Medicinal Plants and the Secondary Metabolites: Potential in Dental Care and Cure

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Abstract: Periodontitis and dental caries are infectious diseases that are claimed to be most widespread among the human population. *S. mutans* has long been considered the major culprit in dental caries formation but the process of odontogenic infections requires the association of more than one species of microbes. It includes both the gram-positive and gram negative bacteria. Plants for oral health mostly had antimicrobial activity against culprit oral microbes that includes gram-positive, gram- negative bacteria and fungal species. Possible role in dentistry of any plant extract or natural product could be verified by knowing their inhibitory activity against dental plaque, GTF (Glucosyltransferase), calculi formation etc.

Keywords: Oral care, Natural products, Higher plants, Plant extracts and fractions, Oral microbes, Dental caries, Antimicrobial activities, MIC, *Streptococcus mutans, Streptococcus sanguis,* Clinical trials.

INTRODUCTION

Periodontal diseases and dental caries are two main common dental pathologies affecting humankind [1]. It has been known since the early 1960s that bacteria play an important role in the initiation and progression of dental diseases [2]. In 1942, *Streptococcus mutans* was isolated from human carious lesion, but subsequently was not thoroughly studied until 1960s when it was identified as a etiological agent of a transmissible caries infection in redent models [3]. *Streptococcus mutans* has long been considered as one of the primary causative agents of dental caries but this notion has now been weakened through more profound and intense researches [9]. Indeed, cavities are the single most common chronic disease of childhood, with a rate five times greater than that seen for the next most prevalent disease, asthma [5]. Incidence of dental caries is most prevalent in industrialized countries. As the treatment is very costly and requires a lot of manpower, the prevention at the primary level is the solution of choice. Dental plaque is formed by the colonization and accumulation of oral microorganisms in the insoluble glucan layer that are synthesized by glucosyltransferase (GTF) from *Streptococcus mutans* [6]. Finding healing powers in plants is an ancient idea. People on all continents have long applied poultices and imbibed infusions of hundreds, if not thousands, of indigenous plants, dating back to prehistory. Historically, therapeutic results have been mixed; quite often cures or symptom relief resulted. Poisonings occurred at a high rate, also. Currently, of the one-quarter to one-half of all pharmaceuticals dispensed in the United States having higher-plant origins, very few are intended for use as antimicrobials, since we have relied on bacterial and fungal sources for these activities. Since the advent of antibiotics in the 1950s, the use of plant derivatives as antimicrobials has been virtually nonexistent [7]. It is well established that antibacterial mouth rinses are effective in decreasing tooth surface plaque. In general, mouth rinses may contain fluorides, alcohols, detergents and other antimicrobial substances. Such synthetic antimicrobials include povidone iodine products, chlorhexidine and cetylpyridinium chloride. Toothpastes also contain fluorides and other antimicrobials including triclosan and zinc citrate. Natural antibacterial substances are now attracting attention as useful antimicrobials to be incorporated into mouth rinses and toothpastes. For example, extracts of miswak, tea tree oil, peppermint, green tea and Manuka honey have all recently been incorporated into such products to enhance their antimicrobial properties [8].

HERBALS IN DENTISTRY

Bacterial Plaque and Bacterial Virulence

Periodontitis and dental caries are infectious diseases that are claimed to be most widespread among the human population. They are the endogenous infections as the etiologic agents of these diseases are the microbial population residing within the oral cavity.

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More than 300 species of microorganisms are isolated from periodontal pockets, among them some are pathogenic. Even from the pathogenic species not all the strains are pathogenic. Microorganisms are widely accepted as the key etiologic factor of the periodontal diseases. They start colonizing in the oral cavity by forming a translucent to yellowish plaque biofilm on the teeth. Actually bacteria itself are not the culprits but their metabolites and constituents are the reason for the disease. This is called bacterial virulence and it activates the host defense mechanism that further aggravates the disease [10].

Etiology of periodontal diseases is associated to microbes. Acute inflammation with infiltrations of neutrophils, collagen degradation, changes in vasculature and epithelial tissues are visible in initial stages of gingivitis the pathological changes are due to the activation of host defense system as a consequence of bacterial influence in the gingival tissues. Chronic gingivitis lesion is due to activation of cell-mediated immunity and is predominant with the accumulation of B-lymphocytes and plasma cells. This is resolved just by removal of plaque without the need of further treatment. Acute necrotizing ulcerative gingivitis (ANUG) occurs when there is tissue infiltration of spirochetes and non-spirochetes. Non-spirochetes are dominated by *Prevotella intermedia* and *Fusobacterium nucleatum.*

Periodontitis is an odontologic infection which can be defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganism or group of specific microorganism, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both [11].

