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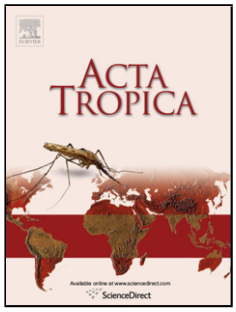

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Plants and other natural products used in the management of oral infections and improvement of oral health

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Graphical abstract

This article reviews plants and other natural products used in oral health: *Punica granatum* L. (pomegranate), *Matricaria recutita* L. (chamomile), *Camellia sinensis* (L.) Kuntze (green tea), chewing sticks made from *Diospyros mespiliformis* Hochst. ex A.DC., *Diospyros lycioides* Desf., and *Salvadora persica* L. (miswak), honey and propolis from the manuka tree (*Leptospermum scoparium* J.R.Forst. & G.Forst.), rhein from *Rheum rhabarbarum* L. (rhubarb), dried fruits of *Vitis vinifera* L. (raisins), essential oils, probiotics and mushrooms.

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Highlights

- A rigorous review of natural products used in oral health was conducted
- *Punica granatum*, *Matricaria recutita*, *Vitis vinifera* and *Camellia sinensis* are used
- Other plants are *Diospyros mespiliformis*, *Diospyros lycioides* and *Salvadora persica*
- Honey, propolis, rhein, essential oils, probiotics and mushrooms are also used
- Data on clinical efficacy and toxicity are urgently needed
- More research and funding are also needed in the field of natural products for oral health

Abstract

Challenges of resistance to synthetic antimicrobials have opened new vistas in the search for natural products. This article reviews plants and other natural products used in oral health: *Punica granatum* L. (pomegranate), *Matricaria recutita* L. (chamomile), *Camellia sinensis* (L.) Kuntze (green tea), chewing sticks made from *Diospyros mespiliformis* Hochst. ex A.DC., *Diospyros lycioides* Desf., and *Salvadora persica* L. (miswak), honey and propolis from the manuka tree (*Leptospermum scoparium* J.R.Forst. & G.Forst.), rhein from *Rheum rhabarbarum* L. (rhubarb), dried fruits of *Vitis vinifera* L. (raisins), essential oils, probiotics and mushrooms. Further, the review highlights plants from Africa, Asia, Brazil, Mexico, Europe, and the Middle East. Some of the plants' antimicrobial properties and chemical principles have been elucidated. While the use of natural products for oral health is prominent in resource-poor settings, antimicrobial testing is mainly conducted in the following countries (in decreasing order of magnitude): India, South Africa, Brazil, Japan, France, Egypt, Iran, Mexico, Kenya, Switzerland, Nigeria, Australia, Uganda, and the United Kingdom. While the review exposes a dire gap for more studies on clinical efficacy and toxicity, the following emerging trend was noted: basic research on plants for oral health is mainly done in Brazil, Europe and Australia. Brazil, China, India and New Zealand generally conduct value addition of natural products for fortification of toothpastes. African countries focus on bioprospecting and primary production of raw plants and other natural products with antimicrobial efficacies. The Middle East and Egypt predominantly research on plants used as chewing sticks. More research and funding are needed in the field of natural products for oral health, especially in Africa where oral diseases are fuelled by human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS).

Keywords: Plants; Natural products; Pathogens; Management; Improvement; Oral health

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1. Introduction

The human oral cavity is heavily colonised by disease-causing microbes such as viruses, protozoa, fungi, Archaea and the true bacteria (Eubacteria). Many species of bacteria have been isolated from the mouth most of which are innocuous. Oral microbes are responsible for two common diseases of humans: dental caries and the periodontal diseases. Dental caries and periodontal diseases are one of the most common infectious diseases affecting humans. Thus, plaque-related diseases are probably the most common bacterial diseases of humans.

Periodontitis involves inflammation around the tooth. It is a serious gum infection that damages the soft tissue and bone that supports the tooth. Periodontitis is associated with oral microbiota including *Aggregatibacter actinomycetemcomitans, Eikenella corrodens, Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Enterococcus faecalis* and *Treponema denticola* (Amir Alireza et al., 2014). *P. gingivalis, P. intermedia* and *A. actinomycetemcomitans* are regarded as the major pathogens in advancing periodontitis (Allaker and Douglas, 2008). Archaea including *Methanobrevibacter oralis*, *Methanobacterium* spp., *Methanosarcina* spp., and *Thermoplasmata* spp. are also responsible for oral diseases (Maeda et al., 2013). *M. oralis* is the dominant archaeal species in sub-gingival plaque.

Gingivitis is a mild and reversible form of periodontal disease, but periodontitis causes permanent damage to tooth-supporting tissues and may lead to tooth loss (Bonifait et al., 2012). While as many as 700 different bacterial species may be present in sub-gingival plaque samples, strong experimental evidence has emerged to implicate *P. gingivalis*, a Gram-negative anaerobic bacterium often found in association with *T. forsythia* and *T. denticola*, as one of the key pathogens in periodontitis (Azelmat et al., 2014).

For a long time, the upkeep of oral hygiene has been premised on the use of chemical agents (Allaker and Douglas, 2008). For instance, mouth rinses are often employed in the prevention and treatment of oral infections. Mouth-rinses may contain fluorides, alcohols, detergents and other antimicrobial substances. Toothpastes also contain fluorides and other antimicrobials

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including triclosan and zinc citrate. Synthetic antimicrobials include povidone iodine products, flourides, phenol derivatives, chlorhexidine and cetyl pyridinium chloride. Antibiotics like ampicillin, erythromycin, penicillin, tetracycline, and vancomycin are also widely used in dentistry to inhibit bacterial growth (Jang et al., 2014).

Nowadays, oral microbes have developed resistance to antibiotics and synthetic chemicals. Thus, many antibiotics and synthetic oral hygiene products have diminished clinical efficacy, especially in persons with HIV/AIDS. Synthetic substances also have several adverse effects such as vomiting, diarrhoea and teeth staining (Alviano et al., 2008). In the wake of these shortcomings, plants and other natural antibacterial substances are now attracting attention as useful and alternative antimicrobials to be incorporated into mouth rinses and toothpastes.

Since plants are the sources of more than 25% of prescription and over-the-counter drugs, conventional medicine is increasingly becoming receptive to the use of antimicrobials derived from plants and other natural products. The rise in the use of herbal medicines has renewed interest in the effects of plant extracts to control plaque and other oral diseases (Lobo et al., 2014). Screening for antimicrobial agents isolated from plants is a feasible approach to the identification of natural compounds with antimicrobial properties against dental pathogens (Tichy and Novak, 1998). In fact, compounds that possess antimicrobial activities against oral pathogens are now being isolated from plants traditionally used as oral remedies (Rivero-Cruz et al., 2008).

The main aim of this review is to document the current status of plants and other natural products used in oral health. Plants and other natural products used for oral health in Africa, Asia, Brazil, Mexico, Europe, and the Middle East are described. Finally, poly-herbal treatments for oral infections and plant compounds for prevention and treatment of oral infections are reviewed. This review is important because the oral cavity is an important site for human diseases in poor settings and during HIV infection.

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2. Oral cavity as a site for diseases

Dental caries, a medical term for tooth decay or cavities, is a poly-microbial disease caused by specific bacteria that produce acid which destroys the tooth's enamel and the layer under it (dentin). Allaker and Douglas (2008) stated that dental caries can progress to inflammation and death of vital pulp tissue, with eventual spread of infection to the periapical area of the tooth and beyond. The disease process involves acidogenic plaque bacteria, including *Streptococcus mutans, Streptococcus sobrinus* and *Lactobacillus* spp. (Maeda et al., 2013).

In individuals who repeatedly ingest high levels of carbohydrates, especially those that drink beer, the frequency of acid production leads to erosion of the buffering capacity of saliva and sustained reductions in pH. In turn, this favours the growth of oral microbiota that grows well in acidic environments. Aciduric bacterial species, particularly *S. mutans* and *Lactobacillus* spp. continue to produce acid and thus exacerbate the damage to dental hard tissues. *S. mutans* and *S. sobrinus*, the main acidogenic components of dental biofilm, break down exogenous dietary carbohydrates to produce lactic acid, resulting in demineralization of tooth enamel (Bonifait et al., 2012).

Biofilm is a dense non-calcified mass composed of microorganisms, *Streptococcus mitis* and *S. sanguis* being the pioneers (Batista et al., 2014). It is a matrix rich in bacterial extracellular polysaccharides and salivary glycoproteins, firmly attached to the teeth and other hard surfaces of the oral cavity. The development of the oral biofilm is a major factor responsible for the emergence of various diseases including dental cavities, gingivitis and periodontitis (Barbieri et al., 2014). As dental biofilm matures, colonization shifts towards facultative and anaerobic bacterial species leading to supra-gingival plaque accumulation and gingival inflammation which are the first clinical signs of periodontal disease (Bonifait et al., 2012).

Dental caries develop due to an increase in strongly acidogenic and aciduric Gram-positive bacteria while common forms of periodontal disease are linked to anaerobic Gram-negative bacteria in subgingival plaque. While caries and periodontitis are bacterial diseases, Wade (2013) makes the case that they are not infectious diseases *sensu stricto* because they result from a

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complex interaction between the commensal microbiota, host susceptibility and environmental factors such as diet and smoking. Periodontitis, in particular, appears to result from an inappropriate inflammatory reaction to the normal microbiota, exacerbated by the presence of some disease-associated bacterial species.

