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Natural chemical compounds from plants extract for prevention and treatment of oral infections: a review

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Abstract

Oral health has a direct link with general health and, when neglected, results in two common oral diseases: dental caries and periodontal diseases. The development of dental caries involves acidogenic and aciduric Gram-positive bacteria, primarily the mutans streptococci (*Streptococcus mutans* and *S. sobrinus*), lactobacilli and actinomycetes, whereas *P. gingivalis, P. intermedia* and *A. actinomycetemcomitans* are regarded as the major pathogens in advancing periodontitis. The management of oral hygiene has been for a long time achieved by the use of synthetic chemical agents. Unfortunately, these remedies have some side effects and are not only, and they are not affordable for people with low incomes, though their effectiveness is proven. So, it is very important to find out substitutes for these synthetics anti-microbial agents. Natural products could play this role, knowing that many of them are proved to be safer and more effective. This is why the present review focuses on natural products that harbor bioactive molecules, which may exert anti-microbial activity against oral pathogenes.

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Introduction

Oral diseases are classified as a major public health problem because of their high prevalence and significant impact on general health (Ndiaye, 2003). In terms of cost, the treatment of these diseases has been classified at the fourth rank in most industrialized countries (Baba- Moussa *et al.,* 2012). The oral cavity is one of the major habitats for a microbe in the human body, including Gram-positive and Gram-negative bacteria, as well as certain yeasts and fungi. This is particularly due to the presence of food particles and shedded epithelial cells in the oral cavity, making it a favorable microbial habitat at 37°C with a neutral pH despite the presence of saliva, which contains anti-bacterial agent agents like lysozyme and lactoperoxidase (Henley-Smith and *al*., 2013). As a matter of fact, the first observed bacteria by a microscope were from the oral cavity. It was a dental plaque that the father of microbiology, Anton van Leeuwenhoek, used as a specimen to observe bacteria under his first-ever microscope (Sintim and Gürsoy, 2016**)**. Successful accumulation and multiplication of pathogenic bacteria in oral biofilms can lead to two common diseases, dental caries and periodontitis. Biofilms are associated with nearly two-thirds of all microbial infections in the US and should not be simply viewed or underestimated as "bacterial accumulations on surfaces" (Sintim and Gürsoy, 2016).

For a long time, the upkeep of oral hygiene has been premised on the use of synthetic chemical agents (Allaker and Douglas, 2009). The drawback to the evident benefits of antibiotic treatment is represented by the undesired effects of their use. On the one hand, there are side effects with repercussions for the patient, such as gastric, hematological, neurological, dermatological, allergic and other disorders. On the other hand, the development of bacterial resistance is of great importance for both individual patients and public health (Bairwa, 2012). Over the past two decades, there has been a tremendous increase in the use of herbal medicine. However, there is still a significant lack of research data in this field (Zhang, 2009).

Three kinds of small molecules that inhibit biofilm formation by oral pathogens have been described. These are inhibitors of cell-to-cell communication, synthetic anti-bacterial agents that have both bactericidal and antibiofilm properties and natural products, mainly isolated from food, leaves, and essential oils, that either inhibit biofilm formation or disperse established biofilms (Sintim and Gürsoy, 2016). In this review, we deal mainly with the third aspect because the use of natural products seems to be an alternative solution to the synthetic antibiotic. So, the objective of the present review is to document the main oral diseases, how they occur and the potential application of plants extracts and isolated molecules in their treatments.

Oral diseases

The World Health Organization (WHO) defines oral health as "a state of being free from mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing" (WHO, 2012). Thus oral diseases are simply malfunctions affecting the human's oral cavity, which are caused by a lack of good oral hygiene (Muhammad and Lawal, 2010).

Good oral health enables us to speak, smile, kiss, breathe, whistle, smell, taste, drink, eat, bite, chew, swallow and express feelings. The oral cavity plays a central role in the intake of basic nutrition and protection against microbial infections.

There are four major natural habitats in the oral cavity, namely the buccal mucosa, dorsum of the tongue, tooth surfaces and crevicular epithelium. The diversity of the oral micro-flora is intimately linked with the habitats of the oral cavity. (Henley-Smith *et al.*, 2013). A number of micro-organisms are found in the oral cavity, but only a few bacteria can be considered true dental pathogens or odontopathogens. These are responsible for the most common bacterial disease in humans (Muhammad and Lawal, 2010).

Gram-positive aerobic bacteria, such as *Actinomyces spp.* and *oral streptococci* are the initial colonizers of the teeth surfaces. These bacteria interact with the pellicle-coated tooth surface and other bacteria as well. New bacterial adherence to immobilized bacteria is called co-adhesion, which is a form of co-aggregation (Sintim and Gürsoy, 2016). Both co-aggregation and co-adhesion happen only between compatible organisms and require cell surface adhesions and cognate receptors. One major bacterial species to co-aggregate with early and late colonizers of oral biofilms is *Fusobacterium nucleatum,* which is a Gram-negative, anaerobic bacterium of the oral cavity, acting as a bridge between early and late colonizers of the oral biofilms (Kolenbrander *et al.*, 2010; Sintim and Gürsoy, 2016).

Biofilm is a dense non-calcified mass composed of micro-organisms, *Streptococcus mitis* and *Streptococcus sanguis* being the pioneers. It is a matrix rich in bacterial extra-cellular polysaccharides and salivary glycoproteins, firmly attached to the teeth and other hard surfaces of the oral cavity (Chinsembu, 2016). Dental plaque is the primary etiologic factor in dental caries, gingivitis, and periodontal disease. It is complex bacterial biofilm communities that contribute to many factors such as cell adherence, congregation, growth and survival in the environment. Plaque bacteria utilize carbohydrates on tooth surfaces to produce acids that result in the cariogenic challenge and lead to dissolving the calcium phosphate in teeth and enamel demineralization and fallowing tooth decay (Borhan-mojabi and Azimi, 2013).

Oral health is an integral part of general health and oral health when neglect results in two common oral diseases: dental caries and periodontal diseases (Digra *et al.*, 2014).

