

Antimicrobial Natural Products in Oral Health

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1. Oral disease

Oral diseases continue to be a major health issue worldwide. These are including oral and pharyngeal cancers and oral soft and hard tissue lesions, orofacial disorders, tooth loss, dental caries and periodontal diseases. These diseases are among the most important oral health problems. Also some of them cause significant health concerns. Despite general progress in the general health status of the people, majority of school-aged children and adults affected by dental caries. Millions of Americans suffer from oral conditions that result in pain and suffering, problem in chewing, swallowing and speaking; and in extreme cases, death. Also oral diseases have had a negative impact on economic efficiency and the learning ability of children.

There is considerable evidence that associated between poor oral health and chronic conditions, such as strong association between aggressive periodontal diseases and poor oral health; systemic diseases, such as diabetes, cardiovascular diseases and heart attacks, strokes, rheumatoid arthritis, lung diseases and osteoporosis. In addition periodontal diseases may associate with risk of pregnancy complications, for example preterm low-birth weight. Up to 20% of tooth loss in adult patients caused by poor periodontal health can result in significant morbidity and may be premature death. [1-7]

1.1. Dental Caries and periodontal disease:

Dental caries is a multi-factorial infectious disease that depends on:

A-diet and nutrition, B-microbial infection, C-host response

The incidence of root caries is increased dramatically in adults. Therefore control of caries is very important in dentistry.

In addition to dental caries, gingivitis and periodontal disease affect most of the adult population, the prevalence of this disease increasing with age. Periodontal disease is chronic inflammatory disease with different manifestation caused by some anaerobic Gram-negative bacteria which, leading to collagen destruction and loss of bone supporting the teeth. Periodontitis occurs at greatly different rates in different group.

Periodontitis has two conditions: A-The chronic forms, B- the aggressive, destructive forms (affects approximately 10% of the population, lead to serious tooth loss before old age). [7-10]



Fig. 1 Dental Caries

1.2. Dental plaque

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, and growth and survival in the environment. Plaque bacteria utilize carbohydrates on tooth surfaces to produce acids that result in cariogenic challenge and leading to dissolve the calcium phosphate in teeth and enamel demineralization and following tooth decay.

Therefore food particles especially fermentable carbohydrates that trapped on the teeth surfaces promoting acid production by plaque bacteria and tooth decay.

Over 750 species of bacteria inhabit the oral cavity and some of them are implicated in oral diseases.

The mutans group of streptococci (MS) is found prominently in dental plaque. It appears that this group of bacteria one of the etiologic agents of dental caries. The formation of dental caries involves acidogenic and aciduric Gram-positive bacteria, especially the mutans streptococci (*Streptococcus mutans* and *S. sobrinus*), lactobacilli and actinomycetes that metabolize sucrose to organic acids that demineralizing teeth, causing decalcification and eventual decay. Hence, the most prominent virulence factors of MS include acidogenicity, aciduricity, and their ability to synthesize adherent glucans from dietary sucrose, facilitating dental plaque formation and its adherence to tooth surfaces.

Periodontal diseases are linked to anaerobic Gram-negative bacteria such as *Porphyromonas gingivalis*, *Actinobacillus* sp., *Prevotella* sp. and *Fusobacterium* sp. In periodontal diseases, the gingival crevice and lower surface of cervical margin are infected by bacteria and result in a inflammatory response in gingiva and surrounding tissue of this area. These inflammatory responses can manifest as gingivitis (inflammation and bleeding of the gingival tissues) or periodontitis (loss of collagen attachment of the tooth to the bone and bone destruction).

Therefore high prevalence and incidence of oral diseases, coupled with the resultant social and economic implications, has led to a constant striving to produce new antimicrobial agents. [6,7]



Fig. 2 Periodontitis

2. Antimicrobial natural products

Natural products have been used from the past for their antibacterial effect, but recently investigation more thoroughly about that as promising agents for the prevention of oral diseases especially plaque-related diseases such as dental caries and periodontal disease. This global need for alternative treatment and use of natural products attracted the attention of the scientific community regarding a search for remedy products those are safer, effective and has economical efficiency.