Caries and gingivitis/periodontitis are plaque-dependent oral pathologies while dental plaque is a bacterial biofilm. As a consequence to pathogens that cause oral diseases, people should always engage in regular oral hygiene practices, especially brushing with toothpastes, or rinsing with mouthwashes. Brushing, a common physical method of biofilm removal is practically important but sometimes difficult to perform as it requires reasonable control, time, motivation and manual dexterity (Batista et al., 2014). Due to high costs, many people hardly buy and use commercial oral hygiene products. Toothpaste and tooth brushes are beyond the reach of the majority poor. Yet, with increasing incidences of oral diseases especially due to HIV/AIDS, many poor folks turn to the use of plant products to prevent and treat oral infections like dental caries and periodontal disease which are the most common infectious diseases of humans.

3. Oral diseases during HIV infection

Oral hygiene is very important in HIV/AIDS. The oral microbiome and the immunobiology of periodontal disease and caries have been reviewed by Costalonga and Herzberg (2014). These authors argue that impairment of the gingival immune response leads to the pathology of periodontal tissue. Oral diseases are intimately linked to HIV/AIDS. During HIV infection, periodontal diseases are a sign of progression to AIDS. Depletion of CD4 cells is the hallmark of HIV infection. Initial immune suppression is indicated by CD4 levels below 500 and signals the first appearance of systemic and oral opportunistic infections.

In HIV-infected subjects, increased progression and aggression of periodontitis is related to lower CD4 counts. High viral load, too, is associated with increased tooth loss. There are significant associations between a CD4 count of less than 200 with periodontitis and oral hairy leukoplakia in HIV-infected pregnant women. Chronic periodontitis was associated with CD4 count lower than 200 cells/mm^3 in HIV-infected women (Pattrapornnan and DeRouen, 2013).

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It is not surprising that more than one third of people who are seropositive for HIV and approximately 90% of people with AIDS develop HIV associated oral lesions during the course of the disease. HIV can also enter the mouth via gingival crevicular fluid (Wade, 2013). Studies have shown that oral health and periodontal status closely reflect the immune status of an individual. HIV-infected patients have an increased risk of developing more aggressive periodontitis. Oxidative stress in the oral cavity also increases the risk of aggressive periodontitis (Avezov et al., 2014). Oral cancer is among the commonest malignancies in HIV/AIDS, with 900,000 new global cases diagnosed annually (Lopes et al., 2012).

In HIV/AIDS persons, oral candidiasis is an opportunistic infection of the oral cavity caused by an overgrowth of *Candida* species, the most common being *Candida albicans* (Bonifait et al., 2012). The most prevalent forms of oral candidiasis are pseudomembranous candidiasis (also called thrush) and erythematous candidiasis, which includes denture stomatitis (Bonifait et al., 2012). Occurrence of opportunistic oropharyngeal candidiasis is a clinical alarm for the onset of AIDS (Alili et al., 2014). Oropharyngeal candidiasis is the commonest fungal infection amongst HIV-positive individuals worldwide (Kwamin et al., 2013). Put differently, there is a strong association between oral candidiasis and AIDS.

The majority of oral candidiases are caused by the opportunistic pathogen *C. albicans*, followed by non-albicans *Candida species* such as *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. dubliniensis*, and *C. guilliermondii*. Due to HIV/AIDS, increased prevalence of resistance against anti-*Candida* agents is widely recognized in the global oral health care community. The yeast *C. albicans* is frequently associated with infections in HIV-positive patients (Sardi et al., 2011).

HIV-associated gingivitis and HIV-associated periodontitis do not respond well to conventional therapy and often progress very rapidly (Gonçalves et al., 2013). HIV-associated periodontitis is characterized by rapid destruction of the periodontal supporting apparatus and severe soft tissue damage. Even worse, in some HIV-associated periodontitis cases, more than 90% of the attachment is destroyed in as little as three to six months, resulting in early tooth loss. In HIV

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infected adults, treatment failure of periodontal diseases and losses of teeth are warning bells for AIDS.

Published research before the introduction of highly active antiretroviral therapy (HAART) indicates a significantly greater prevalence of periodontitis in HIV-infected patients when compared to sero-negative individuals (Gonçalves et al., 2013). However, antiretroviral therapy has markedly helped to de-escalate the proliferation of periodontal pathogens thus reducing the clinical manifestation of periodontitis. HAART provides a protector effect, keeping the pathogenic sub-gingival microbiota under control, even in previous cases of severe immunodeficiency. Indeed, the introduction of HAART has decreased the frequency of several oral diseases such as candidiasis, hairy leukoplakia, and Kaposi's sarcoma. However, it is critical to note that HAART does not provide protection via a direct effect. Rather, HAART reduces the frequency of opportunistic oral infections through indirect reconstitution of immunity.

Despite the importance of HAART in alleviating oral diseases, many have long believed that our indigenous plant species are impregnated with phytochemicals and chemical ingredients that inhibit the growth of oral pathogens. These plant extracts may be included into formulations of commercial toothpastes and mouthwashes or developed into novel drugs for oral pathogens. In retrospect, phytochemical and antimicrobial knowledge of our indigenous flora could play a crucial role in managing oral diseases brought on by HIV/AIDS. In addition, the rapid increase in antibiotic resistance and the side effects they cause has opened real possibilities in the application of natural plant extracts for oral diseases during HIV infection.

4. Plant species and common natural products used in oral health

In their review, Kouidhi et al. (2015) documented the potential use of plant extracts, essential oils and natural compounds as biofilm preventive agents in dentistry, including their origin and mechanism of biofilm inhibition. Inhibition of bacterial biofilms is achieved with extracts of *Salvadora persica* (toothbrush tree), *Juglans regia* L. (Persian walnut), *Vaccinium macrocarpon* Aiton, *Camellia sinensis (L.)* Kuntze, *Morus alba* L. **(**mulberry), *Trachyspermum ammi* Sprague, *Piper betle* L.,, *Vitis vinifera L.*, *Azadirachta indica* A.Juss. (neem), *Sanguinaria canadensis* L.,

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Myristica fragrans Houtt., *Kaempferia pandurata Roxb.*, *Pistacia atlantica* Desf., *Pistacia vera* Mill., *Achyranthes aspera* Guss., *Artocarpus lakoocha* Roxb., *Polygonum cuspidatum* Willd. ex Spreng., *Helichrysum litoreum* Guss., *Rosmarinus officinalis* L., *Mentha spicata* L., and *Eugenia caryophyllata* Thunb.

Earlier, Palombo (2011) also examined studies on plants whose extracts inhibit the growth of oral pathogens, reduce the development of biofilms and dental plaque, decrease the adhesion of bacteria to surfaces and lessen the symptoms of oral diseases. Some of the plants were: *Abies canadensis* (L).Mill., *Albizia julibrissin* Durazz., *Drosera peltata* Willd (contains plumbagin, an anti-HIV ingredient), Ginkgo *biloba* L., *Juniperus virginiana* L., *Pinus virginiana* Mill., *Sassafras albidum* (Nutt.)Nees, *Tanacetum vulgare* L., and *Thuja plicata* Donn ex D.Don. Other plant species with activity against oral pathogens are *Ageratum conyzoides* Sieber ex Steud., *Annona senegalensis* Pers., *Breynia nivosa* (W.Bull) Small, *Harungana madagascariensis* Poir, *Helichrysum italicum* (Roth) G.Don, and *Piper cubeba* Bojer.

For many years now, Listerine^{TM} Essential Oils Rinse, which contains the natural active ingredients menthol, methyl salicylate, eucalyptol, and thymol has been in widespread use (Allaker and Douglas, 2008). Methyl salicylate and menthol act as a cleaning agent and local anaesthetic, respectively. The antimicrobial agent eucalyptol is a colourless organic liquid, a cyclic ether and monoterpenoid.

Thymol, 2-isopropyl-5-methylphenol, is a natural monoterpene phenol derivative of cymene and an isomer of carvacrol (Nabavi et al., 2015). It is an antimicrobial agent and antiseptic commonly used in dental preparations to inhibit foul-odour producing bacteria. Nabavi et al. (2015) mentioned studies where thymol deters the growth of bacteria known to be resistant to antibiotics such as penicillin. Even more important, thymol possesses various biological and pharmacological benefits attributable to its anti-mutagenic, anti-tumour, antioxidant, and anti-inflammatory functions (Bhalla et al., 2013; Deb et al., 2011; Miguel, 2010; Shikov et al., 2014).

Common products like milk, honey, tea, *Vaccinium macrocarpon* Aiton (cranberries), edible mushroom, *Coffea arabica* L (common coffee), *Hordeum vulgare* L (barley coffee), *Vitis*

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vinifera L (grapes), and alcohol-free red wine are some of the representative natural foods and beverages that inhibit adhesion of bacteria in the buccal cavity (Signoretto et al., 2012). *Rosmarinus officianalis* L and *Salvia officianalis* L are useful as antiplaque agents in dental preparations (Smullen et al., 2012).

