mäkinen KK. Can the pentitol-hexitol theory explain the clinical observations made with xylitol? Med Hypotheses, 54: 603–13, 2000.
103. Milgrom P, Ly KA, Roberts MC, Rothen M, Meuller G, Yamaguchi DK. Mutans streptococci dose response to xylitol chewing gum. J Dent Res, 85(2): 177–81, 2006.
104. Mäkinen KK, Alanen PA, Isokangas P, Isotupa K, Söderling E, Mäkinen PL, Wenhui W, Weijan W, Xiaochi C, Yi W, Boxue Z. Thirty-nine-month xylitol chewing gum programme in initially eight year old school children: a feasibility study focusing on *mutans streptococci* and *lactobacilli*. Int Dent J, 58(1): 41–50, 2008.
105. Loesche WJ, Grossman NS, Earnest R, Corpron R. The effect of chewing xylitol gum on the plaque and salivary levels of *Streptococcus mutans*. J Am Dent Assoc, 108(4): 587–92, 1984.
106. Mäkinen KK. Dietary prevention of dental caries by xylitol-clinical effectiveness and safety. J Appl Nutr, 44: 16–28, 1991.
107. Mäkinen KK. Prevention of dental caries with xylitol- A potential dietary procedure for self-care and population-level use in young adults. J Am College Health, 41: 172–80, 1993.
108. Peldyak J, Mäkinen KK. Xylitol for caries prevention. J Dent Hygiene, 76(4): 276–85, 2002.
109. Sanchita Bhattacharya, Salima Virani, Mashenka Zavro, Gerhard J. Haas. Inhibition of *Streptococcus Mutans* and Other Oral Streptococci by Hop (Humulus Lupulus L.) Economic Botany, 57(1): 118–25, 2003.
110. Yamanaka A, Kimizuka R, Kato T, Okuda K. Inhibitory effects of cranberry juice on attachment of oral streptococci and biofilm formation. Oral Microbiol Immunol, 19(3): 150–4, 2004.
111. Chung JY, Choo JH, Lee MH, Hwang JK. Anticariogenic activity of macelignan isolated from Myristica fragrans (nutmeg) against *Streptococcus mutans*. Phytomedicine, 13(4): 261–6, 2006.
112. Bianchini, Bedendo IP. Efeito antibiótic do própolis sobre bactérias fitopatogênicas. Piracicaba: Scientia Agrícola; 1988.
113. Manara LRB, Anconi SI, Gromatzky A, conde MC, Bretz WA. Utilização da própolis em odotnologia. [The use of propolis in dentistry]. Rev Fac Odontol Bauru, 7(3/4): 15–20, 1999.
114. Silva EB. Efeito da a ção da própolis na lamina própria da mucosa buccal de ratos: estudo histologico. Robrac, 9(28): 4–8, 2000.
115. Fernandes A Jr, Orsi RO, Sforcin JM, Rall VLM, Funari SRC, Barbosa L. The antibacterial activity of propolis produced by Apis mellifera L. and Brazilian stingless bees. J Venom Anim Toxins, 7(2): 173–82, 2001.
116. Koo H, Rosalen PL, Cury JA, Park YK, Bowen WH. Effects of compounds found in propolis on Streptococccus mutans growth and on glucosyltransferace activity. Antimicrob Agents Chemother, 46(5): 1302–9, 2002.
117. Silvana Alves de CD, Azizedite GG, Fernando JMA. Effect of a propolis extract on Streptoccocus mutans counts in vivo. J Appl Oral Sci, 15(5): Bauru Sept/Oct, 2007.
118. Uzel A, Sorkun K, Oncag O, Cogulu D, Gencay O, Salih B. Chemical compositions and antimicrobial activities of four different Anatolian propolis samples. Microbiol Res, 160(2): 189–95, 2005.
119. Feres M, Figueiredo LC, Barreto IM, Coelho MH, Araujo MW, Cortelli SC. In vitro antimicrobial activity of plant extracts and propolis in saliva samples of healthy and periodontally-involved subjects. J Int Acad Periodontol, 7(3): 90–6, 2005.
120. Menezes SMS, Cordeiro LN, Viana GSB. Punica granatum (pomegranate) extract is active against dental plaque. J Herb Pharmacotherapy, 6: 79–92, 2006.
121. Vasconcelos LCDS, Sampaio FC, Sampaio MCC, Pereira MDSV, Higino JS, Peixoto MHP. Minimum inhibitory concentration of adherence of Punica granatum Linn (pomegranate) gel against S. mutans, S. mitis and C. albicans. Braz Dent J, 17(3): 223–7, 2006.
122. Sofrata AH, Claesson RL, Lingström PK, Gustafsson AK. Strong antibacterial effect of miswak against oral microorganisms associated with periodontitis and caries. J Periodontol, 79(8): 1474–9, 2008.
123. Akihiro O, Harafumie Saito ,Tsugio Matsuhisa. Screening of Antibacterial Activities of Edible Plants against Streptococcus mutans. Food Sci Technol Res, 14 (2): 190–3, 2008.
124. Wu CD. Grape products and oral health. J Nutr, 139(9): 1818 'S'- 23 'S', 2009.
125. Didry N, Dubreuil L, Trotin F, Pinkas M. Antimicrobial activity of aerial parts of Drosera peltata. Smith on oral bacteria. J Ethnopharmacol, 60(1): 91–6, 1998.