Considering diseases caused by microorganisms, the increasing resistance in many common pathogens. This resistance by pathogenic bacteria to currently used antibiotics and chemotherapeutics and opportunistic infections in immune compromised result in renewed interest in the discovery of novel anti- infective compounds and universal tendency towards the natural medicine. [11-14]

2.1. Herbal Medicine

Plants have been used as traditional method of treatments for many human diseases from the past. Written records about medicinal plants date back at least 5000 years to the Sumerians, and archeological records suggest even earlier use of medicinal plants.

Historically there is strong association between plants and human health. In 1897, Friedrich Bayer et al introduced synthetic acetyl salicylic acid (aspirin) to the world. Aspirin is a safer synthetic analogue of salicylic acid, an active ingredient of willow bark, and it was discovered as a remedy for aches and fevers.

Herbs, botanically speaking, are any plants that lack the woody tissue characteristic of shrubs or trees. More specifically, herbs are plants used medicinally or for their flavor or scent. Herbs with medicinal properties are a useful and effective source of treatment for various disease processes. Many drugs used in Western medical science called allopathic medicine have their origin in medicinal plants.

There are about 5000000 plant species growths in worldwide, but only 1% has been phytochemical investigated, hence, there is enormous potential for discovering new bioactive compounds. [6,13,15]

Some investigator suggested that plant-derived essential oils might be a good alternative to overcome microbial resistance.

Herbs may be used internally as pills, syrups, and infusions, or externally as poultices, plasters, and liniments. Plants can be used as drugs (e.g. aspirin), dietary Supplements (e.g. Garlic or Echinacea extract), functional/medicinal foods (e.g. Canola Oil) or recombinant proteins (not commercialized)[13].

2.2. Antibacterial Activity of Plant (Crude or Total Extracts)

Major classes of antimicrobial compounds from plants consist of: Phenolics (including: simple phenols, Phenolic acids Quinones, Flavonoids, Flavones, Flavonols, Tannins, Coumarins) Terpenoids, essential oils, Alkaloids, Lectins and polypeptides, Polyacetylenes [16].

Researcher, mostly have simply sought to validate the traditional medicinal use of the plant. For example, the use of *Drosera peltata* leaves for dental caries treatment was validated by a study that demonstrate broad-spectrum activity against many bacteria of the oral cavity, especially against *S. mutans* and *S. sobrinus*. Plumbagin was identified as the active component of this product.

Investigator collected 27 medicinal and random plants extracts and identified a number that inhibited the growth of oral streptococci. The most active extracts consist of *Abies canadensis* (Pinaceae), *Albizia julibrissin* (Fabaceae), *Chelidonium majus* (Papaveraceae), *Ginkgo biloba* (Ginkgoaceae), *Juniperus virginiana* (Cupressaceae), *Pinus virginiana* (Pinaceae), *Rosmarinus officinalis* (Lamiaceae), *Sassafras albidum* (Lauraceae), *Tanacetum vulgare* (Asteraceae) and *Thuja plicata* (Cupressaceae) [6].

2.3. Antibacterial Activity of Plants (Purified Phytochemicals)

Purified phytochemicals includes: 1. Flavonoids and Other Polyphenols. 2. Terpenes. 3. Alkaloids. 4. Sugar Alcohols. 5. Other Phytochemicals. Several constituents found in hops, *Humulus lupulus* (Cannabaceae), have been found to display antibacterial activity against *S. mutans*, *S. salivarius* and *S. sanguis* in disc diffusion assays [6]

Table 1 Plant extracts and phytochemicals with antibacterial property against oral bacteria (6).

Solvent	Extract	Class	Phytochemical
Chloroform	<i>Drosera peltata</i>	Terpene	Macrocarpals A,B,C
Ethanol	<i>Mikania laevigata</i>		Bakuchiol
	<i>Mikania glomerate</i>		Compound 2
	<i>Helichrysum italicum</i>		Xanthorrhizol
	Propolis		Erycristagallin
Water	<i>Coptidis rhizoma</i>	Flavonoid	Artocarpin
Aqueous ethanol	<i>Piper cubeba</i>		Artocarpesin
			Macelignan
			Kuwanon G
			Xanthohumol
		Alkaloid	Berberine
		Phenolic	Catechol

2.4. Plants with antibacterial activity against oral pathogen

This section focuses on some of the plants with antibacterial effects on oral pathogens and describing the experimental studies and clinical trails based upon these plants.

