Candida and anti-candidal plant compounds

Subjects: Plant Sciences

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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.

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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 *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. dubliniensis* [2]. Less frequently identified are *C. guilliermondii*, *C. lusitaniae*, *C. rugosa*, *C. orthopsilosis*, *C. metapsilosis*, *C. famata*, *C. inconspicua*, and *C. kefyr* [3].

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][5][6]. Opportunistic infection caused by *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]. *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 *C. glabrata* infection, topical boric acid, nystatin, or flucytosine 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, amphoteticin B is used. In selected cases of candidemia caused by *C. krusei*, voriconazole is recommended [10][11][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, *Candida* species are becoming resistant to drugs. Marak and Dhanashree [13] tested the resistance of 90 *Candida* strains isolated from different clinical samples, such as pus, urine, blood, and body fluid. Their study revealed that about 41% of *C. albicans* strains are resistant to fluconazole and voriconazole. Simultaneously, about 41% of *C. tropicalis* strains are resistant to voriconazole and about 36% of strains to fluconazole. In strains of *C. krusei*, about 23% are resistant to fluconazole and about 18% to voriconazole. Rudramurthy et al. [14] studied resistance in *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 *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 *Candida* biofilm occurrence. Biofilm prevents the spread of antifungals; moreover, fluconazole is bound by the biofilm matrix [18]. The formation of a *Candida* biofilm during infection increases mortality, length of hospital stay, and cost of antifungal therapy [19].

2. 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 (4 species in 3 genera), and Apiacae (4 species in 2 genera).

Plants from the Lamiaceae family had the best antifungal activity, including *Lavandula dentata* (0.045–0.07 mg/L) [20], *Satureja macrosiphon* (0.06–8 mg/L) [21], and *Ziziphora tenuior* (2.5 mg/L) [22]. *Artemisia judaica* (2.5 mg/L) from the Asteraceae family [23], *Lawsonia inermis* (2.5–12.5 mg/L) from the Lythraceae family [24], and *Thymus vulgaris* (12.5 mg/L) from the Lamiaceae family [25] 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 and fluorescence microscopy**	[26]
Allium sativum **L. (Amaryllidaceae)**	**Extract: allicin**	***C. albicans***	**400**	**60**	**Biofilm formation; XTT**	[27]
Aloysia gratissima **(Aff & Hook).Tr (Verbenaceae)**	**EO: E-pinocamphone (16.07%), β-pinene (12.01%), guaiol (8.53%), E-pinocarveol acetate (8.19%)**	***C. albicans***	**15**	**500**	**Biofilm formation; crystal violet**	[28]
Artemisia judaica **L. (Asteraceae)**	**EO: piperitone (30.4%), camphor (16.1%), ethyl cinnamate (11.0%), chrysanthenone (6.7%)**	***C. albicans***	**1.25**	**2.5**	**Mature biofilm; XTT**	[23]
		C. guillermondii	**1.25**	**2.5**		
		C. krusei	**1.25**	**2.5**		
		C. parapsilosis	**1.25**	**2.5**		
		C. tropicalis	**1.25**	**2.5**		
Buchenavia tomentosa **Eichler (Combretaceae)**	**Extract: gallic acid, kaempferol, epicatechin, ellagic acid, vitexin, and corilagin**	***C. albicans***	**625**	**312.5**	**Biofilm formation and mature biofilm; culture**	[29]
Chamaecostus cuspidatus **(Nees & Mart.) C.Specht & D.W.Stev. (Costaceae)**	**Extract: dioscin, aferoside A, aferoside C**	***C. albicans***	**250**	**15.62**	**Biofilm formation and mature biofilm; MTT**	[30]
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**	[31]
		C. dubliniensis	**1000**	**200**		
		C. tropicalis	**1000**	**350**		

