Review

Plant Preparations and Compounds with Activities against Biofilms Formed by Candida spp.

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Abstract: Fungi from the genus Candida are very important human and animal pathogens. Many strains can produce biofilms, which inhibit the activity of antifungal drugs and increase the tolerance or resistance to them as well. Clinically, this process leads to persistent infections and increased mortality. Today, many Candida species are resistant to drugs, including C. auris, which is a multiresistant pathogen. Natural compounds may potentially be used to combat multiresistant and biofilm-forming strains. The aim of this review was to present plant-derived preparations and compounds that inhibit Candida biofilm formation by at least 50%. A total of 29 essential oils and 16 plant extracts demonstrate activity against Candida biofilms, with the following families predominating: Lamiaceae, Myrtaceae, Asteraceae, Fabaceae, and Apiaceae. Lavandula dentata (0.045–0.07 mg/L), Satureja macrocephon (0.06–8 mg/L), and Ziziphora tenuior (2.5 mg/L) have the best antifungal activity. High efficacy has also been observed with Artemisia judaica, Lawsonia inermis, and Thymus vulgaris. Moreover, 69 plant compounds demonstrate activity against Candida biofilms. Activity in concentrations below 16 mg/L was observed with phenolic compounds (thymol, pterostilbene, and eugenol), sesquiterpene derivatives (warburganal, polygodial, and ivalin), chalconoid (lichochalcone A), steroidal saponin (dioscin), flavonoid (baicalein), alkaloids (waltheriones), macrocyclic bisbibenzyl (riccardin D), and cannabinoid (cannabidiol). The above compounds act on biofilm formation and/or mature biofilms. In summary, plant preparations and compounds exhibit anti-biofilm activity against Candida. Given this, they may be a promising alternative to antifungal drugs.

Keywords: Candida; biofilm; treatment; antifungals; natural compounds; essential oil; extract; minimal inhibitory concentration (MIC)

1. Introduction

The genus Candida contains about 150 species; however, most are environmental organisms. The most medically important is Candida albicans, which accounts for about 80% of infections. C. albicans causes more than 400,000 cases of bloodstream life-threatening infections annually, with a mortality rate of about 42% [1]. Candida non-albicans species that
are mainly responsible for infections are \textit{C. glabrata}, \textit{C. parapsilosis}, \textit{C. tropicalis}, \textit{C. krusei}, and \textit{C. dubliniensis} [2]. Less frequently identified are \textit{C. guilliermondii}, \textit{C. lusitaniae}, \textit{C. rugosa}, \textit{C. orthopsilosis}, \textit{C. metapsilosis}, \textit{C. famata}, \textit{C. inconspicua}, and \textit{C. kefyr} [3].

\textit{C. albicans} is a member of the commensal microflora. It colonizes the oral mucosal surface of 30–50% of healthy people. The rate of carriage increases with age and in persons with dental prostheses up to 60% [4–6]. Opportunistic infection caused by \textit{Candida} species is termed candidiasis. At least one episode of vulvovaginal candidiasis (or thrush) concerns 50 to 75% of women of childbearing age [7]. Candidiasis can also affect the oral cavity, penis, skin, nails, cornea, and other parts of the body. In immunocompromised persons, untreated candidiasis poses the risk of systemic infection and fungemia [5,8]. \textit{Candida} can be an important etiological factor in the infection of chronic wounds that are difficult to treat; this is mainly related to the production of biofilm [9].

Treatment of candidiasis depends on the infection site and the patient’s condition. According to guidelines, vulvovaginal candidiasis should be treated with oral or topical fluconazole; however, regarding \textit{C. glabrata} infection, topical boric acid, nystatin, or fluocytosine is suggested. In oropharyngeal candidiasis, the treatment options include clotrimazole, miconazole, or nystatin, and in severe disease, fluconazole or voriconazole. In candidemia and invasive candidiasis, the drugs of choice are echinocandins (caspofungin, micafungin, anidulafungin), fluconazole, or voriconazole; in resistant strains, amphotericin B is used. In selected cases of candidemia caused by \textit{C. krusei}, voriconazole is recommended [10–12]. More details can be found in the Guidelines of the Infectious Diseases Society of America [12] and the European Society of Clinical Microbiology and Infectious Diseases [11]. Increasingly, \textit{Candida} species are becoming resistant to drugs. Marak and Dhanashree [13] tested the resistance of 90 \textit{Candida} strains isolated from different clinical samples, such as pus, urine, blood, and body fluid. Their study revealed that about 41% of \textit{C. albicans} strains are resistant to fluconazole and voriconazole. Simultaneously, about 41% of \textit{C. tropicalis} strains are resistant to voriconazole and about 36% of strains to fluconazole. In strains of \textit{C. krusei}, about 23% are resistant to fluconazole and about 18% to voriconazole. Rudramurthy et al. [14] studied resistance in \textit{C. auris}, which is considered a multiresistant pathogen. Among 74 strains obtained from patients with candidemia, over 90% of strains were resistant to fluconazole and about 73% to voriconazole. Virulence factors of \textit{Candida} species include the secretion of hydrolases, the transition of yeast to hyphae, phenotypic switching, and biofilm formation [15,16]. All microorganisms in biofilm form are more resistant to antimicrobial and host factors, which leads to difficulties in eradication [17]. It has also been shown that resistance to drugs increases significantly in the case of \textit{Candida} biofilm occurrence. Biofilm prevents the spread of antifungals; moreover, fluconazole is bound by the biofilm matrix [18]. The formation of a \textit{Candida} biofilm during infection increases mortality, length of hospital stay, and cost of antifungal therapy [19].