Caries

'Caries' is defined as localized destruction of the tissues of the tooth by bacterial fermentation of dietary carbohydrates. First, the enamel is demineralized and then the dentin by the acid by-products of microbial metabolism of carbohydrates. However, demineralization is followed by remineralization. Cavities occur when the demineralization overtakes remineralization. *Streptococci* such as *S. mutans* are acidogenic and aciduric (acid-tolerant) and reduce plaque pH levels encouraging conditions for other plaque bacteria. Once the pH level falls below 5.5, enamel demineralization occurs (Henley-Smith and *al.*, 2013).

Dental caries is a highly prevalent chronic disease afflicting a significant proportion of the world population, including around 60% to 90% of school-aged children and the vast majority of adults (Petersen, 2004). The fact that dental caries is prevalent globally does not, by itself, merit it as a major issue. However, the significant cost to treat the disease, as well as its impact on individuals and populations who cannot afford or do not have access to dental care, elevate dental caries to an oral health and public health issue (Cummins, 2013**)**. Caries is currently classified by the experts of the World Health Organization (WHO) to the third rank of the world curses, immediately after the cancerous affections and the cardiovascular illnesses. It is about a microbial, multi-factorial illness, which succeeds in destroying the hardest substance of the human body, the enamel, before reaching the dentine (Disadila, 2013).

There is general acceptance that the true risk factors in dental caries are the presence of susceptible tooth surfaces, acid-producing bacteria, including *Streptococcus mutans*, frequent sugar intake; impaired salivary function, poor oral hygiene, past caries experience; inadequate fluoride exposure, limited access to dental care; and low socioeconomic status (Featherstone, 2006).

The development of dental caries involves acidogenic and aciduric Gram-positive bacteria, primarily the mutans streptococci (*Streptococcus mutans* and *S. sobrinus*), lactobacilli and actinomycetes, which metabolize sucrose to organic acids (mainly lactic

acid) that dissolve the calcium phosphate in teeth, causing decalcification and eventual decay or plaque formation. (Borhan-mojabi and Azimi, 2013).

One of the most often documented characteristics of the virulence of *S. mutans* is its ability to produce glucosyltransferases (GTFs), which synthesize intracellular polysaccharides (IPS) and extra-cellular polysaccharides (EPS).

The EPS, especially water-insoluble glucans, mediate the adherence of *S. mutans* and other oral bacterial species to tooth surfaces, contributing to the formation of dental plaque biofilms (Xu *et al.*, 2011).

Table 1. Oil used in dentistry.

Oil	Active components	Use in dentistry	References
Coconut oil	Polyphenols	Active against tooth decay ; Gum disease ; Dental plaque ; Bleeding gums ; Halitosis	Lakshmi and Ruchika, 2013
Tea Tree oil	terpinen-4-ol and alpha-terpineol	Treatment of Herpes labialis ; Dental pain killer ; Halitotsis ; Relieves symptoms of gingivitis ; Treatment of denture stomatitis	Lakshmi and Ruchika 2013
Eucalptus oil	1,8-cincole	A decongestant ; Antimicrobial ; Periodontal disease ; Candidiasis	Lakshmi and Ruchika, 2013
Clove oil	Ecrireles composés responsable	Treat dry socket ; As temporary restorative material ; As local anesthetic agent ; For tooth pain ; Candidiasis	Lakshmi and Ruchika, 2013
Sesame oil	omega3	Tooth pain ; Gum diseases ; Sensitive teeth ; Dental Plaque	Lakshmi and Ruchika, 2013

Several stages occur during plaque formation. As dental caries are generally associated with *S. mutans*, the process of biofilm formation of the bacteria on tooth surfaces will be used to clarify the description. Firstly, sucrose and glucosyltransferases (GTFs) enzymes are required for the accumulation of *S. mutans*. Saliva in the oral cavity produces a film on the tooth surface. This film contains glycoprotein constituents and forms a pellicle on the tooth surface. *Streptococcus mutans* interact with the α-galactosides in the saliva-derived glycoprotein of the pellicle using an adhesion known as antigen I/II.

The cell membrane of *S. mutans* also possesses glucanbinding protein (GBP), serotype carbohydrates and GTFs. This allows for the accumulation of *S. mutans*. Co-aggregation or co-adhesion then takes place as new bacteria attach to those bacteria already attached to the tooth's surface. These steps lead to the formation of a biofilm. (Taubman and Nash, 2006; Henley-Smith *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 favors 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.

Periodontal diseases

Periodontal diseases are 'a collective term ascribed to several pathological conditions characterized by degeneration and inflammation of gums, periodontal ligaments, alveolar bone and dental cementum' (Henley-Smith *et al.*, 2013). Periodontal diseases affect the tissues surrounding the teeth. Gums and bone supporting the teeth come under the term periodontal. Gingivitis, the mildest form of periodontal disease, is generally caused by insufficient oral hygiene. Inadequate oral hygiene can lead to plaque buildup. A variety of triggering factors like bacterial causes, dyscrasias, avitaminosis, cause inflamed gums leading to gingivitis. Salivary tartar has an additive effect to these causative factors in causing gingivitis (Ali *et al.*, 2009). Gingivitis is the inflammation of the periodontal ligament that forms the periodontal pocket.

Table 2. Anti-microbial activity of natural compound.

