Conventional and natural products against oral infections

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In 1674, the Netherlander Antony van Leeuwenhoek (1632 - 1723), recognized as the discoverer of the microorganisms, created a device composed by plates of metal and lens, like a microscope, where he observed from human saliva, teeth and faeces, little movable objects, invisible through the naked eyes, that he called “animalcule” [1].

The oral cavity is an environment highly infected by commensal microorganisms that, initially, play the role of protection of the mucosa. The “resident” microbiota cohabits in a harmonic relationship with the host, as a beneficial infection and as a local host defense, since it makes difficult the implantation of pathogenic species, strange for this microbiota. This resident microbiota can become pathogenic when the host conditions are changed or the harmonic equilibrium is broken [2].

Due to the existence of teeth and periodontal spaces, the oral cavity shows many different ecological sites with peculiar environmental characteristics. The oral microbiota is the most complex inside the human, with more than 30 different genders of bacteria and more than 700 species. There are approximately 350 bacterial cultivable species and more than 200 species identified only by molecular techniques. The total number of oral microorganisms is similar to the intestinal microbiota besides more complex about the number of species [3, 4, 5].

However, the accumulation of the microbial biofilms can develop some diseases. Beyond the bacteria, other microorganisms such as virus and fungi can also colonize and induce oral diseases. The oral infections own specific characteristics, with a predominantly strict anaerobic and/or facultative microbiota, with propitious surfaces for adhesion and suitable nutrients. These microorganisms organize themselves quickly into biofilms, from initial adhesion to the dental enamel surface, gingival epithelium, tongue and mucosa, once they are flooded by saliva. Saliva contains proteins that can favor the molecular adsorption. Some species possess receptors or produce polysaccharides that can facilitate the adhesion and start the multiplication process. The nutrients come from saliva, accumulated food and gingival fluid [3, 5, 6, 7].

In addition, the oral microorganisms have to compete for sites where the receptors are already occupied by initial colonizers, deal with the positive and negative relationships among other microorganisms, resist to host defenses and possess some virulence factors [2, 8].

At the intrauterine life, the mouth is free of microorganisms. Some hours after the birth, the infection starts, with microorganisms coming from people in a strait contact with the baby, especially the mother, as a vertical infection. The facultative anaerobic bacteria are the most adaptable to the new mucosa, mainly the genus Streptococcus. When the teeth appear, new ecological sites are created and the oral microbiota develops more complex and intensely [3, 9].

The most prevalent species capable to adhere to the teeth surfaces are facultative anaerobic species as S. sanguinis, S. gordonii and S. oralis, in addition to some species of Actinomyces. Interproximal areas, enamel grooves and cracks provide conditions for the development of strict anaerobic bacteria. The gingival groove is a niche with very low content of oxygenation and it is conducive to installation of these anaerobes. The toothed adult man can have until $10^8$ bacterial cells per mL of saliva and $10^{10}$ cell per gram of dental biofilm [3, 5].

Bacteria can adhere to the dental surface directly or to other initial colonizers by means of adesins and fimbriae. Some Gram-negative periodontopathogens are not able to adhere to the teeth, however, they have adherence binders toward to the periodontal pocket epithelium and/or to the initial colonizers [4, 8].

Saliva is responsible for the regulation of the supragingival microbiota, since it offers to the adhered microorganisms suitable temperature, pH, and humidity, in addition to some nutrients as proteins, amino acids, carbohydrates, vitamins and inorganic compounds. On the other side, saliva possess antibodies, antimicrobial substances and enzymes as lysozyme and lactoferrin, pH stabilization system and a mechanical drag action due to the salivary flux. This salivary flux is increased during the speech and chewing, what is favorable to the removal of bigger accumulation of microorganisms. In spite of, during the sleep, this flux is greatly reduced, promoting the accumulation of biofilms and maintaining the acid pH [2,10].

The gingival fluid also helps to regulate the subgingival microbiota. Since the biofilm accumulation increases, the inflammatory response develops and the gingival exudate increases too. This fluid possesses many host defense factors as cells and the complement, however, is a great source of nutrients for anaerobic bacteria as proteins, hemin, k vitamin and hormones [3, 4].

