Antibiofilm Potential of Medicinal Plants against Candida spp. Oral Biofilms: A Review

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Abstract: The use of natural products to promote health is as old as human civilization. In recent years, the perception of natural products derived from plants as abundant sources of biologically active compounds has driven their exploitation towards the search for new chemical products that can lead to further pharmaceutical formulations. Candida fungi, being opportunistic pathogens, increase their virulence by acquiring resistance to conventional antimicrobials, triggering diseases, especially in immunosuppressed hosts. They are also pointed to as the main pathogens responsible for most fungal infections of the oral cavity. This increased resistance to conventional synthetic antimicrobials has driven the search for new molecules present in plant extracts, which have been widely explored as alternative agents in the prevention and treatment of infections. This review aims to provide a critical view and scope of the in vitro antimicrobial and antibiofilm activity of several medicinal plants, revealing species with inhibition/reduction effects on the biofilm formed by Candida spp. in the oral cavity. The most promising plant extracts in fighting oral biofilm, given their high capacity to reduce it to low concentrations were the essential oils extracted from Allium sativum L., Cinnamomum zeylanicum Blume. and Cymbopogon citratus (DC) Stapf.

Keywords: Candida spp.; oral disease; oral biofilm; infections; medicinal plants; plant extracts; natural compounds; antibiofilm strategies

1. Introduction

Medicinal plants have been used for several centuries to treat a wide variety of ailments. In recent years, the investigation into molecules derived from these plants, which play a fundamental role in the resistance of various pathogens, has boosted the study of their antibacterial and/or antibiofilm properties [1–3]. Some plant compounds can interact with bacterial proteins and cell membrane structures, damaging them and reducing their fluidity, while inhibiting their nucleic acid synthesis and interfering with the energy metabolism of the microorganisms themselves [2,4,5]. Additionally, the study of the antibiofilm properties associated with these molecules has revealed that, in addition to their fungicidal/bactericidal effect, other underlying mechanisms can lead to biofilm suppression, namely, disturbances at the level of bacterial regulation mechanisms [6].

The biofilm is a more resistant form of microbial existence on solid surfaces and air–liquid interfaces in which microorganisms multiply in a matrix of self-produced extracellular polymeric substances (EPS) [7]. Its resistance is directly related to the natural survival characteristics of the microbial cells that live in these communities. The slower
growth of cells associated with the biofilm, as opposed to free-living microbial cells, and the tight regulation of the cellular processes, stand out, and are mainly caused by the more restricted contact of the cells inside the biofilm with external nutrients. In addition, the presence of an EPS matrix that hinders the action of antimicrobials contributes even more to the resistance of biofilms, since this matrix acts as a diffusion barrier against small molecules [8,9].

Biofilms can be found in a variety of surfaces, both biotic and abiotic. Particularly in the oral cavity, biofilm can be found in the teeth and mucosal surfaces and are thought to consist of approximately 700 bacterial species, 100 fungal species, and some viruses [10]. Since these microorganisms coexist in the same environment, there is the possibility of interactions between different species, a factor that can make an oral infection more difficult to treat, creating an environment of protection and tolerance for microorganisms against conventional antimicrobial agents [11].

One of the main groups of microorganisms that can be found in the normal oral flora is the genus Candida, which is composed of dimorphic commensal yeast. Although Candida species are mainly nonpathogenic, when an imbalance in the oral microbiome occurs, they are the main pathogens responsible for the occurrence of fungal infections in the oral cavity [12]. One of the key virulence factors associated with these microorganisms is their ability to adhere to oral surfaces and form biofilms, which function as a reservoir for this type of fungi, both in teeth and mucosal surfaces [13,14]. Several factors contribute to the unbalanced colonization and biofilm formation in the oral cavity by Candida spp., namely, low salivary flow, low pH and poor oral hygiene among others [15]. As an opportunistic pathogen, this yeast can also cause disease when the host’s immune system is debilitated by the appearance of pathologies such as diabetes mellitus and Human Immunodeficiency Virus (HIV) infection, and by the use of broad-spectrum antibiotics, among others [16]. Additionally, as they are one of the largest acid producers in the oral cavity, Candida fungi can also be at the origin of oral infections through a localized infectious process [17–19].

Once the establishment of pathogenic oral biofilms occurs, the risk of the occurrence of systemic infections increases, as does the resistance of these infections to conventional antimicrobial therapies [20]. Currently, the treatment of Candida infections in the oral cavity is mostly done using broad-spectrum antimicrobials, however, conventional biocidal agents can cause substantial side effects if administered in high concentrations, including vomiting, diarrhea, mucosal desquamation, tooth discoloration, etc. [11,19]. Given the harmful effects of traditional antimicrobial agents, and the increasing microbial resistance to them, natural plant products have been pointed out as a safe and efficient alternative for the treatment of Candida infections in the oral cavity since, together with their anti-inflammatory, antioxidant, and analgesic properties, they also exert antimicrobial and antifungal effects over Candida spp [21].