Due to the above, new antifungal drugs are sought that could effectively combat not only planktonic fungi but also fungal biofilms. The natural compounds offer promise, with many acting on \textit{Candida} species or biofilms in vitro [20].

The aim of this review was to present plant-derived natural compounds that have an effect against biofilms formed by \textit{Candida} species.

2. Materials and Methods

In this review, publications available in PubMed and Scopus databases and through the Google search engine were taken into account. The following keywords and their combinations were used: “antifungal,” “\textit{Candida},” “anti-biofilm,” “biofilm,” “plant,” “compound,” “extract,” and “essential oil.” The principal inclusion criterion was the inhibition of biofilm formation by at least 50%. We focused on biofilm inhibition assays, in which the time of culture allowed for \textit{Candida} biofilm maturation was at least 24 hours. Articles from the year 2000 to the present were taken into account. All articles published in predatory journals were rejected.
3. Results and Discussion

3.1. Plant Preparations That Display Activity against Candida Biofilms

The present review includes 60 articles in which Candida biofilm formation was inhibited by at least 50%. It has been shown that preparations from 34 plants demonstrate activity against Candida biofilms. Among them were 29 essential oils and 16 extracts. The plants from the following families dominated: Lamiaceae (6 species in 5 genera), Myrtaceae (5 species in 4 genera), Asteraceae (4 species in 4 genera), Fabaceae (3 species in 3 genera), and Apiaceae (4 species in 2 genera).

Plants from the Lamiaceae family had the best antifungal activity, including Lavandula dentata (0.045–0.07 mg/L) [21], Satureja macrospiron (0.06–8 mg/L) [22], and Zizia phora tenuior (2.5 mg/L) [23]. Artemisia judaica (2.5–12.5 mg/L) from the Asteraceae family [24], Lawsonia inermis (2.5 mg/L) from the Lythraceae family [25], and Thymus vulgaris (12.5 mg/L) from the Lamiaceae family [26] likewise exhibited good antifungal activity (Table 1). All preparations were essential oils, with the exception of Lawsonia inermis, which was an extract. Most of the plant preparations presented in Table 1 acted on biofilm formation and/or mature biofilms.

**Table 1. Antifungal (MICs) and anti-biofilm (inhibition >50%) activity of plant preparations (essential oils or extracts).**