Other factors that can promote the oral microorganism accumulation are cavities, inadequate restorations, prosthesis, crowding, orthodontic devices, epithelium loss, and in a more effective way, the systemic condition of the host, the diet and the quality of oral hygiene [3, 11].
The more frequent oral diseases as caries, periodontal disease, periimplantitis, pulp space infections and candidiasis are called endogenous diseases, since their etiological agents are part of the resident microbiota, also in the healthy condition although in lower numbers. These diseases caused by biofilms are chronic, with a long duration, low clinical immunity and sporadic episodes of acute manifestations [3, 8].

The main biofilms produced in the oral cavity are: the cariogenic, at the dental surfaces, mainly composed by Gram-positive, facultative, and saccharolytic bacteria and the periodontal biofilm at the gingival sulcus, mainly composed of Gram-negative, anaerobic and proteolytic bacteria distributed in these areas because of the nutritional and respiratory requirements. Also, there are the supra lingual biofilm with an anaerobic microbiota, most responsible for bad breath and the biofilm over dentures with the predominance of the fungi Candida albicans. The products of the metabolism from the cariogenic biofilm include a lot of acids, which can demineralize the enamel and start the dental decay. This process evolves and when it reaches the dental pulp the microbiota changes to anaerobic and proteolytic ones, due to the availability of proteins from dead pulp tissue. The periodontal biofilm generates protein metabolic products that can stimulate the inflammatory and immunological response of the tissue.

Costerton et al. (1987) [12] conceptualize the biofilm as an association of microorganisms attached to a solid surface bathed by a liquid substance and embedded by a polysaccharidic matrix. This organizational form in biofilms gives great resistance to the microorganisms, due to the difficulty of chemical agents and host defense factors to penetrate inside the biofilm mass, besides genetic changes of virulence factors among the microorganisms. According to this idea, the biofilms are only totally removed by physical or mechanical ways. The dental biofilm, called before as “dental plaque” fits perfectly in this concept, since it is adhered to the teeth and mucosa surfaces and it is bathed by saliva. Its removal can be made efficiently by correct oral hygiene, teeth brushing and flossing, besides tongue cleaners [4, 12].

There is a continuing search for the development of effective antiseptics against cariogenic and periodontal biofilms, which may be used as adjuncts in controlling the formation of supragingival biofilm. If the chemical substances can not remove the formed biofilm, at least mouthrinses can impair its new formation (“de-novo” plaque formation). Some circumstances are good to use chemical products as: clean hidden surfaces, clean post surgical areas, for people with problems of coordination and demotivation, people inside hospitals and diminish the generated aerosol from patient mouth under dental treatment to the environment. Several active ingredients were tested in various formulations, especially chlorhexidine, cetylpyridinium chloride, triclosan and essential oils. The chlorhexidine normally is the most effective antimicrobial agent, not aggressive to the host tissue, but it has other adverse effects as teeth and restorations coloration, change of taste and ardecency at the mucosa [13,14].

Parwani et al. (2013) [15] explored a alternative (herbal/natural miswak) to gold standard chlorhexidine gluconate mouthwash for the anti-plaque efficacy. They found that 0.2% chlorhexidine gluconate mouthwash remains the best anti-plaque agent. However, when socio-economic factor and/or side-effects of chlorhexidine need consideration, the tested herbal mouthwash may be considered as a good alternative.

Haffajee et al. (2009) [16] investigated if antimicrobial mouthrinses with different formulations could affect the composition of the subgingival microbiota (by using checkerboard DNA-DNA hybridization) and clinical parameters of adjacent tissues in 116 periodontal maintenance subjects. The mouthrinses were herbal 1, herbal 2, essential oil, and chlorhexidine. Streptococcus and Capnocytophaga species were reduced most in the herbal rinse groups, while Veillonella parvula was reduced most in the essential oil and chlorhexidine groups. Actinomyces were also markedly reduced in the chlorhexidine group. Mean Plaque (PI) and Gingival Indices (GI) were reduced between baseline and three months in each group, especially for chlorhexidine and herbal rinses. The observed microbial changes were accompanied by improvements in clinical parameters.