Periodontitis is not due to progression of gingivitis, then who is the culprit? Periodontal Pathogenic Microorganisms are the culprit and they have the ability of colonizes, evade host defense system and produce toxins that cause periodontium destruction. Bacterial plaque is the main source of bacterial colonization. Plaque is basically a net of bacteria and its degradation products that accumulate on the surface of tooth mostly in unhygienic mouth. Pathogenic microorganisms are able to attach firmly to tissues and other bacteria. These appendages in the bacteria include fimbriae or other molecules such as adhesins. There may be a capsular polysaccharide (*e.g*. in *P. gingivalis*) to resist the host defense mechanisms such as complement system and antibodies. *A. actinomycetemcomitans* , *P. gingivalis* and *Fusobacterium nucleatum* caused destruction of periodontal tissues by direct means (tissue invasion). *A. actinomycetemcomitans* produce leukotoxins toxins capable of causing periodontium destruction. Substances released by host defense mechanism in order to combat microbial attack *i.e*. Interleukin 1, Interleukin 6, Interleukin 8, Tumor necrosis factor alpha, Prostaglandin E2 are capable of collagen destruction and periodontal tissue damage [12].

Natural Products in Dentistry

Natural products could be tested for their antimicrobial activities against oral pathogens and *in vivo* assays that include animal studies and clinical trials.

Although plants have tremendous potential to be used as anti-infective as it was manifested by practice of traditional medicine, there are comparatively less number of phytochemicals used clinically as antimicrobials than used for other disease conditions. This fact itself supports the idea of screening plants as a source of novel antimicrobials [7, 13-15].

Analyzing Herbals for Dentistry

Possible role in dentistry of any plant extract or natural product could be verified by knowing their inhibitory activity/activities on GTF, F-ATPase, salivary alpha amylase, acid production, acid tolerance of *S. mutans* and *S. sobrinus,* biofilm formation, cell surface hydrophobicity of *S. mutans,* sacharolytic capability of *S. mutans,* sucrose induced cellular aggregation of *S. mutans,* adherence of *S. mutans*, calcium phosphate precipitation (calculi formation) and ability to eleviate plaque pH after sucrose or acidogenic challenge. In addition to anti GTF and anti adherence assays (on bacterial biofilms and/or sliva coated hydroxy apatite (sHA) beads/disk), natural products could be tested for their antimicrobial activities against oral pathogens and *in vivo* assays that includes animal studies and clinical trials.

Oral Care Plants and Natural Products

In dentistry the plants could be adapted well, for instances, Cacao bean husk extract lead to reduction in caries development and plaque formation at minimum cariostatic concentration of 1.0 mg/ml in rats infected with either *S. sobrinus* or *S. mutans.* In addition, at >5mg/ml of the husk extract upto 80% inhibition of sucrose dependent cell adherence of *S. mutans* and *S. sobrinus* was observed [16]. Besides, Apigenin, at 135 micrgram/ml, showed 90.5 - 95% inhibition of GTF [17].

In another study, GPE (green propolis extract) at >0.1mg/ml and Bd-LRE (*Baccharis dracunculifolia* leaf rinse exts) at 0.2 mg/ml showed significant reduction in acid production [18]. In addition, *Galla rhois, Psoralea corylifolia, Camellia sinensis* and *Salvia miltirrhiza* can be adapted in dentistry as they inhibited artificial dental plaque and did not reduced the cell viability in human gingival fibroblasts [19]. Also Isothiocyanates from Wasabi showed anticaries effects [20]. Likewise chloroform-methanol fraction of ethanolic extract of *Nidus vespae* showed anti biofilm activity of *S. mutans* at MBIC50=8mg/ml and MBRC50=16mg/ml tested by microdilution method and antiadherence activity of *S. mutans*on S-HA (sliva coated hydroxyapatite) discs and also the extract and chemical fractions of this plant lowered the percentage of polysaccharide compounds and retarded the pH decrease in the biofilm matrix [21, 22]. *Curcuma xanthorrhiza* extract with and without xylitol inhibited the fermentation of polysaccharides by *S. mutans* [23] (Table **1** and **2**). A little later, xanthorrhizol from the same plant extract showed dental plaque inhibition [24]. Also extracts and condensed tannins of *Paullinia cupana* showed *in vitro* dental plaque prevention [25]. Also, a palatal mucoadhesive tablet containing herbal formulation (echinacea, sage, lavender and mastic gum) reduced oral malodor in a clinical study [26].

Antimicrobial Plants

To combat such a vast variety of microorganisms and in a search of newer antimicrobial agents for oral health to be used as anti-plaque and oral care agents with lesser side effects profile, non-other choice is better than phytochemicals and if it is for the dentistry, natural products and botanicals have showed remarkable activity for both dental care and cure [27, 28].

Although plants have tremendous potential to be used as anti-infective as it was manifested by practice of traditional medicine, there are comparatively less number of phytochemicals used clinically as antimicrobials than used for other disease conditions. This fact itself supports the idea of screening plants as a source of novel antimicrobials [7, 13-15].