Extracts of *Melaleuca alternifolia* Cheel (tea tree) oil, *Aloe vera* (L.) Burm.f., miswak, peppermint, and manuka honey have all been incorporated into synthetic oral hygiene products to enhance their antimicrobial efficacies. Tea tree oil gel in Australia with anti-inflammatory properties relieved periodontal disease (Soukoulis and Hirsch, 2004). Bischoff and Guale (1998) also stated that *M. alternifolia* oil was usually added to commercial toothpaste, though it caused poisoning in cats. Aloe Dent Triple Action is a dentifrice containing *A. vera*. Meswak, an Indian toothpaste brand that was valued at US$3.2 million in 2007, is made from extracts of miswak. Pepsodent toothpaste contains green tea. Manuka Health New Zealand also makes a toothpaste and mouth rinse containing mild menthol, natural propolis and manuka honey.

In reducing oral infections and improving oral health, the following sections detail the significance of common natural products such as rhein, raisins, pomegranate, chamomile, honey, propolis, essential oils, green tea, chewing sticks, probiotics, nisin, and edible mushrooms.

4.1 Rhein

Azelmat et al. (2014) studied the effects of rhein, a major anthraquinone found in the roots of *Rheum rhabarbarum* (rhubarb), on the periodontopathogen *P. gingivalis*. The data revealed that rhein had significant inhibitory activity against the oral bacterium *P. gingivalis*, the Gram-negative anaerobe most commonly associated with periodontal diseases. Using polymerase chain reaction assays, they found that rhein impairs the pathogenicity of *P. gingivalis* by reducing transcription of genes coding for important virulence factors. The authors cite other studies where rhein inhibits the action of gingipains, enzymes that provide peptides and amino acids to aid the growth of *P. gingivalis*.

4.2 Raisins

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Rivero-Cruz et al. (2008) demonstrated the power of raisins in improving oral health. Raisins are dried grapes, the fruits of the plant *V. vinifera* (family Vitaceae). Experiments show that phytochemicals in raisins suppress growth of oral bacteria associated with dental diseases. Besides being a traditional and popular snack food, raisins contain polyphenols, antioxidants, flavonoids and iron that favour overall human health.

Various phytochemicals found in raisins include triterpenes, fatty acids, flavonoids, amino acids, hydroxycinnamic acids and 5-hydroxymethyl-2-furaldehyde (Rivero-Cruz et al., 2008). Oleanolic acid, oleanolic aldehyde, and 5-(hydroxymethyl)-2-furfural stall the growth of *P. gingivalis*, with minimum inhibitory concentration (MIC) values ranging from 3.5 to 488 µg/mL (Rivero-Cruz et al., 2008). Besides its antibacterial benefits, oleanolic acid also plays valuable pharmacological functions due to its anti-inflammatory, anti-tumour, and anti-HIV properties.

4.3 Pomegranate and chamomile

Bailly (2009) maintains that good old drugs from plants and microbes remain essential. In this light, Batista et al. (2014) conducted a randomized controlled clinical trial to evaluate the effectiveness of a mouth rinse with *Punica granatum* and *Matricaria recutita* plant extracts, compared to 0.12% chlorhexidine in gingival bleeding subjects. The mouth rinses with the herbal products were equally effective in alleviating this oral condition, producing antimicrobial and anti-inflammatory properties similar to that of chlorhexidine.

According to Batista et al. (2014), *M. recutita* contains flavonoids and volatile oil rich in terpenoids such as alpha-bisabolol, azulene, matricine and chamazulene. These components provide the anti-inflammatory, antispasmodic and antibacterial activity of *M. recutita*. *P. granatum* prevents and has the potential to fight oral diseases due to its antioxidant, antiviral, antiparasitic, antifungal and anti-cancer properties. It has antibacterial action against *Staphylococcus aureus* and *Salmonella typhi*, and its anti-inflammatory, healing and antiseptic activities are attributable to the large amounts of tannin in the fruit skin (Batista et al., 2014).

4.4 Honey and propolis

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In their review of novel antimicrobial therapies for dental plaque-related diseases, Allaker and Douglas (2008) documented that manuka honey derived from the flowers of *Leptospermum scoparium* (manuka tree) in New Zealand, is widely utilised in the treatment of cariogenic and periodontopathic bacteria. Along a similar trajectory, propolis is added to Colgate Herbal Propolis toothpaste manufactured by Colgate Palmolive in Brazil, and exported to many African countries including Namibia and Zambia.

Propolis is a resinous product collected by honeybees from various plant sources (Kujumgiev et al., 1999). It is a substance used in defence of the beehive including embalming invaders which bees have killed but cannot transport out of the hive. A multifunctional material which bees use as a glue to make and maintain their hives, propolis contains flavonoids, phenolic acids and their esters (Kujumgiev et al., 1999; Gekker et al., 2005). In relation to the external environment, propolis lowers the concentration of bacteria and fungi in the hive (Gekker et al., 2005).

Activity of propolis against oral bacteria has been demonstrated in experiments (Koo et al., 2000). Consequently, propolis is an old remedy in modern medicine. Due to its pharmaceutical properties, it is utilised in biocosmetics, food supplements, and formulations of medicinal natural products. It has long been known as a relatively non-toxic natural remedy with antibiotic, antifungal, and antiviral activities (Kujumgiev et al., 1999).

Interestingly, propolis suppresses HIV-1 replication and increases immune responses in humans (Gekker et al., 2005). The addition of propolis to the Colgate toothpaste is clearly aimed at utilising its well established activities against periodontopathogenic microorganisms. A herbal Colgate toothpaste incorporating chamomile, eucalyptus, myrrh, and sage is made by Colgative-Palmolive (China) Co. Ltd., Guangzhou, China.

However, since there have been very few clinical trials, many manufacturers do not necessarily add natural products to their commercial oral hygiene products based on available evidence of clinical efficacy. In fact, it is possible that without supporting evidence of clinical efficacy, perhaps the addition of natural products or their derivatives to commercial toothpastes or

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mouthwashes may be a marketing strategy rather than to prevent or treat diseases of the oral cavity.

4.5 Essential oils

Essential oils are complex mixtures of low molecular weight compounds obtained from plants by steam distillation and various solvents. All over the world, traditional healers prescribe essential oils for a variety of diseases. Ocheng et al. (2015) found that essential oils from ten Ugandan aromatic medicinal plants show significant growth inhibitory effects on periodontopathic *A. actinomycetemcomitans* and *P. gingivalis*, moderate effects on cariogenic *S. mutans*, and the least outcome on *L. acidophilus*. In their status review vis-à-vis the medicinal properties of essential oils, Raut and Karuppayil (2014) refer to various pharmacological and biological activities such as anti-inflammatory, antibacterial, antifungal, anticancer, anti-mutagenic, antiviral, and anti-protozoal properties.

Raut and Karuppayil (2014) stated the characteristic aroma and biological properties of essential oils are founded in their two major constituents: terpenoids and phenylpropanoids. Emergence of drug resistant strains of oral pathogens, increasing cases of immune-compromised individuals due to HIV/AIDS, and several limitations of current regimens of pharmaceutical drugs have motivated people to use essential oils for oral health. Essential oils of medicinal importance distributed in selected plant families have been provided by Raut and Karuppayil (2014).

Thymus vulgaris M.Bieb. essential oil exhibits extremely strong activity against 120 strains of *Staphylococcus*, *Enterococcus*, *Escherichia*, and *Pseudomonas genera*, isolated from patients with infections of the oral cavity (Nabavi et al., 2015). Through a multiplicity of evidence-based examples, Allaker and Douglas (2008) state that essential oils extracted from *M. alternifolia*, eucalyptus, lavandula and rosmarinus (rosemary) are widely applied as inhibitory agents against cariogenic and periodontopathic bacteria.

Curcuma longa L. essential oil prevents cytogenetic damage to oral sub-mucous cells (Raut and Karuppayil, 2014). Leaning on experimental evidence from other studies, Sardi et al. (2011)

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found that the essential oils of *Achillea millefolium* L., *Mikania glomerata* Spreng. and *Stachys byzantina* K.Koch all had strong activities against oral *C. albicans*. In addition, essential oils obtained from the leaves of *Coriandrum sativum* L. displayed antifungal activity against established biofilm and planktonic cells of *C. albicans* isolated from periodontal pockets.

Carson et al. (2006) stated that *M. alternifolia* oil has many antimicrobial and medicinal properties. Antifungal and antibacterial efficacies of *M. alternifolia* oil are well known (Hammer et al., 2004; Hammer et al., 2003; Halcón and Milkus, 2004). *M. alternifolia* oil causes K+ leakage and inhibits respiration in *Escherichia coli* (Cox et al., 1998). *M. alternifolia* oil contains about 100 chemical components, mostly monoterpenes, sesquiterpenes and associated alcohols. Of all these chemicals, terpinen-4-ol which acts through the disruption of microbial cell membranes has the greatest antimicrobial activity.

Allaker and Douglas (2008) reviewed that essential oil mouth rinses effectively destroy oral pathogens through various mechanisms: disruption of the cell wall, inhibition of key enzymes, slowing down replication, reduction of endotoxin release, and disaggregation of bacteria in the early plaque matrix. On the other hand, chlorhexidine acts through three mechanisms: it mediates loss of cellular contents through leakages in the cell wall, disrupts pellicle formation, and inhibits formation of the plaque matrix.

In terms of clinical efficacy against plaque and gingivitis, Allaker and Douglas (2008) wrote that essential oil inhibits supragingival plaque by up to 56% and gingivitis by up to 36%, while chlorhexidine decreases plaque by up to 61% and reduces gingivitis by up to 80%. Notwithstanding the superior clinical effects of chlorhexidine, the authors admit the superior personal appeal and acceptability of essential oils. They point out that in comparison to chlorhexidine, essential oil natural remedies offer four advantages: they do not cause teeth staining, do not alter taste perception, do not promote calculus formation, and their efficacy is not diminished in the presence of toothpaste.