2. The Bioactive Compounds of Plants

Folk knowledge about the medicinal use of plants has been transmitted for centuries [22]. In recent years, much of the ethnopharmaceutical research has been focused on more specific approaches in order to evaluate and understand the biological and pharmaceutical effects of medicinal and aromatic plants [22]. Plants are rich in a wide variety of secondary metabolites which play an important role in the defense against numerous pathogens. These molecules are also involved in adaptation to biotic and abiotic stresses, protection against ultraviolet radiation, oxidation of molecules, nutritional and water stresses, while performing functions at the tissue level structure, being able to add flavor and color to plant products [23].

Presently, about 200,000 different plant secondary metabolites have been isolated and identified [24]. They can be classified based on their chemical structures and/or biosynthetic pathways [25]. A simple classification includes three main groups: terpenoids (polymeric isoprene derivatives and biosynthesized from acetate via the mevalonic acid pathway), phenolics (biosynthesized from shikimate pathways, containing one or more
hydroxylated aromatic ring), and alkaloids (nonprotein nitrogen-containing compounds, biosynthesized from amino acids, such as tyrosine) [26]. Terpenoids, the condensation products of C5 isoprene units, are the main components of plant volatiles and essential oils [27]. They present many important properties, including anti-insect, antimicrobial, antiviral, and antiherbivore properties [28]. Phenolic compounds are widely found in fruits, seeds, leaves, roots, and stems, and are known for their strong antioxidant ability and their anticancer, anti-inflammatory, hypolipidemic, and hypoglycemic properties [29,30]. They have at least one aromatic ring with one or more hydroxyl groups attached, ranging from low molecular weight molecules to large and complex ones [31]. Alkaloids are usually cyclic organic compounds that contain at least one nitrogen atom in an amine-type structure [32]. These compounds are known to possess varied biological activities such as antimicrobial and antimalarial properties, among others [33].

Many studies have been published regarding bioactive properties such as antioxidant [34,35], antitumoral [31,36], analgesic/anti-inflammatory [29,37], immunostimulant [38], antiseptic, and antimicrobial [39–41]. The antimicrobial and/or biofilm activity linked with some of these compounds is closely related to their ability to inhibit the synthesis of nucleic acids, disrupt the plasma membrane, inhibit efflux pumps, elicit mitochondrial dysfunction, impair cell division and/or growth, and impair cell-wall formation, as shown in Figure 1 [42,43].

Figure 1. Mechanisms of action of phytocompounds against Candida spp. (Created with BioRender.com).

Given their strong bioactive potential, various types of phytocompounds are currently used in a wide range of fields such as food, pharmaceuticals, biomaterials, and environmental purification [44]. Regarding the ability of these compounds as antimicrobials, multiple studies have been conducted to determine their capability to fight oral infections caused by opportunistic pathogens such as Candida species [45–48]. The increased virulence of some Candida species such as Candida albicans is largely related to their ability to form biofilms which, as mentioned before, makes oral infections caused by these microorganisms very difficult to treat [49]. Taking this information into account, the use of plant-derived products to fight oral pathologies caused by Candida appears as an alternative to conventional antifungal therapy. In oral care, the use of natural products to prevent candidiasis is receiving much attention and many studies have reported the effects of medicinal plant extracts on the inhibition of oral pathogen growth and inhibition of surfaces adhesion to surfaces [50]. Some of the most prescribed antifungal agents that are currently used target
the synthesis of fungal cell membrane components that are not found in human cells, such as ergosterol [51]. However, there are few available antifungal compounds that show low levels of cytotoxicity, given the similarities between human and fungal cells, making it urgent to search for and identify new molecules capable of disrupting biofilms formed by *Candida* spp. and increase the arsenal of antifungal agents [52,53]. Knowing this, screening plants as potential sources of molecules with antifungal and/or antibiofilm properties can be considered an excellent approach to combat the formation of *Candida* spp. oral biofilms and the establishment of infections [54].