2.4.1. Green Tea

The source of tea is in the plant *Camellia sinensis*. It grows mainly in China and in southeast of Asia. After water tea is the most popular beverage allover the world. Green tea as suggestive of healthy beverage was common for thousands years. Nowadays there is a growing interest in green tea due to scientific findings that show the health potentials of this tea.

Many investigations examined green tea as an antioxidant, anti-mutagenic and anti-carcinogenic, and its role in hypertension prevention, cardiovascular risk modification, ultraviolet radiation protection, body weight management and oral health improvement.

Green tea has a unique composition that consists of proteins, considerable parts of it are enzymes, Carbohydrates such as: cellulose, pectin, glucose, fructose and sucrose and lipid components: linoleic and linolenic acids and sterols such as stigmaterol. In addition to macronutrients, also green tea consist of vitamins (B, C, E), xanthic bases such as caffeine (27 mg/240 ml tea infusion) and theophylline; pigments such as chlorophyll and carotenoids; volatile components such as aldehydes and alcohols, minerals and trace elements such as Ca, Mg, Cr, Mn, Fe, Cu, Zn, Mo, Se, Na, P, Co, Sr, Ni, K, F and Al [17-22].

2.4.1.1. Green tea and oral health

Green tea has many special antibacterial effects on oral cavity. They are includes: effect on Dental caries, Antiviral properties and Abolition of halitosis.

Investigation shows that tea consumption may decrease dental caries. In one research mouth rinsing with green tea extract (0.61%) protected dentine from erosion and abrasion similarly to mouth rinsing with fluoride extract (250 ppm) or chlorhexidine extract (0.06%). Moreover, one week of green tea mouthwash (3 times a day) was able to significantly reduce the salivary levels of the virulent cariogenic pathogens *Streptococcus mutans* and *lactobacilli* that will probably decrease the susceptibility to dental caries. But there is some study with conflicting evidence. It seems that green tea has indirect antibacterial activity through mediation of protective saliva components such as secretory immunoglobulins, oral peroxidases, lysozyme, mucins or others.

In addition, Green tea has antiviral properties which are based on the polyphenols ability to act as antioxidants, inhibit enzymes that damage cellular membranes and prevent binding and penetration of viruses to cells. Considering various viruses are found the in oral cavity, this property is extremely important.

Bacterial halitosis caused mainly as a result of volatile sulphur compounds (such as H₂S and CH₃SH). There are some studies demonstrate that green tea succeeded to abate the creation of those sulphur compounds and consequently halitosis. Accordingly, some bad breath treatment products such as chewing gum and mouth spray contain tea polyphenols [17].

2.4.2. Grape product

Raisins are dried grapes, fruits of *Vitis vinifera* L. (Vitaceae). Raisins contain polyphenols, flavonoids, and high levels of iron that may benefit human health. There are some investigations about antimicrobial compounds in raisins against oral pathogens. The antimicrobial compounds present in raisins have ability to suppressing growth and virulence of oral pathogens, and investigation identified this property.

Through antimicrobial assay-guided compounds identified with growth inhibition against oral pathogens were oleanolic acid, oleanolic aldehyde, linoleic acid, linolenic acid, betulin, betulinic acid, 5- (hydroxymethyl)-2-furfural, rutin, b-sitosterol, and b-sitosterol glucoside. Studies (in-vitro) demonstrate that oleanolic acid inhibited insoluble glucan synthesis of *mutans streptococci* in the oral cavity. Multiple pharmacological properties demonstrated for oleanolic acid: anti inflammatory, antitumor, cytotoxic, antibacterial, anti-HIV activities and so on. It was observed that oleanolic acid inhibited the in vitro biofilm formation of *S. mutans*.

