Review

Antimicrobials from Medicinal Plants: An Emergent Strategy to Control Oral Biofilms

Catarina Milho 1, J. Jani Silva 1,2,*, Rafaela Guimarães 1, Isabel C. F. R. Ferreira 3, Lillian Barros 3,* and Maria José Alves 1,3

1 AquaValor—Centro de Valorização e Transferência de Tecnologia da Água—Associação, Rua Dr. Júlio Martins n.º 1, 5400-342 Chaves, Portugal; catarina.milho@aquavalor.pt (C.M.); jani.silva@aquavalor.pt (J.S.); rafaela.guimaraes@aquavalor.pt (R.G.)
2 Molecular Oncology and Viral Pathology Group, IPOP Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Rua Dr. António Bernardino de Almeida 865, 4200-072 Porto, Portugal
3 Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal; lferreira@ipb.pt
* Correspondence: lillian@ipb.pt (L.B.); maria.alves@ipb.pt (M.J.A.)
† These authors contributed equally to this work.

Abstract: Oral microbial biofilms, directly related to oral diseases, particularly caries and periodontitis, exhibit virulence factors that include acidification of the oral microenvironment and the formation of biofilm enriched with exopolysaccharides, characteristics and common mechanisms that, ultimately, justify the increase in antibiotics resistance. In this line, the search for natural products, mainly obtained through plants, and derived compounds with bioactive potential, endorse unique biological properties in the prevention of colonization, adhesion, and growth of oral bacteria. The present review aims to provide a critical and comprehensive view of the in vitro antibiofilm activity of various medicinal plants, revealing numerous species with antimicrobial properties, among which, twenty-four with biofilm inhibition/reduction percentages greater than 95%. In particular, the essential oils of Cymbopogon citratus (DC.) Stapf and Lippia alba (Mill.) seem to be the most promising in fighting microbial biofilm in Streptococcus mutans, given their high capacity to reduce biofilm at low concentrations.

Keywords: medicinal plants; oral diseases; oral biofilm; drug resistance; antibiofilm strategies

1. Introduction

Oral diseases triggered by pathogenic bacteria persevere as a worldwide problem with high impact on human health. More than 750 bacteria species inhabit the oral cavity, some of which are opportunistic species capable of causing infections related to oral biofilm. Epithelial cells, dental surfaces and orthodontic prostheses are examples of oral surfaces favorable to the creation of multispecies biofilms that promote the development of infectious diseases, such as dental caries, gingivitis, and periodontitis, which represent some of the most common chronic oral diseases in adults and children [1–4]. Dental caries, a medical term for tooth decay or cavities, are part of a group of polymicrobial diseases caused by specific acid-producing bacteria, mainly Gram-positive species, such as Streptococcus mutans, Streptococcus sobrinus and Lactobacillus spp., responsible for the destruction of the dental enamel and its lower layer, the dentin [5,6]. These bacteria metabolize sucrose into organic acids, mainly lactic acid, which dissolve calcium phosphate from the teeth causing decalcification and possible decay [7]. On the other hand, periodontal diseases are characterized by the occurrence of severe gum infections that damage the soft tissue and the bone that supports the tooth, most of which caused by...
the pathogens Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis and Prevotella intermedia [5,8].

Several chemical compounds have been used in the control of oral infectious diseases, like chlorhexidine, fluorine and their combinations [9]. Chlorhexidine is generally accepted as a chemical antibiofilm agent, widely used in dentistry to preserve the healthy oral microbiome [10]. However, some unwanted side effects have been reported, arising from its use for prolonged periods, which may include tooth pigmentation, burning sensation in the mouth, altered taste, and restocking of the oral cavity by resistant strains [11], the latter being mainly due to an increased resistance to antibiotics and to other synthetic chemicals, with a consequent decrease in their clinical efficacy [2]. Given this, in recent years, one of the adopted strategies to overcome these and other related issues is the use of medicinal plants [12,13], which have been used as traditional treatments for thousands of years and throughout the world, given their composition in natural bioactive compounds with multiple recognized biological activities [14]. There are several reports of antibacterial and/or antibiofilm activity linked to extracts from a huge variety of plants, mostly related with the presence of secondary metabolites such as flavonoids, phenolic acids, and tannins [15], which play an important role in the resistance to various microbial pathogens and in the protection against free radicals and toxins [16,17]. Regarding phenolic compounds, several mechanisms through which antimicrobial activity is promoted have been described, since these compounds interact with bacterial proteins and cell membrane structures, damaging and reducing their fluidity, inhibiting the synthesis of nucleic acids, and interfering with the microorganisms’ own energy metabolism [16,18,19]. On the other hand, the investigation of antibiofilm properties derived from phenolic compounds present in plants has revealed that, in addition to their bactericidal effect, other mechanisms can lead to biofilm suppression, namely through disturbances in its bacterial regulatory mechanisms, such as quorum sensing (QS) [20]. As an example, many catechin-based polyphenols, flavonoids, proanthocyanin oligomers, and some other plant-derived compounds, compromise the formation of biofilm through the inhibition of glucosyltransferases (GTFs) from one of the most important oral pathogens, S. mutans [21].

In modern medicine, natural compounds are considered valuable and with undeniable therapeutic assets, showing reduced toxicity and increased efficiency [22]. Therefore, the search for natural phytochemicals is seen as a good alternative to synthetic substances in the prevention and treatment of oral diseases. The present review focuses on the potential of plant extracts to inhibit the growth and adhesion of oral pathogens, and the development of biofilms, thus reducing the progress of oral diseases.

A literature search in PubMed and Science Direct was conducted using the search terms “oral biofilm”, “dental biofilm” “medicinal plants”, “aromatic plants”, “natural products”, “antibiofilm”, “cariogenic biofilms” and “natural antimicrobials”. Literature analysis included scientific papers published in the last 11 years (between 2010 and 2021). Obtained scientific papers were manually curated and selected by relevance of their findings, namely, selected by relevance of their findings and focusing on antibiofilm activity.

The inclusion criteria for the collected papers (54 papers) were as follows: (1) medicinal plants extracts, (2) oral biofilm-associated bacteria, (3) inhibition of biofilm formation and/or eradication of preformed biofilm.

2. Oral Microbiome

The oral cavity has an actual diverse microbiome, comprising bacteria, protozoa, fungi, archaea, and viruses, with the most abundant group (96%) being composed by bacteria belonging to the phyla Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes, and Fusobacteria [23,24]. The remaining microorganisms belong to the phyla Euryarchaeotic, Chlamydia, Chloroflexi, SR1, Sinergistetes, Tenericutes, and TM7. Although present in small percentages, species from the Archaea domain, such as
Methanobrevibacter oralis, Methanobacterium curvum/congolense and Methanosarcina mazei, are also part of the oral microbiome [25]. About fungi, Candida species are the most found, being present in almost 50% of the healthy world population [26]. Other frequently fungi found in the oral cavity belong to Aspergillus, Saccharomyces, Cryptococcus, Fusarium genera [27]. When it comes to viruses, the most frequently found include those that cause sores in the oral cavity, chicken pox, herpes simplex, among others [28]. Moreover, Trichomonas tenax and Entamoeba gingivalis are the main protozoa found as members of the oral microbiome, the majority of which being saprophytes [29].

Microorganisms that make up the oral microbiome can reside on two types of surfaces, the hard faces of the teeth and the soft tissues of the oral mucosa [30]. Usually, these microorganisms are present in the oral cavity in the form of a biofilm, playing an extremely important role in oral homeostasis, maintenance, and prevention of oral pathologies [31]. However, under certain conditions, changes in the composition and properties of the biofilm can lead to oral illnesses, such as tooth decay and periodontitis. Increased sugar intake, for instance, promotes the proliferation of acidogenic and aciduric bacteria, such as S. mutans and Lactobacillus acidophilus, which, in turn, create an acidic environment that stimulates the development of dental caries [32–34]. Other bacteria that are usually present in the tooth biofilm include P. gingivalis, Tannerella forsythia and Treponema denticola, closely related to periodontal diseases, which may result from a set of inflammatory conditions that affect the supporting tissues of the teeth [35]. Thus, the biofilm formation may represent the start of the development of different oral diseases.

3. Oral Biofilm Formation

In general, biofilm formation encompasses a series of sequential steps (Figure 1), which begins with the formation of a conditioning film on a surface. In the oral cavity, specifically, an acquired salivary surface, composed of glycoproteins and other molecules, is developed on the tooth surface [36].

![Figure 1](image_url)  
**Figure 1.** Sequence of pathogenic oral biofilm development. (1) Initially, a salivary pellicle is formed, derived from salivary glycoproteins attached to the tooth surface. (2) Then, initial adhesion starts, as early colonizer bacteria in saliva recognize the binding proteins in acquired pellicle and attach to them. (3) As the biofilm grows, different bacterial species attach, and the biofilm matures. (4) Finally, bacteria disperse from the biofilm and spread to colonize new surfaces. (Created with BioRender.com accessed on 27 April 2021).

Subsequently, a reversible fixation of microorganisms to the tooth occurs, whose approximation of their cell walls occurs randomly or directed through chemotaxis and motility, as well as through weak interactions such as electrostatic and van der Waals forces, and hydrophobic interactions, established between them and the surface [37]. Thus, the mechanisms that occur during the first stages of biofilm formation allow the interaction and adhesion of bacteria to proteins in the acquired salivary film, such as α-
amylose and glycoproteins rich in proline [38]. The physical–chemical properties of the oral environment, the presence of nutrients, the physiological state of the bacteria and the presence of bacterial structures, such as fimbriae and flagella, also influence bacterial fixation. In dental caries, the main bacterial colonizers that stick to the tooth surface belong to the genus Actinomyces, Streptococcus, Haemophilus, Capnocytophaga, Veillonella and Neisseria [39]. At this stage, if the oral environment is unfavorable to fixation, bacteria can be easily removed from the adhered surface. However, under favorable conditions, bacteria can become irreversibly linked, with different forces in this process, such as dipole-dipole interactions, hydrogen, ionic and covalent bonds, and hydrophobic interactions [37]. This attachment is strengthened by bacterial surface structures such as ligands located on pili, fimbriae, and fibrillae [40,41]. The following production of extracellular polymeric substances (EPS), the most important phase of the irreversible attachment, will support the adhesion of bacteria to oral surfaces. EPS is mainly composed by polysaccharides, containing, also, nucleic and amino acids, glycoproteins and phosphoproteins, phospholipids, uronic acids, and phenolic compounds [42]. In addition to strengthening bacterial adhesion to the tooth surface, EPS is also responsible for reducing diffusional transport, causing decreased growth and metabolism rates of incorporated bacterial cells, nutrient storage, and increased resistance to antimicrobial agents [43]. At the end of this stage, if a physical or chemical procedure is not applied, the bacterial fixation becomes irreversible. Fusobacterium nucleatum, Treponema spp., T. forsythensis, P. gingivalis, and A. actinomycetemcomitans, are some of the main colonizing bacterial species that are late attached to the biofilm in expansion [44]. After this stage, bacterial cells proliferate, communicating with each other through chemical signals, and potentiating the production of EPS. The continuous growth of bacteria leads to the formation of biofilm that can cover the entire exposed surface, and whose complexity increases not only through the constant fixation and growth of these microorganisms, but also through the production of greater amounts of EPS, originating several layers of cells incorporated into the matrix [45]. In the biofilm itself, there are also water-filled channels responsible for transporting nutrients and removing waste products. At this step, the formation of a mature biofilm, with a complex three-dimensional structure, is completed and, as the biofilm matures, the cells become detached and dispersed, as a result of nutrient depletion, decreased pH or oxygenation, and accumulation of toxic products [46]. Additionally, enzymes that degrade EPS can also be produced by different microorganisms, further increasing the detachment of biofilm cells, which will later colonize new niches and start the formation of new biofilms.