At the same way, Ferreira et al. (2006) [17] compared the antimicrobial effect of a commercial chlorhexidine, propolis and water mouthwashes over the total number of oral microorganisms, Candida albicans and Streptococcus mutans from saliva of healthy students. They observed that chemical solutions acted more efficiently over the species, chlorhexidine over C. albicans and S. mutans, and propolis over C. albicans. The total number of microorganisms was reduced equally by the three solutions showing the mechanical effect of the mouthwashes.

The subgingival biofilms can induce periodontal diseases. The environment inside the gingival sulcus or pockets has a low amount of oxygen, about 1 to 2%, while in the normal air this rate is 21% [3].The nutrients are composed of protein from the gingival fluid, them the proteolytic and strict anaerobic microorganisms can establish in this site. It is a complex microbiota that stimulates the immunological response at the periodontal tissue. The main pathogens of this disease (chronic disease) are Porphyromonas gingivalis (Figure 1), Treponema denticola and Tannerella forsythia, besides many others associated. These three species compose the red complex of Socransky & Haffajee (2002). Recently, Jiao et al. (2013) [18] using molecular techniques, found a new bacterium in periodontal disease which stimulates a cell receptor, which is responsible for the recruitment of elastic cells, increasing the bone resorption. This last one can also be associated with the aggressive periodontitis, which is caused by a facultative Gram-negative bacterium Aggregatibacter actinomycetemcomitans. This microorganism is very persistent and treated with systemic antibiotic therapy.
The treatment of chronic periodontitis is based on mechanical removal procedures such as self performed oral hygiene, scaling and root planing or in a last option periodontal surgery. The elimination of pockets or the removal of supragingival plaque will provide a less favorable environment for the growth of subgingival species, particularly those associated with disease [4, 13]. The treatment can affect the composition of the bacterial plaque but is also influenced by the genetic background of the subject, environmental influences such as smoking and the systemic well-being of the patient [4].

The periodontal pockets can be a reservoir of important pathogens for other areas of organism. For example, mouths of patients with gingivitis or with chronic periodontitis, who are positive for H. pylori in their stomachs, may be considered as reservoirs of these bacteria [19]. For these situations, the use of antimicrobial mouthrinses is also suitable.

At the cariogenic biofilm, the most prevalent microbiota is composed by acidogenic and aciduric microorganisms, especially Streptococcus mutans and Lactobacillus species. S. mutans can produce an insoluble extra cell polysaccharide, called “mutan”, which can adhere to the enamel surface. Mutan also gives protection to the bacteria and gives supply of sugar nutrient when the environment is not favorable. In addition, this polysaccharide maintains amounts of produced acids contiguous to the enamel surface, causing the demineralization (Figure 2). Because of these virulence factors, besides the resistance to survive in an acidic environment, S. mutans is considered not the only, but the main microorganism involved in etiology of dental caries [6].

Many authors have been researching S. mutans for a long time, stating that caries and S. mutans are transmissible. Caufield et al. (1993) [9] established an infectivity window, where children acquire S. mutans for the first time from their mothers or caregivers. At the age of 19 to 31 months from birth, the eruption of deciduous molars occurs, with retentive surfaces, favoring the installation of S. mutans. Following this thinking, many researchers investigated the
genetic profile of the mutans strains from mothers and children, to verify the transmission. The dental treatment in mothers could prevent caries in children in the future. In one of these works, Pieralisi et al. (2010) [20] observed by molecular techniques, horizontal transmission (from colleagues each other in schools) besides vertical transmission (from mother to child) of S. mutans.

On the other side, the etiology of dental caries has been investigated in order to identify other pathogens, also highly involved in caries process, since they survive in a acid pH, as Bifidobacterium and Actinomyces species [21].

Under normal conditions, the dentin-pulp complex is free of microorganisms and isolated from the oral environment. The coating dental structures (enamel and cementum) act as a barrier against the entry of microorganisms to the pulp cavity. When these structures are lost, either by decay, trauma or periodontal disease, the pulp will be unprotected and can evolve to necrosis, allowing the entry of micro-organisms via dentinal tubules or by exposure of the pulp tissue to the oral cavity. Deficient restorations and anachoises are other ways for entry of microorganisms to the endodontic space [22, 23].