Plant species (Extract)	Plant part	Isoleted compound		MIC (µg/mL) of isoleted compound aginst oral Micro-organism							Reference
		Group	Name	*S. sa*	*S. so*	*S. mu*	*S. mi*	*S. sali*	*P. inter*	*P. ging*	
Lippia sidoides	leaves	Phenolic compound	Thymol	5000	ND	5000	5000	5000	ND	ND	Botelho *et al.*, 2007
Lippia sidoides	Leaves	Phenolic compound	Carvacrol	2500	ND	2500	2500	2500	ND	ND	Botelho *et al.*, 2007
Vitis vinifera	Fruit	Triterpene acid	oleanolic acid	ND	ND	625	ND	ND	ND	488	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	oleanolic aldehyde	ND	ND	488	ND	ND	ND	250	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	Betulin	ND	ND	1000	ND	ND	ND	1000	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	betulinic acid	ND	ND	1000	ND	ND	ND	1000	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	5-(hydroxymethyl)-2-furfural	ND	ND	31	ND	ND	ND	16	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	Rutin	ND	ND	250	ND	ND	ND	NA	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	3-Acetyloleanolic acid	ND	ND	79	ND	ND	ND	1000	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	Methyl 3-acetyloleanolic acid	ND	ND	781	ND	ND	ND	NA	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	Methyl oleanolic acid	ND	ND	1000	ND	ND	ND	1000	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	3-O-(20,20-dimethylsuccinyl)-oleanolic acids	ND	ND	NA	ND	ND	ND	156	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	3-O-(30,30-dimethylsuccinyl)-oleanolic acids	ND	ND	500	ND	ND	ND	98	Rivero-Cruz *et al.*, 2008
Vitis vinifera	Fruit	Triterpene acid	Sodium salt of oleanolic acid	ND	ND	78	ND	ND	ND	39	Rivero-Cruz *et al.*, 2008
Diospyros lycioides	Twigs	naphthalene glucosides	diospyroside A.	39	ND	1250	ND	ND	39	78	Cai *et al.*, 2000
Diospyros lycioides	Twigs	naphthalene glucosides	diospyroside B	39	ND	625	ND	ND	156	78	Cai *et al.*, 2000
Diospyros lycioides	Twigs	naphthalene glucosides	diospyroside C	625	ND	156	ND	ND	39	312	Cai *et al.*, 2000
Diospyros lycioides	Twigs	naphthalene glucosides	diospyroside D	312	ND	156	ND	ND	156	156	Cai *et al.*, 2000
Diospyros lycioides	Twigs	Quinone	juglone	39	ND	78	ND	ND	19	39	Cai *et al.*, 2000
Diospyros lycioides	Twigs	Quinone	7-methyljuglone	78	ND	156	ND	ND	78	39	Cai *et al.*, 2000
Psoralea corylifolia	Seeds	phenolic isoprenoid	Bakuchiol	ND	1.6	1.4	ND	ND	ND	4	Katsura *et al.*, 2001.
Salvia officinalis	Aerial parts	Diterpene	Manool	ND	24	6	12	24	ND	ND	Moreira *et al.*, 2013
Propolis	-	Sesquiterpene	tt-farnesol	ND	14	28	ND	ND	ND	ND	Koo *et al.*, 2002
Propolis	-	Flavone	Baicalein	ND	134	134	ND	ND	ND	ND	Koo *et al.*, 2002
Propolis	-	Flavanone	Pinocembrin	ND	128	64	ND	ND	ND	ND	Koo *et al.*, 2002
Propolis	-	Flavanone	Sakuranetin	ND	135	NA	ND	ND	ND	ND	Koo *et al.*, 2002
Propolis	-	Flavanone	Isosakuranetin	ND	135	67	ND	ND	ND	ND	Koo *et al.*, 2002
Propolis	-	Dihydroflavonol	Pinobanksin-3-acetate	ND	145	72	ND	ND	ND	ND	Koo *et al.*, 2002
Morus alba	Leave	Iminosugar	1-deoxynojirimycin	ND	ND	15.6	ND	ND	ND	ND	Islam *et al.*, 2008
Myristica fragrans	Seed	Phenylpropane	Macelignan	2	15.6	3.9	ND	3.13	ND	125	Chung *et al.*, 2004
Trachyspermum ammi	Seed	Naphthalene	(4aS, 5R, 8aS) 5, 8a-di-1-propyloctahydro-naphthalen-1-(2H)-one	ND	ND	156	ND	ND	ND	ND	Khan *et al.*, 2010
Psidium guajava	Leave	Flavonoid	quercetin-3-O-α-L-arabinopyranoside (guaijaverin)	ND	ND	2000	ND	ND	ND	ND	Prabu *et al.*, 2005
Rheedia	Fruit	prenylated	7-epiclusianone	ND	ND	1.25-	ND	ND	ND	ND	Almeidaa *et al.*, 2008

brasiliensis		benzophenone				2.50					
Camellia sinensis	Leave	Polyphenol	epigallocatechin gallate	ND	ND	31.25	ND	ND	ND	ND	XU *et al.*, 2010
Miconia fallax	aerial parts	triterpene acid	ursolic acid	ND	50	80	50	50	ND	ND	Cunha *et al.*, 2007
Miconia albicans	aerial parts	triterpene acid	oleanolic acid	ND	50	70	40	30	ND	ND	Cunha *et al.*, 2007
Miconia fallax	aerial parts	triterpene acid	Sumaresinolic acid	ND	90	200	40	70	ND	ND	Cunha *et al.*, 2007
Miconia stenostachya	aerial parts	triterpene acid	Gypsogenic acid	ND	100	200	50	70	ND	ND	Cunha *et al.*, 2007
Miconia stenostachya	aerial parts	triterpene acid	ursolic acid and oleanolic acid	ND	80	90	30	60	ND	ND	Cunha *et al.*, 2007
Miconia sellowiana	aerial parts	triterpene acid	maslinic acid and 2α-hydroxyursolic acid	ND	200	200	60	80	ND	ND	Cunha *et al.*, 2007
Aspilia foliacea	aerial parts	Diterpene	ent-kaur-16(17)-en-19-oic acid	ND	10	10	10	100	ND	ND	Ambrosio *et al.*, 2008
Artocarpus heterophyllus	heart wood	Flavonoid	Artocarpin	6.25-12.5	6.25-12.5	6.25	3.13-6.25	6.25-12.5	ND	3.13	Sato *et al.*, 1996
Artocarpus heterophyllus	heart wood	Flavonoid	Artocarpesin	6.25-12.5	6.25-12.5	6.25-12.5	6.25	6.25-12.5	ND	3.13	Sato *et al.*, 1996
Alcea longipedicellata	Flower	Flavonoid	Malvidin-3,5-diglucoside (malvidin)	220	220	160	ND	ND	ND	ND	Esmaeelian *et al.*, 2007
Zanthoxylum zanthoxyloides	Root's bark	Phenylpropane derivative	4'-O-(3"-méthylbut-2"-enyloxy)-3-phénylpropanol	ND	ND	500	ND	ND	ND	ND	Kouri, 2004
Cinnamomum zeylanicum	Bark	phenylpropanoid	Cinnamaldehyde	ND	ND	0.40	0.40	0.40	ND	0.30	Zainal-Abidinand *et al.*,. 2013
Cinnamomum zeylanicum	Bark	phenylpropanoid	Eugenol	ND	ND	0.40	0.40	0.40	ND	0.80	Zainal-Abidin *et al.*, 2013
Rosmarinus officinalis	Leave	Terpenoid	Camphor	ND	1500	1500	300	400	ND	ND	Bernardes *et al,*. 2010
Rosmarinus officinalis	Leave	Terpene	Verbenone	ND	1000	1000	300	400	ND	ND	Bernardes *et al.* 2010
Rosmarinus officinalis	Leave	Terpene	α-Pinene	ND	1000	2000	400	400	ND	ND	Bernardes *et al.*, 2010
Rosmarinus officinalis	Leave	Terpene	β-Myrcene	ND	2000	400	400	400	ND	ND	Bernardes *et al.*, 2010
Rosmarinus officinalis	Leave	Terpenoid	1,8-Cineole	ND	1500	1500	300	400	ND	ND	Bernardes *et al.*, 2010
Rosmarinus officinalis	Leave	Sesquiterpene	β-Caryophyllene	ND	400	300	300	400	ND	ND	Bernardes *et al.*, 2010