In the oral cavity, the subsistence in a multispecies biofilm confers ecological advantages when compared to biofilms colonized by a single species. Moreover, once in the EPS matrix, oral bacteria are protected from microenvironmental damage, from the host’s immune defenses and from antimicrobial agents [47]. The presence of persistent dormant cells in the biofilm is crucial, given their high tolerance to antimicrobial agents, reason why they are pointed out as the main parties responsible for the biofilm recalcitrancy to these agents [48].

4. Oral Biofilms: From Dental Caries to Systemic Diseases

Chronic and progressive oral diseases are estimated to affect more than 3.5 million people worldwide. Although preventable, this public health problem can disproportionately affect low-income people and, consequently, their longevity and quality of life, factors directly related to social and economic disparities [49]. As previously mentioned, dental caries, periodontal diseases and other problems related to the oral cavity, result from a complex interaction between the microbiome and the oral microenvironment, the pathogens, and specific characteristics of the host, sharing common risk factors between them [47,50] (Figure 2A). Both the appearance and progression of these pathologies are closely related to bacterial biofilms characteristics, which present themselves as complex microbial groups that interact with each other,
triggering immunological/inflammatory responses and modulating the action of antimicrobial agents [51].

![Figure 2. Dysbiosis as a trigger of oral diseases. (A) Development of oral biofilm from health to disease conditions, the associated risk factors, and the antimicrobial resistance mechanisms. (B) Development of periodontitis and related risk factors. (Created with BioRender.com accessed on 27 April 2021).](image)

The extracellular insoluble glucans converted from the dietary sucrose that feeds the assembly of the EPS matrix are essential in bacterial adhesion and subsequent formation of dental plaque, and in the formation of the EPS matrix nucleus of the biofilm, which can be the starting point for the development of diseases such as periodontitis [47,52–54]. Cariogenic biofilms are naturally acidic and hypoxic; however, they are rich in carbohydrates, which creates an environment conducive to the growth of opportunistic microorganisms, such as the lactobacilli, Lactobacillus casei and Lactobacillus reuteri, thus accelerating the development of dental caries [47], which passes from the enamel to the dentin, and may be associated with continuous microbial dysbiosis owed to an increased bacterial diversity and to species with proteolytic capacity, such as F. nucleatum [55].

In contrast, endodontic infections are characterized by the presence of bacterial infections in the tooth pulp that can be caused by initial dental caries. In fact, sequencing of the 16S rRNA gene showed that polymicrobial biofilms can be identified within the infected root canals, which are mostly composed of Firmicutes spp. (>50%) [50,56,57]. Thus, the morphological structure of the oral biofilm may vary from case to case, in which the time of infection, the type and availability of nutrients in the oral microenvironment and the arrangement of the established microbiota are at the origin of this structure [58,59].

Periodontitis, in turn, is defined as a chronic inflammatory disease induced by biofilm, that affects the integrity of the periodontium, which consists in the periodontal ligament, gingiva and alveolar bone (Figure 2B). Destructive inflammation of the tissue, as well as increased dysbiosis, results in bone loss, that may culminate in tooth decay and, ultimately, systemic complications. This type of inflammation is associated with variations in the subgingival polymicrobial community, which changes from a predominantly aerobic Gram-positive biofilm to a Gram-negative anaerobic biofilm [50]. Chronic periodontitis has been associated with a predominance of “red complex bacteria”, namely P. gingivalis, T. forsythia and T. denticola [50,60]. The most aggressive forms of this
disease can result in faster periodontal destruction and bone loss, modulated by a set of pathogenic species that act in conjunction with *A. actinomycetemcomitans* strains [50,58].

Increasing evidence has shown that the dysbiotic oral microbiota can not only be a source of oral inflammation, but may also contribute to systemic ones, by releasing toxins or microbial by-products into the bloodstream. Thus, the synergistic effect between oral and systemic inflammation is a crucial step for the subsequent damaging effects on various organ systems, increasing the risk of developing oral and non-oral diseases [61] (Figure 3).

![Figure 3. Schematic representation of different systemic diseases and their association with oral keystone pathogens. (Created with BioRender.com accessed on 27 April 2021).](image)

In fact, a meta-analytical study showed that patients with periodontal disease are more susceptible to the development of oral cancer [62]. Recently, a study performed by Michaud et al. [63] also provided supporting data for a positive correlation between periodontal disease and risk of oral, lung, and pancreatic cancers. In line with these information, *P. gingivalis* was found at significantly higher levels in both oral and esophagus squamous cell carcinoma patients [64]. Moreover, other studies have shown that *F. nucleatum* can migrate from the oral cavity to the intestinal tract, promoting a pro-inflammatory microenvironment and suggesting a possible role of these bacteria in the development of colorectal cancer [65,66]. Also, Alzheimer’s disease and diabetes mellitus seem to be bidirectionally associated with periodontal disease [61]. According to Mealey et al. [67], diabetic patients have a 3-fold increase risk of developing periodontitis when compared with healthy controls. On the other hand, Teeuw et al. [68] suggest that periodontal treatments lead to an improvement of glycemic control of type 2 diabetes, which may be related, in part, with periodontal infection and inflammatory response [69]. As so, these data show that periodontal disease management could positively control the glycemic levels in diabetic individuals. Also, Kothari et al. [70] found that individuals with acquired brain injuries had a series of unstable oral, dental and periodontal parameters, translated into generalized chronic periodontitis. In contrast, the systemic production of pro-inflammatory cytokines in response to oral bacterial infection suggests that periodontal disease can lead to cerebral inflammatory state, related to Alzheimer’s disease [71,72]. Actually, higher levels of antibodies against *A.
Actinomyetemcomitans, P. gingivalis, T. forsythia were found in elderly patients with Alzheimer’s disease when compared to healthy individuals [72]. Likewise, the presence of periodontopathic virulence factors, namely lipopolysaccharides (LPS) from P. gingivalis and T. denticola, could figure in the development of brain inflammation and, ultimately, in Alzheimer’s disease [73]. Other studies have also shown that individuals with periodontal disease had a 1.14 to 2 times greater risk of developing coronary heart disease when compared to a control group [74]. The presence of oral bacteria DNA, namely P. gingivalis, A. actinomyetemcomitans, T. forsythia, Eikenella corrodens, F. nucleatum and Campylobacter rectus in atheromatous plaques of endarterectomy, were also detected [75]. Reinforcing the previous results, DNA from periodontal bacteria P. gingivalis, A. actinomyetemcomitans, P. intermedia, T. forsythia and cariogenic S. mutans, was noticed in atherosclerotic plaques, suggesting that these oral pathogens have the ability to migrate from the oral cavity to distant body sites [76,77]. In addition, the oral cavity, especially the saliva and dental plaque of individuals with periodontal disease, appears to be the source of accumulation and dissemination of pathogens to the lower respiratory tract. Several oral pathogens have already been implicated in lung infections, including A. actinomyetemcomitans, Actinomyces israelii, Capnocytophaga spp., Chlamydophila pneumoniae, Eikenella corrodens, F. nucleatum, Fusobacterium necrophorum, P. gingivalis, P. intermedia and Streptococcus constellatus [78–80]. It has been also reported that periodontal infection increases the likelihood of developing nosocomial pneumonia [81]. Genetic similarities between microorganisms isolated on dental plaque and bronchoalveolar lavage fluid suggest that the former may function as a reservoir for respiratory and/or opportunistic pathogens [82]. Porto et al. [83], in turn, showed that toothed and toothless individuals hospitalized in intensive care units and submitted to orotracheal intubation presented large amounts of A. actinomyetemcomitans, P. gingivalis and T. forsythia, suggesting that the oral microenvironment favors the pathogenic bacterial growth. Additional studies also express that systemic dissemination of periodontal-related oral pathogens, endotoxins, and inflammatory mediators can cross the placental barrier and contribute to adverse pregnancy outcomes [84,85], with F. nucleatum and P. gingivalis being detected in placental and fetal tissues [86], and in the placenta of preterm delivery patients, respectively [87,88]. An increasing number of epidemiological, serological and clinical evidences, observed between the pathogenesis of rheumatoid arthritis and periodontitis, have been presented, with A. actinomyetemcomitans and P. gingivalis being recognized as the main triggers of this disease, associating autoimmunity with periodontal diseases [89]. P. gingivalis is referred as the only human pathogen known to express the peptidyl arginine deiminase enzyme and to produce citrullinated epitopes that are recognized by anti-citrullinated protein antibodies, that ultimately culminate in clinical manifestations of rheumatoid arthritis [50,89].

5. Biological Properties of Plants

Traditional knowledge on medicinal plants, used for different health purposes, has attracted much attention among the scientific community due to their effectiveness in the treatment of several diseases [90]. Medicinal plants are a rich source of bioactive compounds, or bionutrients, which may be present in seeds, roots, leaves, flowers, or even in the whole plant, thus assuming themselves as important sources of compounds with characteristics of food additives, flavorings and other valences at an industrial level [91]. Bioactive compounds are secondary metabolites that can be classified based on their composition, the pathway by which they are synthesized, or through their chemical structure. A simple classification of bioactive compounds includes three main groups, consisting of phenolic compounds, terpenoids, and alkaloids, which represent about 90% of all secondary metabolites [92]. The minor groups of secondary metabolites include saponins, lipids, carbohydrates, ketones, and others [93,94]. Currently, phenolic compounds are among the most studied natural products, given their chemical and structural diversity and bioactive properties [95,96], which may include antioxidant, antimutagenic, antitumor, antiallergenic, anti-inflammatory, antiviral, antiulcer,
Antidiarrheal, antihelmintic, antihepatitic, and antiproliferative properties [97,98]. Medicinal plants are composed of a wide range of phenolic compounds with antimicrobial properties that provide protection against aggressive agents. Some of these compounds can deliver sustainable solutions for combating drug-resistant microorganisms [99]. These secondary metabolites are biosynthesized from the shikimate pathway, containing benzene, hydrogen and oxygen rings, the majority of which being flavonoids, the largest and most studied group of compounds in plants [100]. Flavonoids are found to be effective against a wide range of microorganisms, and their antimicrobial activity is thought to be shaped through their ability to form complexes with both extracellular and soluble proteins, as well as with bacterial membranes, increasing their permeability and disruption [101]. In addition, these compounds may also act to inhibit the activities of DNA gyrase and β-hydroxyacyl-acyl transport protein dehydratase [102]; for example, catechins belonging to this group exhibit inhibitory activity against both Gram-positive and Gram-negative bacteria [103]. In its turn, apigenin showed inhibitory activity to both GTF and fructosyltransferase proteins of S. mutans without major impact on bacterial viability [104]. Quercetin derivate inhibited S. mutans biofilm production by reducing the synthesis of both water-soluble and insoluble glucans and suppressing several virulence genes [105]. On the other hand, the antimicrobial mechanism by which terpenoid compounds act is not clearly defined, but is attributed to the rupture of microorganisms membrane [106,107]. Finally, alkaloids, which are biosynthesized from amino acids, such as tyrosine, hold an antimicrobial mechanism attributed to their ability to intercalate with DNA, thereby resulting in impaired cell division and death [108]. The plant-extracted product may exert its antimicrobial activity, not by killing the microorganism itself, but by affecting several key events in the pathogenic process [109,110].