The bacteria in infected root canals include a restricted group of species [24]. The root canals have specific conditions, the availability of nutrients, low oxygen tension and bacterial interactions are important ecological determinants [25].

The first researcher to observe microorganisms in the root canals was Miller (1894)[26], by means of an optical microscope, finding cocci, bacilli and spirochetes. He suggested that the presence of bacteria inside root canal is the cause of apical periodontitis. Seventy years after this, Kakehashi et al (1965)[27] confirmed their assumptions. They evaluated the response of dental pulps exposed to the oral environment of conventional and germ-free mice. In conventional mice, there were necroses of the pulp tissue and periapical lesions, while germ-free mice showed viable pulp with a minimal inflammatory response and in some cases a dentin barrier, protecting the tissue of the oral cavity. Möller et al (1981) [28] conducted a study that also showed that microorganisms are the main cause of apical periodontitis and the absence of microorganisms leads to healing tissue.

The endodontic infection can be classified to primary, secondary (endodontic retreatment) or persistent, when the composition of the microbiota may vary [29]. In the primary, the root canal infections present polymicrobial, predominantly anaerobic bacteria, Gram-negative or Gram-positive, in proportions that vary according to the painful symptomatology. The number of bacterial species in root canals may vary from 1 to 12, and the number of bacterial cells recovered is between less than 10^2 to more than 10^8. There is a correlation between the size of the periapical lesion and the number of bacterial species and cells present in the root canal. Thus, teeth with large lesions usually harbor more bacterial species and have a higher density of bacteria [25, 30,31].

The root canal microbiota is dominated by anaerobic bacteria. Facultative anaerobic bacteria such as Streptococcus also play a significant role in the infection, particularly in the coronal portion of the canal in the tooth pulp chamber exposed to the cavity [24]. Studies on the dynamics of root canal infections have shown that the relative proportions of anaerobic microorganisms and bacterial cells increase with time and that the facultatively anaerobic bacteria are outnumbered when the canals have been infected for 3 months or more [32].

Bacterial species commonly found in primary infections belong to the Gram-negative genera of Fusobacterium, Dialistes, Porphyromonas, Prevotella, Tanerella, Treponema, Campylobacter and Veillonella and Gram-positive Parvimonas, Filifactor, Pseudoramibacter, Olsenella, Actinomyces, Peptostreptococcus, Streptococcus, Propionibacterium and Eubacterium. Differences in availability of nutrients and oxygen tension in the apical region compared with the main root canal are important reasons for the dominance of slow growing, obligatory anaerobic bacteria in the apical region.

The endodontic treatment aims to eliminate or significantly reduce micro-organisms in the root canal system through irrigating solutions and dressings with antiseptic properties. Moreover, with the step of the filling and subsequent sealing the crown prevent introduction of new microorganisms. However, faults can occur during the treatment and some micro-organisms can resist causing failure and persistence of periapical inflammation, resulting in persistent symptoms and flare-ups.

The composition of the microbiota after root canal treatment failure differs from that found in untreated teeth [33,34]. Gram-negative bacteria, which are common members of primary infection, are usually eliminated. Most studies revealed that Gram-positive bacteria are more frequently present [30]. They include streptococci, Parvimonas micra, Actinomyces species, Propionibacterium species, Pseudoramibacter alactolyticus, Lactobacilli, Enterococcus faecalis and Olsenella uli. The number of present species in the secondary or persistent infections is smaller than occurs in primary infections, an average of one to five bacterial species per case, with counts reaching 10^5 to 10^8 cells per sample. Enterococcus faecalis is the species most often found in cases of treatment failure [35]. In addition to the bacterial species, fungi can also be found in cases of secondary infection or persistent, as Candida albicans [36]. This species has the ability to colonize and invade the dentin and seems to be resistant to calcium hydroxide dressing [37].

The presence of microorganism in root canals can cause apical periodontitis, which function is act as a barrier to separate the infection of root canal from alveolar bone and other body sites. However, in some cases the microorganisms colonize and break this barrier to the apical area establishing an extra-radicular infection. Persistent extraradicular infection is not affected by the action of antimicrobial agents such irrigants and medicaments using during root
canal treatment. Apical surgery may be the only method for definitive removal of an established extra-radicular infection promoting repair in therapy-resistant cases (Figure 3) [38].