3. Opportunistic Fungal Infections Caused by *Candida* spp.

Currently, fungal infections affect millions of people every year, being the fourth leading cause of hematogenous infections worldwide. *Candida* spp., commensal microorganisms present in the normal microbial flora of the skin and mucosal surfaces (oral cavity, gastrointestinal tract, and vagina) of healthy individuals [55], are presented as the main responsible for the development of candidiasis, the most common invasive fungal disease in developed countries [56]. As commensals, *Candida* species are harmless; however, if the balance of normal flora is disrupted or immune defenses are compromised, these fungi can overrun the normal flora and cause disease. When the host’s immune status is impaired, two main types of *Candida* infection can be observed: superficial or invasive candidiasis. Superficial infections of the mucosal epithelial tissues are frequent in immunocompromised patients and include chronic atrophic stomatitis, chronic mucocutaneous candidiasis, and vulvovaginitis. In more severe cases, *Candida* species can enter the bloodstream (candidemia) and penetrate almost every organ in the body [57].

Seven *Candida* species are classified as clinically relevant, namely, *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. stellatoidea*, *C. krusea*, and *C. kyfer*, with the species *C. albicans* being the most relevant since it is the most often isolated from deeper tissues, blood, and organs [58,59].

*Candida* species has been related, majorly, to *C. albicans* species, a dimorphic fungal organism that is normally present in the oral cavity in a nonpathogenic state but which, under propitious conditions, can transmute into pathogenic hyphae form due to changes in the normal conditions of the oral cavity, especially in patients with reduced immune function or in antibiotic treatment [60–62]. A variety of local and systemic predisposing factors can lead to the transition from commensal to pathogenic *Candida*, namely the use of dentures, corticosteroid inhalers, and xerostomia, and systemic factors such as immunosuppressive states, HIV infection, malnutrition, diabetes, systemic chemotherapy, and radiotherapy, among others [63]. Therefore, about 65% of oral candidiasis are identified in the elderly, usually due to the use of dentures, and other pathologies associated with this age group, and about 16.7% in patients with hematological disorders [64]. Other factors, such as the diversity of microorganisms, the presence of saliva, vascularization, contamination by food residues, and trauma resulting from lack of hygiene, increase the inflammatory process, healing time, and patient discomfort [65,66].

*Candida* spp. express a variety of virulence factors so that it can cause disease. Biofilm formation in *Candida* spp. and the transition from planktonic to sessile form are mainly associated with a high resistance to antimicrobials. Other mechanisms include the expression of resistance genes, particularly those encoding efflux pumps, and the presence of persistent cells [67]. The interaction of bacteria and *Candida* within the biofilm is increasingly evident, however, the role of fungi in the progression of inflammation and the prognosis of oral infections remains uncertain [68].

Currently, there are only four main classes of antifungals in clinical use: azoles, polyenes, echinocandins, and pyrimidine analogs. The lack of antifungal diversity dramatically decreases the chances of treatment success and increases the probabilities of a fatal outcome if the pathogen is resistant to one or more drugs [69]. Therefore, the search for alternative products and phytochemicals isolated from plants and used in traditional medicine is considered a good alternative to conventional synthetic drugs, offering
a wide range of molecules with antimicrobial and/or antibiofilm properties to combat oral candidiasis.

4. Plant Extracts against Oral Biofilm Formed by *Candida* spp.

Most of the available antifungals are either ineffective against *Candida* biofilms or exhibit activity at very high concentrations [70]. Concerning microbial resistance, pharmacotherapy has reached its limit, threatening the effective prevention and treatment of an ever-increasing range of infections. These limitations have led to the search for novel molecules with antibiofilm potential. Plants are rich sources of bioactive molecules exhibiting various biological and pharmaceutical properties. Therefore, in recent years, new clinical approaches using natural phytocompounds have been the subject of several types of research, considering the composition of natural plant products in molecules with antimicrobial and/or antibiofilm potential. Table 1 presents some of the plant species whose extracts hold compounds with antifungal/antibiofilm activity against *Candida* spp. Moreover, extracts able to inhibit biofilm formation and/or eradication in more than 99%, at concentrations ≤ 1 mg·mL\(^{-1}\), were chosen for discussion.

*Allium sativum* L. (Amaryllidaceae) is an aromatic herbaceous annual plant, one of the oldest authenticated and most important herbs that have been used since ancient times in traditional medicine. It is one of the most described plant species with proven antifungal, antimicrobial, anti-aging, as well as anticancer properties, which have been confirmed by epidemiological data from human clinical studies [71]. This specie and its active components have been also reported to reduce the risk of diabetes and cardiovascular diseases [72,73]. *A. sativum* antibiofilm properties against oral cavity yeast were studied by Fahim et al. [74] who demonstrated that, for a concentration of 8.00 µg·mL\(^{-1}\), *A. sativum* L. essential oil presented > 99.9% of growth reduction on biofilm of *C. albicans* ATCC 14053. The ability of this essential oil to inhibit biofilm formation seems to be correlated with its phenolic profile, with allicin, alliin and ajoene being the major compounds found in it [75].