S. sa: *Streptococcus sanguis ;* S. so: *Streptococcus sobrinus ; S. mu* : *Streptococcus mutans ;* S. mit: *Streptococcus mitis ; S. sali* : *Streptococcus salivarius ; P. inter*: *Prevotella intermedia ; P. ging* : *Porphyromonas gingivalis* ; ND : not done ; NA : not active.

Clinical features include redness, swelling and bleeding of the gums. Periodontitis usually develops from untreated gingivitis and can involve loss of bone and tissue decay. The combined activities of micro-organisms within the subgingival biofilms and the host responses to them lead to the progression of the disease and tissue damage. Periodontal diseases are subgingival conditions that have been linked to anaerobic Gram-negative bacteria such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythus*, *Aggregatibacter actinomycetemcomitans*, *Fusiobacterum nucleatum* and *Capnocytophaga* species. (Henley-Smith *et al.*, 2013). *P. gingivalis, P. intermedia* and *A. actinomyces temcomitans* are regarded as the major pathogens in advancing periodontitis (Allaker and Douglas, 2009; Chinsembu, 2016). Periodontal disease is recognized as a major public health problem throughout the world and is the most common cause of tooth loss in adults. Pain, discomfort and cosmetic considerations are some of the factors that demonstrate the severity of the

problems associated with dental diseases and hence, it is of utmost importance to minimize and control dental diseases (Ali *et al.*, 2009). Periodontopathic bacteria play a key role in producing volatile sulfure compounds, especially hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH) and dimethylsulfide [$(CH_3)_2S$] involved in bad breath. These compounds result from the proteolytic degradation by predominantly anaerobic Gram-negative oral micro-organisms of various sulfur-containing substrates in food debris, saliva, blood and epithelial cells (Arab *et al.*, 2011).

Prevention and treatment

Prevention

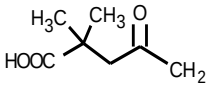
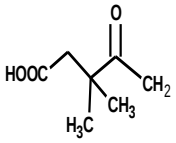
Maintaining oral hygiene should be a lifelong habit. An infant's gum and later teeth should be kept clean by wiping them with moist cloth/cotton wool or a soft toothbrush. However, only a very small amount of toothpaste (pea-sized) containing fluoride should be used since too much fluoride may be toxic to infants (Muhammad and Lawal, 2010). An adult who has partial or full denture is also expected to maintain good oral hygiene. Bridges and dentures must be kept clean to prevent gum disease. The denture should be relined and adjusted by a dentist as necessary to maintain proper fit so that the gums do not become red, swollen and tender (Muhammad and Lawal, 2010). Oral health and general health share common risk factors related to diet, the use of tobacco, and the excessive consumption of alcohol and the solutions to control the oral disease are to be found through shared approaches with integrated chronic disease prevention (Petersen, 2005). Bacteria adherent to surfaces has a higher resistance to clearance by normal cleansing methods as well as to bacteriolytic enzymes and antibiotics. The adherent state is therefore advantageous to survival and a key step in pathogenesis. By preventing microbial adhesion, disease formation can be prevented as well (Henley-Smith *et al.*, 2013). Modern toothpaste, mouthwashes, dentifrices etc. are available in different forms, types, sizes, colors, and in different packs. Most toothpaste is clearly marked out with fluoride, which is an element that is expected to prevent tooth decay. Some other chemical components of toothpaste are aqua, hydrated silica, sorbitol, glycerin, sodium lauryl sulphate, flavour, titanium dioxide, xanthan gum, sodium saccharin, sodium fluoride and a number of others. All these are good for health (Muhammad and Lawal, 2010). Plant extracts can also be used in the prevention of oral diseases. Huang *et al.* (2012) evaluated the effect of *Galla chinensis* extract and its main components on the prevention of enamel demineralization *in vitro*. They suggested that Gallic Acid could be the main effective constituent of *Galla chinensis* extract in inhibiting enamel demineralization, and could be a potential source for the development of promising anti-cariogenic agents. Smullen *et al.* (2012) investigated the inhibition effect of propanone extract of leaves of *Rosmarinus officianalis* and *Salvia officianalis* on growth and acid production from glucose and sucrose by *Streptococcus mutans*. Prevention of plaque formation on bovine teeth initiated by *Streptococcus mutans* was also studied using an artificial mouth. The plant extracts inhibited the growth of oral bacteria and prevented acid production by *Streptococcus mutans*. The results of this study suggest that the extracts of *R. officianalis L.* and *S. officianalis L.* may be useful as antiplaque agents in foods and dental preparations.