The effect of raisins and raisin-containing bran cereal was examined in 7- to 11-y-old children; for plaque acidogenicity, and it was found that raisins did not reduce the plaque pH decline below pH 6 over the 30-min test period. Authors conclude that compared with commercial bran flakes or raisin bran cereal, a lower plaque pH drop was noted in children who consumed a raisin and bran flake mixture when no sugar was added. Also, Grape seed extract, high in proanthocyanidins, affected the demineralization and remineralization processes of artificial root caries lesions, and it seems that it's potential as a promising natural agent for root caries therapy in noninvasive way [7].

2.4.3. *Salvia officinalis* (Sage)

Salvia officinalis (sage) is a perennial, evergreen subshrub, with woody stems, grayish leaves. Also it has blue to purplish flowers. It belongs to the Lamiaceae family and is native to the Mediterranean area, though it has naturalized in many places throughout the world. It consists of about 900 species and has an ancient history of medicinal and pharmacological use such as analgesic and anti-inflammatory, antioxidant, hepatoprotective and hypoglycemic activities.

The volatile oil of sage contains the constituent alpha- and beta-thujone, camphor, and cineole. It also contains rosmarinic acid, tannins and flavonoids. In modern European herbal medicine, a gargle of sage tea is commonly recommended to treat a sore throat, inflammations in the mouth, and gingivitis. Sage oil has antibacterial, antifungal, and antiviral activity, which may partially explain the effectiveness of sage for these indications. The antifungal effect against *Candida albicans* was evaluated [13,23].

2.4.3.1. Antibacterial activity of essential oil from *Salvia leriifolia* Benth

Salvia leriifolia that was introduced in the flora Iranica in 1982 geographically grows in the south and tropical regions of Khorassan and Semnan provinces, I.R. Iran. The aerial parts of *S. leriifolia* were collected at full flowering stage and essential oil was obtained by steam distillation method. The effects of different concentrations of essential oil against *Streptococcus mutans*, *Streptococcus sanguis*, and *Actinomyces viscosus* were evaluated.

Results showed that there were significant differences between the effect of essential oil and chlorohexidine on all bacteria and its antibacterial effects were even better than chlorohexidine. Besides, *S. mutans* was the most sensitive bacterium. Therefore the essential oil from *S. leriifolia* was found as a potent antimicrobial compound with appropriate effects on the oral pathogen. Authors suggested more studies for production of herbal mouthwashes [24].

2.4.4. *Lippia*

Lippia sidoides Cham (Verbenaceae), popularly known as “Alecrim-pimenta” is a typical shrub commonly found in the Northeast of Brazil. Many plant species belonging to the genus *Lippia* yield are used by the industry for the production of perfumes, creams, lotions, and deodorants. Also, the leaves of *L. sidoides* are highly used in medicine for the treatment of skin wounds and cuts [25,26].

The antimicrobial activity of the oil and the main components was examined against cariogenic bacterial species such as *Streptococcus* and *Candida albicans*. The essential oil and its major components thymol and carvacrol show potent antimicrobial activity against examined organisms with minimum inhibitory concentrations. The most sensitive microorganisms were *C. albicans* and *Streptococcus mutans*. The essential oil of *L. sidoides* and its major components exert promising antimicrobial effects against oral pathogens and suggest its probable efficiency to combat oral microbial growth [12].

2.4.5. *Achillea millefolium* (Yarrow)

Latin name of this plant is named after Achilles, the legendary hero of Greece. It is said that during the Trojan war (about 1200 BC) the extract was used to treat wounds and stop bleeding and infection. It is a perennial plant, 20 to 90 cm in height, and even the leaves without petiole long, covered with long and narrow cuts. Yarrow is a weed in fields and grows along the road and mountainous, Europe and northern Iran Alborz mountains.

The combination of different materials such as amino acids, alkaloids, flavonoids and tannins in plant cause analgesic, antispasmodic and anti-inflammatory effects. There are some investigations about antibacterial effect of this plant. Also researcher evaluated antibacterial effect of leaves of this plant against oral pathogen including *Streptococcus Salivarius*, *Sabrynv*, *sanguinis* and *actinomyces viscosus* and *Candida albicans* and conclude that this product has antibacterial effect against these oral pathogen [27].

2.4.6. *Matricaria recutita* (Chamomile)

Chamomile is a common name for several daisy-like plants of Asteraceae family. These plants are best known for their ability to be made into an infusion, which is commonly used to help with sleep.