Through a randomized double-blind controlled trial, Lobo et al. (2014) verified the use of essential oil from the plant *Lippia sidoides* Cham., in the treatment of dental caries in children.

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The plant is popularly known as Alecrim-Pimenta in north-eastern Brazil. Lobo and co-workers convincingly showed that toothpaste containing *L. sidoides* essential oil produced significant reductions in salivary *S. mutans* in children with dental caries.

In the trial, *L. sidoides* essential oil toothpaste demonstrated a reduction of salivary *S. mutans* after 5 days of treatment. More originally, Lobo and collaborators discovered that significantly low colonies of *S. mutans* were maintained throughout the study and these numbers did not revert to baseline during subsequent analysis at 30, 60, 180 and 365 days. Baseline numbers of *S. mutans* were significantly higher than after treatment. The toothpaste formulation of *L. sidoides* essential oil mainly has a Gram-positive antibacterial spectrum in addition to a limited action against Gram-negative bacteria. The two major constituents of *L. sidoides* oil are thymol (50–59%) and carvacrol (7–16%). Current experimental data are unanimous about the remarkable broad-spectrum antimicrobial actions of essential oils extracted from *L. sidoides*. Phenolic compounds such as carvacrol and thymol also have established wide spectrum antimicrobial activities against yeasts and bacteria.

Takarada et al. (2004) tested manuka oil, *M. alternifolia* oil, eucalyptus oil, lavandula oil, and romarinus oil on cariogenic and periodontopathic bacteria. While all these essential oils inhibited the growth of the bacteria, manuka oil was the most effective. Minimum bactericidal concentration values showed that lavandula oil acts bacteriostatically, and the remaining oils, bactericidally. Periodontopathic bacterial strains tested were killed completely by exposure for 30 seconds to 0.2% manuka oil, *M. alternifolia* oil or eucalyptus oil. *M. alternifolia* oil and manuka oil showed significant adhesion-inhibiting activity against *P. gingivalis*. All the essential oils tested inhibited the adhesion of *S. mutans*. Takarada et al. (2004) showed that manuka oil and *M. alternifolia* oil had strong antibacterial activity against periodontopathic and cariogenic bacteria.

4.6 Green tea

Experimental evidence appears to be decisive that green tea contains multi-purpose antimicrobial phytochemicals. It is therefore not surprising that Narotzki et al. (2012) point to the beneficial role of green tea in oral health. Based on their review, green tea works against dental caries

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induced by bacteria. That is not all. Tea polyphenols possess antiviral properties and abolish bad breath (halitosis) through modification of odourant sulphur components. Narotzki et al. (2012) explain that green tea polyphenols diminish oral cavity oxidative stress and inflammation, especially caused by nicotine and acrolein, the two most harmful compounds in cigarette smoke. In Japan, there is a popular notion that green tea makes the mouth clean as well as an old tradition that those who drink copious amounts of green tea rarely get tooth decay (Signoretto et al., 2012).

Allaker and Douglas (2008) also indicated that data from animal and human trials support the use of green tea in the control of dental caries. They cited studies which show that flavonoids in green tea control plaque-related diseases and dental caries. Extracts of green tea destroy oral bacteria *S. mutans* and *S. sobrinus* through the inhibition of three factors: bacterial adherence, acid production, and glucosyl transferase activity, an enzyme involved in the formation of extracellular polysaccharides. In relation to periodontitis, Allaker and Douglas (2008) opined that the killing of the periodontal pathogens *P. gingivalis* and *P. intermedia* has been demonstrated with extracts of green tea. They also quote studies where green tea extracts inhibit cysteine proteinase, one of the key enzymes in the virulence of *P. gingivalis*. Experiments in diseased animals also show that extracts of green tea decrease periodontal pocket depths and proportions of black pigmented Gram-negative bacteria.

In addition, Avezov et al. (2014) indicated that consumption of products with antioxidant activity promotes oral health. In this regard, green tea as an excellent source of the polyphenol and antioxidant epigallocatechin-3-gallate plays a beneficial role in alleviating oral oxidative stress and inflammation. In the main, green tea defends healthy oral cells from malignant transformation and induces local apoptosis in oral cancer cells (Avezov et al., 2014). Smullen et al. (2012) stated that extracts of green tea, because of the presence of catechins, inhibit the growth of *S. mutans in vitro* and prevent its attachment to tooth enamel by inhibiting glucosyltransferase activity (GTA). Oolong tea extracts inhibit experimental dental caries infected with *S. mutans*. Green tea extract completely inhibits plaque formation but results in a greenish discolouration of the teeth which cannot be removed by scrubbing.

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4.7 Chewing sticks

The World Health Organisation (WHO) supports the use of chewing sticks as an effective tool for oral hygiene because chewing sticks contain many antimicrobial substances. Allaker and Douglas (2008) explained that in many African and Middle East countries, a number of plants are used as chewing sticks to maintain good oral health. Africans that use chewing sticks have fewer carious lessons than those using tooth brushes (Oshomoh and Idu, 2012). The twigs of the Namibian plant *Diospyros lycioides* Desf., commonly known as Muthala, are frequently used as chewing sticks for the cleaning of teeth by rural and urban people in Namibia. In Saudi Arabia, Arak chewing sticks are used by Muslims for cleaning of teeth during the whole day (Ibrahim et al., 2014). The use of *Diospyros mespiliformis* as a chewing stick is even more significant because the plant has antipyretic, anti-inflammatory, antibacterial, anti-parasitic, anti-HIV and antifungal properties. *D. mespiliformis* is found in many parts of Central, Southern, Eastern and West Africa where it is also utilised in the treatment of fever, whooping cough, wounds, malaria, pneumonia, syphilis, leprosy, dermatomycoses, helminths, and facilitation of childbirth.

Many plants are used as chewing sticks: *Acacia arabica* (Lam.) Willd., *Anogeissus leiocarpus* (DC) Guill. and Perr., *A. indica* , *D. lycioides*, *Distemonanthus benthamianus* Baill., *Fagara zanthoxyloides* Lam., *Garcinia kola* Heckel, *Glyphaea brevis* (Spreng.) Monach., *Massularia acuminata* (G.Don) Bullock ex Hoyle, *Sorindeia warneckei* Engl., *Terminalia glaucescens* Planch. ex Benth., *Vernonia amygdalina* Delile, and *Vitex doniana* Sweet (Alili et al., 2014). Chewing sticks are derived from a wide range of plant species, but within an individual stick, the active antimicrobial ingredients may be heterogeneous. *F. zanthoxyloides*, a chewing stick in Nigeria, consists of antimicrobial alkaloids, and the species *S. wernecki* inhibits the growth of the periodontal pathogens *P. gingivalis* and *Prevotella melaninogenica* (Allaker and Douglas, 2008). *A. leiocarpus* has antifungal properties and *G. brevis* twigs are also utilized in Nigeria as antimicrobial chewing sticks for cleaning teeth (Oshomoh and Idu, 2012).

Globally, the most commonly used chewing stick is *Salvadora persica* (Aboul-Enein, 2013). *S. persica* (family Salvadoraceae) has many synonyms such as Arak, Galenia asiatica, Meswak, Peelu, Pilu, Mustard tree, *Salvadora indica* Royle or natural toothbrush tree (Chaurasia et al.,

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2013). In India, it is commonly known as Arak tree, Meswak, Peelu, Kharjal or Jhank. It also serves as natural toothpaste with antibacterial, anti-caries, and anti-periopathic disinfectant having anti-plaque and anti-fungal properties (Chaurasia et al., 2013). *S. persica* sticks are used by many people in rural areas of developing countries who cannot afford commercial western toothbrush and toothpaste.

S. persica has strong anti-cariogenic properties and contains cleaners such as sinigrin, sodium bicarbonate, calcium oxalate, as well as astringents such as gallic acid and volatile oils; all these chemical constituents, it is believed, strengthen gingival tissues. On the authority of Chaurasia et al. (2013), *S. persica* is used in commercial preparations of a number of toothpastes worldwide e.g. Sarkan toothpaste (United Kingdom), QualiMeswak toothpaste (Switzerland) Epident toothpaste (Egypt), Siwak-F toothpaste (Indonesia), Fluoroswak, Miswak (Pakistan), and Dentacare Miswak Plus (Saudi Arabia).

Natural chewing sticks made of *S. persica* may be considered to be the first toothbrush of human beings. Its use has been documented by ancient Babylonians, Greeks, Romans, Jews, and Egyptians. In addition to its mechanical properties on plaque removal, *S. persica* also possesses antibacterial and antifungal properties (Aboul-Enein, 2013). Twigs of the *S. persica* tree have a selective inhibitory effect on the level of certain bacteria in saliva, particularly the oral streptococci (Allaker and Douglas, 2008). In Saudi Arabia, scientists found that *S. persica* extracts have high antioxidant activities mainly due to the presence of flavonoids and phenolics (Ibrahim et al., 2014). Non-enzymatic antioxidants like flavonoids and phenolics reduce oral pathogenesis by preventing the disintegration of biomolecules (lipids, proteins, and nucleic acids) and cell membranes.