There are several reports on plant extracts activity against a wide range of microbial pathogens from the oral cavity. Some of these studies are focused on the investigation of the ability of plant-derived products to inhibit the formation of biofilms in the oral cavity, interfering and reducing the adhesion of microbial pathogens to different oral surfaces, which constitutes the first step in the formation of dental plaque, and in the progression to cavities and periodontal diseases. It has been shown that crude plant extracts and purified phytochemicals can act as bactericides, inhibiting one or all stages of plaque formation, by interfering with biofilm adhesion/aggregation/formation, or inhibiting the production of glycolytic acid in cariogenic bacteria [111]. Several studies report the polyphenols inhibitory effects on oral biofilm formation and on dental biofilm production and accumulation. Many compounds such as catechins, flavonoids, alkaloids, terpenoids, proanthocyanin oligomers and some other plant-derived compounds, inhibit S. mutans GTFs, one of the crucial virulence factors of S. mutans with a key role in the synthesis of glucans, an important component of the biofilm matrix [21]. The use of traditional medicines clearly shows how potential biologically active compounds can suppress pathogens and prevent disease progression [94]. Thus, the use of herbal extracts and their products on a daily basis is a promising and interesting alternative to synthetic compounds in the control of oral diseases.

6. The Most Promising Medicinal Plant Extracts in the Control of Oral Biofilms

The antibiotic therapy has reached its limits regarding antimicrobial resistance, threatening the effective prevention and treatment of an increasing range of infections. Thus, new therapeutic approaches based on natural phytochemicals have been the target of several research, considering their bioactive assets, namely antimicrobial properties. Knowing that the number of medicinal plants that potential possess antimicrobial/antibiofilm properties is quite large, only published works investigating the extracts obtained from plants’ aerial parts, roots and seeds were considered. Hence, Table 1 presents some of the plant species whose extracts hold compounds with antimicrobial/antibiofilm activity, among others, up to 95%, against specific
microorganisms, i.e., extracts with the potential to inhibit biofilm formation and/or eradicate it, with concentrations <1 mg.mL⁻¹.

One of the described plant species with proven antimicrobial [112], antiulcerative [113] and antifungal [114] activity is *Baccharis dracunculifolia* D.C., considered to be the most important botanical source of South-Eastern Brazilian propolis [115]. The antibiofilm properties against oral cavity bacteria were studied by Galvão et al. [9], through essential oils extracted from the aerial parts of the plant in question. These authors showed that, for a concentration of 31.2 μg.mL⁻¹, *B. dracunculifolia* extracts present 95% of inhibition growth of biofilms of *S. mutans* NCTC 1091. The ability of this extract to inhibit biofilm formation seems to be related to its composition in oxygenated sesquiterpenes, such as spathulanol and trans-nerolidol, described in the literature as antibiofilm/antimicrobial mediators [116,117].

Different phenolic compounds are responsible for the wide diversity of bioactive properties of plant extracts, which, in addition to their antimicrobial assets, may also take part in the healing process. An example of this statement is the species *Camellia japonica* L., whose extract holds antioxidant, anti-inflammatory and antimicrobial properties [118–120]. Additionally, *Chelidonium majus* subsp. *asiaticum* H.Hara, commonly known as greater celandine, is a medicinal plant widely used in traditional medicine due to its anti-inflammatory and antimicrobial effects [121,122], properties also attributed to the *Thuja orientalis* L. species, a perennial conifer tree of the family Cupressaceae [123,124]. Choi et al. [125] investigated the antimicrobial and antibiofilm activities of mancholian extracts of *C. japonica, C. majus* subsp. *asiaticum, C. flagelliferum* and *T. orientalis* against oral pathogens. Notably, all these plant extracts were able to inhibit the GTF function of *S. mutans* ATCC 25175, an important virulence factor in the biofilm formation, by 99.0%, at a concentration of 1.00 mg.mL⁻¹. The total phenolic compounds concentration of these extracts is quite high, which may be the reason of their superior antimicrobial effect [126,127].

The essential oil extracted from *Cinnamomum zeylanicum* Blume, a perennial tree from which cinnamon is obtained [128], is described in the literature as an antimicrobial agent that acts against various biofilm-forming bacteria present in the oral cavity [129,130], such as *S. mutans* ATCC 25,175. When used in the management of biofilms of *S. mutans*, the essential oil from *C. zeylanicum* skin was able to inhibit their formation by up to 99%, at a concentration of 0.224 mg.mL⁻¹ [131]. β-linalool and (E)-cinnamaldehyde are the two main compounds present in this oil, and can be pointed out as responsible for its antibiofilm properties [132,133]. In addition, the essential oils of *Coriandrum sativum* L., a medicinal plant with nutritional benefits, commonly named coriander, exhibit antibacterial and antibiofilm properties against *S. mutans*, in addition to holding antioxidant and anesthetic properties [134,135]. Galvão et al. [9] used a chemical fraction of *C. sativum* essential oil as an antibacterial against *S. mutans* UA 159, at a concentration of 31.2 μg.mL⁻¹, being able to inhibit the growth of *S. mutans* biofilms by more than 95%. The fatty alcohol 1-decanol is one of the major components found in *C. sativum* essential oil, and it has been described as an antibacterial and antibiofilm agent [136,137].

*Copaifera pubiflora* Benth. is a flowering plant whose oleoresin is widely used in Brazilian medicine due to its anti-inflammatory, analgesic, and antimicrobial properties [138–140]. In a study performed by Moraes et al. [141], oleoresin from *C. pubiflora* was used as an alternative agent for the removal of oral pathogenic biofilms. This work showed satisfactory data regarding the antimicrobial activity of the used extract against microorganisms normally present in the oral cavity, which included *S. sanguinis* ATCC 10,556 and *P. micro* clinical isolate (CI), and it was able to eliminate more than 99.9% of preformed biofilms of these species, at a concentration of 50.0 μg.mL⁻¹. The antimicrobial effect of *C. pubiflora* oleoresin was attributed to the presence of ent-hardwickiic acid, which was found to be the main compound present in this plant [142]. *Cymbopogon citratus* (DC.) Stapf, in turn, usually known as lemon grass, is a perennial aromatic plant that is cultivated in tropical and sub-tropical regions [143]. Its essential oil has been found to
have many different biological properties, including anxiolytic, antibacterial and antibiofilm incomes [144–146]. When it comes to oral health, it has been shown that C. citratus exerts an antibiofilm effect on pathogenic bacteria from the oral cavity. As an example, 93.0% of growth inhibition of S. mutans biofilms was obtained at a concentration of 1.00 μg.mL⁻¹ of C. citratus essential oil [147]. In another study, the essential oil from this plant, at a concentration of 0.100 μg.mL⁻¹, led to a reduction of more than 95% of S. mutans ATCC 35,668 preformed biofilms [148]. In addition, C. citratus oil was tested against S. mutans ATCC 35,688 and L. acidophilus ATCC 4356 single-species biofilms, also inhibiting their growth by more than 95%, although at higher concentrations (26.1 mg.mL⁻¹ and 13.2 mg.mL⁻¹, respectively). Regarding its chemical composition, the compounds that are usually found in C. citratus essential oil are citral and myrcene, which are described to have good antimicrobial properties [149].

Eucalyptus globulus Labill is an evergreen tree native to Australia whose leaves have been widely used in pharmaceutical products, given their antimicrobial and antioxidant properties [150]. Tsukatani et al. [151] reported that the E. globulus ethanolic extract exhibited up to 99% eradication activity against P. gingivalis JCM 12257 at a minimum biofilm eradication concentration (MBEC) of 49.1 μg.mL⁻¹, and S. mutans NBRC13955 at a MBEC of 393 μg.mL⁻¹. The extracts of Eucalyptus species were found to equally contain antimicrobial compounds, such as macarcarps, eucalyptine and 1,8-cineol [152,153]. Macarcarp A, B and C are phloroglucinol derivatives referred to inhibit virulence factors of the periodontopathic bacteria P. gingivalis, including specific cysteine proteinases, which appear to be essential for the growth and survival of this bacterium in the periodontal pocket [152]. The presence of specific groups of bioactive compounds can also influence the progression stages of the oral bacterial biofilm’s formation.

Derris reticulata Craib, a climbing medicinal plant used in folk medicine [154], has prenylated flavonones as its main constituents, whose presence has been linked to several pharmacological outcomes, particularly antibacterial activity [154,155]. According to Pulbutr et al. [155], the ethanolic extract from stems of D. reticulata was able to inhibit S. mutans DMST 1877 biofilm formation by up to 99.9%, at the highest tested concentration, 750 μg.mL⁻¹. These results are in accordance with the capability of D. reticulata to inhibit both sucrose-dependent and independent S. mutans adherence in a concentration dependent manner, at sub-MIC concentrations (<625 μg.mL⁻¹).

Dodonaea viscosa var. angustifolia leaf decoction extracts have been reported to have anti-inflammatory and antimicrobial activity [156,157], and they are traditionally used as mouthwashes for toothaches and related problems [158]. The bioactivities present in this plant can be attributed to the major compounds found in D. viscosa extract, namely xylopyranoside; 2,2′-methylenedioxy [6-(1,1-dimethyl)-4-methyl]; 2-(3-Hydroxy-4-methoxy-phenyl)-3,7-dimethoxy-4H-chromen-4-one; trans-3′,4′,5′-Trimethoxy-4-(methylthio)chalcone and stigmasteryl [159]. Naidoo et al. [159] studied the inhibitory effect of this plant methanolic extract against S. mutans NCTC 1091 biofilm, verifying that biofilm reduction was dependent on the exposure time and concentration.

The tapered roots and rhizomes of Glycyrrhiza glabra L. hold most of the bioactive components responsible for this plant medicinal and culinary features [160]. Its phytochemical compounds, namely glycyrrhizin, an oleanane-type triterpene saponin, stands out as its major constituent with antibiofilm activity [160,161]. Suwannakul and Chaibenjawong [162] found that the inhibition pattern and eradication of P. gingivalis biofilm by G. glabra ethanol extract were concentration-dependent. At the concentration of 500 μg.mL⁻¹, the extract exhibited up to 90% inhibition of P. gingivalis biofilm formation. In addition, the eradication of P. gingivalis biofilm was achieved at a MBEC of 62.5 μg.mL⁻¹, being higher at a concentration of 500 μg.mL⁻¹. The authors also found that the Rgp- and Kgp-proteinase activities of P. gingivalis, which are important virulence factors, were also reduced by approximately 50% [162]. Interestingly, Kim et al. [163] showed that G. glabra main bioactive compound, namely 18α-glycyrrhetinic acid, significantly inhibits the P. gingivalis LPS-induced endothelial permeability, both in vitro and in vivo assays.
Lippia alba (Mill.) flowering plant which essential oil presents several pharmacological properties such as sedative, analgesic, antispasmodic, anti-inflammatory and antimicrobial assets [164]. In a work published by Tofino-Rivera et al. [148], the essential oil from L. alba was used as an antibacterial agent against S. mutans ATCC 35,668 biofilms, and it was shown that, at a concentration of 0.100 μg.mL⁻¹, this natural product was able to reduce the number of viable cells present in the biofilm by 95.8%. In this case, isomeric monoterpenes geraniol and citral are two of the main components found, which are known to hold antimicrobial properties [149,165].