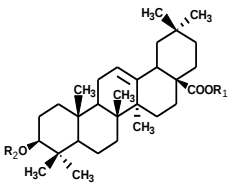
Treatment

Conventional treatment

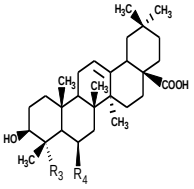
For a long time, the upkeep of oral hygiene has been premised on the use of synthetic chemical agents (Allaker and Douglas, 2009). For instance, mouth rinses are often employed in the prevention and treatment of oral infections. Mouth rinses may contain fluorides, alcohols, detergents and other anti-microbial substances. Toothpaste also contains fluorides and other anti-microbials, including triclosan and zinc citrate. Synthetic anti-microbials include povidone-iodine products, florides, phenol derivatives, chlorhexidine, cetyl pyridinium chloride and antibiotics like ampicillin, erythromycin, penicillin, tetracycline, and vancomycin are also widely used in dentistry to inhibit bacterial growth (Jang *et al.*, 2014).

Table 3. Structures of molecules with oral anti-microbial activity.

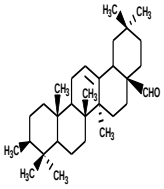
	R_1	R_2
oleanolic acid	H	H
3-Acetyloleanolic acid	H	CH_3CO
3-O-(2',2'-dimethylsuccinyl)-oleanolic acids	H	
3-O-(3',3'-dimethylsuccinyl)-oleanolic acids	H	
Sodium oleanolic acid	Na^+	H



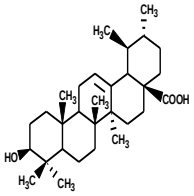
	R_3	R_4
oleanolic acid	H	H
Sumaresinolic acid	CH_3	OH
Gypsogenic acid	COOH	H



2-hydroxyursolic acid



Oleanolic aldehyde



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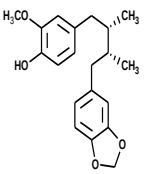

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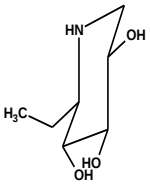

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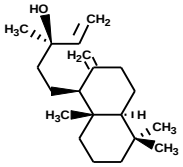
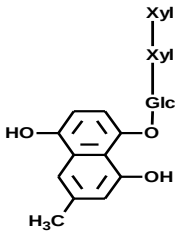


Manool



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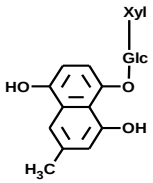

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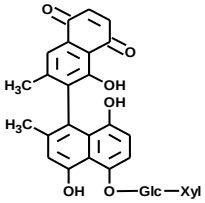

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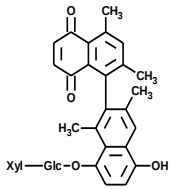
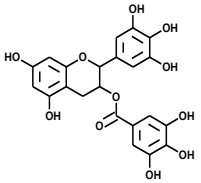


Diospyroside D



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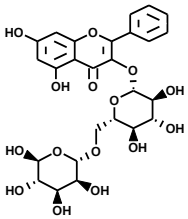
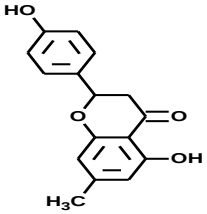


Rutin



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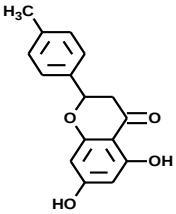

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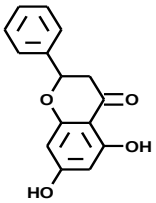

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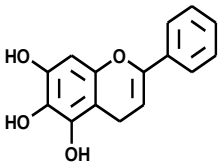

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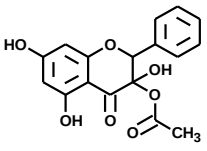

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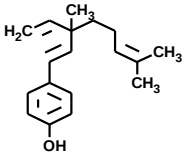
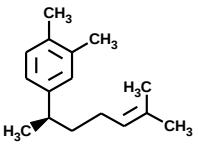


bakuchiol



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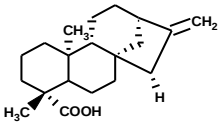

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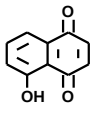
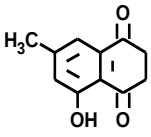
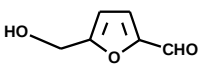


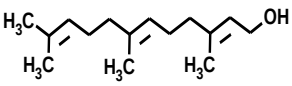
Juglone



7-Methyl-juglone



5-(hydroxymethyl)-2-furfural



tt-farnesol

Fluoride dentifrices, and other topical fluoride products, reduce dental caries by targeting the tooth surface and reducing its susceptibility to acid attack. Fluoride arrests the caries process, reducing demineralization and increasing remineralization of demineralized tissues. However, conventional fluoride toothpaste and mouth rinses have their limitations for high-risk individuals, especially those with high plaque levels and frequent sugar intake. Fluoride does not act upon the plaque biofilm, an

important modifiable factor in dental caries, to reduce the cariogenic challenge. Specifically, fluoride does not primarily reduce total biofilm biomass, inhibit bacterial acid production, or promote microbial homeostasis within the plaque biofilm and a dynamic balance favoring organisms associated with "health". Thus, topical fluoride products help to control but cannot completely prevent dental caries (Cummins, 2013). Since synthetic products have side effects and are costly, plant products are of interest as a source of safer or more effective substitutes for synthetically produced anti-microbial agents and, as such, could have an anti-cariogenic role in food products oral products and medicines (Smullen *et al.,* 2012). Fig. 1 presents the chemical structures of common synthetic molecules found in mouthwashes and toothpaste with anti-microbial and anti-biofilm properties (Sintim and Gürsoy, 2016).

Table 4. Classification of herbal drugs used in dentistry based on their actions (Sinha and Sinha, 2014).