Aboul-Enein (2013) revealed evidence-based studies and clinical trials where the use of *S. persica* (tooth brush tree) is an effective oral hygiene plant used as a chewing stick in different cultures since ancient times. According to this author, WHO recommends and encourages the use of *S. persica* as a readily-available, low-cost, simple and effective plant tool to promote oral hygiene. *S. persica* diminishes foul breath, polishes teeth, and strengthens gums. Alili et al. (2014) demonstrated that *S. persica* exhibits antifungal activity against all *Candida* species. In

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particular, the plant's volatile compounds produce strong inhibition of *Candida* growth, indicating that volatile compounds are the principal agents of anti-fungal inhibition.

Several studies corroborate that *S. persica* contains many different natural chemical compounds essential for good oral and dental hygiene (Chaurasia et al., 2013): fluorides, silica, tannic acid, resins, alkaloids (salvadorine), volatile oils (simgrins), sulfur, vitamin C, sodium bicarbonate, chlorides, calcium, benzyl isothoicyanate, salicylic acids, sterols, trimethylamine, saponins, flavonoids, B-sitosterol, manisic acid, salvadourea [1,3-bis-(3-methoxy-benzyl)-urea, elemental sulfur, and sulfur containing mustard oil. Studies cited by Chaurasia et al. (2013) indicate different biological actions of *S. persica*'s chemical ingredients.

For example, silica in *S. persica* acts as an abrasive material to remove stains on teeth. Denture bases treated with tannic acid show reduced counts of *C. albicans*. Salvadorine has bactericidal activity while essential oils confer characteristic aroma and antiseptic action. The sulfur compounds in *S. persica* have bactericidal properties and sodium bicarbonate is a mild abrasive and dentifrice.

Aboul-Enein (2013) quoted several studies linking benzyl isothiocyanate, one of the active ingredients of *S. persica*, as the main bactericidal agent against oral pathogens that mediate periodontal disease. Benzyl isothiocyanate is mostly active against Gram-negative bacteria, although Amir Alireza et al. (2014) showed that plant extracts were effective against both Gram-negative and positive bacteria.

4.8 Probiotics

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Not less important, probiotics like yoghurts also control the growth of microorganisms including cariogenic streptococci associated with oral diseases (Allaker and Douglas, 2008). Probiotics such as *Lactobacillus salivarius*, *Lactobacillus rhamnosus* CG, *Lactobacillus casei*, *Lactobacillus reuteri* and *Bifidobacterium* DN-173 010 have all demonstrated the capacity to change colonization of cariogenic bacteria and thus prevent

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dental caries (Caglar et al., 2005; Mayanagi et al., 2009). The oral administration of probiotics controls periodontal disease. For example, application of *L. reuteri* to subjects with moderate and severe gingivitis reduces plaque levels and gingival inflammation.

4.9 Nisin

Nisin is a natural antimicrobial peptide or bacteriocin, first isolated from *Lactococcus lactis* by Mattick and Hirsch in 1947 (Tong et al., 2014). Nisin is the oldest known and most widely studied lantibiotic. Tong and co-workers have elucidated the antibacterial efficacy of nisin against pathogenic bacteria related to dental caries. They observed that nisin is a caries-preventive agent due to its inhibition of common cariogenic-relevant bacteria: *S. sanguinis*, *Streptococcus gordonii*, *S. mutans*, *S. sobrinus*, *Lactobacillus acidophilus*, *L. casei*, *Lactobacillus fermenti*, *A. viscosus* and *Actinomyces naeslundii*. Nisin was effective in killing *E. faecalis* and *S. gordonii* cells (Turner et al., 2004). When used together with thymol, nisin had synergistic antibacterial effects against *Listeria monocytogenes* and *Bacillus subtilis* (Ettayebi et al., 2000).

4.10 Edible mushrooms

Contrary to the common assumption that food has a negative impact on oral health, the common edible mushroom shiitake, *Lentinula edodes* (Berk) Pegler, protects against dental caries (Zaura et al., 2011). Shiitake mushroom contains several therapeutic actions such as antioxidant and antimicrobial properties (Kitzberger et al., 2007). Frequent mouth rinses with shiitake mushroom extracts may reduce the metabolic activity of the dental biofilm (Lingström et al., 2012). Shiitake mushroom extracts also have antibiotic action that may be harnessed by incorporating them into mouthwashes and toothpastes (Signoretto et al., 2011).

5. African plants and natural products

Medicinal plants such as *Conyza sumatrensis* (Retz.) E.Walker, *Aeschynomene abyssinica* Vatke, *Sida rhombifolia* L., and *Triumfetta rhomboidea* Jacq. are used to manage carcinoma of the gums in Kenya (Ochwang'i et al., 2014). Ocheng et al. (2014) studied the antibacterial activities of

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extracts from Ugandan medicinal plants used for oral care (**Table 1)**. Pulp juice prepared from fresh roots of *Zanthoxylum chalybeum* Engl. and *Euclea latidens* Stapf show activities against bacteria associated with periodontal disease and dental caries (Ocheng et al., 2014). Antibacterial activities were also demonstrated for solvent extracts of *Helichrysum odoratissimum* Sweet, *Z. chalybeum*, *Lantana trifolia* L., and *Cymbopogon nardus* (L.) Rendle (Ocheng et al., 2014).

The antimicrobial effects of South African plants commonly utilised as ethnomedicines for oral diseases were studied by More et al. (2008). The plants *Annona senegalensis* Pers., *Englerophytum magalismontanum* (Sonder) T.D.Penn., *Dicerocarym senecioides* (Klotzsch) Abels., *Euclea divinorum* Hiern, *Euclea natalensis* A.DC., *Solanum panduriforme* E.Mey. and *Parinari curatellifolia* Planch. Ex Benth displayed MIC values ranging from 25.0 mg/ml to 0.8 mg/ml. All plant extracts showed moderate cytotoxicity on the Vero cell line with 50% inhibitory concentration (IC50) of all plants tested ranging from 92.3 to 285.1 µg/ml. *A. senegalensis* and *E. natalensis* had excellent therapeutic indices greater than 20. Also, *D. lycioides* demonstrated growth inhibitory activity against the oral pathogens *S. mutans* and *P. gingivalis*.

In South Africa, a leaf decoction of *Dodonaea viscosa* (hopbush) is traditionally used for the treatment of oral thrush and as a mouth wash for toothaches and related problems (Naidoo et al., 2012). Crude extracts of *D. viscosa* were bactericidal to *S. mutans* and significantly reduced its biofilm formation thus demonstrating potency in ameliorating oral infections (Naidoo et al., 2012). *E. natalensis* suppressed the growth of *S. mutans* (Stander and Van Wyk, 1991), *A. viscosus* and *C. albicans* (Khan et al., 1978).

6. Asian plants and natural products

Rasingam et al. (2012) enumerated eleven plant tooth twigs used by the inhabitants of Andaman and Nicobar Island, India, to treat dental caries. Some of the plants are *Acacia nilotica* Delile, *A. indica*, *Ficus benghalensis* L., *Jatropha curcas* L., and *Pongamia pinnata* (L.) Pierre. *A. indica* is used as a chewing stick throughout the world. In Tamilnadu, India, a fruit paste from *Solanum surattense* Burm.f. is applied to heal toothache while the young stems of *A. nilotica* are

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employed as toothbrush in addition to being a treatment for toothache (Munuswamy et al., 2013). *Bixa orellana* L., commonly known as Annatto or the lipstick tree, is also useful in alleviating cancer of the mouth.

Ziech et al. (2012) reported that Withaferin A, a steroid lactone derived from the roots and leaves of *Withania somnifera*, heals oral cancer. Roots of *Scutellaria baicalensis* Georgi, known as Huang-Qin plant in China, cause apoptosis of cancerous cells in the mouth. Twigs of *J. curcas* are utilized as toothbrush and alleviate gum problems in Nepal. *P. pinnata* contains antimicrobial and antioxidant compounds like chalcones, flavones, furanoflavonoids, isoflavones, and pyranoflavonoids.

In Japan, kampo herbal medicines are useful in treating periodontal disease and drug-induced gingival overgrowth (Ara et al., 2010). One of the kampo medicines is sho-saiko-to, a seven-plant traditional Chinese and Japanese medicinal mixture which inhibits the growth of cancer cells in the mouth, decreases lipopolysaccharide-induced prostaglandin production by gingival fibroblasts, and reduces inflammation of periodontal tissue. It also modulates the immune system: makes macrophages engulf antigens more efficiently and increases the levels of interleukin-1α (IL-1α) in epithelial cells. The action of IL-1α helps oral epithelial cells prevent bacterial infection in the oral cavity by producing antimicrobial peptides. Thus, sho-saiko-to increases the expression of calprotectin, a broad-spectrum antimicrobial peptide in oral epithelial cells (Hiroshima et al., 2010).

Sho-saiko-to contains active ingredients such as baicalin, baicalein and saikosaponin. A panel of 15 oral bacterial pathogens were inhibited by baicalein, a flavonoid originally isolated from the roots of the traditional Chinese medicinal plant *S. baicalensis* (Jang et al., 2014). Baicalein bestows numerous pharmacological benefits including antiviral, antibacterial, antifungal, antioxidant, anti-cancer, and anti-inflammatory activities. There is a synergistic effect between baicalein and antibiotics (ampicillin or gentamicin) against oral bacteria.