![Image](image_url)

**Fig. 3** Periapical biofilm of a persistent endodontic lesion, showing presence of a fungus joined to the filling material – guta-percha (A) and a streptococci chain inside this biofilm in the extrarradicular area.

Irrigating solutions such as sodium hypochlorite and chlorhexidine have a wide spectrum of action on the microorganisms present in endodontic infections. However, during the treatment they act for a short time and often cannot penetrate inside some parts of the root canal system. Therefore, the use of the dressings is necessary to allow a longer action against microorganisms in root canal and prevent the proliferation of microorganisms, acting as a mechanical barrier to reinfection [39].

The use of calcium hydroxide in clinical situations involving necrotic pulp is advantageous as a result of its antiseptic action on the microorganisms present in the main root canal, its ramifications, in the dentinal tubules, as well as in the apical cementum [40]. The addition of other antiseptic substances to calcium hydroxide has been proposed to enhance its antimicrobial effect [41], like phytotherapics, such as *Casearia sylvestris* [42].

The use of propolis in Endodontics, a beehives product, as intracanal dressing, has been shown to be effective against several bacterial species found in endodontic infections, such as *E. faecalis* and certain anaerobes. Its antimicrobial effect is similar to other drugs used, such as chlorhexidine gel 2%, formocresol, and camphorated parachlorophenol, and better than calcium hydroxide. Its biocompatibility is another great advantage [43,44].

A recently study conducted by the Department of Endodontics, Bauru Dental School, São Paulo, Brazil, evaluated the antimicrobial effect of calcium hydroxide pastes associated to propolis inside the root canals. Bovine dentin tubes previously infected with *Enterococcus faecalis* were used and these pastes remained inside root canals for 15 days. By analysis with Confocal Laser Scanning Microscopy and microbiological culture, the Propolis addition in the calcium hydroxide pastes showed lower cell viability as compared to the calcium hydroxide paste alone. The authors concluded that there are advantages in using Propolis in calcium hydroxide pastes, increasing intratubular penetration which improves the performance against these micro-organisms (Figure 4) [45].
Photodynamic therapy is a reaction between photosynthetic dyes and light, generating a cytotoxic effect over the microorganisms, usually via oxidative reactions that result in cell death through apoptosis. In Endodontics, photodynamic therapy has shown good results [46, 47], being an interesting tool to obtain better antisepsis in endodontic treatment [48].

Ozonated water can also be applied during the biomechanical preparation in Endodontics, as an auxiliary substance to irrigation, and should be used as end-irrigating [49]. Furthermore, its use significantly reduced the number of Candida albicans and Enterococcus faecalis in root canals of human teeth [50]. The ozone can also be used in the process of intracanal medicament in form of ozonized oil, and has shown satisfactory results when compared to similar calcium hydroxide [51].

Candida spp. are considered opportunistic pathogens as they are both colonizers and have the ability to cause infections in response to alterations in the host’s physiology [52]. The presence of these yeasts in the oral cavity of healthy individuals varies from 35 to 60%. C. albicans is the most prevalent species, totaling 60 to 70% of the isolates, followed by C. tropicalis and C. glabrata [53,54]. Therefore, the isolation of Candida spp. from oral cavity is not a confirmatory evidence of infection and clinical signs and symptoms must be also considered for the diagnosis of candidiasis [55].

Occurrence of disease is a result of an imbalance between host’s factors (local or systemic predisposing factors) and candidal virulence factors. The most frequently related systemic factors are use of broad-spectrum antibiotics and corticosteroids, diabetes mellitus and immunosuppression [56-59]. Inadequate oral hygiene, use of dentures, orthodontic devices, chronic periodontitis, smoking, and xerostomia have been cited as oral local factors [60-63].

Capacity of adherence to mucosa, growth at 37°C, hydrophobicity, yeast-to-hyphae transition, biofilm formation, production of histolytic enzymes (such as aspartyl proteases and phospholipases) have been cited as the main C. albicans virulence factors [64,65].