Uses in dentistry	Names of the herbal agents
Anti-microbial action	*Acacia nilotica, Aloe barbadensis, Arctium lappa, Azadirachta indica*, Carvacrol, *Casearia sylvestris, Allium sativum, Marticaria recutitia, Camellia sinensis, Citrus limonum, Morinda citrifolia*, Propolis, *Psidium guajava, Psoralea corylifolia, Rhus lancia, Salavadora persica, Syzigium aromaticum, Melaleuca alternifolia, Curcuma longa, Glycyrrhiza glabra*
Anti-inflammatory action	*Casearia sylvestris, Marticaria recutitia, Camellia sinensis, Morinda citrifolia*, Propolis, *Psidium guajava, Rhus lancia, Salavadora persica, Glycyrrhiza glabra*
Sedative and anxiolytics	*Arctium lappa, Marticaria recutitia*
Miscellaneous action (endodontic irrigants, medicaments and endodontic retreatment)	*Arctium lappa, Azadirachta indica, Casearia sylvestris, Allium sativum, Morinda citrifolia Camellia sinensis, Citrus limonum*, Orange Oil, Propolis, *Salavadora persica, Melaleuca alternifolia, Triphala, Curcuma longa*

Herbal remedies

Recently, many plant-derived products have been used in oral care products. These natural products are incorporated in different dosage forms that have a very good value in the market. In this section, we present these different dosage forms of natural products used against oral diseases.

Mouth bath

Oral rinses deliver their therapeutic ingredients and benefits to all accessible surfaces of the oral cavity. Depending on their composition, oral rinses can remain active for an extended period of time. Clinicians often recommend oral rinses to patients to reduce biofilm formation, which aids in controlling gingivitis (Smullen *et al.*, 2012).

Usually, mouthwashes are an antiseptic solution intended to reduce the microbial load in the oral cavity. Herbal mouthwashes help in the prevention of cavities, restore enamel, strengthen teeth, kill bad breath germs, clean the whole mouth and freshen breath (Vijayaalakshmi and Geetha, 2015).

Vijayaalakshmi and Geetha (2015) studied the anti-bacterial effect of herbal mouth wash in comparison with a conventional mouth wash (Chlorhexidine) in reducing *Streptococcus mutans* count. The research was done with herbal mouth wash, which has ingredients as follows, *Syzygium aromaticum*, *Mentha piperita*, *Eucalyptus globulus*, *Cinnamon zeylanicum*, *Myristica Fragrans*, *Ocimum basilicum*. The minimum inhibition concentrations of herbal and conventional chlorhexidine mouth wash for *S. mutans* were 7.81 and 3.9 (µg/mL). The results showed that herbal mouth is equivalent to conventional mouth wash in use. Botelho *et al.* (2007) examined the short-term efficacy and safety of *Lippia sidoides* essential oil mouth rinse on gingival inflammation and bacterial plaque in a high-caries risk population of Northeastern Brazil. The findings of this study demonstrated that the *Lippi sidoides*-based mouth rinse was safe and efficacious in reducing bacterial plaque and gingival inflammation. In addition, it was shown that such a decrease was statistically similar to the positive control, 0.12% chlorhexidine, whose choice was due to the fact that it

appears to be the most effective chemical agent for plaque control (Botelho *et al.*, 2007).

Toothpaste containing natural product

Many kinds of toothpaste contain plant extract. For instance, Al Sadhan *et al.* (1999) listed some of the known commercial toothpaste produced from *Salvadora persica* plant. These are Sarkan toothpaste, UK, Quali-Meswak toothpaste, Switzerland, Epident toothpaste, Egypt, Siwak-F toothpaste, Indonesia. Fluoroswak Miswak, Pakistan.1 Dentacare Miswak Plus, Saudi Arabia.

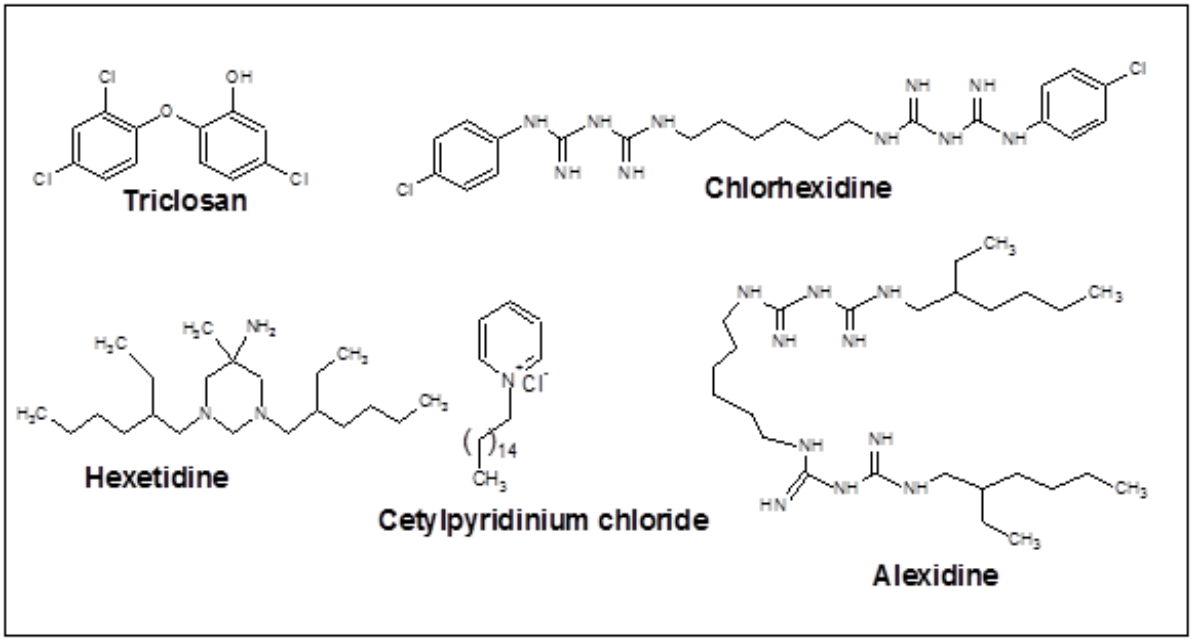


Fig. 1. Common molecules found in mouthwashes and toothpastes with anti-microbial and anti-biofilm properties (Sintim and Gürsoy, 2016).