Meanwhile, a time-kill study showed that the growth of the tested bacteria was completely attenuated after 1–6 hours after treatment with baicalein, regardless of whether baicalein was

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administered alone or with ampicillin or gentamicin (Jang et al., 2014). In the treatment of oral pathogens, these results are important because *S. baicalensis* extracts and pure baicalein (5,6,7-trihydroxyflavone) are not antagonist to antibiotics in addition to being effective antibacterial agents in their own right. This means the two natural agents can be safely administered either independently or together with antibiotics, without loss of their functions.

Barbieri et al. (2014) refer to studies in South Korea where *Polygonum cuspidatum* Siebold & Zucc. (Polygonaceae) roots are traditionally used to maintain good oral health. Extracts of *P. cuspidatum* reduce the viability of *S. mutans* and *S. sobrinus* cells, inhibit sucrose dependent adherence, decrease synthesis of water-insoluble glucan formation, and reduce glycolytic acid production and acid environment tolerance. The inhibitory effects of *P. cuspidatum* are linked to the presence of alkaloids, phenolics and sterol/ terpenes compounds.

Fucoidan, a complex sulphated polysaccharide found in the cell walls of several edible brown algae including *Fucus vesiculosus* L., is an important agent against oral bacteria (Lee et al., 2013). Fucoidan inhibits bacterial cell wall synthesis. Apart from being a natural antibiotic, fucoidan also boosts the immune system by enhancing the action of natural killer cells and macrophages. Corollary to these findings, fucoidan may be a useful candidate in the treatment of cariogenic and periodontopathogenic bacteria (Lee et al., 2013).

In India, Rao et al. (2011) found that *Moringa oleifera* Lam. leaf extracts inhibited the growth of dental plaque bacteria: *S. mutans* (MTCC 890), *S. mutans* (MTCC 497), *Streptococcus salivarius* (MTCC 1938), *S. mitis* (MTCC 2696), *L. fermenti* (MTCC 903), *Streptococcus anginosus* (MTCC 1929), *S. gordonii* (MTCC 2695), *L. acidophilus* (MTCC 447) and *S. aureus* (MTCC 96). *Microcystis aeruginosa* (Kützing) Lemmermann and *Phormidium corium* Agardh (Gomont) are effective against oral diseases in India (Madhumathi and Vijayakumar, 2014). *M. alba* is chewed by Indians with toothache to avoid further destruction or cavitation of the tooth (Islam et al., 2008). ***M. alba*** is used for its antioxidative and antidiabetic effects and is an important ingredient of herbal tea.

The leaf juice of *Phyllanthus reticulatus* Lodd., a shrub that grows in India, Bangladesh, China and the Malay Islands, heals bleeding gums (Kumar et al., 2014). *P. reticulatus* contains tannins

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and phenolic compounds, and increases the immune system's phagocytic activity and neutrophil adhesion. In view of its immune-stimulatory properties, *P. reticulatus* is also used in the management of HIV/AIDS.

Rhodomyrtus tomentosa (Aiton) Hassk. is an evergreen shrub native to Southeast Asia. Its active chemical compound, rhodomyrtone, is isolated from leaves. Studies in Thailand show leaf extracts of *R. tomentosa* have antibacterial activity against oral microorganisms including *S. aureus* ATCC 25923, *S. mutans* (clinical isolate), and *C. albicans* ATCC 90028 with MICs of 31.25, 15.62, and 1000 µg/ml, respectively (Limsuwan et al., 2014). Rhodomyrtone also displays antibacterial activity with MICs of 0.78 and 0.39 µg/ml against *S. aureus* ATCC 25923 and *S. mutans*, respectively. *R. tomentosa* leaf extracts and rhodomyrtone could be useful in prophylaxis and therapy of oral infections.

In Malaysia, extracts of two local ethnomedicinal plants *Piper betel* Blanco and *Brucea javanica* (L.) Merr. inhibit the adherence of seven oral *Candida* species (Nordin et al., 2013). *P. betel* extracts drastically reduce the adherence of *C. tropicalis*, *C. albicans* and *C. krusei* by 86.01%, 61.41% and 56.34%, respectively (Nordin et a., 2013). *B. javanica* exhibits similar effects on *C. tropicalis* (89.86%), *C. lusitaniae* (88.95%), *C. albicans* (79.74%), *C. glabrata* (76.85%) and *C. krusei* (67.61%).

7. Brazilian and Mexican folk medicines

In Brazilian folk medicine, extracts of the plants *Aristolochia cymbifera* Mart., *Cocos nucifera* L., *Caesalpinia pyramidalis* Tul. and *Ziziphus joazeiro* Mart. are popularly used to treat oral diseases (Alviano et al., 2008). Laboratory assays confirmed that *A. cymbifera* extract induced the highest bactericidal effect against oral bacteria, followed by *C. nucifera*, *Z. joazeiro* and *C. pyramidalis* extracts, respectively. *Caesalpinia ferrea* Mart. ex Tul. fruit extract inhibits *in vitro* growth of oral pathogens in planktonic and biofilm models justifying its traditional use in the management of oral infections (Sampaio et al., 2009). The crude extract of *C. ferrea* contains tannins (major constituent), anthraquinones, alkaloids, depsides, depsidones, flavonoids,

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lactones, saponins, sugars, sesquiterpenes and triterpenes. These phytochemicals confer many oral health benefits.

In ethnobotanical surveys of plants used to treat oral diseases in Brazil, the following plants were frequently cited: *A. vera*, *Anacardium occidentale* L., *Schinus terebinthifolius* Raddi, *Chenopodium ambrosioides* Hance and *P. granatum* (Vieira et al., 2014). Determination of MIC demonstrated that *P. granatum*, *Psidium guajava* L. and *S. terebinthifolius* had similar activity to 0.12% chlorhexidine, the positive control. Surprisingly, *C. ambrosioides*, though widely used, did not display any antimicrobial activity at all (Vieira et al., 2014).

Barbieri et al. (2014) reviewed that *S. terebinthifolius* and *Croton urucurana* Baill. inhibit biofilms formed by *S. mutans* and *C. albicans* strains. Their results show biofilms of *C. albicans* were more efficiently inhibited by extracts of *S. terebinthifolius* than *C. urucurana*. The anti-adherent potential of both plants on *in vitro* biofilms formed by *C. albicans* and *S. mutans* were confirmed, suggesting the importance of these extracts in the prevention of oral diseases mediated by oral biofilms. Barbieri et al. (2014) found that compounds produced by *S. terebinthifolius* exhibit antimicrobial, anti-inflammatory and anti-ulcer properties. Phenolic compounds, anthraquinones, terpenoids, and alkaloids are believed to confer these pharmacological functions. *S. terebinthifolius* contains the compounds apigenin, methyl gallate and gallic acid which inhibit adherence of biofilms. *C. urucurana* has anti-inflammatory, anti-haemorrhagic and anti-fungal properties.

Other Brazilian herbal products with the potential to control oral biofilms were cited by Barbieri et al. (2014): extracts of peas (*Pisum sativum* L.), lectins from pitombeira (*Talisia esculenta* Radlk.), and crude extracts from mulberry leaves (*Morus alba* L.). Having undergone pharmaceutical evaluations, these plant extracts are now added to mouthwashes, toothpastes, and other oral hygiene products; in order to make the oral hygiene products more amenable to the prevention of oral biofilm formation. *Eugenia calycina* Cambess. (family Myrtaceae), an endemic plant species in Brazil, produces an essential oil with remarkable activity against anaerobic bacteria *Prevotella nigrescens* and *P. gingivalis* (Sousa et al., 2015). At low MIC, *E. calycina* essential oil has a higher selectivity against oral bacteria and lower toxicity towards

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HeLa cells (Sousa et al., 2015). These findings illustrate that *E. calycina* is a promising plant for the management of oral pathogenic bacteria.

In Mexico, traditional healers and patients use many plants as medicines to treat oral diseases. Rosas-Piñón et al. (2012) obtained high inhibitory effects against oral pathogens *S. mutans* and *P. gingivalis* with ethanolic extracts of *Haematoxylon brasiletto* Karst. commonly known as Palo Brasil, *P. granatum*, *Iostephane heterophylla* (Cav.) Benth. ex Hemsl., *Bursera simaruba* Sarg., *Cedrela odorata* Cham. & Schltdl. and *Rhus standleyi* F.A.Barkley (12.5–65.0 µg/mL) as well as water extracts of *H. brasiletto*, *P. granatum*, *I. heterophylla*, *Amphipterygium adstringens* (Schltdl.) Schiede ex Standl., *Argemone mexicana* L., *C. odorata*, *Eysenhardtia polystachya* (Ortega) Sarg., *Persea americana* Mill., *S. aromaticum*, *Cinnamomum zeylanicum* Blume, *Cnidoscolus multilobus* (Pax) I.M.Johnst. and *Rhus standleyi* F.A.Barkley (10.5–78.0 µg/mL). These laboratory results no doubt mean the plants have antibacterial effects thus justifying their use in traditional medicines for oral infections. However, it is important to note that the use of natural products or their derivatives by indigenous peoples or in folk medicines for particular oral conditions do not represent evidence of clinical efficacy.