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Citrus limon (L.) Osbeck (Rutaceae)	EO: limonene (53.4%), neral (11%), geraniol (9%), *trans*-limonene oxide (7%), nerol (6%)	*C. albicans*	500	2000	Biofilm formation and mature biofilm; XTT	[32]
		C. glabrata	250	1000		
		C. krusei	500	125		
		C. orthopsilosis	500	1000		
		C. parapsilosis	500	2000		
		C. tropicalis	250	2000		
Copaifera paupera (Herzog) Dwyer (Fabaceae)	Extract: galloylquinic acids, quercetrin, afzelin	*C. glabrata*	5.89	46.87	Biofilm formation and mature biofilm; XTT	[33]
Copaifera reticulata Ducke (Fabaceae)	Extract: galloylquinic acids, quercetrin, afzelin	*C. glabrata*	5.89	46.87	Biofilm formation and mature biofilm; XTT	[33]
Coriandrum sativum L. (Apiaceae)	EO: 1-decanol (33.91%), E-2-decen-1-ol (23.59%), 2-dodecen-1-ol (13.06%), E-2-tetradecen-1-ol (5.46%)	*C. albicans*	7	250	Biofilm formation; crystal violet	[28]
	EO: decanal (19.09%), *trans*-2-decenal (17.54%), 2-decen-1-ol (12.33%), cyclodecane (12.15%)	*C. albicans*	15.6	62.5–125	Biofilm adhesion; crystal violet	[34]
		C. dubliniensis	31.2	62.5–125		
		C. rugosa	15.6	62.5		
		C. tropicalis	31.2	31.25–250		
Croton eluteria (L.) W.Wright (Euphorbiaceae)	EO: α-pinene (29.37%), β-pinene (19.35%), camphene (10.31%), 1,8-cineole (9.68%)	*C. albicans*	4000	5–500	Biofilm formation; confocal laser microscopy	[35]
Cupressus sempervirens L. (Cupressaceae)	EO: sabinene (20.3%), citral (20%), terpinene-4-ol (15.4%), α-pinene (8%)	*C. albicans*	250	1000	Biofilm formation and mature biofilm; XTT	[32]
		C. glabrata	31.25	250		
		C. krusei	62.5	62.5		
		C. orthopsilosis	31.25	125		
		C. parapsilosis	62.5	500		
		C. tropicalis	250	500		
Cymbopogon citratus (DC.) Stapf (Poaceae)	EO: no composition	*C. albicans*	180–360	22.5–180	Biofilm formation; XTT	[36]
Cymbopogon martini (Roxb.) W.Watson (Poaceae)	EO: no composition	*C. albicans*	16,800	800	Biofilm formation; XTT	[37]
Cymbopogon nardus (L.) Rendle (Poaceae)	EO: citronellal (27.87%), geraniol (22.77%), geranial (14.54%), citronellol (11.85%), neral (11.21%)	*C. albicans*	1000	2500–5000	Biofilm adhesion; XTT	[38]
		C. krusei	250–500	2500		
		C. parapsilosis	500–1000	5000–10,000		