Essential oils from some plants have shown high antifungal and/or antibiofilm activity against *Candida* species. An example of this are the species of *Cinnamomum cassia* (L.) J. Presl, *Cinnamomum zeylanicum* Blume, *Cymbopogon citratus* (DC.) Stapf, *Cymbopogon nardus* L. Rendle, and *Cymbopogon winterianus* Jowitt. *C. cassia* (L.) J.Presl (Lauraceae), also known as “Chinese cinnamon,” is a well-known aromatic plant that has been widely cultivated and utilized to treat diabetes, ovarian cysts, stomach spasms, kidney disorders, high blood pressure, and menstrual disorders [76], and presents antimicrobial, antioxidant and antifungal properties [77]. *C. zeylanicum* Blume (Lauraceae) is an ever-green perennial plant that is used as a culinary herb [78]. This species presents several pharmacological properties such as antimicrobial, antioxidant, antifungal, and anticancer [79]. When it comes to oral health, a study performed by Almeida et al. [80] demonstrated that *C. cassia* essential oil, at a concentration of 1.00 mg·mL\(^{-1}\), exerts more than 99.9% reduction in oral biofilm formation caused by *C. albicans* ATCC 90028, while *C. zeylanicum*, at a concentration of 1.6 µg·mL\(^{-1}\), leads to more than 99.75% reduction in oral biofilm formation caused by *C. albicans* ATCC 10231. The high percentage of biofilm reduction shown by these two plants is attributed to the major phytocompound found in both species, the cinnamaldehyde. Cinnamaldehyde is a phenylpropanoid that may act on the cell membrane, likely binding to enzymes involved in the formation of the cytoplasmic membrane in fungal cells [81].

*C. citratus* (DC.) Stapf (Poaceae), commonly known as lemongrass, is an aromatic plant widely distributed around the world. It is used as a food flavouring, and is commonly consumed in teas and soups, but it may also be served with poultry, fish, beef, and seafood. Lemongrass essential oil exhibits a number of biological activities, including antioxidant [82], anti-inflammatory [83], antimicrobial [84], antifungal, and antibiofilm properties [85]. Almeida et al. [80] used the essential oil from *C. citratus* as an antifungal agent against *C. albicans* ATCC 10231 biofilms, and reported that, at the concentration of 6.4 µg·mL\(^{-1}\), this essential oil was able to reduce the number of viable cells present in the
biofilm by 99.79%. In this case, citral and neral were two of the main compounds found, which are known to hold antifungal properties [86,87].

*C. nardus* L. (Poaceae), popularly known as citronella, is a grass cultivated in subtropical and tropical regions of Asia, Africa, and America, including Brazil [88]. The essential oil extracted from its leaves is commonly used in perfumes, the production of cosmetics, and as an insect repellent. Several studies have demonstrated the antiviral [89], antibacterial [90], and antifungal activities [91] of this oil. *C. winterianus* Jowitt (Poaceae) is an important aromatic plant cultivated in India and Brazil. In folk medicine, it is used for the treatment of anxiety, as a sedative, and for pain disorders [92]. Some studies demonstrated that the plant has anticonvulsant effects [93], anti-larvicidal effects against *Aedes aegypti* [94], and antibacterial and antifungal effects, including anti-*Candida* action [95]. The essential oils extracted from *C. nardus* L. and *C. winterianus* Jowitt species showed, in different studies, to be highly effective in combating *C. albicans* oral biofilms. *C. nardus* showed, at a concentration of 32.0 µg·mL⁻¹, an adherence inhibition of *C. albicans* ATCC 76645 higher than 99.0%, [68] and the application of *C. winterianus* essential oil, at a concentration of 1.00 mg·mL⁻¹, led to a reduction of *C. albicans* ATCC 90028 oral biofilm formation by more than 99.0%. In both species, the authors attributed the antibiofilm potential to the main compound identified in these species, namely citronellal. Citronellal is known to affect *C. albicans* cell growth by interfering with cell-cycle progression through the arrest of cells in S phase and affecting membrane integrity [96].

*Solidago virgaurea* L. (Asteraceae), commonly known as goldenrod, is a medicinal plant that is common throughout the world. In the literature, this plant is described as possessing a variety of medicinal properties such as antioxidant, anti-inflammatory, analgesic, spasmyloytic, antihypertensive, antibacterial, antifungal and antitumor, among others [97]. Chevalier et al. [98] evaluated the effect of the extracts from two *S. virgaurea* subspecies, *S. virgaurea* subsp. *alpestris* and *S. virgaurea* subsp. *virgaurea*, on *C. albicans* oral biofilm growth. The results obtained showed that, at an extract concentration of 250 µg·mL⁻¹, *S. virgaurea* subsp. *alpestris* inhibition of oral biofilms from *C. albicans* IM003 was higher than 99.5%, and that *S. virgaurea* subsp. *virgaurea* inhibited the oral biofilm formation by *C. albicans* IM001 by more than 99.2%. Regarding the chemical composition of this plant, the compounds usually found in *S. virgaurea* are saponins, which have been attributed to the ability to inhibit the transition from yeast to hyphal growth [98]. This attribution seems reasonable considering the inherent surfactant properties of saponins, as well as their iron chelator qualities, iron being necessary for the growth and development of *Candida* spp. [99].
Table 1. Medicinal plants with antimicrobial/antibiofilm activity against oral *Candida* spp. and the respective bioactive compounds present in their extracts.