The flowers of chamomile contain 1–2% volatile oils. Other active constituents include the flavonoids, apigenin, luteolin, and quercetin. These active ingredients contribute to chamomile's anti-inflammatory, antispasmodic, and smooth muscle relaxing action, particularly in the gastrointestinal tract. Applications of chamomile topically have been shown to be effective moderately in the treatment of eczema. One double-blind trial found it to be about 60% as effective as 0.25% hydrocortisone cream. Flowers of Shirazi type of this plant had been effective against *Streptococcus Salivarius*, *Sabrynv*, *sanguinis* and *actinomyces viscosus* and *Candida albicans* [13,27]. Azulene compounds found in *Matricaria recutita* are reported to possess anti-allergic, anti-inflammatory and mild anti-bacterial activities. *Matricaria recutita* is used for washing the mouth wounds and external use of *M. recutita* is approved for mucous membrane inflammations including those of the oral cavity and gums [28].

2.4.7. Rheum: palmantum officinal (Rhubarb)

Rhubarb is a perennial plant of the Polygonaceae grass family. Rhubarb has different materials such as anthraquinone, starch, magnesium, and iron, tannins and vitamins B and C, which is Anti-infection, astringent and laxative. Investigation shows that root of this plant has antibacterial effect against common oral pathogens [27].

2.4.8. Thymus vulgaris (Thyme) Zataria multiflora

Avishan-e Shirazi in Persian is a native plant in Iran. In the Iranian botanical sources the Avishan term has been used as a Persian name for three different herbs: a; *Thymus kotschanus* b; *Ziziphora clinopodioides* and c; *Zataria multiflora*. In another clinical study, *Z. multiflora* essential oil mouthwash has shown to be more efficacious than placebo. Antibacterial and anti-fungal effects of *Z. multiflora* are also reported [28].

The primary constituents are the volatile oils, which include the phenols, thymol and carvacol. These are complemented by the actions of flavonoids. Investigators find antifungal effect of this plant against *Candida albicans*, one of common oral pathogen [13,29].

2.4.9. Myrtus Communis, Myrtaceae (Myrtle)

Myrtus (myrtle) is a genus of one or two species of flowering plants in the family Myrtaceae, native to southern Europe and North Africa. The leaf is 3–5 cm long, with a fragrant essential oil.

In several countries, particularly in Europe and China, there has been a tradition for prescribing this substance for sinus infections.

This plant has antibacterial, antifungal, anti-inflammatory and analgesic effect. And effective in the control of diseases such as diabetes, lung disease, cancer, and is highly effective as an antioxidant. This plant has bacteriostatic properties and has bactericidal effects at higher concentrations. There are many researches about antibacterial effect of myrtle. In a study antibacterial effect of myrtle extract was analyzed on gram-positive and gram-negative bacteria and showed that this extract has no effect on gram-negative bacteria. But investigators showed antibacterial effect of this plant against some oral bacteria (*S. Salivarius*, *S. Sanguis*, *S. mutans*, *Lactobacillus*, *Diphtheroides*, *Staph. aureus*, *Staph. epidermidis*, *Neisseria sicca*, *Pseudomonas aeruginosa*) [30-36].

2.4.10. Mentha longifolia

Mentha longifolia is a species in the genus *Mentha* (mint) native to Europe, western and central Asia (east to Nepal and the far west of China), and northern and southern (but not tropical) Africa. It is a very variable herbaceous perennial plant with a peppermint-scented aroma.

This plant is edible. Investigation of the essential oil of this plant has shown its strong antibacterial effects. Methanol extracts also has antibacterial and antifungal effects against a range of Gram-positive and Gram-negative bacteria. The extract of plant includes piperitone, beta caryophyllene, cineole and flavonoids.

In one study antibacterial effect of this plant evaluated against oral bacterial including *S. mutans*, *Lactobacillus*, *Streptococcus* and *Actinomyces viscosus* [37].