The Mentha genus includes diverse aromatic herbs that are commonly used in herbal teas, flavoring agent, and as medicinal plants. Infusion, decoction, and distillate water of the aerial parts have been used for centuries as tonics, carminative, digestive, stomachic, antispasmodic, and anti-inflammatory preparations [166]. Traditionally, these plants have been also used for teeth whitening, and their distilled oils used to flavor toothpastes and chewing gum, until this day. Knowing this, several works were conducted in order to study the ability of these plants to eliminate oral pathogenic biofilms. As an example, Shafiei et al. [167] investigated the effects of Mangifera sp. and Mentha sp. aqueous extracts towards the eradication of S. sanguinis ATCC BAA-1455 and S. mutans ATCC 25,175 biofilms. Both extracts showed to be more effective in reducing the biofilm population of S. mutans than S. sanguinis. At a concentration 0.50 mg.mL⁻¹, Mangifera sp. and Mentha sp. extracts reduced 99.4% and 98.5% the S. mutans biofilms, respectively. Previous reports showed that Psidium sp. and Mentha sp. extracts, as well as their mixtures, have antibacterial and anti-adherence activities against S. sanguinis and S. mutans in single species biofilms [168,169]. Moreover, the phenolic profile of Mangifera sp. extract revealed that quinic acid, benzophenone C-glycoside isomer, benzophenone C-glycoside and quercetin-3-O-glucoside were its main compounds, while in the Mentha sp. extract, methyl 2-[cyclohex-2-en-1-yl(hydroxy)methyl]-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxoprolinate was mainly found [170], all presenting inhibiting virulence properties of S. mutans.

Myrtus communis L. is an important aromatic and medicinal plant species from the Mediterranean area, widely used for culinary, cosmetic, pharmaceutical, therapeutic, and industrial purposes [171]. Antimicrobial and antioxidant proprieties of M. communis have been reported in numerous studies [172]. Sateriale et al. [173] described the antibiofilm activity of hydroethanolic extracts from its leaves against the oral pathogens S. mutans ATCC 25,175, S. oralis (CI), S. mitis (CI), and R. dentocariosa (CI). Curiously, the hydroethanolic extract of M. communis produced a significant (p < 0.05) inhibition in all tested oral pathogens biofilms. MBEC values, assigned to the lowest concentration of each antimicrobial agent that is able to eradicate preformed biofilms, ranged between 40 mg.mL⁻¹ (S. oralis and S. mitis) and 120 mg.mL⁻¹ (S. mutans and R. dentocariosa). In a previous study, the same authors were able to identify gallic acid derivatives, tannins, myricetin, and quercetin derivatives as the most abundant phenolic compounds in the hydroalcoholic extract of M. communis [174]. The authors also refer that the antibiofilm properties of M. communis have been directly correlated with its phenolic compounds’ arrangement.

Rhodiola rosea L. is medicinal plant that has been used due to its therapeutic properties and as a potential source of antimicrobial, antioxidant, anti-inflammatory agents, among others [175,176]. This plant has been recognized to present a broad spectrum of biological activities mainly attributed to its major phytochemical compounds, which include phenylethanes and phenylpropanoids (rosavin, salidroside, rosin, cinnamyl alcohol, and tyrosol) [175,177]. In a study performed by Zhang et al. [178], the R. rosea root ethanolic extract inhibited the biofilm formation of S. mutans UA159 by 95%, at a concentration of 0.50 μg.μL⁻¹, with the highest reduction of EPS synthesis being observed at the same concentration. R. rosea also suppressed the expression of virulence genes and QS system as well as the enzymatic activity of GTF proteins in both 0.25 μg.μL⁻¹ and 0.50 μg.μL⁻¹ concentration groups [178]. At a concentration of 0.12 μg.μL⁻¹, no significant cytotoxic
effect was observed, and 0.50 μg.mL⁻¹ and 0.25 μg.mL⁻¹ slightly inhibited the cell proliferation [178].

Rosmarinus officinalis L. is recognized as a fragrant medicinal plant, native to the Mediterranean region and cultivated worldwide. In addition to its therapeutic and prophylactic effects, this plant is extensively used as a condiment, food preservative and for ornamental purposes [179]. Extensive research has been developed regarding the characterization of the antibiofilm properties of this plant. Tsukatani et al. [151] found that the R. officinalis ethanolic extract was able to eliminate P. gingivalis JCM12257 and S. mutans NBRC13955 biofilm formation at a concentration of 195.5 μg.mL⁻¹ and 97.8 μg.mL⁻¹, respectively. Additionally, the phytochemical profile of this medicinal herb was determined, and it showed that carnosic acid presented the lowest MBEC against P. gingivalis (25.0 μg.mL⁻¹) and S. mutans (12.5 μg.mL⁻¹). This bioactive component is a plastidial catechol diterpene with recognized antioxidative, anti-inflammatory and antimicrobial properties [179,180]. Syzygium aromaticum L., another plant traditionally used as a spice and as a food preservative, holds a wide spectrum of pharmacological properties. As reported by Tsukatani et al. [151], the biofilm eradication activity of S. aromaticum ethanolic extract against P. gingivalis JCM 12,257 and S. mutans NBRC 13,955 was observed, respectively, at a concentration of 435.5 and 871 μg.mL⁻¹. Regarding its phytochemical signature, eugenol, eugenol acetate and β-caryophyllene are acknowledged as antimicrobial components present in this plant extract [181]. Eugenol was reported to inhibit P. gingivalis and S. mutans biofilms at higher concentrations, 800 and >800 μg.mL⁻¹, respectively [151]. In addition, other minor compounds, such as β-caryophyllene, exhibited eradication activities against P. gingivalis and S. mutans at lower concentrations (400 and 50 μg.mL⁻¹, respectively), and eugenol acetate against S. mutans, at 400 μg.mL⁻¹ [151].

Spirostachys africana Sond., a tree originally from South America, is traditionally used as a remedy for toothache [182]. Although used as an antibacterial product, its bioactive properties have not been extensively described in the literature. As an example, the dichloromethane:methanol extract from S. africana leaves was used against S. mutans ATCC 25,175 oral pathogen, being able to inhibit the growth of S. mutans biofilms by more than 97% at a concentration 0.25 mg.mL⁻¹ [183]. Unfortunately, no studies have been found describing the chemical profile of S. africana leaf extracts. Another plant commonly used for its interesting properties is Thymus vulgaris L., commonly named thyme, whose essential oil bioactive properties include antioxidant, anti-inflammatory, antitumor, and antimicrobial effects [184]. Several studies have been conducted regarding the antibacterial activity of T. vulgaris essential oil against oral pathogens, namely S. aureus [185]. Interestingly, when used at a concentration of 0.156 mg.mL⁻¹, this essential oil was capable of inhibiting the formation of S. aureus biofilms by 96%. The antibiofilm effect of T. vulgaris essential oil may be due to the presence in its composition of different chemical compounds, in particular thymol, a monoterpenoid phenol that is extensively described as having antibiofilm properties [186].

Trachyspermum ammi L., a plant rich in thymol, is a known herb with recognized medical properties, widely cultivated in the west and northwest of Iran [187]. Its seeds hold several medicinal features, including antibacterial, antioxidants and antifungal properties, among others [188,189]. With respect to its application as an antibacterial product against oral bacteria, Khan et al. [90] found that, at a 160 μg.mL⁻¹ concentration, the ethanolic extract of T. ammi seeds was able to reduce the number of viable cells in S. mutans ATCC 700,610 biofilms by 89%. On the other hand, the petroleum ether fraction of the ethanol extract, applied at 40.0 μg.mL⁻¹, caused the complete inhibition of S. mutans biofilms growth (100%), probably due to its higher concentration in antimicrobial compounds. As mentioned before, thymol, a monoterpenoid phenol, is the major component found in ethanol extracts of T. ammi seeds, which is known to exert antibiofilm effects [186].
Table 1. Medicinal plants with verified antimicrobial/antibiofilm activity against oral cavity bacteria, and the respective bioactive compounds present in their extracts.

| Plant Name                  | Plant Extract                          | Compound                | Microorganism          | Results                        | References |
|-----------------------------|----------------------------------------|-------------------------|-------------------------|--------------------------------|------------|
| *Acacia karroo* Hayne       | Dichloromethane: methanol (leaves)     | -                       | *S. mutans* ATCC 25175  | MIC 0.50 mg.mL⁻¹, 88.8% inhibition, 0.25 mg.mL⁻¹ | [183]      |
| *Achyranthes aspera* L.    | Methanol                               | Betulin, 3,12-oleandione| *S. mutans* (CI)        | MIC 125 μg.mL⁻¹, IZD 23.0 mm (250 mg.mL⁻¹), 94.9% inhibition, 125 μg.mL⁻¹ | [190]      |
|                            | Essential oil (leaves)                  | -                       | *S. mutans* UA159       | MIC 31.2-62.5 μg.mL⁻¹, >90% inhibition, 62.5 μg.mL⁻¹ | [9]        |
| *Aloysia gratissima* (Aff & Hook) Tr | Essential oil (leaves) | (E)-pinocamphone; β-pinene; guaiol | *F. nucleatum* ATCC 25586 | MIC 0.125 mg.mL⁻¹, 55.83% inhibition |            |
|                            |                                        |                         | *P. gingivalis* ATCC 33277 | MBC 0.250 mg.mL⁻¹       |            |
|                            |                                        |                         | *S. sanguis* ATCC 10556   | MIC 0.500 mg.mL⁻¹, 60.83% inhibition | [136]      |
|                            |                                        |                         | *S. mitis* ATCC 903       | MBC 0.25 mg.mL⁻¹, 9.00% inhibition |            |
| *Artemisia princeps* Pamp. | Ethanol (leaves)                        | -                       | *S. mutans* ATCC 25175  | MIC 0.40 mg.mL⁻¹, =80.0% inhibition, 0.40 mg.mL⁻¹ | [191]      |
| *Artocarpus lakoocha* Roxb. | Aqueous                                | Oxyresveratrol          | *S. mutans* ATCC 25175  | MIC 0.10 mg.mL⁻¹, ≥90.0% inhibition, 3.12 mg.mL⁻¹ | [192]      |
|                            |                                        |                         | *S. mutans* ATCC 25175  | MBC 0.20 mg.mL⁻¹, ≥90.0% reduction, 6.25 mg.mL⁻¹ |            |
|                            |                                        |                         | IZD 30.5 mm (10% (w/v)) | MBC 0.100 mg.mL⁻¹, ≥90.0% inhibition, 0.39 mg.mL⁻¹ |            |
|                            |                                        |                         | IZD 29.5 mm (10% (w/v)) | MBC 0.200 mg.mL⁻¹, ≥90.0% reduction, 3.12 mg.mL⁻¹ |            |