| Plant Name                  | Plant Extract                           | Compound                                      | Microorganism                  | Results                                                                 | References |
|-----------------------------|-----------------------------------------|-----------------------------------------------|---------------------------------|-------------------------------------------------------------------------|-----------|
| *Allium sativum* L.         | Essential oil (bulbs)                   | Allicin, alliiin, ajoene [75]                 | *C. albicans* ATCC 14053        | MIC 8.0 µg·mL⁻¹, IZD 19.0 mm (50.0 µg·mL⁻¹), >99.9% reduction 8.00 µg·mL⁻¹ | [74]      |
| *Aloysia gratissima* (Aff & Hook) Tronc. | Essential oil (leaves)                  | (E)-pinocamphone, β-pinene, guaiol Piperitone, camphor, ethyl cinnamate, chrysanthenone | *C. albicans* CBS 562           | MIC 0.015 mg·mL⁻¹, MFC 0.062 mg·mL⁻¹, 12.3% inhibition 1.00 mg·mL⁻¹ | [64]      |
| *Artemisia judaica* L.      | Essential oil (aerial plant parts)       | Piperitone, camphor, ethyl cinnamate, chrysanthenone | *C. albicans* ATCC 10231        | MIC 1.25 µg·mL⁻¹, 50.0% reduction 2.5 µg·mL⁻¹                          | [100]     |
| *Bracea javanica* (L.) Merr. | Aqueous extract (seeds)                  | Quassinoids, alkaloids,                        | *C. albicans* ATCC 14053        | -                                                                      |           |
|                             |                                        |                                               | *C. dubliniensis* ATCC MYA-2975  | 94.5% CSH reduction 79.7% adherence reduction 90.4% CSH reduction    | [101]     |
|                             |                                        |                                               | *C. glabrata* ATCC 90030         | 27.9% adherence reduction 84.8% CSH reduction 76.8% adherence reduction 97.0% CSH reduction |           |
|                             |                                        |                                               | *C. krusei* ATCC 14243           | 67.6% adherence reduction 91.1% CSH reduction 89.0% adherence reduction 98.8% CSH reduction |           |
|                             |                                        |                                               | *C. lusitaniae* ATCC 64125       | 49.0% adherence reduction 88.4% CSH reduction 89.9% adherence reduction |           |
|                             |                                        |                                               | *C. parapsilosis* ATCC 22019     | 50.0% reduction 2.5 µg·mL⁻¹                                           |           |
|                             |                                        |                                               | *C. tropicalis* ATCC 13803       | 99% inhibition 6.25 mg·mL⁻¹                                           |           |
| *Cassia spectabilis* DC.    | Methanol extract (leaves)                | (+)-spectaline; (−)-iso-6-cassine [102]       | *C. albicans* 1 (CI)            | MIC 6.25 mg·mL⁻¹, IZD 20 mm (100 mg·mL⁻¹), 97% inhibition 6.25 mg·mL⁻¹ | [103]     |
|                             |                                        |                                               | *C. albicans* 2 (CI)            | IZD 6.25 mg·mL⁻¹                                                      |           |
|                             |                                        |                                               | *C. albicans* 3 (CI)            | IZD 6.25 mg·mL⁻¹                                                      |           |
| *Chenopodium ambrosioides* L. | Aqueous extract (leaves)                 | Kaempferol, quercetin Cinnamaldehyde, benzyl benzoate, α-pinene | *C. albicans* ATCC 90028        | MIC 0.250 mg·mL⁻¹, MFC 0.250 mg·mL⁻¹, >99.0% reduction 1.25 mg·mL⁻¹ | [104]     |
| *Cinnamomum cassia* L. J.Presl | Essential oil (leaves, bark, stalk)      | Cinnamaldehyde, benzyl benzoate, α-pinene   | *C. albicans* ATCC 90028        | MFC 65.5 µg·mL⁻¹                                                      |           |
|                             |                                        |                                               | *C. albicans* ATCC MYA-2876      | >99.9% reduction 1.00 mg·mL⁻¹                                          |           |
| *Cinnamomum verum* J.Presl  | Essential oil (leaves)                   | Eugenol, benzyl benzoate, trans-caryophyllene, acetyl eugenol, linalool | *C. tropicalis* ATCC 750        | MIC 1.0 mg·mL⁻¹                                                      |           |
|                             |                                        |                                               | *C. dubliniensis* ATCC MYA-646   | 50% reduction 0.15 mg·mL⁻¹, 50% inhibition 1.0 mg·mL⁻¹, 50% reduction 0.35 mg·mL⁻¹ | [105]     |
| Plant Name                          | Plant Extract          | Compound                                                                 | Microorganism       | Results                | References |
|------------------------------------|------------------------|---------------------------------------------------------------------------|---------------------|------------------------|------------|
| *Cinnamomum zeylanicum* Blume      | Essential oil (leaves) | Cinnamaldehyde, cinnamyl acetate, cinnamyl benzoate [79]                  | *C. albicans* ATCC 10231 | MIC 0.1 μg·mL⁻¹         | [106]      |
|                                    |                        |                                                                           |                     | MFC 0.4 μg·mL⁻¹         |            |
|                                    |                        |                                                                           |                     | IZD 42.5 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           |                     |                        |            |