Andiara *et al.* (2014) investigated the anti-microbial efficacy of toothpaste containing triclosan, chlorhexidine, or plant extracts from *Echinacea angustifolia* (0.954 g), *Commiphora myrrha* (0.624 g), *Krameria triandra* (1.248 g), *matricaria chamomilla* (0.624 g) compared with the one of a conventional toothpaste (Sorriso®) against multiple species of Gram-positive bacteria, Gram-negative bacteria and yeasts. This study demonstrated that the toothpaste containing natural extracts, as well as the one containing chlorhexidine or triclosan have anti-microbial efficacy against a variety of micro-organisms involved in most common oral diseases, including caries and periodontal diseases, using the standard disk diffusion method. The plant extract-based dentifrice was the only product able to inhibit the growth of Gram-negative bacteria (*Psudomona aeruginosa*) associated with periodontal diseases. Gibraiel *et al.* (2014) investigated the anti-microbial efficacy of conventional and an herbal toothpaste containing: *Anacyclus pyrethrum, Embeliaribes, Azadirachta indi, Curcuma longa, Acacia arabica, Salvadora persica, Xantho xylumalatum, Quercus infectoria, Syzygium aromaticum, Piper sylvaticum, Barleria prionitis, Mimusop selengi.* The result of this study shows that the herbal formulations studied appeared to be equally effective as the fluorides-containing formulations.

Chewing stick

Plants have very effective and important roles to play in oral hygiene. A number of popular plants are fashioned into chewing sticks, most of which have different substances in them that can keep the buccal cavity healthy as a whole (Muhammad and Lawal, 2010).

Even though many people have abandoned the traditional toothbrush sticks and adapted to the conventional tooth brushing method, some societies

still make use of chewing sticks as a daily ritual to maintain oral hygiene. This is especially true in developing countries where economics, customs, religion and the availability of oral hygiene tools play a role in their continued use. The chewing sticks, termed as such due to the need for the user to chew the stick prior to brushing, have been used throughout the Greek, Roman, Jewish and Islamic Empires (Van Vuuren and Viljoen, 2006).

In Africa, the use of chewing sticks is still widespread and chewing sticks are widely used in Sudan, Nigeria and Namibia. Throughout the world, 182 species of plants have been used as chewing sticks, with 158 known to Africa. In Ghana and Nigeria, Teclea vardo-ordniana, Garcinia and Acacia species are preferred. In Nigeria, about 80-90% of the population in rural areas use chewing sticks, mainly because they are readily available, cheap and efficacious (El-Desoukey, 2015).

The World Health Organization (WHO) supports the use of chewing sticks as an effective tool for oral hygiene because chewing sticks contain many anti-microbial substances. The anti-microbial activity of chewing sticks is well documented and studies have demonstrated that some of these chewing sticks have better anti-microbial than many conventional kinds of toothpaste. For example, Odeleye *et al.* (2016) evaluated the anti-microbial activities of ethanolic and aqueous extracts of *Zanthoxylum zanthoxyloides, Vernonia amygdalina and Massularia acuminata* and two common brands of toothpaste (Macleans and Close Up) for the prevention of tooth decay. Both brands of toothpaste were inferior to the ethanol extracts of all the chewing sticks in anti-caries activity. It is noteworthy that many plants are used as chewing sticks in the Benin Republic, but their anti-microbial activity is not yet known.

The twigs of *Diospyros lycioides* are frequently used as chewing sticks for the cleaning of teeth by rural and urban people in Namibia. Preliminary studies showed that a methanol extract of *D. lycioides* inhibited the growth of selected oral pathogens. Subsequent bioassay-guided fractionation led to the isolation of four novel bioactive naphthalene glycosides, 1,4,5-trihydroxy-7-methylnaphthalene-4-O-β-xylopyranosyl (1→ 4)-β-xylopyranosyl (1→ 6)-β-glucopyranoside (diospyroside A) ; 5,8-dihydroxy-2-methyl[1,4]naphthoquinone-5-O-β-xylopyranosyl(1→6)-β-glucopyranoside (diospyroside B) ; 8,6'-binaphthalene-1',4'-one-7,7'-dimethyl-1,4,5,5'-tetrahydroxy-4-O-β-xylopyranosyl (1→6)-β-glucopyranoside (diospyroside C) ; 6,8'-binaphthalene-1',4'-one-7,7'-dimethyl-1,4,5,5'-tetrahydroxy-4-O-β-xylopyranosyl(1→6)-β-glucopyranoside (diospyroside D), and two known bioactive naphthoquinones, 5-hydroxy-1,4-naphthoquinone (juglone) and 5-hydroxy-7-methyl-1,4-naphthoquinone (7-methyljuglone). These compounds inhibited the growth of oral cariogenic bacteria (*Streptococcus mutans* and *Streptococcus sanguis*) and periodontal pathogens (*Porphyromonas gingivalis* and *Prevotella intermedia*) at minimum inhibitory concentrations ranging from 0.019 to 1.25 mg/mL. Juglone exhibited the strongest inhibitory activity among these compounds (Cai *et al.*, 2000). Kothai (2012) evaluated the antifungal activity of chewing sticks used by the inhabitants of Jimma-Ethiopia, namely *Clausenia anisata*, *Clematis simensis, Cleodendrum myricoides*, *Juniperus procera*, *Justicia schimperiana*, *Olea europea*, *Phoenix reclinata* and *Rubus apitalus*. The minimum inhibitory concentration (MIC) varied from 12.5 to 100µg/ml for the chewing sticks.

Essential oil

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 (Chinsembu, 2016).

Essential oils and their components have been recently investigated more thoroughly as promising agents for the prevention or treatment of dental plaque-related diseases (Botelho *et al.*, 2007). The same authors studied a comparative evaluation of the

activity of separate and combined compounds against micro-organisms related to caries and oral infection. This study shows that the essential oil from *Lippia sidoides* has a lower anti-bacterial potential when compared to two of it major constituents (thymol and carvacrol), suggesting that the minor components may contribute to an antagonistic effect on the activity of the essential oil (Botelho *et al.*, 2007). This fact was also confirmed by Islam *et al.* (2008) by comparing the activity of 1,5 deoxy-1,5-imino-D-glucitol, commonly known as 1-deoxynojirimycin (DNJ), a purified compound from *Morus alba,* with its ethanol crude extract against *Streptococcus mutans* biofilm formation. The MIC of the crude extract (125 mg/L) shows a decrease by ~8-fold when compared with the one of the purified compounds (15.6 mg/L), reflecting the higher activity of the purified compound when compared with that of the crude extract.