MIC = Minimum Inhibitory Concentration; MBC = Minimum Bactericidal Concentration; IZD = Inhibitory Zone Diameter.
| Species                          | Compounds (leaves)          | Pathogens | MIC (μg.mL⁻¹) | MBC (μg.mL⁻¹) | Inhibition (%) | Reference |
|---------------------------------|-----------------------------|-----------|---------------|---------------|----------------|-----------|
| *Azadirachta indica* A.Juss.    | Aqueous                     | E. faecalis ATCC 29212 | -             | -             | 53.6% reduction | [193]     |
|                                 |                             | S. aureus ATCC 25923   | -             | -             | 48.2% reduction |           |
| *Baccharis dracunculifolia* DC. | Essential oil               | S. mutans ATCC 35688   | MIC 6.0% (v/v) | -             | 39.3% reduction |           |
|                                 |                             | S. mutans 22 (Cl)      | -             | -             | 78.9% reduction |           |
|                                 |                             | S. mutans 24 (Cl)      | -             | -             | 90.9% reduction |           |
|                                 |                             | S. mutans 28 (Cl)      | -             | -             | 91.1% reduction |           |
|                                 | Essential oil               | Trans-nerolidol; spathulenol | -             | MIC 15.6-31.2 μg.mL⁻¹ | 95.0% inhibition | [9]       |
|                                 |                             | S. mutans UA159        | MBC 125-250 μg.mL⁻¹ | -             | 37.7% inhibition | [183]     |
| *Berula erecta* (Huds.) Coville | Dichloromethane: methanol   | S. mutans ATCC 25175   | MIC 0.5 mg.mL⁻¹ | -             | 37.7% inhibition | [183]     |
|                                 | (rhizome)                   | -                      | -             | -             | 46.0% reduction |           |
| *Betula schmidtii* Regel.       | Methanol                    | S. mutans ATCC 25175   | MIC 31.3 mg.mL⁻¹ | -             | 46.0% reduction | [195]     |
| *Camellia japonica* L.          | Methanol                    | S. mutans ATCC 25175   | MIC 0.5 mg.disk⁻¹ | IZD 12 mm (2 mg.disk⁻¹) | 99.0% GTFs inhibition | [125]     |
| *Chelidonium majus* subsp.      | Methanol                    | S. mutans ATCC 25175   | MIC 1.0 mg.disk⁻¹ | IZD 8 mm (1.0 mg.disk⁻¹) | 99.0% GTFs inhibition | [125]     |
| asiaticum* H. Hara              |                             | -                      | -             | -             |               |           |
| *Chrysosplenium flagelliferum*  | Methanol                    | S. mutans ATCC 25175   | MIC 1.0 mg.disk⁻¹ | IZD 12 mm (2 mg.disk⁻¹) | 99.0% GTFs inhibition | [125]     |
| F.Schmidt                       |                             | -                      | -             | -             |               |           |
| *Cinnamomum burmannii* (Nees & | Aqueous                     | S. mutans UA159        | MIC 2.5 mg.mL⁻¹ | -             | >99% inhibition | [196]     |
| T.Nees) Blume                   |                             | -                      | -             | -             |               |           |
|                                 | Essential oil               | S. mutans ATCC 25175   | MIC 0.056 mg.mL⁻¹ | IZD 10 mm (50 mg.mL⁻¹) | 99.0% inhibition | [185]     |
|                                 | β-linalool; (E)-cinnamaldehyde; | -                        | -             | -             |               |           |
| Study System  | Medicinal Plant | Main Constituent | Organism | MIC (mg.mL⁻¹) | IZD | % Inhibition | MBC (mg.mL⁻¹) | % Reduction |
|---------------|-----------------|-----------------|-----------|---------------|-----|-------------|---------------|-------------|
| Cinnamomum zeylanicum Blume | Essential oil (bark) | Cinnamyl acetate | *E. faecalis* ATCC 19433 | 0.315 | 10 mm (50 mg.mL⁻¹) | 47.0% inhibition | 1.26 mg.mL⁻¹ | |
|  | | | *S. aureus* ATCC 29213 | 0.315 | 11 mm (50 mg.mL⁻¹) | 93.0% inhibition | 0.315 mg.mL⁻¹ | |
|  | | | *S. mutans KPSK2* | | | | | |
|  | Essential oil (bark) |  | *P. gingivalis ATCC 5397* | | | | | |
|  | Essential oil (bark) | Cinnamaldehyde | *P. gingivalis ATCC 33177* | 6.25 μg.mL⁻¹ | | 74.5% inhibition | 4.17 μg.mL⁻¹ | |
| Cistus creticus L. Methanol (aerial plant parts) | | Quercetin; 3-O-β-D-glucopyranoside | *S. mutans DSM 20523* | 5 mg.mL⁻¹ | 10 mg.mL⁻¹ | =80% inhibition | 0.600 mg.mL⁻¹ | |
| Cistus monspeliensis L. Methanol (aerial plant parts) | | Cistodioic acid | *S. mutans DSM 20523* | 2.5 mg.mL⁻¹ | | =60% inhibition | 0.600 mg.mL⁻¹ | |
| Copaifera pubiflora Benth. Oleoresin | | | *S. sanguinis ATCC 10556* | 12.5 μg.mL⁻¹ | | MBIC50 6.25 μg.mL⁻¹ | |
|  | | | *S. sanguinis* (CI) | 25.0 μg.mL⁻¹ | | MBEC 50.0 μg.mL⁻¹ | |
|  | | | *S. mutans ATCC 25175* | 12.5 μg.mL⁻¹ | | MBIC50 6.25 μg.mL⁻¹ | |
|  | | | *L. paracasei* (CI) | 12.5 μg.mL⁻¹ | | MBIC50 12.5 μg.mL⁻¹ | [141] |
|  | | | *P. gingivalis ATCC 33277* | 12.5 μg.mL⁻¹ | | MBIC50 12.5 μg.mL⁻¹ | |

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[197] [198] [200]
| Compound                                | MIC          | MBC          | MBIC50  | MBC  |
|----------------------------------------|--------------|--------------|---------|------|
| *P. gingivalis* (CI)                   | 50.0 μg.mL⁻¹ | MBIC50       | 100 μg.mL⁻¹ |
| *F. nucleatum* (CI)                    | 25.0 μg.mL⁻¹ | MBIC50       | 400 μg.mL⁻¹ |
| *P. micra* (CI)                        | 12.5 μg.mL⁻¹ | MBIC50       | 25.0 μg.mL⁻¹ |
| *S. mutans* UA159                      | 15.6-31.2 μg.mL⁻¹ | MBC | >95% inhibition | 31.2 μg.mL⁻¹ | [9] |
| *F. nucleatum* ATCC 25586              | 0.015 mg.mL⁻¹ | MBC         | 55.8% inhibition |
| *P. gingivalis* ATCC 33277             | 0.125 mg.mL⁻¹ | MBC         | 39.7% inhibition |
| *S. sanguis* ATCC 10556                | 0.250 mg.mL⁻¹ | MBC         | 58.3% inhibition |
| *S. mitis* ATCC 903                    | 0.062 mg.mL⁻¹ | MBC         | 1.5% inhibition |
| *S. mutans* ATCC UA159                 | -            | MBC         | 34% inhibition | 0.007 mg.mL⁻¹ | [201] |
| *S. mutans* NBRC13955                  | -            | MBC         | 99.1% reduction | 5.0% (v/v) | [151] |
| *L. acidophilus* ATCC 4356             | -            | MBC         | 93% inhibition | 1.0 μg.mL⁻¹ | [147] |
| *L. acidophilus* ATCC 4356             | 2.61 mg.mL⁻¹ | MBC         | 95% inhibition | 26.1 mg.mL⁻¹ | [202] |

**Coriandrum sativum L.**

| Compound | MIC          | MBC          | MBIC50  | MBC  |
|----------|--------------|--------------|---------|------|
| *F. nucleatum* ATCC 25586              | 0.015 mg.mL⁻¹ | MBC         | 55.8% inhibition |
| *P. gingivalis* ATCC 33277             | 0.125 mg.mL⁻¹ | MBC         | 39.7% inhibition |
| *S. sanguis* ATCC 10556                | 0.250 mg.mL⁻¹ | MBC         | 58.3% inhibition |
| *S. mitis* ATCC 903                    | 0.062 mg.mL⁻¹ | MBC         | 1.5% inhibition |

**Curcuma longa L.**

| Compound | MIC          | MBC          | MBIC50  | MBC  |
|----------|--------------|--------------|---------|------|
| *P. gingivalis* JCM12257               | -            | MBC         | 99.7% reduction |
| *S. mutans* NBRC13955                  | -            | MBC         | 99.1% reduction | 5.0% (v/v) | [151] |