|                                    |                        | Decanal, trans-2-decenal, 2-decen-1-ol, cyclodecane, cis-2-dodecenal      | *C. albicans* CBS 562 | MIC 15.6 μg·mL⁻¹        | [107]      |
|                                    |                        |                                                                           |                     | MFC 31.2 μg·mL⁻¹        |            |
|                                    |                        |                                                                           |                     | IZD 15.0 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           | *C. tropicalis* CBS 94 | MIC 15.6 μg·mL⁻¹        | [107]      |
|                                    |                        |                                                                           |                     | MFC 31.2 μg·mL⁻¹        |            |
|                                    |                        |                                                                           |                     | IZD 15.0 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           | *C. krusei* CBS 573  | MIC 31.2 μg·mL⁻¹        | [107]      |
|                                    |                        |                                                                           |                     | MFC 62.5 μg·mL⁻¹        |            |
|                                    |                        |                                                                           | *C. dubliniensis* CBS 7987 | MIC 31.2 μg·mL⁻¹        |            |
|                                    |                        |                                                                           |                     | MFC 62.5 μg·mL⁻¹        |            |
|                                    |                        |                                                                           | *C. rugosa* CBS 12   | MIC 15.6 μg·mL⁻¹        | [107]      |
|                                    |                        |                                                                           |                     | MFC 31.2 μg·mL⁻¹        |            |
|                                    |                        |                                                                           | *C. albicans* ATCC 10231 | MIC >99.9% inhibition |            |
|                                    |                        |                                                                           |                     | IZD 9.6 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           | *C. albicans* CBS 18804 | MIC >99.9% inhibition | [112]     |
|                                    |                        |                                                                           |                     | IZD 9.6 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           | *C. albicans* CBS 76645 | MIC >99.0% inhibition | [113]     |
|                                    |                        |                                                                           |                     | IZD 9.6 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           | *C. albicans* ATCC 90028 | MIC >99.0% inhibition | [80]       |
|                                    |                        |                                                                           |                     | IZD 9.6 mm (50 μg·mL⁻¹) |            |
|                                    |                        |                                                                           | *C. albicans* CBS 562 | MIC 0.125 mg·mL⁻¹       | [112]     |
|                                    |                        |                                                                           |                     | IZD 0.125 mg·mL⁻¹       |            |
|                                    |                        |                                                                           | *C. albicans* ATCC 14053 | MIC 0.219 mg·mL⁻¹       | [115]     |
|                                    |                        |                                                                           |                     | IZD 0.219 mg·mL⁻¹       |            |
|                                    |                        |                                                                           | *C. tropicalis* ATCC 66029 | MIC 0.219 mg·mL⁻¹       |            |
|                                    |                        |                                                                           |                     | IZD 0.219 mg·mL⁻¹       |            |
|                                    |                        |                                                                           | *C. glabrata* ATCC 66032 | MIC 0.219 mg·mL⁻¹       | [115]     |
|                                    |                        |                                                                           |                     | IZD 0.219 mg·mL⁻¹       |            |
|                                    |                        |                                                                           | *C. albicans* CAD1   | MIC >2.17 mg·mL⁻¹       | [116]     |
|                                    |                        |                                                                           |                     | IZD >96 mg·mL⁻¹         |            |
|                                    |                        |                                                                           | *Lippia sidoides* Cham. | MIC 0.250 mg·mL⁻¹       | [117]     |
|                                    |                        |                                                                           |                     | IZD 0.250 mg·mL⁻¹       |            |
|                                    |                        |                                                                           | *C. albicans* CBS 562 | MIC 0.500 mg·mL⁻¹       |            |