| Name of Plant (Family) | Main Compounds Presented in the Reference (EO: Essential Oil) | Targeted Species of Candida | MICs (mg/L; mL/L) | Inhibition of Biofilm Formation by at Least 50% (mg/L; mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|------------------------|---------------------------------------------------------------|-----------------------------|------------------|-------------------------------------------------------------|--------------------------------------------------------|------|
| Acorus calamus var. angustatus Besser = A. tatarinowii Schott (Acoraceae) | EO: asaraldehyde, 1-(2,4,5-trimethoxyphenyl)-1,2-propanediol, α-asarone, β-asarone, γ-asarone, acotatarone C | C. albicans | 51.2 | 50–200 | Mature biofilm; crystal violet | [27] |
| Allium sativum L. (Amaryllidaceae) | Extract: allin | C. albicans | 400 | 60 | Biofilm formation | [28] |
| Aloysia gratissima (All & Hook) Tr (Verbenaceae) | EO: E-pipercamphone (16.5%), β-pinene (12.01%), guaoli (8.53%), E-pipercarveol acetate (8.19%) | C. albicans | 15 | 50 | Biofilm formation; crystal violet | [29] |
| Artemisia judaica L. (Asteraceae) | EO: piperitone (30.4%), camphor (16.1%), ethyl cinnamate (11.0%), chrysanthone (6.7%) | C. albicans | 1.25 | 2.5 | Mature biofilm; XTT | [24] |
| Buchea totentosa Eichler (Comrertaceae) | Extract: gallic acid, kaemoperol, epicatechin, elagic acid, vitexin, and corilagin | C. albicans | 625 | 312.5 | Biofilm formation and mature biofilm, culture | [30] |
| Chamomilla recutita (L.) Gaertn. (Asteraceae) | EO: E-pinocarveol acetate (8.19%) | C. albicans | 250 | 15.62 | Biofilm formation and mature biofilm; MTT | [31] |
| Cinnamomum verum J. Presl (Lauraceae) | EO: eugenol (77.22%), benzyl benzoate (4.53%), trans-caryophyllene (3.39%), acetyl eugenol (2.75%), linalool 2.11% | C. albicans | 1000 | 150 | Biofilm adhesion; XTT | [32] |
| Citrus limon (L.) Osbeck (Rutaceae) | EO: limonene (53.4%), nerol (11%), geraniol (9%), trans-limonene oxide (7%), nerol (6%) | C. glabrata | 250 | 1000 | Biofilm formation and mature biofilm, XTT | [33] |
| Coriandrum sativum L. (Apiaceae) | EO: 1-decanol (33.91%), E-2-decen-1-ol (23.59%), 2-decanol-1-ol (13.06%), E-2-tetradecen-1-ol (5.46%) | C. albicans | 7 | 250 | Biofilm formation; crystal violet | [29] |
| Copaifera paupera (Herzog) Dwyer (Fabaceae) | Extract: galloylquinic acids, quereotrin, afzelin | C. glabrata | 5.89 | 46.87 | Biofilm formation and mature biofilm, XTT | [34] |
| Copaifera reticulata Ducke (Fabaceae) | Extract: galloylquinic acids, quereotrin, afzelin | C. glabrata | 5.89 | 46.87 | Biofilm formation and mature biofilm, XTT | [34] |
| Copaifera reticulata Ducke (Fabaceae) | EO: decanol (19.09%), trans-2-decanol (17.54%), 2-decan-1-ol (12.33%), cyclohexane (12.15%) | C. albicans | 31.2 | 62.5–250 | Biofilm adhesion; crystal violet | [35] |
### Table 1. Cont.

| Name of Plant (Family) | Main Compounds Presented in the Reference (EO: Essential Oil) | Targeted Species of Candida | MICs (µg/L; mL/L) | Inhibition of Biofilm Formation by at Least 50% (µg/mL; mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|-----------------------|---------------------------------------------------------------|-----------------------------|------------------|-------------------------------------------------------------|--------------------------------------------------------|------|
| Croton elateria (L.) W.Wright (Euphorbiaceae) | EO: α-pinene (29.3%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 4000 | 5–500 | Biofilm formation; confocal laser microscopy | [36] |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 250 | 1000 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 31.25 | 250 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 62.5 | 62.5 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 31.25 | 125 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 62.5 | 500 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 250 | 500 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 180-360 | 22.5–180 | Biofilm formation; XTT | [37] |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 16,800 | 800 | Biofilm formation; XTT | [38] |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 1000 | 2500–5000 | Biofilm adhesion; XTT | [39] |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 500–1000 | 5000–10,000 | | |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 219 | 11,250–22,500 | Mature biofilm; scanning electron microscopy | [40] |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 219 | 11,250–22,500 | Mature biofilm; scanning electron microscopy | [41] |
| Capparis spinosa L. | EO: α-pinene (29.4%), β-pinene (19.3%), camphene (10.31%), 1,8-cineole (9.68%) | C. albicans | 885 | 11,250–22,500 | | |
| Capparis spinosa L. | EO: no composition | C. albicans | 8400 | 500 | Biofilm formation; XTT | [38] |
| Capparis spinosa L. | EO: no composition | C. albicans | 15.62–31.25 | 156 | Mature biofilm; scanning electron microscopy | [42] |
| Capparis spinosa L. | EO: no composition | C. albicans | 15.62–250 | 156 | Mature biofilm; scanning electron microscopy | [42] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 6000 | 10–500 | Biofilm formation; confocal laser microscopy | [36] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 1250 | 6300 | Biofilm formation; confocal laser microscopy | [43] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 1250 | 6300 | Biofilm formation; confocal laser microscopy | [43] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 5000 | 10,000 | Biofilm formation; confocal laser microscopy | [43] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 5000 | 10,000 | Biofilm formation; confocal laser microscopy | [43] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 7500 | 15,000 | Biofilm formation; MTT | [29] |
| Helichrysum italicum (Roth) (Asteraceae) | EO: α-pinene (27.64%), γ-terpinene (22.84%), β-caryophyllene (13.05%), α-longipinene (11.25%) | C. albicans | 7500 | 37,500 | Biofilm formation; MTT | [29] |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 0.15–0.18 | 0.045–0.07 | Mature biofilm; XTT | [37] |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 10 | 2.5–12.5 | Mature biofilm; MTT | [29] |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 10 | 2.5–12.5 | Mature biofilm; MTT | [29] |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 500 | 2000 | | |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 250 | 500 | | |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 500 | 2000 | | |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 250 | 500 | | |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 250 | 500 | | |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 250 | 500 | | |
| Lavandula dentata L. (Lamiaceae) | EO: eucalyptol (42.66%), α-pinene (8.59%), trans-α-bisabolene (6.34%), pinocarveol (6.3%) | C. albicans | 250 | 500 | | |
Antibiofilm activity may vary between plants in the same family. For example, in the Lamiaceae family, essential oil from *Lavandula dentata* acted against *C. albicans* biofilm at concentrations of 0.045–0.07 µg/mL [21], while essential oil from *Satureja hortensis* acted against the same biofilm at concentrations of 400–4800 mg/L [51]. There may also be large differences within the same species, due to various reasons. This may be influenced by, for example, different research methodologies, the use of different strains of fungi, and different chemical compositions depending on the plant variety, country, and season of harvest. A notable example of such a difference is observed with *Mentha piperita*. In studies by Benzaid et al. [44], essential oil of *M. piperita* acted against *Candida* biofilm at a concentration of 10 µL/mL. However, the work of Agarwal et al. [38] showed that the same essential oil was active at 800 µL/mL.