**Cymbopogon citrates** (DC.) Stapf

| Compound | MIC          | MBC          | MBIC50  | MBC  |
|----------|--------------|--------------|---------|------|
| *S. mutans* ATCC 35688                  | 10.54 mg.mL⁻¹ | MBC         | 95% inhibition | 26.1 mg.mL⁻¹ | [202] |
| IZD      | 11 mm (100% (v/v)) | MBC         | 99.6% inhibition | 13.2 mg.mL⁻¹ | [202] |
| Essential oil | Geraniol; neral; myrcene | S. mutans ATCC 35668 | MIC | MBC | IZD | Reduction | Concentration |
|---------------|---------------------------|-----------------------|-----|-----|-----|-----------|--------------|
| Cymbopogon martini (Roxb.) W. Watson | S. mitis (CI) | 0.25 mg.mL⁻¹ | 0.25 mg.mL⁻¹ | 28% reduction | 0.25 mg.mL⁻¹ | [148] |
| Essential oil | Geraniol; geranyl acetate | E. faecalis (CI) | 0.25 mg.mL⁻¹ | 0.25 mg.mL⁻¹ | 36% reduction | 1.0 mg.mL⁻¹ | [203] |
| | S. mitis + S. sanguinis + E. faecalis | - | - | - | 20% reduction | - | |
| Cyperus articulatus L. | Essential oil (bulbs) | α-pinene; mustakone; α-bulnesene | F. nucleatum ATCC 25586 | 0.250 mg.mL⁻¹ | 61.67% inhibition | - | |
| | | | P. gingivalis ATCC 33277 | 0.250 mg.mL⁻¹ | 43.53% inhibition | - | |
| | | | S. sanguis ATCC 10556 | 0.250 mg.mL⁻¹ | 63.96% inhibition | - | |
| | | | S. mitis ATCC 903 | 0.500 mg.mL⁻¹ | 5.00% inhibition | - | |
| Derris reticulata Craib | Ethanol (stem) | - | S. mutans DMST 1877 | 0.875 mg.mL⁻¹ | 102.8% inhibition | 750 μg.mL⁻¹ | [155] |
| Dodonaea viscosa var. angustifolia (L.f.) Benth | Methanol (leaves) | Xylopyranoside; 2,2′-methylenebis[6-(1,1-dimethyl)4-methyl]; 2-(3-Hydroxy-4-methoxyphenyl)-3,7-dimethoxy-4H-chromen-4-one; trans-3′,4′,5′- | S. mutans NCTC 1091 | 0.78 mg.mL⁻¹ | 99% inhibition | 0.78 mg.mL⁻¹ | [159] |
| Plant Species                        | Solvent          | Compound                        | Organism          | End-point        | MIC            | Inhibition       | MBC            | [Reference] |
|-------------------------------------|------------------|---------------------------------|-------------------|-----------------|----------------|-----------------|----------------|-------------|
| **Englerophytum magalismontanum**   | Dichloromethane: | Trimethoxy-4-                   | *S. mutans* ATCC 25175 | MIC             | 0.83 mg.mL⁻¹  | 49.28% inhibition | 0.25 mg.mL⁻¹  | [183]       |
| (Sond.) T.D.Penn.                   | methanol (stems) | (methylthio)chalcone;           |                   |                 |                |                 |                |             |
|                                     |                  | stigmasterol                    |                   |                 |                |                 |                |             |
| **Erythrina lysistemon**            | Dichloromethane: | -                               | *S. mutans* ATCC 25175 | MIC             | 0.50 mg.mL⁻¹  | 72.54% inhibition | 0.25 mg.mL⁻¹  | [183]       |
| Hutch.                              | methanol (stems) | -                               |                   |                 |                |                 |                |             |
| **Eucalyptus sp.**                  | Essential oil    | -                               | *E. faecalis* ATCC 29212 | -              |                | 71.6% reduction   | 100% (v/v)    | [204]       |
| **Eucalyptus galbie**               | Methanol         | -                               | *E. faecalis* PTCC 1237 | MIC            | 12.5 mg.mL⁻¹  | 77.7% adherence  | 6.25 mg.mL⁻¹  | [205]       |
|                                    | Ethanol          | Essential oil (leaves)           | *S. mutans* ATCC 700610 | MIC            | 0.013 mg.mL⁻¹ | 81.1% reduction   | 2.0 mg.mL⁻¹  | [206]       |
| **Eucalyptus globulus**             | Ethanol          | 1,8-cineole; α-pinene            | *S. mutans* NBRC13955 | MBEC           |                | 49.1 μg.mL⁻¹   |                |             |
| Labill.                             |                  | eucalyptin; 1,8-cineole          |                   | MBEC           |                | 393 μg.mL⁻¹     |                |             |
| **Eucalyptus x urograndis**         | Essential oil (leaves) | 1,8-cineole; α-pinene           | *S. mutans* ATCC 700610 | IZD            | 23.0 mm (100% v/v) | 35.1% reduction | 2.0 mg.mL⁻¹  | [206]       |
|                                    | Essential oil (leaves) | 1,8-cineole; α-pinene           | *S. mutans* ATCC 700610 | IZD            | 34.7 mm (100% v/v) | 81.1% reduction | 2.0 mg.mL⁻¹  | [206]       |
| **Firmiana simplex**                | Methanol (bark)  | -                               | *S. mutans* ATCC 25175 | IZD            | 9 mm (1.0 mg.disk⁻¹) | 35.7% GTFs inhibition | 1.0 mg.mL⁻¹  | [125]       |
| (L.) W.Wight                        | Essential oil (seeds) | -                               | *S. mutans* KPSK2 | MIC            | 1.25% (v/v)   | 84.4% inhibition | 5.0% (v/v)    | [197]       |
| **Foeniculum vulgare**              | Essential oil (seeds) | -                               | *S. mutans* KPSK2 | MBC            | 2.50% (v/v)   | 69.7% reduction | 5.0% (v/v)    | [197]       |
| Plant                          | Ethanol          | MIC                  | MBC                  | GTFs inhibition | MIC                  | MBC                  | MBC                  |
|-------------------------------|------------------|----------------------|----------------------|-----------------|----------------------|----------------------|----------------------|
| *Geranium sibiricum* L.       | Methanol (whole plant) | S. mutans ATCC 25175 | 0.5 mg.dish⁻¹ | 69.3 % GTFs inhibition | 1.0 mg.mL⁻¹ |             |                       |
| *Ginkgo biloba* L.            | Methanol         | S. mutans ATCC 25175 | 62.5 μg.mL⁻¹ | ≈38.5 % reduction | 125 mg.mL⁻¹ |             |                       |
| *Glycyrrhiza glabra* L.       | Ethanol (roots)  | P. gingivalis ATCC 33277 | 62.5 μg.mL⁻¹ | 92.3 % inhibition | 500 μg.mL⁻¹ | 62.5 μg.mL⁻¹ |                       |
| *Hibiscus sabdariffa* L.      | Ethanol (calices) | S. mutans Ingbrit | 7.2 mg.mL⁻¹ | 99.0 % inhibition | 3.60 mg.mL⁻¹ |             |                       |
|                               |                  | S. sanguinis ATCC 10556T | 28.8 mg.mL⁻¹ | 97.0 % inhibition | 14.4 mg.mL⁻¹ |             |                       |
|                               |                  | L. casei ATCC 4646   | >57.6 mg.mL⁻¹ | 92.0 % inhibition | 28.8 mg.mL⁻¹ |             |                       |
|                               |                  | A. naeslundii ATCC 12104T | 14.4 mg.mL⁻¹ | 97.0 % inhibition | 14.4 mg.mL⁻¹ |             | [207]               |
|                               |                  | A. actinomycetemcomitans ATCC 29522 | 28.8 mg.mL⁻¹ | 97.0 % inhibition | 28.8 mg.mL⁻¹ |             |                       |
|                               |                  | F. nucleatum JCM 6328 | 7.2 mg.mL⁻¹ | 83.0 % inhibition | 1.8 mg.mL⁻¹ |             |                       |
|                               |                  | P. gingivalis ATCC 33277T | 7.2 mg.mL⁻¹ | 98.0 % inhibition | 14.4 mg.mL⁻¹ |             |                       |
|                               |                  | P. intermedia ATCC 25611T | 14.4 mg.mL⁻¹ | 89.0 % inhibition | 7.2 mg.mL⁻¹ |             |                       |
| *Houttuynia cordata* Thunb.   | Ethanol (leaves) | S. mutans MT8148     | 1.09 μg.mL⁻¹ | ≈80.0 % reduction | 10 % (v/v) |             |                       |
|                               |                  | F. nucleatum JCM8532  | 0.543 μg.mL⁻¹ | ≈90.0 % reduction | 10 % (v/v) |             |                       |
| Plant Compound | Bacterial Strain | MIC (μg.mL⁻¹) | MBIC₅₀ (μg.mL⁻¹) |
|----------------|-----------------|---------------|-----------------|
| Ethanol        | S. mutans ATCC 21752 | 64.0          | 18.0            |
|                | S. sobrinus ATCC 6715 | 16.0          | 7.23            |
|                | L. plantarum ATCC 80141 | 32.0          | 29.9            |
|                | E. faecalis ATCC 29912 | 32.0          | 18.1            |
| Hexane         | S. mutans ATCC 21752 | 64.0          | 16.3            |
|                | S. sobrinus ATCC 6715 | 16.0          | 7.29            |
|                | L. plantarum ATCC 80141 | 32.0          | 27.6            |
|                | E. faecalis ATCC 29912 | 32.0          | 16.1            |
| Chloroform     | S. mutans ATCC 21752 | 32.0          | 17.2            |
|                | S. sobrinus ATCC 6715 | 16.0          | 8.03            |
|                | L. plantarum ATCC 80141 | 32.0          | 27.5            |
|                | E. faecalis ATCC 29912 | 32.0          | 17.2            |
| Hypericum perforatum L. | S. mutans ATCC 21752 | 32.0          | 17.2            |
|                | S. sobrinus ATCC 6715 | 16.0          | 7.52            |
|                | L. plantarum ATCC 80141 | 16.0          | 25.1            |
|                | E. faecalis ATCC 29912 | 16.0          | 17.7            |
| Acetic acid    | S. mutans ATCC 21752 | 32.0          | 17.5            |
|                | S. sobrinus ATCC 6715 | 16.0          | 7.25            |
|                | L. plantarum ATCC 80141 | 16.0          | 27.3            |
|                | E. faecalis ATCC 29912 | 16.0          | 17.5            |
| Butanol        | S. mutans ATCC 21752 | 32.0          | 20.1            |
|                | S. sobrinus ATCC 6715 | 16.0          | 7.60            |
|                | L. plantarum ATCC 80141 | 8.00          | 24.9            |
|                | E. faecalis ATCC 29912 | 16.0          | 20.1            |
| Aqueous        | S. mutans ATCC 21752 | 32.0          | 20.1            |
|                | S. sobrinus ATCC 6715 | 8.00          | 7.60            |
|                | L. plantarum ATCC 80141 | 8.00          | 24.9            |
|                | E. faecalis ATCC 29912 | 16.0          | 20.1            |
| Laurus nobilis L. | S. aureus ATCC 6538 | 31.25         |                 |
| Essential oil (from Gafsa) | S. aureus L36 (CI) | S. aureus L37 (CI) | S. aureus ATCC 6538 |
|--------------------------|------------------|------------------|------------------|
| 1,8-cineole; methyl eugenol; α-terpinyl acetate; linalool | 15.625 mg.mL⁻¹ | 15.625 mg.mL⁻¹ | 31.25 mg.mL⁻¹ |
| | 78.4 % eradication | 86.07% inhibition | 78.4 % eradication |
| | 31.25 mg.mL⁻¹ | 15.625 mg.mL⁻¹ | 100 mg mL⁻¹ |
| | 100% (v/v) | 100% (v/v) | 100% (v/v) |
| Essential oil (from Sousse) | S. aureus L36 (CI) | S. aureus L37 (CI) | S. mutans UA159 |
| 1,8-cineole; methyl eugenol; α-terpinyl acetate; linalool | 3.91 mg.mL⁻¹ | 3.91 mg.mL⁻¹ | 0.40% (w/v) |
| | 88.22% inhibition | 93.00% inhibition | =35.0% inhibition |
| | 3.91 mg.mL⁻¹ | 3.91 mg.mL⁻¹ | MBIC-0.8% (w/v) |
| | 45.0% eradication | 31.0% eradication | 0.10% (w/v) |
| | 100% (v/v) | 100% (v/v) | [211] |
| Ligustrum robustum (Roxb.) | S. mutans C1 (CI) | S. mutans C2 (CI) | S. mutans C3 (CI) |
| Methanol (roots) | 0.25% (w/v) | 0.25% (w/v) | 0.25% (w/v) |
| Ligurobustoside B, N, J and C | 0.50% (w/v) | 0.50% (w/v) | 0.50% (w/v) |
| | =61.0% inhibition | =62.0% inhibition | =61.0% inhibition |
| | MBIC-0.5% (w/v) | MBIC-0.5% (w/v) | MBIC-0.5% (w/v) |
| | 0.10% (w/v) | 0.10% (w/v) | 0.10% (w/v) |
|                  | MIC          | MBC          | MBIC (% (w/v))       |
|------------------|--------------|--------------|----------------------|
| **S. mutans C4 (Cl)** | 0.25% (w/v)  | 0.50% (w/v)  | =54.0% inhibition    |
| **S. mutans C5 (Cl)** | 0.25% (w/v)  | 0.50% (w/v)  | =57.0% inhibition     |
| **S. mutans C6 (Cl)** | 0.25% (w/v)  | 0.50% (w/v)  | =47.0% inhibition     |
| **S. mutans C7 (Cl)** | 0.30% (w/v)  | 0.50% (w/v)  | =42.0% inhibition     |
| **S. mutans C8 (Cl)** | 0.35% (w/v)  | 0.50% (w/v)  | =40.0% inhibition     |

**Lindera glauca** (Siebold & Zucc.) Blume
Methanol (leaves)

|                  | MIC          | MBC          | MBIC (% (w/v))       |
|------------------|--------------|--------------|----------------------|
| **S. mutans ATCC 25175** | 1.0 mg. disk⁻¹ | -           | 85.9% GTFs inhibition |

**Lippia alba** (Mill.) N.E.Br. ex Britton & P.Wilson
Essential oil

|                  | MIC          | MBC          | MBIC (% (w/v))       |
|------------------|--------------|--------------|----------------------|
| **S. mutans ATCC 35668** | -            | 0.30% (w/v)  | =95.8% reduction     |