2.4.11. Garlic (Allium sativum)

Garlic (*Allium sativum*) is one of the most extensively investigated medicinal plants in use since ancient times due to its antibacterial, antifungal, and antiviral properties. Allicin is produced by the enzymatic activity of alliinase (a cysteine sulfoxide lyase) after crushing a garlic clove. There is extensive support that allicin and other thiosulfonates are responsible for the range of remedial effects described for garlic. Garlic extract has been

shown to have a wide spectrum inhibitory effect on the growth of various gram positive and gram-negative bacteria such as: *Micrococcus*, *Enterobacter*, and gram-negative bacteria such as: *Micrococcus*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Lactobacilli*, *Pseudomonas*, *Salmonella*, *Shigella*, *Proteus*, *Helicobacter pylori*, *Staphylococcus*, and *Streptococcus* species. Moreover, it is also active against multi-drug resistant (MDR) organisms such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Mycobacterium tuberculosis*. Garlic extract mouth wash is effective at reducing total salivary bacterial counts. Antimicrobial agent of raw garlic extract is more effective than presently used antibiotics. The inhibition of DNA or RNA syntheses has a similar mechanism in both garlic and antibiotics. Strong antifungal activities of garlic extract inhibit the formation of mycotoxins, which is similar to the aflatoxin of *Aspergillus parasiticus*. Responsible for inhibition of fungal growth, pure allicin has a high anticandidal activity with minimum inhibitory concentrations of 7 µg/mL.

Antiviral properties of fresh garlic extracts have been illustrated by in vitro and in vivo experimental studies against human cytomegalovirus, influenza virus type 3, vaccine virus, vesicular stomatitis virus and human rhinovirus type 2.

According to recent studies, garlic extract is effective in the reduction of an oral microbial population. It may be useful as an alternative product and new treatment modality with fewer side effects. [38]

2.4.12. Purslane (*portulaca oleracea*)

Purslane is an herbaceous weed from the Portulacaceae family that contains numerous biologically active compounds including omega-3 fatty acids, minerals, B-carotene, melatonin and vitamins A, C and E. This herbal medicine possesses anti-inflammatory, antiulcerogenic, antifungal & antioxidant properties and has been used for urinary, digestive, febrile & infectious problems worldwide. Antimicrobial, along with antifungal effects have also been reported in different extracts of purslane. Also, purslane is clinically effective in the treatment of oral lichen planus.[39]

2.4.13. Other plants with antibacterial activity

There are many researches about antibacterial effect of plants on oral pathogens, following mentioned herbs that are useful for tooth and gingiva:

Fumaria parviflora [40], *Pimpinella anisum* [37], *Carum copticum* [41], *Walnut (juglans regia)* [42], *Cinnamon* [29], *Clove* [29], *Miswak* [43], *Bloodroot (Sanguinaria Canadensis)*[13], *Caraway (Carum carvi)* [13], *Echinacea (Purple coneflower)*[13], *Myrrh (Commiphora molm)* [13], *Peppermint (Mentha piperita)*[13], *Rosemary (Rosmarinus officinalis)*[13], *Aloe vera* [13]

2.5. Antimicrobial effects of propolis extract

Propolis is a wax- or resin-like substance that is collected by bees from fresh flowers, or other botanical sources, and used to reinforce the structural stability of the hive, acting as a barrier in preventing diseases and parasites from entering the hive.

There is evidence that propolis has some broad antimicrobial activity and that it may have anti-inflammatory effects. These properties make it useful in the treatment of some forms of arthritis, among other disorders. There is also some evidence of anti-cancer activity. It seems that Flavonoids in propolis responsible for the antifungal activity. There are differences in Propolis property produced around the world; there are many research about antimicrobial effect of propolis on oral pathogens.

In one study researcher compare the antimicrobial effects of the Propolis produced in Hamedan province, Iran, with Nystatin (antifungal drug) and Chlorhexidine (antibacterial mouthwash). The antimicrobial effect of 30% ethanol extract of Propolis was demonstrated against *S. mutans*, *C. albicans* and *A.a.commitans*. The antimicrobial effects of Ethanol-extract of Propolis and Chlorhexidine solution were evaluated at eight different times against *S.mutans*, *C.albicans* and *A.a.commitans*. Based on these findings they conclude that 30% ethanol extract of Propolis is very effective on oral pathogenic microorganisms [13,44].

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