|                                    |                        |                                                                           |                     | IZD 0.500 mg·mL⁻¹       |            |
|                                    |                        |                                                                           | *Melaleuca alternifolia* (Maiden & Bettle) Cheel | MIC 1.95 mg·mL⁻¹       | [118]     |
|                                    |                        |                                                                           |                     | IZD 1.95 mg·mL⁻¹       |            |
| Plant Name            | Plant Extract                  | Compound                                                                                      | Microorganism       | Antimicrobial Activity | Antibiofilm Activity | References |
|-----------------------|--------------------------------|-----------------------------------------------------------------------------------------------|---------------------|------------------------|----------------------|------------|
| **Antimicrobial Activity** |                               |                                                                                              |                     |                        |                      |            |
|                       |                                | C. albicans ATCC 10231                                                                      | MIC 3.40 mg·mL⁻¹    | 131% adherence reduction | 76.0% adherence reduction | [119]      |
|                       |                                | C. albicans SC5314                                                                          | MIC 0.84 mg·mL⁻¹    |                        |                      |            |
| *Mikania glomerata* Spreng | Essential oil (leaves)          | Germacrene D, α-caryophyllene, bicyclogermacrene                                              | C. albicans CBS 562 | MIC 0.250 mg·mL⁻¹      | 22.7% inhibition      | [117]      |
|                       |                                |                                                                                                | C. albicans ATCC 14053 | MFC 0.250 mg·mL⁻¹     |                      |            |
|                       |                                |                                                                                                | C. dublinensis ATCC MYA-2975 | -               |                      |            |
|                       |                                |                                                                                                | C. glabrata ATCC 90030 | -                |                      |            |
|                       |                                |                                                                                                | C. krusei ATCC 14243 | -                |                      |            |
|                       |                                |                                                                                                | C. lusitaniae ATCC 64125 | -            |                      |            |
|                       |                                |                                                                                                | C. parapsilosis ATCC 22019 | -       |                      |            |
|                       |                                |                                                                                                | C. tropicalis ATCC 13803 | -              |                      |            |
| *Piper betle* L.     | Aqueous extract (leaves)        | Hydroxycavicol, cinnamoyl derivatives, luteolin, apigenin [120]                              | C. albicans F81 (CI)| MIC 0.78 mg·mL⁻¹      | 99.9% reduction      | [101]      |
|                       |                                |                                                                                                | C. albicans F81 (CI)| MMC 3.13 mg·mL⁻¹      |                      |            |
|                       |                                |                                                                                                | C. albicans F94 (CI)| 300 μg·mL⁻¹           | 91.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F94 (CI)| 400 μg·mL⁻¹           | 91.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F87 (CI)| 200 μg·mL⁻¹           | 90.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F87 (CI)| 300 μg·mL⁻¹           | 80.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F87 (CI)| 400 μg·mL⁻¹           | 86.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F49 (CI)| 300 μg·mL⁻¹           | 76.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F49 (CI)| 400 μg·mL⁻¹           | 92.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F82 (CI)| 400 μg·mL⁻¹           | 92.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F82 (CI)| 600 μg·mL⁻¹           | 89.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F82 (CI)| 600 μg·mL⁻¹           | 89.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F95 (CI)| 400 μg·mL⁻¹           | 81.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F95 (CI)| 600 μg·mL⁻¹           | 81.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F92 (CI)| 300 μg·mL⁻¹           | 90.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F92 (CI)| 400 μg·mL⁻¹           | 90.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F60 (CI)| 400 μg·mL⁻¹           | 80.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F60 (CI)| 600 μg·mL⁻¹           | 80.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F86 (CI)| 200 μg·mL⁻¹           | 87.0% reduction      |            |
|                       |                                |                                                                                                | C. albicans F86 (CI)| 300 μg·mL⁻¹           | 87.0% reduction      |            |