**Lippia sidoides** Cham.
Essential oil (leaves)

|                  | MIC          | MBC          | MBIC (% (w/v))       |
|------------------|--------------|--------------|----------------------|
| **F. nucleatum ATCC 25586** | 62.5–125 μg.mL⁻¹ | -          | >90% inhibition     |
| **P. gingivalis ATCC 33277** | 0.125 mg.mL⁻¹    | 125–250 μg.mL⁻¹ | 58.33% inhibition      |
| **S. sanguis ATCC 10556** | 0.125 mg.mL⁻¹    | 0.500 mg.mL⁻¹ | 58.13% inhibition     |
| Plant          | Formulation          | Bacterial Strain               | MIC Concentration | MBC Concentration | Inhibition Effect |
|---------------|----------------------|--------------------------------|-------------------|-------------------|-------------------|
| **Mangifera sp.** | Aqueous (leaves)      | S. mutis ATCC 25175            | 0.250 mg.mL⁻¹     | >1.0 mg.mL⁻¹      | 5.50% inhibition  |
|               |                      | S. sanguinis ATCC BAA-1455     |                   |                   | 99.4% reduction   |
| **Mangifera indica L.** | Aqueous (leaves)      | E. faecalis ATCC 29212         |                   | 0.50 mg.mL⁻¹      | 61.4% reduction   |
|               |                      | S. aureus ATCC 25923           |                   |                   |                  |
| **Matricaria aurea (Loefl.) Sch.Bip.** | Ethanol (flowers)      | P. gingivalis (CI)             | 0.78 mg.mL⁻¹      | 1.56 mg.mL⁻¹      | 78% inhibition    |
|               |                      | T. denticola (CI)              | 1.56 mg.mL⁻¹      | 3.12 mg.mL⁻¹      | 74% inhibition    |
|               |                      | T. forsythia (CI)              | 0.39 mg.mL⁻¹      | 0.78 mg.mL⁻¹      | 86% inhibition    |
|               |                      | A. actinomycetemcomitans (CI)  | 1.56 mg.mL⁻¹      | 3.12 mg.mL⁻¹      | 62% inhibition    |
| **Matricaria recutita L.** | Essential oil (leaves) | A. actinomycetemcomitans ATCC 29522 |                   |                   | 87.6% reduction   |
|               |                      | T. denticola ATCC 35405        |                   |                   | 99.1% reduction   |
| **Melaleuca alternifolia** | Essential oil         | S. mutis ATCC 25175            | 0.125% (v/v)      |                   | ≈94% reduction    |
|               |                      | (metabolic activity)           |                   |                   | 1.0% (v/v)        |
| Plant Species | Plant Part | Compound | Microorganism | MIC | MBC | IZD | Reduction |
|---------------|------------|----------|---------------|-----|-----|-----|-----------|
| (Maiden & Betch) Cheel | Myrtaceae | Methyl-2-[cyclohex-2-en-1-yl(hydroxy)methyl]-3-hydroxy-4-(2-hydroxyethyl)-3-methyl-5-oxoprolinate | S. mutans ATCC 25175 | - | 0.25% (v/v) | 20.3 mm [20% (v/v)] | =85% reduction (biomass) | 0.5% (v/v) |
| Mentha sp. | Aqueous (leaves) | - | S. mutans KPSK2 | 1.25% (v/v) | 1.25% (v/v) | - | 83.42% inhibition | 98.5% reduction | 0.50 mg.mL⁻¹ [167] |
| Mentha × piperita L. | Essential oil (leaves) | - | S. sanguis ATCC BAA-1455 | - | - | 11.33 mm [20% (v/v)] | 85.5% reduction | 0.5% (v/v) |
| Mentha spicata L. | Methanol (leaves) | - | S. mutans KPSK2 | 0.25% (v/v) | 0.5% (v/v) | - | >90.0% inhibition | 0.25% (v/v) [215] |
| Mikania glomerata Spreng | Essential oil (flowers) | Germacrene D; α-caryophyllene; bicyclogermacrene | P. gingivalis ATCC 33277 | 0.5% (v/v) | 0.25% (v/v) | 0.062 mg.mL⁻¹ | 58.96% inhibition | 54.79% inhibition |
| Myracrodruon urundeuva All. | Hydroalcoholic (leaves) | - | S. mutans ATCC 25175 | 0.125 mg.mL⁻¹ | 0.125 mg.mL⁻¹ | - | 1.00% inhibition | 1.00% inhibition |
| | | | | | | | | | [136] |
| | | | | | | | | | [173] |
| Plant                      | Hydroethanolic (leaves) | Essential oil (leave) | Ethanol (seeds) | Methanol (aerial plant parts) | Ethanol (bark) | Aqueous (leaves) | 4-chromanol |
|---------------------------|-------------------------|-----------------------|-----------------|-------------------------------|----------------|------------------|-------------|
| Myrtus communis L.        |                         |                       |                 |                               |                |                  |             |
| S. oralis (CI)            |                         |                       |                 |                               |                |                  |             |
| S. mitis (CI)             |                         |                       |                 |                               |                |                  |             |
| R. dentocariosa (CI)      |                         |                       |                 |                               |                |                  |             |
| Ocimum basilicum L.       | Hydroethanolic (leaves) | Essential oil (leave) | Ethanol (seeds) | Methanol (aerial plant parts) | Ethanol (bark) | Aqueous (leaves) | 4-chromanol |
| S. mutans KPSK2           | MIC 0.31% (v/v)         | MBC 0.31% (v/v)       |                 |                               |                |                  |             |
|                         | IZD 14.7 mm (20% (v/v)) |                       |                 |                               |                |                  |             |
| P. gingivalis JCM12257    | S. mutans NBRC13955     | Ethanol (seeds)       |                 |                               |                |                  |             |
|                         |                         |                       |                 |                               |                |                  |             |
| S. mutans DSM 20523       | MIC 2.5 mg.mL\(^{-1}\) | MBC 5.0 mg.mL\(^{-1}\) |                 |                               |                |                  |             |
|                         | IZD =60.0% inhibition   |                       |                 |                               |                |                  |             |
| S. mutans ATCC 25175      | MIC 0.315 mg.mL\(^{-1}\) |                         |                 |                               |                |                  |             |
|                         | IZD =97.0% inhibition   |                       |                 |                               |                |                  |             |
| S. aureus ATCC 29213      | MIC 0.625 mg.mL\(^{-1}\) |                         |                 |                               |                |                  |             |
|                         | IZD =60.0% inhibition   |                       |                 |                               |                |                  |             |
| S. mutans UA159           | MIC 0.313 mg.mL\(^{-1}\) |                         |                 |                               |                |                  |             |
|                         | IZD =100% inhibition    |                       |                 |                               |                |                  |             |
| E. faecalis ATCC 19433    | MIC 0.625 mg.mL\(^{-1}\) |                         |                 |                               |                |                  |             |
|                         | IZD =94% inhibition     |                       |                 |                               |                |                  |             |
| S. aureus ATCC 29212      | MIC 0.625 mg.mL\(^{-1}\) |                         |                 |                               |                |                  |             |
|                         | IZD 7.0 mm (50 mg.mL\(^{-1}\)) |                 |                 |                               |                |                  |             |
| Phellodendron amurense Rupr. | Ethanol (bark)       | S. mutans UA159        |                 |                               |                |                  |             |
| S. mutans ATCC 25175      | MIC 1.56 mg.mL\(^{-1}\) |                         |                 |                               |                |                  |             |
|                         | IZD =90% inhibition     |                       |                 |                               |                |                  |             |
| S. aureus ATCC 25923      | Aqueous (leaves)        | E. faecalis ATCC 29212 |                 |                               |                |                  |             |
|                         |                          | S. aureus ATCC 25923  |                 |                               |                |                  |             |
|                         |                          | S. mutans ATCC 25175  |                 |                               |                |                  |             |

| MBEC | MBIC (CI) | MBIC (CI) | MBIC (CI) | MBIC (CI) | MBIC (CI) | MBIC (CI) | MBIC (CI) |
|------|----------|----------|----------|----------|----------|----------|----------|
| 120 μg.mL\(^{-1}\) | 20 μg.mL\(^{-1}\) | 40 μg.mL\(^{-1}\) | 20 μg.mL\(^{-1}\) | 40 μg.mL\(^{-1}\) | 20 μg.mL\(^{-1}\) | 40 μg.mL\(^{-1}\) | 120 μg.mL\(^{-1}\) |
| Plant/Liquid                  | Compound                  | MIC       | MBC       | Reduction (%) | MIC       | MBC       | Reduction (%) |
|------------------------------|---------------------------|-----------|-----------|---------------|-----------|-----------|---------------|
| **A. actinomycetemcomitans**  | ATCC 33384                | 1.04 mg.mL⁻¹ | 2.08 mg.mL⁻¹ | 90% inhibition | 0.39 mg.mL⁻¹ | 3.13 mg.mL⁻¹ | 90% reduction |
| **Piper nigrum L.**          | Methanol (seed)           | 1.25% (v/v) | 2.50% (v/v) | 82.7% inhibition | 5.0% (v/v) |            |               |
|                             | S. mutans KPSK2           | 2.08 mg.mL⁻¹ | >50.0% (v/v) | MBIC > 50% (v/v) |
|                             | A. actinomycetemcomitans  | 1.04 mg.mL⁻¹ | 2.08 mg.mL⁻¹ | 90% inhibition | 0.39 mg.mL⁻¹ | 3.13 mg.mL⁻¹ | 90% reduction |
|                             | E. faecalis ATCC 29212    | -         | 49.1% reduction | 44.2% reduction | 30.0 mg.mL⁻¹ | [197]      |               |
|                             | S. aureus ATCC 25923      | -         | 49.1% reduction | 44.2% reduction | 30.0 mg.mL⁻¹ | [193]      |               |
| **Pistacia lentiscus L.**    | Essential oil (berry)     | -         | 50.0% (v/v) | MBIC 25.0-3.0% (v/v) |
|                             | Phenols; free unsaturated-saturated fatty acids | -         | 50.0% (v/v) | MBIC 25.0-3.0% (v/v) |
|                             | S. salivarius K12         | >50.0% (v/v) | >50.0% (v/v) | MBIC > 50% (v/v) |
|                             | S. salivarius M18         | >50.0% (v/v) | >50.0% (v/v) | MBIC > 50% (v/v) |
|                             | S. pyogenes (CI)          | 50.0% (v/v) | 50.0% (v/v) | MBIC 25.0-3.0% (v/v) |
|                             | S. agalactiae (CI)        | 50.0% (v/v) | 50.0% (v/v) | MBIC 25.0-3.0% (v/v) |
|                             | S. mutans CIP103220       | 50.0% (v/v) | 50.0% (v/v) | MBIC 25.0-3.0% (v/v) |
|                             | S. intermedius DSM 20573  | 6.0-3.0% (v/v) | 50.0% (v/v) | MBIC <4.0% (v/v) |
|                             | S. mitis (CI)             | 6.0-3.0% (v/v) | 50.0% (v/v) | MBIC <4.0% (v/v) |

| **Pistacia vera L.**         | Purified oleoresin        | -         | >2048 μg.mL⁻¹ | 49.4% inhibition | 256 μg.mL⁻¹ | [219]     |               |
|                             | α-pinene; β-pinene        | -         | 49.4% inhibition | 256 μg.mL⁻¹ | [219]     |               |               |
| **Psidium sp.**             | Aqueous (leaves)          | -         | 93.8% reduction | 0.5 mg.mL⁻¹ | [167]     |               |               |
| Plant Name | Infusion/Extract | Pathogen | MIC (mg.mL⁻¹) | MBC (mg.mL⁻¹) | Reduction |
|------------|-----------------|-----------|---------------|----------------|----------|
| **Psidium cattleianum** Sabine | Aqueous (leaves) | E. faecalis ATCC 51299 | 0.5 | >99.9% | 5.0 mg.mL⁻¹ |
| | Hydroethanol (leaves) | P. aeruginosa ATCC 15442 | 4.0 | - | - |
| **Punica granatum** L. | Flowers infusion | E. faecalis ATCC 51299 | 0.5 | >99.9% | 2.5 mg.mL⁻¹ |
| | | P. aeruginosa ATCC 15442 | 4.0 | >99.9% | 40 mg.mL⁻¹ |
| | | S. mutans ATCC 35608 | 50.0 | 84.4% | 25 mg.mL⁻¹ |
| | | S. sanguinis ATCC 10556 | 6.25 | 100% | 1.56 mg.mL⁻¹ |
| | | S. sobrinus ATCC 27607 | 25.0 | 99.9% | 12.5 mg.mL⁻¹ |
| | | S. salivarius ATCC 9222 | 25.0 | 86.5% | 12.5 mg.mL⁻¹ |
| | | E. faecalis CIP 55142 | 50.0 | 56.3% | 50 mg.mL⁻¹ |
| **Pyrostegia venusta** (Ker Gawl.) Miers | Hydroalcoholic (flowers) | S. mutans ATCC 25175 | 500 | 68.9% inhibition | 500 mg.mL⁻¹ |
| | | | 1000 | | |
| | | S. mutans ATCC 25175 | 5.0 | | 5.0 mg.mL⁻¹ |