8. Natural products for oral health in Europe

In the United Kingdom, flow microcalorimetry showed that Rosemary, myrrh and *M. alternifolia* had antimicrobial activity against *S. mutans*, one of the oral pathogens responsible for dental caries (Morgan et al., 2001). Lauk et al. (2003) conducted an evaluation of the antibacterial activity of *Althaea officinalis* L. roots, *Arnica montana* L. flowers, *Calendula officinalis* L. flowers, *Hamamelis virginiana* L. leaves, *Illicium verum* Hook. fruits and *Melissa officinalis* L. leaves, against anaerobic and facultative aerobic periodontal bacteria: *P. gingivalis, Prevotella* spp., *F. nucleatum, Capnocytophaga gingivalis, Veilonella parvula, E. corrodens, Peptostreptococcus micros* and *Actinomyces odontolyticus.*

The methanol extracts of *H. virginiana*, *A. montana* and *A. officinalis* had inhibitory activity (MIC ≤ 2048 mg/L) against many of the species tested. However, *M. officinalis* and *C. officinalis* extracts had lower inhibitory action (MIC ≥ 2048 mg/L) against all the tested species except

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Prevotella spp. *Illicium verum* methanol extract was not very active though it had a particular good activity against *E. corrodens*. Lauk et al. (2003) recommended the use of alcohol extracts of *H. virginiana, A. montana* and *A. officinalis* as topical medications in periodontal prophylactics.

9. Natural products for oral health in the Middle East

Delfan et al. (2014) conducted an ethnobotanical study of medicinal plants used to relieve toothache in Lorestan Province, Iran. Some of the plants used to treat toothache were *Daphne mucronata* Royle (mazerion), *V. vinifera*, and *Glycyrrhiza glabra* L. (liquorice). A study by Mansourian et al. (2014) found that the plant extracts of *Syzygium aromaticum* (L.) Merr. & L.M.Perry (clove) oil and *P. granatum* had good activity against oral *C. albicans*.

Remarkably, the antifungal action of *S. aromaticum* was better than that for nystatin, an anti-fungal drug first isolated from *Streptomyces noursei* (Mansourian et al., 2014). *S. aromaticum* contains a high percentage of eugenol, a known anti-fungal agent. *P. granatum* has definite anti-*Candida* activity, but the magnitude of this activity is less than for nystatin or *S. aromaticum*. Against cariogenic and periodontopathogenic bacteria, clove oil and eugenol are effective natural antibacterial agents; both have synergistic effects with ampicillin or gentamicin (Moon et al. 2011).

10. Poly-herbal treatments of oral infections

Resistance of oral pathogens to single plant extracts is giving way to the new treatments involving plant combinations. The growth of dental bacteria was inhibited by a poly-herbal tablet of the plants *A. indica*, *Mangifera indica* L., *Hemidesmus indicus* (L.) R.Br., *Caryophyllus aromaticus* L., *Cinnamomum zeylanicum* Blume, *Quercus infectoria* Oliv., *Emblica officinalis* Gaertn., *Terminalia* belerica Roxb., and *Terminalia chebula* Retz. (Thombre et al., 2012). Sho-saiko-to is another medicinal plant mixture used in China and Japan to treat oral infections (Ara et al., 2010; Hiroshima et al., 2010).

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11. Natural chemical compounds for prevention and treatment of oral infections

Many plants used in the management of oral infections are infused with several useful antimicrobial phytochemicals such as simple phenols, phenolic acids, quinones, flavones, flavonoids, flavonols, tannins, coumarins, terpenoids, essential oils, alkaloids, lectins, and antimicrobial peptides. The actions of flavonoids are classically attributed to their antioxidant properties. According to Petti and Scully (2009), polyphenols help prevent oral diseases via mechanisms like antioxidant activity and neutralization or modulation of human and microbial enzymes. Regular and frequent dietary intake of polyphenols helps alleviate symptoms of oral cancer. Shi et al. (2014) indicate that several alkaloids isolated from natural herbs exhibit anti-proliferation, antibacterial, antiviral, and anti-metastatic effects on various types of oral cancers both *in vitro* and *in vivo.*

Oxyprenylated acetophenones are secondary metabolites extracted from plants belonging to the Rutaceae family, especially from the fruits of *Evodia merrillii*, aerial parts of *Boronia ramosa*, fruits and aerial parts of *Melicope obscura*, *Melicope obtusifolia*, and *Melicope semecarpifolia*. Bonifait et al. (2012) elucidated that oxyprenylated acetophenones such as 2′,6′-dihydroxy-4′-geranyloxyacetophenone and 2′,6′-dihydroxy-4′- farnesyloxy-acetophenone can be harnessed as natural agents for the prevention and treatment of common oral infections including dental caries, periodontal disease, and candidiasis. The compound 2′,6′-dihydroxy-4′-geranyloxyacetophenone showed stronger antimicrobial activity than 2′,6′-dihydroxy-4′-farnesyloxy-acetophenone against major oral pathogens including Gram positive bacteria (*S. mutans, S. sobrinus*), Gram negative bacteria (*P. intermedia, P. gingivalis*) and *C. albicans* (Bonifait et al., 2012). Oxyprenylated acetophenones also inhibit proliferation of oral cancer cells.

Cai and Wu (1996) isolated the compounds 5,7-dihydroxy-2-methylchromone 8-*C*-β-D-glucopyranoside, biflorin, kaempferol, rhamnocitrin, myricetin, gallic acid, ellagic acid, and oleanolic acid from *S. aromaticum*. These clove compounds had activity against oral bacterial pathogens including *S. mutans*, *Actinomyces viscosus*, *P. gingivalis*, and *P. intermedia*. The

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flavones (kaempferol and myricetin) demonstrated potent growth-inhibitory activity against the periodontal pathogens *P. gingivalis* and *P. intermedia*.

According to Li et al. (1997), a methanol extract of the plant *Ceanothus americanus* demonstrated antimicrobial activity against selected oral pathogens. Through bioassay-guided fractionation and purification, three triterpenes (ceanothic acid, 27-hydroxy ceanothic acid and ceanothetric acid) and two flavonoids (maesopsin and maesopsin-6-*O*-glucoside) were identified. Ceanothic acid and ceanothetric acid demonstrated growth inhibitory effect against *S. mutans, A. viscosus, P. gingivalis*, and *P. intermedia* with MICs ranging from 42 to 625 μg/ml.

Cai et al. (2000) showed that a methanol extract of *D. lycioides* found in Namibia inhibited the growth of selected oral pathogens. Subsequent bioassay-guided fractionation led to the isolation of four novel bioactive naphthalene glycosides, four diospyrosides A-D, and two known bioactive naphthoquinones, juglone and 7-methyljuglone. These compounds inhibited the growth of oral cariogenic bacteria (*S. mutans, S. sanguis*) and periodontal pathogens (*P. gingivalis, P. intermedia*) at MICs ranging from 0.019 to 1.25 mg/ml. Of all these compounds, juglone exhibited the strongest inhibitory activity. The broad antimicrobial functions of *D. mespiliformis* are accredited to the presence of two active compounds, diosquinone and plumbagin. Diosquinone also displays anti-cancer activity while plumbagin (also present in *Drosera peltata*) is a known anti-HIV agent.

Chemical compounds from the leaves of *M. oleifera* including β-sitostirol, niazinin A, stigmasterol, kaempferol-3-o-β-D-glucopyranoside and quercetin-3-o-β-D-glucopyranoside were all active against the bacterial strains *S. mutans, S. salivarius, S. mitis, L. fermenti, S. anginosus, S. gordonii, L. acidophilus* and *S. aureus* (Rao et al., 2011). Kuwanon G, a flavone derivative containing a condensed dihydrochalcone partial structure and isolated from the ethyl acetate fraction of the methanol extract of *M. alba*, completely inactivated *S. mutans* at the concentration 20 μg/ml in 1 minute and significantly inhibited the growth of other cariogenic bacteria such as *S. sobrinus* and *S. sanguis*, and *P. gingivalis* causing periodontitis (Park et al., 2003). Kuwanon G works by lysing the cell wall and compressing the cytoplasm.

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According to Madhumathi and Vijayakumar (2014), *M. aeruginosa* and *P. corium* contain phytochemicals like alkaloids, phenolics, and steroids; these phytochemicals inhibit the growth of oral *C. albicans* and *S. mutans*. Antimicrobial action of these two blue-green algae is also premised on their novel chemical active ingredients such as microginins and cyalobolide B, present in *M. aeruginosa* and *P. corium*, respectively. In antimicrobial assays, *P. corium* extracts show activity against HIV reverse transcriptase and *S. aureus*. But caution should be taken because extracts of *M. aeruginosa* are known to contain hepato- and neuro-toxins commonly called microcystins; these toxins kill even the larvae of mosquitoes *Aedes aegyptii*.

Palombo (2011) stated that 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 MIC values of 160–200 μg/ml. The compound macelignan is also isolated from *Myristica fragrans*, main source of the spices nutmeg and mace and an ever-green tree indigenous to the Moluccas of Indonesia. Chemical agents in extracts for oral health include alkaloids (berberine), flavonoids (erycristagallin, artocarpin, artocarpesin, macelignan, xanthohumol), terpenes (macrocarpals A-C, bakuchiol, xanthorrhizol), sugar alcohols, catechol (phenolic), tetra iso-alpha acid, and beta acid (Palombo, 2011).

In the search for potential anti-plaque agents from natural sources, several compounds of plant origin show plenty of growth inhibitory activity against oral pathogens. Some of these natural compounds are the naphthalene glucosides, diospyrosides A–D, and some flavonoids, including kaempferol, myricetin, and rhamnocitrin.