Changes in the content of active substances were described by Gonçalves et al. [56]. They showed that in essential oil from *Mentha cervina* collected in August, the amount of

### Table 1. Cont.

| Name of Plant (Family) | Main Compounds Presented in the Reference (EO: Essential Oil) | Targeted Species of *Candida* | MICs (µg/mL) | Inhibition of Biofilm Formation by at Least 50% (µg/mL) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|------------------------|---------------------------------------------------------------|-------------------------------|--------------|-------------------------------------------------------|------------------------------------------------------|------|
| *Myrtus communis* L. (Myrtaceae) | EO: α-pinene (39.8%), 1,8-cineole (24.8%), limonene (10.7%), linalool (6.4%) | *C. albicans* | 1250–10,000 | None or 1250 | No data; no data | [45] |
| *Ononis spinosa* L. (Fabaceae) | Extract: kaempferol-O-dihexoside, kaempferol-O-hexose-pentoside, kaempferol-O-hexose, quercetin-O-hexose-pentoside, acetylquercetin-O-hexose | *C. albicans* | 620 | 10,000 | Mature biofilm; luminescence | [46] |
| *Pelargonium graveolens* (Miq.) C. P. | EO: neralidios | *C. albicans* | 125 | 4000–8000 | Mature biofilm; XTT | [47] |
| *Piper longum* L. (Piperaceae) | EO: neralidios | *C. albicans* | 125 | 4000–8000 | Mature biofilm; XTT | [48] |
| *Portulaca oleracea* L. (Portulacaceae) | Extract: no composition | *C. albicans* | 10 | 12.5 | Mature biofilm; MTT | [25] |
| *Punica granatum* L. (Lythraceae) | Extract: ellagic acid | *C. albicans* | 1000 | 100–750 | Biofilm formation and mature biofilm; crystal violet | [49] |
| *Santolina impresta* Hoffmanns. & Link (Asteraceae) | EO: β-pinene (22.5%), 1,8-cineole (10.0%), limonene (9.1%), camphor (8.1%), β-phellandrene (8.0%) | *C. albicans* | 540 | 70–1050 | Biofilm formation; XTT | [50] |
| *Satureja hortensis* L. (Lamiaceae) | EO: thymol (45.9%), gamma-terpinen (16.71%), carvacrol (12.81%), p-phenylen (9.61%) | *C. albicans* | 200–400 | 400–4800 | Biofilm adhesion, formation, and mature biofilm; MTT | [51] |
| *Satureja macrophylla* (Coms.) = *Mircromeria macrophylla* Coms. (Lamiaceae) | EO: linalool (28.46%), borneol (16.22%), terpinen-4-ol (14.58%), cis-sabinene hydrate (12.96%) | *C. albicans* | 0.06–4 | 0.06–8 | Biofilm formation; XTT | [22] |
| *Syzygium aromaticum* (L.) Merr. & L.M.Perry = *Eugenia Caryophyllus* (Sparr.) Bullf. & S.G. Harrison (Myrtaceae) | EO: no composition | *C. albicans* | 100–200 | 50 | Biofilm formation; XTT | [37] |
| *Thymus vulgaris* L. (Lamiaceae) | EO: thymol (54.73%), carvacrol (12.42%), terpinol (4.0%), neral acetate (2.86%), fenol (0.5%) | *C. albicans* | 1.56–25 | 12.5 | Biofilm formation; absorbance, crystal violet, and scanning electron microscopy | [26] |
| *Warburgia agrodendron* Sprague (Cameliaceae) | Extract: ugarionial A, warbuganal, polygodial, alpha-linollenic acid ALA | *C. albicans* | Lack of data | 1000 | Biofilm formation and mature biofilm; XTT and confocal laser microscopy | [52] |
| *Ziziphus mauritiana* L. (Lamiaceae) | EO: pulegone (46.8%), p-metho-3-en-5-ol (12.5%), isomenthol (6.6%), 1-hydroxymenthol (6.2%), isomenthop (4.7%) | *C. albicans* | 1.25 | 2.5 | Mature biofilm; XTT | [23] |
| *Zuccagnia punctata* L. (Fabaceae) | Extract: no composition | *C. albicans* | 400 | 100 | Biofilm formation and mature biofilm; XTT and crystal violet | [53] |