2,6-dihydroxy-3-methyl-4-O-(6”-O-galloyl-β-D-glucopyranosyl)-benzophenone

S. sanguinis ATCC BAA-1455 48.6% reduction
| Qualea grandiflora Mart. | Hydroalcoholic (leaves) | MBEC | 10.0 mg.mL⁻¹ |
|-------------------------|-------------------------|------|--------------|
| Rhodiola rosea L. | Ethanol (root) | S. mutans UA159 | MIC | 1.0 mg.disk⁻¹ |
| | | | IZD | 12 mm (2.0 mg.disk⁻¹) |
| | | =95.0% inhibition | ≈48.6% reduction |
| | | | 0.50 μg.μL⁻¹ |
| Rosa rugosa Thunb. | Methanol (leaves) | S. mutans ATCC 25175 | MIC | 1.0 mg.disk⁻¹ |
| | | | IZD | 12 mm (2.0 mg.disk⁻¹) |
| | | 64.9% GTFs inhibition | |
| | | | 1.0 mg.mL⁻¹ |
| | | | [125] |
| Rosmarinus officinalis L. | Ethanol Carnosic acid; carnosol; rosmarinic acid | S. mutans NBRC13955 | MBEC | 97.8 μg.mL⁻¹ |
| | | P. gingivalis JCM12257 | MBEC | 195.5 μg.mL⁻¹ |
| | | | | [151] |
| | Extract (leaves) S. aureus ATCC 6538 | MIC | 25 mg.mL⁻¹ | 99% reduction |
| | | MMC | >50 mg.mL⁻¹ | |
| | E. faecalis ATCC 4083 | MIC | 50 mg.mL⁻¹ | |
| | | MMC | >50 mg.mL⁻¹ | 80% reduction |
| | S. mutans ATCC 35688 | MIC | 25 mg.mL⁻¹ | |
| | | MMC | >50 mg.mL⁻¹ | 80% reduction |
| | P. aeruginosa ATCC 15442 | MIC | 6.25 mg.mL⁻¹ | 70% reduction |
| | | MMC | | |
| | Methanol (aerial plant parts) 7-methoxyrosmanol, rosmanol isomers; rosmarinic acid | S. mutans DSM 20523 | MIC | 0.60 mg.mL⁻¹ | >90% inhibition |
| | | MBC | 2.50 mg.mL⁻¹ | 1.25 mg.mL⁻¹ |
| | | | [200] |
| | Extract (leaves) S. mutans ATCC 35688 | MBC | 200 mg.mL⁻¹ | 32% reduction of total biofilm protein |
| | | | | [224] |
| Salvadora persica L. | Methanol Benzy (6Z,9Z,12Z)-6,9,12-octadecatrienoate; 3-benzylxoxy-1-nitro-butan-2- | S. mutans CI | MIC | 2.60 mg.mL⁻¹ | 87.9% inhibition |
| | | | IZD | 24.0 mm (2.5 g. mL⁻¹) | 2.6 mg.mL⁻¹ |
| | | | | [225] |
| Plant Name                  | Solvent (Parts) | Compound            | Microorganism     | MIC          | MBC          | Inhibition Effect | MIC          |
|-----------------------------|----------------|---------------------|-------------------|--------------|--------------|-------------------|--------------|
| Salvia sclarea L.           | Methanol (aerial plant parts) | Rosmarinic acid | *S. mutans* DSM 20523 | 1.25 mg.mL⁻¹ | 5.0 mg.mL⁻¹ | 60% inhibition    | 2.5 mg.mL⁻¹ |
| Schinus terebinthifolia Raddi. | Methanol (leaves) | p-anisaldehyde | *S. mutans* UA159 | -            | -            | 41% inhibition    | 0.0035 mg.mL⁻¹ |
| Sophora flavescens Aiton.   | Methyl-alcohol | -                   | *S. mutans* ATCC 25175 | 62.5 mg.mL⁻¹ | 1.25 mg.mL⁻¹ | ≈88.5% reduction  | 125 mg.mL⁻¹ |
| Spirostachys africana Sond. | Dichloromethane: methanol (leaves) | - | *P. gingivalis* ATCC 53978 | 0.50 mg.mL⁻¹ | 125 mg.mL⁻¹ | 97.56% inhibition  | 0.25 mg.mL⁻¹ |
| Syzygium aromaticum (L.) Merr. & L.M.Perry | Essential oil (flower buds) | Eugenol; eugenol acetate; β-caryophyllene | *P. gingivalis* JCM12257 | -            | -            | 78.6% inhibition  | 5.0 mg.mL⁻¹ |
| Tarchonanthus camphoratus L. | Hydroethanol (buds) | Eugenol; eugenol acetate; β-caryophyllene | *E. faecalis* ATCC 19433 | -            | -            | 76.2% reduction  | 1.25 mg.mL⁻¹ |
|                            | Dichloromethane: methanol (bark) | - | *S. mutans* ATCC 25175 | 0.67 mg.mL⁻¹ | 1.25 mg.mL⁻¹ | 86.37% inhibition  | 0.08 mg.mL⁻¹ |

**Note:** MIC = Minimum Inhibitory Concentration, MBC = Minimum Bactericidal Concentration, IZD = Inhibitory Zone Diameter, MBEC = Minimum Bactericidal Essential Concentration.
| Plant                        | Solvent/Extract                        | Organism                | MIC/MMC/MBC (mg/mL) | Inhibition/IZD (mm) |
|-----------------------------|----------------------------------------|-------------------------|---------------------|---------------------|
| Tecoma capensis (Thunb.) Lindl. | Dichloromethane: methanol (leaves)     | S. mutans ATCC 25175    | 0.67 mg/mL<sup>−1</sup> | 53.10% inhibition   |
|                            |                                        |                         | 0.25 mg/mL<sup>−1</sup> |                     |
| Thuja orientalis L.         | Methanol (leaves and stems)            | S. mutans ATCC 25175    | 0.1 mg/disk<sup>−1</sup> | 99.0% GTFs inhibition |
|                            |                                        |                         | 1.0 mg/mL<sup>−1</sup>  |                     |
| Thymus longicaulis C.Presl. | Methanol (aerial parts) Rosmarinic acids; flavonoids; triterpenic acids | S. mutans DSM 20523     | 0.60 mg/mL<sup>−1</sup> | >95% inhibition     |
|                            |                                        |                         | 5.0 mg/mL<sup>−1</sup>   |                     |
| Thymus vulgaris L.          | Extract (leaves)                        | S. aureus ATCC 6538     | >50.0 mg/mL<sup>−1</sup> | 66% reduction       |
|                            |                                        | E. faecalis ATCC 4083   | >50.0 mg/mL<sup>−1</sup> | 82% reduction       |
|                            |                                        |                         | MMC                  | 200 mg/mL<sup>−1</sup> |
|                            |                                        | S. mutans ATCC 35688    | >50.0 mg/mL<sup>−1</sup> | 64% reduction       |
|                            |                                        | P. aeruginosa ATCC 15442| MMC                  | 88% reduction       |
| Thymus zygis L.             | Essential oil Thymol; p-cymene; terpinene; linalool; carvacrol | S. mitis (CI)           | 0.625 mg/mL<sup>−1</sup> | 96% inhibition       |
|                            |                                        | E. faecalis (CI)        | 0.625 mg/mL<sup>−1</sup> | 55% inhibition       |
|                            |                                        | S. sanguinis (CI)       | 0.625 mg/mL<sup>−1</sup> | 55% inhibition       |
|                            |                                        | E. faecalis (CI)        | 0.625 mg/mL<sup>−1</sup> | 55% inhibition       |
|                            |                                        | S. mitis + S. sanguinis + E. faecalis | - | 16% inhibition |

**Notes:**
- MIC: Minimum Inhibitory Concentration
- MMC: Minimum Micotbicidal Concentration
- MBC: Minimum Bactericidal Concentration
- IZD: Inhibitory Zone Diameter
- GTFs: Gluconic acid production
- E. faecalis (CI): E. faecalis (Clinical Isolate)
- S. mitis (CI): S. mitis (Clinical Isolate)
- S. sanguinis (CI): S. sanguinis (Clinical Isolate)
|                  |          | 2-isopropyl-5-methyl- |          |          |          |          |
|------------------|----------|------------------------|----------|----------|----------|----------|
|                  |          | phenol; oleic acid;    |          |          |          |
|                  |          | octadecanoic acid      |          |          |          |
| **Trachyspermum** | Ethanol  | *S. mutans* ATCC 700610 | MIC      | 320 μg.mL⁻¹ | 61% inhibition | 160 μg.mL⁻¹ |
| **ammi L.**      | (seeds)  |                        |          |          |          | [90]     |
| Petroleum ether  |          | *S. mutans* ATCC 700610 | MIC      | 40 μg.mL⁻¹ | 100% inhibition | 40 μg.mL⁻¹ |
| fraction (seeds) | 2-isopropyl-5-methyl- |                        |          |          | 100% reduction | 80 μg.mL⁻¹ |
|                  |          | phenol; oleic acid     |          |          |          |          |
| **Zingiber officinale** | Ethanol | *P. gingivalis* JCM12257 |          |          | 99.9% reduction |          |
| Rosco.           |          |                        |          |          |          | [151]    |
|                  |          | *S. mutans* NBRC13955  |          |          | 97.6% reduction | 5.0% (v/v) |

CI, clinical isolate; CSH, cell surface hydrophobicity; IZD, inhibition zone diameter; GTFs, glucosyltransferase; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; MFC, minimum fungicidal concentration; MMC, minimum microbial concentration; MBIC, minimum biofilm inhibitory concentration; MBBC, minimum biofilm bactericidal concentration; MBEC, minimum biofilm eradication concentration; NA, no activity observed; -, not tested.
7. Conclusions

Medicinal plants are still a greatly unexplored source of powerful natural products with antibiofilm potential, especially when antibiotic resistances continue to rise. The focus of this review was to emphasize the potential of extracted products from medicinal plants such as essential oils and plant extracts, to treat common oral diseases, like dental caries and periodontitis, which are mainly caused by the formation of bacterial oral biofilms. Although the extracts of many medicinal plants have shown promising results in the control of oral biofilms, the two most promising extracts exerting this activity were found to be the essential oils extracted from two aromatic plants, namely *C. citratus* and *L. alba*. Interestingly, the terpenoid citral is one of the main components found in both plants, which is in accordance with several studies that point the powerful antibiofilm effect of this compound. The use of essential oils from *C. citratus* and *L. alba* could be a great alternative to antibiotics in the treatment of oral diseases since they show low cytotoxicity levels and do not induce resistance in bacterial pathogens. Nonetheless, research regarding the use of medicinal plants on the treatment of oral ailments continues to be an extremely interesting topic, mainly due to the extensive variety of unscreened plants that potentially have antimicrobial and antibiofilm properties.

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