Crevelin *et al.* (2015) investigated the anti-microbial activity of the essential oil obtained from the leaves of *Plectranthus neochilus* against a representative panel of oral pathogens.

This essential oil displayed moderate activity against *Enterococcus faecalis* (MIC = 250 μg/mL) and *Streptococcus salivarus* (MIC = 250 μg/mL), significant activity against *Streptococcus sobrinus* (MIC = 62.5 μg/mL), *Streptococcus sanguinis* (MIC = 62.5 μg/mL), *Streptococcus mitis* (MIC = 31.25 μg/mL), and *Lactobacillus casei* (MIC = 31.25 μg/mL), and interesting activity against *Streptococcus mutans* (MIC = 3.9 μg/mL). Samples with MIC values lower than 100 μg/mL, between 100 and 500 μg/mL, and between 500 and 1000 μg/mL were considered to be promising, moderately active, and weak anti-microbials, respectively. Samples with MIC values greater than 1000 μg/mL were deemed inactive (Kouri, 2004; Crevelin *et al.*, 2015).

Many essential oils are used in dentistry to prevent or to treat oral diseases and their anti-microbial activity is well documented. Table 1 presents a list of essential oil used in dentistry.

Natural products and compounds with anti-microbial against oral microbes

Plant products are of interest as a source of safer or more effective substitutes for synthetically produced anti-microbial agents and, as such, could have an anti-cariogenic role in food products, oral products and medicines (Smullen *et al.,* 2012). Consumption of products with antioxidant activity promotes oral health. Many plants used in the management of oral infections are infused with several useful anti-microbial phytochemicals such as simple phenols, phenolic acids, quinones, flavones, flavonoids, flavonols, tannins, coumarins, terpenoids, essential oils, alkaloids, lectins, and anti-microbial peptides (Chinsembu, 2016).

Rivero-Cruz *et al.* (2008) isolated eight known compounds, oleanolic acid, oleanolic aldehyde, linoleic acid, linolenic acid, betulin, betulinic acid, 5-(hydroxymethyl)-2-furfural, rutin, β -sitosterol and β-sitosterol glycoside through bioassay-guided fractionation of Thompson seedless raisins (*Vitis vinifera*). The anti-microbial screening against two oral pathogens revealed that most of the compounds inhibited the growth of *S. mutans* and *P. gingivalis*, with MIC values ranging from 16 to 1000 µg/mL.

Studies have demonstrated that isolated pure compounds are more effective against oral bacterial than essential oil or crude extracts containing them. For example, Xu *et al.* (2011) studied the effect of Epigallocatechin Gallate (EGCg) extracted from the leaves of the plant *Camellia sinensis* (Tea) on Cariogenic Virulence Factors of *Streptococcus mutans*. They discovered that EGCg inhibited growth of *S. mutans* planktonic cells at a MIC of 31.25 µg/ml and a minimal bactericidal concentration (MBC) of 62.5 µg/ml. EGCg also inhibited *S. mutans* biofilm formation at 15.6 µg/ml (minimum concentration that showed at least 90% inhibition of biofilm formation) and reduced viability of the preformed biofilm at 625 µg/ml. In their review, Arab *et al.* (2011) cited studies that show that anti-microbial polyphenols, especially Epigallocatechin Gallate (EGCg) in green tea, can improve bad breath by

suppressing Gram-negative bacteria. The deodorizing effect of EGCg involves a chemical reaction between EGCg and methyl mercaptan (MSH). The reaction involves the introduction of a methylthio and/or a methylsulfinyl group into the Brink of EGCg. During this reaction, a methylthio group is added to the orthoquinone form of the catechin generated by oxidation with atmospheric oxygen and helps in reducing halitosis (Arab *et al*., 2011).

A crude methanolic extract of *Syzygium aromaticum* (clove) exhibited preferential growth-inhibitory activity against Gram-negative anaerobic periodontal oral pathogens, including *Porphyromonas gingivalis* and *Prevotella intermedia*. By means of bioassay-directed chromatographic fractionation, eight active compounds were isolated from this extract and were identified as 5,7-dihydroxy-2-methylchromone 8-*C*-β-d-glucopyranoside, biflorin, kaempferol, rhamnocitrin, myricetin, gallic acid, ellagic acid, and oleanolic acid, based on spectroscopic evidence. The anti-bacterial activity of these pure compounds was determined against *Streptococcus mutans*, *Actinomyces viscosus*, *P. gingivalis*, and *P. intermedia*. The flavones, kaempferol and myricetin, demonstrated potent growth-inhibitory activity against the periodontal pathogens *P. gingivalis* and *P. intermedia* (Cai et Wu, 1996).

Pure compounds displaying MIC values lower than or equal to 10 μg/mL are very promising for the development of anti-bacterial drugs (Ambrosio *et al*., 2008).

Table 2 shows the anti-microbial activity of the natural compound against oral pathogens. It is noteworthy that the anti-microbial activity is in the function of the isolated compound against oral Micro-organism. Many of the effective compounds against oral health belong to the terpene class or their derivative. Also, some plants presented a good anti-microbial activity, but their bioactive compounds are not yet known. The chemical structure of the majority of a compound that yields a good capacity to fight against oral pathogens is described in Table 3. Table 4 reveals the classification of herbal drugs used in dentistry based on their actions. It notifies that many plants display an anti-inflammatory, miscellaneous, anti-microbial, sedative and anxiolytics action.

Conclusion and perspectives

The present review reveals the importance of plants and their compounds in the process of discovery of novel drugs or natural medicine that will be effective and alternative to synthetize molecules in the fight against oral diseases. Many plants and their bioactive components have prospected for their anti-microbial activity against oral diseases causing bacteria and the results are promising. For this reason, they have been successfully incorporated in toothpaste and mouth rinses. This study also reveals the important role of the chewing stick in maintaining good oral hygiene. Though plants are effective against oral diseases, their toxicological effect is still not well established. So more biological, toxicological and structure-activity relationship studies must be undertaken for the safe use of plants in oral care.

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