Legend: MIC—minimal inhibitory concentration; XTT—reduction assay of 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[carboxylphenylamino]-2H-tetrazolium hydroxide; MTT—reduction assay of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide [54,55].
isomenthone was 8.7% and pulegone was 75.1%. However, in essential oil collected in February, the ratio of the two compounds reversed and amounted to 77.0% for isomenthone and 12.9% for pulegone. The method of obtaining the compounds likewise had an influence on their content in the final essential oil. In a study by Čavar et al. [57], the composition of essential oils of *Calamintha glandulosa* differed depending on the extraction method. The level of menthone was 3.3% using aqueous reflux extraction, 4.7% using hydrodistillation, and 8.3% using steam distillation, while the concentration of shisofuran was only 0.1% using hydrodistillation and steam distillation, while aqueous reflux yielded 9.7%.

3.2. Plant Compounds That Display Activity against Candida Biofilm

It has been shown that 69 compounds obtained from plants demonstrate activity against *Candida* biofilms (Table 2). Among these, the most common are monoterpenes (20), followed by sesquiterpene lactones (7) and sesquiterpenes (6). Another big group is also phenolic compounds, including phenols (6), phenolic acids (5), phenolic aldehydes (2), polyphenols (2), and phenolic alcohol (1).

In terms of activity, large differences were found, depending on the authors cited. Eugenol and thymol serve as good examples. Both compounds exhibited excellent activity in some studies (from 12.5 mg/L for eugenol [58] and 1.56 mg/L for thymol [26]), and in other studies, the activity was very poor (up to 80,000 for both [59]). These differences may be related, for example, to a different purity of the compound, a different fungal suspension density, or even to the use of other *Candida* strains with different sensitivities to chemical substances. A number of other factors, such as the type of culture medium, pH of the medium, incubation time, and temperature may likewise influence the antimicrobial activity [20].

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the antifungal clinical breakpoints are between 0.001 mg/L and 16 mg/L [60]. Using EUCAST guidelines in this review, the most active compounds that inhibit (>50%) *Candida* biofilm formation are lichochalcone A (from 0.2 mg/L) [61], thymol (from 3.12 mg/L) [26], dioscin (from 3.9 mg/L) [31], baicalein (from 4 mg/L) [62], warburganal (4.5 mg/L) [52], pterostilbene, waltheriones and riccardin D (both from 8 mg/L) [63–65], polygodial (10.8 mg/L) [52], cannabidiol and eugenol (both from 12.5 mg/L) [58,66], and ivalin (15.4 mg/L) [67]. It is interesting that monoterpenes, which represent the highest percentage of substances listed in Table 2, are not the most active compounds. The two larger groups with the best activity are phenolic compounds (thymol, pterostilbene, and eugenol), and sesquiterpene derivatives (warburganal, polygodial, and ivalin). Single compounds with the highest observed activity belong to chalconoids (lichochalcone A), steroidal saponins (dioscin), flavonoids (baicalein), alkaloids (waltheriones), macrocyclic bisbibenzyls (riccardin D), and cannabinoins (cannabidiol). Most of the compounds presented in Table 2 acted on biofilm formation and/or mature biofilm.