Oral candidiasis is common among immunocompromised individuals, while systemic infection can be observed in more severe cases of immunosuppression [66]. Although C. albicans is more frequently isolated in cases of oral candidiasis, C. parapsilosis, C. glabrata, C. krusei, C. guilliermondii, C. lipolytica and C. kefyr have been considered as emergent pathogens. Several studies showed that patients with systemic predisposing factors have higher incidence of non-albicans species when compared to healthy controls [67-71]. Oral candidiasis can be observed basically as three different clinical variants: pseudomembranous, erythematous and hyperplastic [72]. Candida albicans has been also cited as a putative endodontic pathogen. More recently, the capacity of C. albicans to survive and form biofilm for over six months under anaerobic and nutrient-limited conditions was reported [73], corroborating the ability of these yeasts in surviving inside root canals.

Conventional therapeutic options for oral candidiasis range from topical polyene antifungals to azole agents. However, the increase in the occurrence of resistance of Candida spp. to conventional antifungals has been related in the last decades. Even though the prevalence of resistant oral isolates seems to be still low, they have been found in particular among patients with predisposing factors [69, 74]. Besides, antifungal drugs show relevant limitations, such as low spectrum, interaction with other drugs, high cost and toxic effects. Markedly, the toxic effects are result of the similarities between yeast and host cells (both eucariotic), are very relevant in clinical context. In particular for
against Plants extracts, essential oils and compounds have been an important source of research for new antifungal options experimentally infected root canals [88].

In investigations on the dental applications of propolis for candida infections have been done. The use of propolis ethanolic extract inhibited in vitro growth of C. albicans experimentally inoculated in root canals in vitro at immediate sampling. However, no residual effect was observed since increased values of CFU were detected after 7 days [83]. Vinegar and sodium bicarbonate can be also considered promising alternative substances with efficacy for the disinfection of acrylic resin inoculated with C. albicans, due to their low cost and availability [84,85].

Investigations on the dental applications of propolis for candida infections have been done. The use of propolis ethanolic extract inhibited in vitro growth of C. albicans isolates from oral candidiasis [86]. Moreover, this extract showed similar clinical effectiveness for the treatment of patients with denture-associated candidiasis when compared to miconazole [87]. On the contrary, propolis as intracanal medicament was not able to reduce counts of C. albicans experimentally infected root canals [88].

Plants extracts, essential oils and compounds have been an important source of research for new antifungal options against Candida spp. Effectiveness of Coriandrum sativum L. essential oil on the biofilm formation by C. albicans isolates from patients with periodontal disease was reported [89]. Cytopogon citratus and Syzygium aromaticum essential oils inhibited C. albicans biofilm formation and were more active against pre-formed biofilms when compared to amphotericin B and fluconazole in vitro [90].

Methanol extract of Mentha piperita, Rosmarinus officinalis, Arrabidoea chica, Tabebuia avellanedae, Punica granatum and Syzygium cumini showed antifungal activity on Candida species [91]. Methanol extract of Ficus deltoidea showed in vitro activity on C. albicans [92]. Seed and leaf extracts of Abelmoschus moschatus were tested against C. albicans cells, using microdilution test, and showed similar inhibitory effect when compared to nystatin [93]. A paste containing ethyl acetate fraction (AcOEt) extracted from Arctium lappa inhibited the growth of C. albicans besides of other endodontically related microorganisms [94].

Some studies already evaluate isolated substances or secondary metabolites from plants. The effects of licorice and its isolated compounds (licochalcone A, glabridin and glycyrrhizic acid) on C. albicans also show promising results. Glabridin and licochalcone A showed potent antifungal activity and prevented yeast-hyphal transition. Besides, licochalcone Z showed a significant effect on C. albicans biofilm formation [95,96]. The in vitro and in vivo anti-Candida activities of pogostone that is isolated from Pogostemon cablin (Blanco) Benth have been also reported. Pogostone was equally effective against fluconazole-resistant C. albicans strains when compared to voriconazole [97]. A-type cranberry proanthocyanidins prevented C. albicans biofilm formation and reduced the adherence to oral epithelial cells and saliva-coated acrylic resin specimen [98]. The compounds 2',6'-dihydroxy-4'-geranyloxyacetophenone and 2',6'-dihydroxy-4'-farneslyoxy-acetophenone, extracted from plants belonging to the Rutaceae family, showed high antimicrobial activity on C. albicans [99].

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