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Cyperus articulatus L. (Cyperaceae)	EO: α-pinene (5.72%), mustakone (5.66%), α-bulnesene (5.02%), α-copaene (4.97%)	*C. albicans*	125	250	Biofilm formation; crystal violet	[28]
Eucalyptus sp. (Myrtaceae)	EO: no composition	*C. albicans*	8	8	Mature biofilm; luminescence	[39]
Eucalyptus globulus Labill. (Myrtaceae)	EO: 1,8-cineole (75.8%), p-cymene (7.5%), α-pinene (7.4%), limonene (6.4%)	*C. albicans*	219	11,250–22,500	Mature biofilm; atomic force microscopy	[40]
		C. glabrata	219	11,250–22,500		
		C. tropicalis	885	11,250–22,500		
	EO: no composition	*C. albicans*	8400	500	Biofilm formation; XTT	[37]
Eugenia brasiliensis Lam. (Myrtaceae)	Extract: no composition	*C. albicans*	15.62–31.25	156	Mature biofilm; scanning electron microscopy	[41]
Eugenia leitonii Legrand *nom. inval.* (Myrtaceae)	Extract: no composition	*C. albicans*	15.62–250	156	Mature biofilm; scanning electron microscopy	[41]
Helichrysum italicum (Roth) G.Don (Asteraceae)	EO: α-pinene (27.64%), γ-elemene (23.84%), β-caryophyllene (13.05%), α-longipinene (11.25%)	*C. albicans*	6000	10–500	Biofilm formation; confocal laser microscopy	[35]
Laserpitium latifolium L. (Apiaceae)	Extract: laserpitine	*C. albicans*	1250	6300	Mature biofilm; luminescence	[42]
		C. krusei	1250	6300		
Laserpitium ochridanum Micevski (Apiaceae)	Extract: isomontanolide, montanolide, tarolide	*C. albicans*	5000	10,000	Mature biofilm; luminescence	[42]
		C. krusei	5000	10,000		
Laserpitium zernyi Hayek = *L. siler* subsp. *zernyi* (Hayek) Tutin (Apiaceae)	Extract: isomontanolide, montanolide, tarolide	*C. albicans*	7500	15,000	Mature biofilm; luminescence	[42]
		C. krusei	7500	37,500		
Lavandula dentata L. (Lamiaceae)	EO: eucalyptol (42.66%), β-pinene (8.59%), *trans*-α-bisabolene (6.34%), pinocarveol (6.3%)	*C. albicans*	0.15–0.18	0.045–0.07	Mature biofilm; XTT	[20]
Lawsonia inermis L. (Lythraceae)	Extract: no composition	*C. albicans*	10	2.5–12.5	Mature biofilm; MTT	[24]
Lippia sidoides Cham. (Verbenaceae)	EO: thymol (65.76%), p-cymene (17.28%), α-caryophyllene (10.46%), cyclohexanone (6.5%)	*C. albicans*	250	500	Biofilm formation; crystal violet	[28]

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Litsea cubeba (Lour.) Pers. (Lauraceae)	EO: limonene (37%), neral (31.4%), citral (12%), linalool (4%)	*C. albicans*	500	2000	Biofilm formation and mature biofilm; XTT	[32]
		C. glabrata	250	2000		
		C. krusei	62.5	250		
		C. orthopsilosis	250	2000		
		C. parapsilosis	500	1000		
		C. tropicalis	1000	2000		
Mentha × *piperita* L. (Lamiaceae)	EO: menthol (32.93%), menthone (24.41%), 1,8-cineole (7.89%)	*C. albicans*	1–10	10	Biofilm formation; MTT	[43]
	EO: no composition	*C. albicans*	11,600	800	Biofilm formation; XTT	[37]
Mikania glomerata Spreng (Asteraceae)	EO: germacrene D (38.29%), α-caryophyllene (9.49%), bicyclogermacrene (7.98%), caryophyllene oxide (4.28%)	*C. albicans*	250	500	Biofilm formation; crystal violet	[28]
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	[44]
		C. parapsilosis	1250 to >16,000	1250		
		C. tropicalis	1250–16,000	1250		
Ononis spinosa L. (Fabaceae)	Extract: kaempherol-O-dihexoside, kaempherol-O-hexoside-pentoside, kaempherol-O-hexoside, quercetin-O-hexoside-pentoside, acetylquercetin-O-hexoside	*C. albicans*	620	10,000	Mature biofilm; luminescence	[45]
		C. krusei	620	5000		
		C. tropicalis	310	10,000		
Pelargonium graveolens L'Hér. (Geraniaceae)	EO: geraniol (42.3%), linalool (20.1%), citronellol (11.1%), menthone (8.0%)	*C. albicans*	125	4000–8000	Mature biofilm; XTT	[46]
Piper claussenianum (Miq.) C. DC. (Piperaceae)	EO: nerolidols	*C. albicans*	4100–9600	2400–12,600	Mature biofilm; MTT	[47]
Portulaca oleracea L. (Portulacaceae)	Extract: no composition	*C. albicans*	10	12.5	Mature biofilm; MTT	[24]
Punica granatum L. (Lythraceae)	Extract: ellagic acid	*C. albicans*	1000	100–750	Biofilm formation and mature biofilm; crystal violet	[48]
Santolina impressa 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	[49]
Satureja hortensis L. (Lamiaceae)	EO: thymol (45.9%), gamma-terpinen (16.71%), carvacrol (12.81%), p-cymene (9.61%)	*C. albicans*	200–400	400–4800	Biofilm adhesion, formation, and mature biofilm; MTT	[50]