| Active Compound (alkaloid) | Example of Plant Origin | Targeted Fungus | MICs (mg/L, mL/L) | Inhibition of Biofilm Formation by at Least 50% (mg/L, mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|---------------------------|-------------------------|----------------|-----------------|----------------------------------------------------------|----------------------------------------------------------|------|
| Waltheria indica, W. brachypetala | C. albicans | 32 | 16 | Mature biofilm, XTT | [63] |
| C. glabrata | >32 | 16 |
| C. krusei | 16 | 16 |
| C. parapsilosis | 4 | 16 |
| C. tropicalis | >32 | 16 |

| Active Compound (phenolic aldehyde) | Example of Plant Origin | Targeted Fungus | MICs (mg/L, mL/L) | Inhibition of Biofilm Formation by at Least 50% (mg/L, mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|-----------------------------------|-------------------------|----------------|-----------------|----------------------------------------------------------|----------------------------------------------------------|------|
| Pimpinella anisum, Foeniculum vulgare | C. albicans | 500 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [68] |
| Pimpinella anisum | C. albicans | 4000 | 4000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [68] |
| Pimpinella anisum | C. albicans | 31 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [68] |
| Scutellaria baicalensis, S. lateriflora | C. albicans | No data | 4–32 | Biofilm formation, XTT | [62] |
| Active Compound | Example of Plant Origin | Targeted Fungus | MICs (mg/L, mL/L) | Inhibition of Biofilm Formation by at Least 50% (mg/L, mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|-----------------|--------------------------|-----------------|------------------|----------------------------------------------------------|--------------------------------------------------------|------|
| Camphene (monoterpenes) | Croton eluteria, Cinnamomum verum | C. albicans | No data | 500 | Biofilm formation; confocal laser microscopy | [36] |
| | | C. albicans | 1000 | 2000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Campher (bicyclic monoterpenes) | Cinnamomum camphora, Artemisia annua | C. albicans | 125–250 | Not or 62.5–250 | Biofilm formation; crystal violet and absorbance | [70] |
| | | C. glabrata | 175 | Not | | |
| | | C. kruzei | 350 | Not | | |
| | | C. parapsilosis | 125 | Not | | |
| | | C. tropicalis | 175 | 175 | | |
| Cannabidiol (cannabinoid) | Cannabis sativa | C. albicans | No data | 12.5–100 | Biofilm formation; confocal laser microscopy | [66] |
| Carvacrol (phenol) | Thymus serpyllum, Cuminum carvi, Origanum vulgare | C. albicans | 250 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | C. glabrata | 100–20,000 | 300–1250 | Mature biofilm, XTT | [71] |
| | | 1000 | 750–1500 | Biofilm formation; MTT | [72] |
| | C. parapsilosis | 100–20,000 | 300–1250 | Mature biofilm, XTT | [71] |
| | | C. tropicalis | 100–20,000 | 300–1250 | | |
| | Citrus × aurantium, Citrus limon | C. albicans | 1000 | 4000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | C. kruzei | >4000 | 250 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | | | | | |
| | Helichrysum italicum, Capparis spinosa | C. albicans | No data | 100–500 | Biofilm formation; confocal laser microscopy | [36] |
| 1,4-Cineole (monoterpenes) | Rosmarinus officinalis, Thymus vulgaris | C. albicans | >4000 | 4000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | C. glabrata | 4000 | 4000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
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| | | C. tropicalis | 8 | 4 | Mature biofilm, luminescence | [46] |
| | | Eucalyptus globulus, Salvia officinalis, Pinus sylvestris | | | | |
| | 1,8-Cineole/Eucalyptol (monoterpenes) | | | | | |
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| Active Compound | Example of Plant Origin | Targeted Fungus | MICs (mg/L, mL/L) | Inhibition of Biofilm Formation by at Least 50% (mg/L, mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|-----------------|-------------------------|----------------|------------------|-------------------------------------------------------------|--------------------------------------------------------|------|