**References**

[119] [117] [101] [122] [123]
Table 1. Cont.

| Plant Name                        | Plant Extract                  | Compound                                | Microorganism | Results | References |
|-----------------------------------|--------------------------------|-----------------------------------------|---------------|---------|------------|
| Schinus terebinthifolia Raddi.    | Methanol extract (leaves)      | Phenolic compounds, anthraquinones, terpenoids, alkaloids | C. albicans ATCC 10231 | 47.0% inhibition | 0.007 mg·mL⁻¹ | [109] |
| Solidago virgaurea subsp. alpestris Waldst. & Kit. ex Willd. | Aqueous extract (aerial plant parts) | Saponins                               | C. albicans ATCC 10231 | 47.0% inhibition | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM001 (CI)                | 95.9% inhibition | 0.750 mg·mL⁻¹ | [98] |
|  |                                |                                          | C. albicans IM003 (CI)                | 96.0% inhibition | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM007 (CI)                | 99.5% inhibition | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans ATCC 10231                | 92.4% reduction | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM001 (CI)                | 96.0% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM003 (CI)                | 76.3% reduction | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM007 (CI)                | 75.1% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans ATCC 10231                | 98.4% reduction | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM001 (CI)                | 77.9% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM003 (CI)                | 92.9% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM007 (CI)                | 91.9% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans ATCC 10231                | 99.2% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM001 (CI)                | 99.3% reduction | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM003 (CI)                | 91.9% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM007 (CI)                | 97.3% reduction | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans ATCC 10231                | 96.5% reduction | 0.250 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM001 (CI)                | 96.5% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM003 (CI)                | 90.9% reduction | 0.750 mg·mL⁻¹ |
|  |                                |                                          | C. albicans IM007 (CI)                | 90.9% reduction | 0.750 mg·mL⁻¹ |
| Terminalia catappa L.            | Ethanol extract (leaves)         | Caffeic acid, quercitrin, kaempferol, gallic acid, chlorogenic acid, isoquercitrin [124] | C. albicans ATCC 90028 | MIC 6.25 mg·mL⁻¹ | >98.0% reduction |
|  | n-butanol fraction from ethanol extract (leaves) | | C. albicans ATCC 90028 | MFC 12.5 mg·mL⁻¹ | 62.5 mg·mL⁻¹ | [125] |
|  |                                |                                          | C. albicans ATCC 90028                | >99.5% reduction | 2.50 mg·mL⁻¹ | [126] |
|  |                                |                                          | C. glabrata ATCC 2001                 | >99.0% reduction | 2.50 mg·mL⁻¹ |
Table 1. Cont.

| Plant Name          | Plant Extract                          | Compound                               | Microorganism          | Results                        | References |
|---------------------|----------------------------------------|----------------------------------------|-------------------------|-------------------------------|------------|
| Trachyspermum ammi  | Aromatic water (aerial plant parts)    | Thymol, carvacrol, carvotanacetone     | C. albicans CBS1905    | 95.2% inhibition 0.5% (v/v)   | [127]      |
| (L.) Sprague        | Aqueous extract (whole plant)          |                                        |                         |                               |            |
| Zataria multiflora  | Ethanolic extract (whole plant)        | Thymol, hydroxyl benzoic acid, and cymene | C. albicans PTCC-5027 | 87% reduction 25 mg·mL⁻¹     | [129]      |
| Boiss.              |                                        |                                        |                         |                               |            |

1 IZD: Inhibition zone diameter; MIC: Minimum inhibitory concentration; MFC: minimum fungicidal concentration; MMC: minimum microbiocidal concentration; MBIC: Minimum biofilm inhibitory concentration; MBEC: Minimum biofilm eradication concentration; NA: No activity; -: Not tested; CI: clinical isolate; CSH: Cell surface hydrophobicity.
5. Conclusions

Medicinal plants are still an untapped source of powerful natural products with great antimicrobial and/or antibiofilm potential, especially in a backdrop of increasing antibiotic resistance. This review aimed to identify medicinal plant products, such as essential oils and plant extracts for the treatment of common oral Candida infections, mainly caused by the formation of fungal biofilms. Although extracts from many medicinal plants have shown exciting results in controlling these biofilms, the most promising plant extracts were from A. sativum L., which reduced C. albicans ATCC 14053 oral biofilm formation by more than 99.9% at a concentration of 8.0 µg mL⁻¹; the essential oil extracted from C. zeylanicum Blume, which showed, at a concentration of 1.6 µg mL⁻¹, a reduction in oral biofilm formation by C. albicans ATCC 10231 higher than 99.75%; and the essential oil obtained from C. citratus (DC) Stapf, which exhibited a reduction in the oral biofilm formation by C. albicans ATCC 10231 greater than 99.79% at 6.4 µg mL⁻¹. Interestingly, in all of these medicinal plant species, organic compounds with proven bioactive properties such as antimicrobial and antibiofilm effects were identified.

The use of essential oils and plant extracts from medicinal plants can be a great alternative to conventional antimicrobials in the treatment of fungal infections in the oral cavity since they have low levels of cytotoxicity and, to date and to our knowledge, do not induce resistance in microorganisms. However, research on the use of medicinal plants in the treatment of oral ailments remains an extremely interesting and unexplored topic, mainly due to the wide variety of plants whose phytochemical profiles are still unknown, and which will likely show good antimicrobial and antibiofilm properties.

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