12. Modes of action

In the prevention and treatment of oral infections, phytochemicals and natural compounds exhibit several modes of action such as bacterial growth inhibition, anti-adhesion to buccal surfaces, bacteriostatic and bactericidal effects on oral bacteria, inhibition of glucan production, inhibition of amylases, and biofilm disruption (Palombo, 2011). Other mechanisms of action are prevention of co-aggregation of the microorganisms, disruption of signal transduction pathways (Zaura et al., 2011), inhibition of acid production in bacteria, reduction of the hydrophobicity of

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bacteria, and down-regulation of genes involved in metabolic pathways like lactic acid production or glycolysis (Palombo, 2011).

That said, innate protection against microbial infections is provided by the oral mucosa membrane which acts as a mechanical and physical barrier, and saliva which contains unique host defense peptides, also known as antimicrobial peptides. The mechanical shield of the oral epithelium consists of stratified keratinocytes which form a strengthened structure. Okumura (2011) enumerated several types of host defense peptides including defensins, cathelicidins, and histatins. Host defense peptides are mostly cationic, have amphipathic structures, and provide non-specific, rapid defenses against invading oral pathogens.

13. A closer look at natural products against oral infections

It is ironic to note that although most common infectious diseases of humans are oral diseases, they have not been given comparable attention like HIV/AIDS or tuberculosis. Nowadays, the increasing incidence of dental caries and periodontitis is inextricably linked to dysfunctional immunity experienced during HIV/AIDS. In fact, oral diseases are one of the clear manifestations of AIDS, a hidden but very painful morbidity of the AIDS complex that evolves when CD4 counts are as low as 200. In developing countries, the numbers of oral health facilities and practitioners including dentists are very low, too inadequate to meet demand. There is less than one dentist for every 100,000 people in Africa; the least number of dentists is in Angola. The increasing incidence of oral diseases due to HIV/AIDS, coupled with the lack of oral health facilities and person-power, has created a natural demand for the use of plant products to treat oral diseases.

But there is another reason for the shift to natural products. Resistance of pathogens to conventional drugs for oral therapy is increasing public interest towards natural products for oral health. Whilst natural products are not a replacement for oral antibiotics, fungicides or virucides, they provide more options of antimicrobial agents to treat oral diseases. Even without bioprospecting, many common natural products alleviate oral infections. Milk, honey, green tea, cranberries, edible mushrooms, liquorice, alcohol-free red wine, raisins, essential oils, rhein,

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pomegranate, chamomile, and probiotics such as those in yoghurt have been shown to reduce symptoms of oral diseases. Green tea has polyphenol antioxidants like epigallocatechin-3-gallate which reduce oral oxidative stress, inflammation and malignancy.

Apart from plants, blue-green algae such as *M. aeruginosa* and *P. corium* are also useful in the treatment of oral diseases. Chemical ingredients have also been isolated from fungal and bacterial species. In general, these species are impregnated with several useful antimicrobial phytochemicals that fight oral diseases: phenols, phenolic acids, quinones, flavones, flavonoids, flavonols, tannins, coumarins, terpenoids, essential oils, alkaloids, monoterpenes, sesquiterpenes, lectins, naphthalene glucosides, diospyrosides, kaempferol, myricetin, rhamnocitrin, eugenol, oleanolic acid, oleanolic aldehyde, and antimicrobial peptides.

Specifically, many active chemical ingredients isolated from natural products ward off oral infections, for example: 2′,6′-dihydroxy-4′-geranyloxyacetophenone, 2′,6′-dihydroxy-4′-farnesyloxy-acetophenone, 5-(hydroxymethyl)-2-furfural, benzyl isothiocyanate, alpha-bisabolol, salvadourea [1,3-bis-(3-methoxy-benzyl)-urea, azulene, matricine and chamazulene. While many of these active chemical ingredients may be laced into drugs and other oral health products, use of their raw source plant materials is significantly justifiable, as is the case with *S. persica* chewing sticks which are recommended by WHO.

It is apparent that the use of natural products for oral health is quite prominent especially in resource-poor settings. But a closer scrutiny of the literature cited in this review shows that bioprospecting for and antimicrobial studies of natural products for oral health were mainly conducted in the following countries (in decreasing magnitude): India, South Africa, Brazil (where 8 million people do not have teeth), Japan, France, Egypt, Iran, Mexico, Kenya, Switzerland, Nigeria, Australia, Uganda, and the United Kingdom.

There is somewhat an emerging dichotomy when one looks at natural products for oral health in these countries. Work on basic research, mouth washes and value-addition is synonymous with Brazil, European countries and Australia. Already Brazil and China are adding natural products to Colgate toothpaste. On the other hand, African and Asian countries mostly focus on the

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antimicrobial testing of natural products. Countries in the Middle East (e.g. Iran) and Egypt conduct substantial research on plants used as chewing sticks.

Of note is the point that oral infections seem to be a hidden yet highly prevalent health issue associated with HIV/AIDS. Thus, in Africa, research on natural products for treating oral diseases is far much less when compared to other natural remedies for AIDS-associated diseases such as skin diseases, sexually transmitted infections, tuberculosis, and malaria. The reasons for this imbalance are not entirely clear, but one possibility is that because morbidity and mortality due to oral infections are usually inconspicuous, natural products for oral diseases have not received their fair share of research attention and funding.

Against this backdrop, there is an urgent need to accelerate bioprospecting efforts, antimicrobial testing, and isolation of active compounds from African plants and other natural products that may be used to manufacture new drugs and hygiene products for oral health. Oral diseases can be so painful that they can obstruct food mastication and ingestion, and this can impair the nutritional status and immune function of the body. In Southern Africa where HIV infection is taking a heavy toll on health, oral diseases are an important prognosis for wasting and weight loss characteristic of AIDS. Use of plants and other natural products to fight oral diseases becomes particularly very important as it can improve the overall health of many people because the mouth becomes amenable to food nutrient intake.

To improve our understanding of the link between food and oral health, an international European Union sixth framework programme consortium project (NUTRIDENT, FOOD-CT-2006-36210) was commissioned with the overall aim of identifying beverage/food constituents that are able to reduce the risk of two major dental diseases, caries and gingivitis (Zaura et al., 2011). This 2.2 million Euro project was implemented between 2006 and 2010. Despite this EU project, there is still a global paucity of data about the quality, safety and efficacy of herbal products used in oral health. Therefore, given the possible adverse interactions between natural product formulations and conventional drugs, caution should be exercised when using herbal medicines. Natural products can destroy oral health as much as they can help restore its bright future.

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14. Conclusions and recommendations

This is a rigorous review of the current status of plants and other natural products used in oral health. The data suggest an opportunity of leads for inventing new drugs and oral hygiene products from natural sources. Several common natural products are used to improve oral health: rhein, raisins, pomegranate, chamomile, honey, essential oils, green tea, probiotics, mushrooms, and chewing sticks. Some active chemical principles have been isolated from medicinal plants used against oral pathogens. Further, the review describes the folk pharmacopeia of plants and other natural products used for oral health in Africa, Asia, Brazil, Mexico, Europe, and the Middle East. Many plants and plant-derived antimicrobial agents are used as traditional medicines for the treatment of periodontal disorders and for the purposes of oral hygiene. Some have been evaluated for possible use in modern medicine, while thousands of other potentially useful plants have not yet been evaluated. The review exposes the lack of data on clinical efficacy and toxicity regarding natural products used in oral hygiene.

Therefore, with respect to natural products for oral health, there is an urgent need to increase research efforts and funding aimed at identifying more natural products that possess antimicrobial efficacy targeting oral pathogens. More studies should also focus on toxicological safety of natural products, clinical trials on efficacy and safety, isolation and characterisation of active chemical compounds. These endeavours may lead to value-addition and commercialisation of natural products that may be used to manufacture novel products and drugs for the treatment of oral infections. Africa should take more interest in plants and other natural products for oral health care because oral diseases are very common during HIV infection. Although the mouth is a hive of activity for microorganisms and protozoal parasites, many oral microbes become increasingly pathogenic in the course of HIV infection. Therefore, oral infections are becoming poignant and serious opportunistic diseases associated with AIDS. Oral diseases should therefore be part and parcel of current HIV/AIDS research and interventions.

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Table 1: Putative medicinal plants used in the improvement of oral health in Uganda

Plant's scientific name	**Plant's local name/ Ugandan tribe**	**Plant parts and preparation**	**Diseases whose symptoms are alleviated**
Bidens pilosa L.	Enyabarashana/Rukiga	Chew fresh leaves	Toothache
Vernonia amygdalina Delile	Okello-okello/Langi	Stems used to brush teeth; fresh twigs are chewed	Dental caries
Euclea latidens Stapf	Amuru-dyek/Langi	Roots used to brush teeth	Dental caries
Hoslundia opposita Vahl	Kamunye/Baganda	Chew fresh leaves	Mouth sores
Ocimum gratissimum Forssk.	Omujaja/Rukiga	Chew fresh leaves	Toothache
Cymbopogon citratus (DC.) Stapf.	Kasubi/Baganda	Fresh leaves taken as tea or chewed	Bad breath, toothache
Clematis hirsuta Guill. & Perr.	Adwe/Langi	Fresh leaves are pounded and applied as paste on painful tooth; infusion is drunk	Toothache and sore throat
Teclea nobilis Delile	Nzo/Baganda	Stems used as tooth brush	Dental caries
Zanthoxylum chalybeum Engl.	Owucu/Langi Songowowo/ Pokot	Roots used as tooth brush; fresh stem bark is chewed	Dental caries, toothache

Adapted from Ocheng et al. (2014).