| 4α,5α-Epoxy-10β,14β,11-epi-muurol-8(9)-ene (sesquiterpene lactone) | Carposium macrophleum | C. albicans | >128 | | Biofilm formation and mature biofilm, XTT | [67] |
| Eugenol (phenol) | Syzygium aromaticum | C. albicans | 50–400 | 12.5–200 | Mature biofilm, XTT | [58] |
| | | | 250 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | | 500 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [68] |
| | | | 1200 | 10,000–30,000 | Mature biofilm, XTT | [69] |
| Farnesol (sesquiterpene) | Tilia sp., Cymbopogon sp. | C. albicans | 1000 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [58] |
| | | | 1000 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Gallic acid (phenolic acid) | Polygonum sp., Buchenavia tomentosa | C. albicans | 5000 | 2500 | Biofilm formation and mature biofilm, culture | [58] |
| Geraniol (monoterpane) | Pelargonium graveolens, Ros sp. | C. albicans | 1000 | 1000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | | 100–20,000 | 300–1250 | Mature biofilm, XTT | [71] |
| | | | No data | 1000–4000 | Mature biofilm, XTT | [47] |
| | | | 100–20,000 | 300–1250 | Mature biofilm, XTT | [71] |
| Guaiaicol (phenol) | Cunicium officinale, Atriplex graveolens | C. albicans | 50 | 1000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [68] |
| Hydroxysuccinicol (phenol) | Piper betle | C. albicans | 125–500 | 125–1000 | Biofilm formation and mature biofilm, XTT | [74] |
| β-limonene (carotenoid) | Laurus nobilis, Camellia sinensis | C. albicans | 250 | 250 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | | 50 | 250 | Mature biofilm; luminescence | [58] |
| | | | 200 | 250 | Mature biofilm; luminescence | [58] |
| Isopulegol (monoterpane) | Mentha rotundifolia, Melissa officinalis | C. albicans | >4000 | 250 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Ivalin (sesquiterpene lactone) | Geigeria aegyptiaca, Carposium macrophleum | C. albicans | >128 | 15.4 | Biofilm formation and mature biofilm, XTT | [67] |
| Laserpitoline (sesquiterpene lactone) | Laserpitium latifolium, Laserpitiumhalleri | C. albicans | 200 | 400 | Mature biofilm; luminescence | [58] |
| Lichochalcone A (chalconoid) | Glycyrrhiza sp. | C. albicans | 6.25–12.5 | 0.2–20 | Biofilm formation, crystal violet | [58] |
| Linanol (monoterpane) | Laranula officinalis, Pelargonium graveolens | C. albicans | No data | 100–500 | Biofilm formation; confocal laser microscopy | [36] |
| | | | 2000 | 1000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| | | | No data | 1000–8000 | Mature biofilm, XTT | [47] |
| α-Longipinene (sesquiterpene lactone) | Croton eluteria, Helichrysum italicum | C. albicans | No data | 100–500 | Biofilm formation; confocal laser microscopy | [36] |
| Menthol (monoterpane) | Mentha sp. | C. albicans | >4000 | 2000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Montanellide (sesquiterpene lactone) | Laserpitium ochridanum, L. zernyi | C. albicans | 200 | 400 | Mature biofilm, XTT | [59] |
| | | | 200 | 400 | Mature biofilm, luminescence | [43] |
| Morin (flavonoid) | Prunus dulcis, Morus alba | C. albicans | 150 | 37.5–600 | Biofilm formation, crystal violet | [75] |
| Myrcene (monoterpane) | Hamulus lapulus, Cassinia sativa | C. albicans | 1000 | 2000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Nerol (monoterpane) | Citrus × aurantium, Hamulus lapulus | C. albicans | 2000 | 500 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Nerolidol (sesquiterpene lactone) | Citrus × aurantium, Pimpinella dracaenifolia | C. albicans | 15,600–62,500 | 2500–10,000 | Mature biofilm, MT | [48] |
| α-Pinene (monoterpane) | Pinus sylvestris, Picea abies | C. albicans | 3125 | 3125 | Biofilm formation, XTT | [76] |
| β-Pinene (monoterpane) | Pinus sylvestris, Picea abies | C. albicans | 2000 | 4000 | Mature biofilm, XTT, crystal violet, and inverted light microscopy | [69] |
| Polygodial (sesquiterpene lactone) | Warburgia angononos, Polygous hipadloper | C. albicans | 4.1 | 10.8 | Biofilm formation and mature biofilm, XTT and confocal laser microscopy | [52] |
Table 2. Cont.