126. Hu JP, Takahashi N, Yamada T. Coptidis rhizoma inhibits growth and proteases of oral bacteria. Oral Dis, 6(5): 297–302, 2000.
127. Park KM, You JS, Lee HY, Baek NI, Hwang JK. Kuwanon G, An antibacterial agent from the root bark of Morus alba against oral pathogens. J Ethnopharmacol, 84(2–3): 181–5, 2003.
128. Nostro A, Cannatelli MA, Crisafi G, Musolino AD, Procopio F, Alonzo V. Modifications of hydrophobicity, in vitro adherence and cellular aggregation of Streptococcus mutans by Helichrysum italicum extract. Lett Appl Microbiol, 38(5): 423–7, 2004.
129. Nagata H, Inagaki Y, Yamamoto Y, Maeda K, Kataoka K, Osawa K. Inhibitory effects of macrocarpals on the biological activity of Porphyromonas gingivalis and other periodontopathic bacteria. Oral Microbiol Immunol, 21(3): 159–63, 2006.
130. Sterer N. Antimicrobial effect of mastic gum methanolic extract against Porphyromonas gingivalis. J Med Food, 9(2): 290–2, 2006.
131. Prabu GR, Gnanamani A, Sadulla S. Guaijaverin. A plant flavonoid as potential antiplaque agent against Streptococcus mutans. J Appl Microbiol, 101(2): 487–95, 2006.
132. Song JH, Kim SK, Chang KW, Han SK, Yi HK, Jeon JG. In vitro inhibitory effects of Polygonum cuspidatum on bacterial viability and virulence factors of Streptococcus mutans and Streptococcus sobrinus. Arch Oral Biol, 51(12): 1131–40, 2006.
133. Silva ML, Coimbra HS, Pereira AC, Almeida VA, Lima TC,Costa ES. Evaluation of Piper cubeba extract, cubebin and its semi-synthetic derivatives against oral pathogens. Phytother Res, 21(5): 420–2, 2007.

134. Smullen J, Koutsou GA, Foster HA, Zumbe A, Storey DM. The antibacterial activity of plant extracts containing polyphenols against Streptococcus mutans. Caries Res, 41(5): 342–9, 2007.
135. Tsui VW, Wong RW, Rabie AB. The inhibitory effects of naringin on the growth of periodontal pathogens in vitro. Phytother Res, 22(3): 401–6, 2008.
136. Bispo MD, Mourao RHV, Franzotti EM et al. Antinociceptive and antiedematogenic effects of the abueous extract of Hyptis pectinata leaves in experimental animals. J Ethnopharmacol, 76(1): 81–6, 2001.
137. Alviano WS, Mendonca-Filho RR, Alviano DS et al. Antimicrobial activity of Croton cajucara Benth linalool-rich essential oil on artificial biofilms and planktonic microorganisms. Oral Microbiol Immunol, 20: 1–5, 2005.
138. Hammer KA, Dry L, Johnson M, Michalak EM, Carson CF, Riley TV. Susceptibility of oral bacteria to Melaleuca alternifolia (tea tree) oil in vitro. Oral Microbiol Immunol, 18(6): 389–92, 2003.
139. Shapiro S, Meir A, Guggenheim B. The antimicrobial activity of essential oils and essential oil components towards oral bacteria. Oral Microbio Immunol, 9(4): 202–8, 1994.
140. Groppo FC, Bergamaschi C, Cogok, Franz-Montan M, Motta RH, de Andrade ED. Use of phytotherapy in dentistry. Phytother Res, 22(8): 993–8, 2008.
141. Sanjib Bhattacharya. Phytosomes: Emerging Strategy in Delivery of Herbal Drugs and Nutraceuticals. Pharma Times, 41 (3): 9–12, 2009.
142. Bombardelli E, Curri SB, Loggia RD, Del NP, Tubaro A, Gariboldi P. Complexes between phospholipids and vegetal derivatives of biological interest. Fitoterapia, 60: 1–9, 1989.
143. Murray. Phytosomes-Increase the absorption of herbal extract. Available at: www.doctormurray.com/articles/silybin.htm Accessed-Sept. 28, 2008.
144. Bombardelli E, Spelta M, Loggia RD, Sosa S, Tubaro A. Aging skin: Protective effect of silymarin-Phytosome. Fitoterapia, 62(2): 115–22, 1991.
145. Kidd P, Head K. A review of the bioavailability and clinical efficacy of milk thistle Phytosome: a silybinphosphatidylcholine complex. Altern Med Rev, 10(3): 193–203, 2005.
146. Yanyu x, Yunmei S, Zhipeng C, Quineng P. The preparation of silybinphospholipid complex and the study on its pharmacokinetics in rats. Int J Pharm, 3; 307(1): 77–82, 2006.
147. Vitamedics, Phytosome products. Available at www.vitamedics.com. Accessed-Sept. 19, 2008.
148. Barzaghi N, Crema F, Gatti G, Pifferi G, Perucca E. Pharmacokinetic studies on IdB 1016, a silybin phosphatidylcholine complex in healthy human subjects. Eur J Drug Metab Pharmacokinet, 15: 333–8, 1990.
149. Bombardelli E. Phytosomes in functional cosmetics. Fitoterapia, 65(5): 320–7, 1994.