Besides, aqueous, methanolic and mixed aqueous-methanolic extracts of stem bark of *Bridelia grandis* showed antibacterial activity against oral streptococci [29] Further, isopanduratin A from *Kaempferia pandurata* showed damage to the cell membrane and cell wall of *S. mutans* by transmission electron microscopy (TEM) [30]. In addition, *Ginkgo biloba* showed anti-adhesion to *S. mutans* with a MIC of 5g/l [31] (Table **1** and **2**, Figure **1** and **2**).

Moreover, recommended *Vernonia amygdalina, Fagara zanthoxyloides, Terminalia glaucescens, Camellia sinensis, Melaleuca alternifolia, Arctium lappa, Hyptis divaricat, Allium cepa, Allium sativum* and *Massularia acuminata,* to have potential to be used in dentistry due to their antimicrobial potential against oral pathogens; Eucalyptus oil, orange oil*, Matricaria*

Table 1: Antimicrobial Activities of Natural Products Against Oral Microbes

Plant	Natural Products	MIC* Against *S. mutans*	MIC* Range**	MBC* Against *S. mutans*	MBC* Range**	References
Saphora flavescens (roots)	SophoraflavanoneG	3.2	0.2-6.4	3.2	0.8-12.8	[33]
Eucalyptus globulus	Macrocarpals C	0.39	0.20-1.56	-	-	[34]
Green tea leaves	Polyphenols	500	< 1->2000	-	-	[35]
Kaempferia pandurata	Isopanduratin A	4	4	-	-	[30]
-	Sanguinarine	12	-	-	-	[30]
-	Carvacrol	125	-	-	-	[30]
-	Thymol	250	-	-	-	[30]
-	Iso eugenol	500	-	-	-	[30]
-	Eucalyptol	500	-	-	-	[30]
Pinus pinaster (B)	Pycogenol (standardized extract 0.025%)	-	-	-	20-250	[36]
Moutan cortex	Gallic acid	312.5	-	-	-	[37]

*The values of MIC and MBC are in microgram/ml.
**Range of MIC or MBC for other oral microbes tested.

Table 2: Antimicrobial Activities of Plant Extracts and Fractions Against Oral Microbes

Plant	Plant Part	Extract/fraction	MIC* Against *S. mutans*	MIC* Range**	MBC* Against *S. mutans*	MBC* Range**	References
Curcuma xanthorrhiza	-	-	5	5	-	-	[23]
Curcuma xanthorrhiza extract+xylitol	-	-	10	5-10	-	-	[23]
Propolis (southern specy)	-	Hexane fraction	20-50	12.5-50	50-100	-	[14]
Red propolis	-	Chloroform extract	25-50	25-50	100-200	100-200	[4]
Rheum undulatum	Rhei rhizoma (roots)	Dichloromethane fraction of methanol extract	250	50-500	-	-	[39]
Salvia miltiorrhiza bunge	-	EtOH	62500	15620-62500	-	-	[38]

*The values of MIC and MBC are in microgram/ml.
**Range of MIC or MBC for other oral microbes tested.

Figure 1: Some medicinal products for dentistry: *Kaempferia pandurata, Rheum undulatum, Salvia miltiorrhiz*, Propolis, Green tea (up to down, left to right).

recutita L. and the tea tree oil could be used as endodontic irrigants; Guaco, *M. laevigata* and *M. involucrate, Kalanchoe brasiliensis, Plumeria acuminate, M. chamomilla* could be used as anti-inflammatory and *Melissa officinalis, Valeriana officinalis, Passiflora incarnate* and *Piper methysticum* could be used as hypnosis and anxiolytics in the field of dentistry [32].

CONCLUSION

Major dental and gum diseases are due to microbial growth. Key ingredient in the initiation and progression of the disease are the plaque bacteria. These bacteria initiate and progress the disease in both direct and indirect means [12]. *S. mutans* and *S. sobrinus* are supposed to initiate the carious lesions in teeth in

human kind. They released GTF which synthesize insoluble glucan from sucrose. The glucan synthesizes the plaque which accumulates and adheres the culprit bacteria and acids which leads to demineralization of teeth, dental caries and periodontal diseases. *S. mutans* also synthesize organic acids [16]. Although, *S. mutans* has long been considered the major culprit in dental caries formation but the process of odontogenic infections requires the association of more than one species of microbes. It includes both the gram-positive and gram negative bacteria [9]. Plants for oral health mostly had antimicrobial activity against culprit oral microbes that includes gram-positive, gram-negative bacteria and fungal species [16].

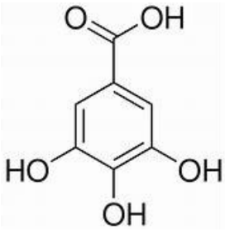

Figure 2: Structure of Gallic acid.

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