| Active Compound | Example of Plant Origin | Targeted Fungus | MICs (mg/L, mL/L) | Inhibition of Biofilm Formation by at Least 50% (mg/L, mL/L) | Inhibited Stage of Biofilm; Method of Biofilm Detection | Ref. |
|-----------------|-------------------------|-----------------|-------------------|-------------------------------------------------------------|--------------------------------------------------------|------|
| Pterostilbene   | *Pterocarpus marsupium*, *Pterocarpus santalinus*, *Vitis vinifera* | *C. albicans* | No data           | 8–32                                                        | Biofilm formation and mature biofilm; XTT              | [65] |
| Riccardin D     | *Dunorina hirsuta*      | *C. albicans*   | 16                | 8–64                                                        | Mature biofilm; XTT                                    | [64] |
| Salicylaldehyde  | *Filipendula ulmaria*, *Fagopyrum esculentum* | *C. albicans*   | 31                | 125                                                         | Mature biofilm; XTT, crystal violet, and inverted light microscopy | [68] |
| Salicylic acid   | *Salis sp.*, *Filipendula ulmaria* | *C. albicans*   | 4000              | 2000                                                        | Mature biofilm; XTT, crystal violet, and inverted light microscopy | [68] |
| Scopoletin      | *Mitracarpus frigidus*, *Scopolia carniola* | *C. tropicalis* | 50                | 50                                                          | Biofilm adhesion, formation, and mature biofilm, absorbance and digital scanning | [77] |
| 6-Shogaol       | *Zingiber officinale*   | *C. auris*      | 32–64             | 16–64                                                       | Mature biofilm; crystal violet                         | [78] |
| Tarodil (sesquiterpene lactone) | *Laserpitium schidigianum*, *L. terryi* | *C. albicans*   | 400               | 1000                                                        | Mature biofilm; luminescence                           | [63] |
| Telekin (sesquiterpene lactone) | *Carpeolus macrocephalus*, *Telesia speciosa* | *C. albicans*   | >128              | 36                                                          | Biofilm formation and mature biofilm; XTT             | [67] |
| Terpinolene     | *Cannabis sativa*, *Citrus limon* | *C. albicans*   | 2000              | 4000                                                        | Mature biofilm; XTT, crystal violet, and inverted light microscopy | [69] |
| Tetramethoxyflavone (flavonoid) | *Psidium punciulale*, *Kamptera parviflora* | *C. albicans*   | >4000             | 500                                                         | Mature biofilm; XTT, crystal violet, and inverted light microscopy | [69] |
| Thymol (phenol) | *Thymus vulgaris*, *Thachipormum cyprium* | *C. albicans*   | 250               | 250                                                         | Mature biofilm; XTT, crystal violet, and inverted light microscopy | [69] |
| Tn-AFP1 (protein) | *Trapa natans* | *C. tropicalis* | 1.56–50 | 3.12 | Biofilm formation; absorbance, crystal violet, and scanned electron microscopy | [26] |
| 5,6,8-Trihydroxy-7,4'-dimethoxy flavone (flavonoid) | *Thymus membranaceus subsp. membranaceus*, *Dalenaea vicosa var. angustifolia* | *C. albicans*   | 32–128            | 128                                                         | Biofilm adhesion and mature biofilm; XTT               | [60] |
| 5(R)-Vanessine  | *Waltheria indica*      | *C. albicans*   | 100               | 40                                                          | Biofilm formation; crystal violet                      | [79] |
| 5,6,8-Trihydroxy-7,4'-dimethoxy flavone (flavonoid) | *Thymus membranaceus subsp. membranaceus*, *Dalenaea vicosa var. angustifolia* | *C. albicans*   | 390              | 390                                                         | Biofilm formation and mature biofilm; MTT              | [63] |
| Valininc acid   | *Angelica sinensis*, *Solium tuberosum* | *C. albicans*   | >4000             | 4000                                                        | Biofilm formation and mature biofilm; XTT              | [68] |
| Vanillin (phenol) | *Vanilla plantifera* | *C. albicans*   | 1000              | 500                                                         | Mature biofilm; XTT, crystal violet, and inverted light microscopy | [68] |
| Walthorosines (alkaloid) | *Waltheria indica*, *W. microsperma* | *C. albicans*   | 4–32              | 8–32                                                        | Mature biofilm; XTT                                    | [63] |
| Warburganal (sesquiterpene) | *Wurbergia sp.* | *C. albicans*   | 4                 | 4.5                                                         | Biofilm formation and mature biofilm; XTT and confocal laser microscopy | [52] |

Legend: MIC—minimal inhibitory concentration; XTT—reduction assay of 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(carbonyl[phenylamino])-2H-tetrazolium hydroxide; MTT—reduction assay of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide [54,55].
4. Conclusions

Plant preparations (essential oils and extracts) and pure compounds exhibit anti-biofilm activity against Candida species. Some of them are characterized by high activity in concentrations below 16 mg/L. Given this activity at relatively low concentrations, some may prove to be promising alternatives to antifungal drugs, especially in the cases of resistant or multiresistant strains of Candida. Moreover, the simple chemical structures involved and relative ease of extraction from natural sources warrant further research into the development of new, promising, and much-needed plant-based antifungals.

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