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Satureja macrosiphon **(Coss.) =** ***Micromeria macrosiphon*** **Coss. (Lamiaceae)**	**EO: linalool (28.46%), borneol (16.22%), terpinene-4-ol (14.58%),** ***cis*****-sabinene hydrate (12.96%)**	***C. albicans***	**0.06–4**	**0.06–8**	**Biofilm formation; XTT**	[21]
		C. dubliniensis	**0.25–4**	**2–8**		
Syzygium aromaticum **(L.) Merr. & L.M.Perry =** ***Eugenia caryophyllus*** **(Spreng.) Bullock & S.G.Harrison (Myrtaceae)**	**EO: no composition**	***C. albicans***	**100–200**	**50**	**Biofilm formation; XTT**	[36]
	EO: no composition	***C. albicans***	**48,000**	**3300**	**Biofilm formation; XTT**	[37]
Thymus vulgaris **L. (Lamiaceae)**	**EO: thymol (54.73%), carvacrol (12.42%), terpineol (4.00%), nerol acetate (2.86%), fenchol (0.5%)**	***C. albicans***	**1.56–25**	**12.5**	**Biofilm formation; absorbance, crystal violet, and scanning electron microscopy**	[25]
		C. tropicalis	**25–50**	**12.5**		
Warburgia ugandensis **Sprague (Canellaceae)**	**Extract: ugandenial A, warburganal, polygodial, alpha-linolenic acid ALA**	***C. albicans***	**Lack of data**	**1000**	**Biofilm formation and mature biofilm; XTT and confocal laser microscopy**	[51]
		C. glabrata	**Lack of data**	**1000**		
Ziziphora tenuior **L. (Lamiaceae)**	**EO: pulegone (46.8%), p-menth-3-en-8-ol (12.5%), isomenthone (6.6%), 8-hydroxymenthone (6.2%), isomenthol (4.7%)**	***C. albicans***	**1.25**	**2.5**	**Mature biofilm; XTT**	[22]
Zuccagnia punctata **L. (Fabaceae)**	**Extract: no composition**	***C. albicans***	**400**	**100**	**Biofilm formation and mature biofilm; XTT and crystal violet**	[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 [53][54].

3. 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 monotherpenes (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).

Table 2. Antifungal and antibiofilm activity of plant compounds.

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.
Antidesmone (alkaloid)	*Waltheria indica*, *W. brachypetala*	*C. albicans*	32	16	Mature biofilm; XTT	[55]
		C. glabrata	>32	16		
		C. krusei	16	16		
		C. parapsilosis	4	16		
		C. tropicalis	>32	16		
Anisaldehyde (phenolic aldehyde)	*Pimpinella anisum* , *Foeniculum vulgare*	*C. albicans*	500	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[56]
Anisic acid (phenolic acid)	*Pimpinella anisum*	*C. albicans*	4000	4000	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[56]
Anisyl alcohol (phenolic alcohol)	*Pimpinella anisum*	*C. albicans*	31	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[56]
Baicalein (flavonoid)	*Scutellaria baicalensis*, *S. lateriflora*	*C. albicans*	No data	4–32	Biofilm formation; XTT	[57]
Camphene (monotherpene)	*Croton eluteria*, *Cinnamomum verum*	*C. albicans*	No data	500	Biofilm formation; confocal laser microscopy	[35]
		C. albicans	1000	2000	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
Camphor (bicyclic monotherpene)	*Cinnamomum camphora*, *Artemisia annua*	*C. albicans*	125–250	Not or 62.5–250	Biofilm formation; crystal violet and absorbance	[59]
		C. glabrata	175	Not		
		C. krusei	350	Not		
		C. parapsilosis	125	Not		
		C. tropicalis	175	175		
Cannabidiol (cannabinoid)	*Cannabis sativa*	*C. albicans*	No data	12.5–100	Biofilm formation; confocal microscopy	[60]

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.
Carvacrol (phenol)	*Thymus serpyllum*, *Carum carvi*, *Origanum vulgare*	*C. albicans*	250	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
			100–20,000	300–1250	Mature biofilm; XTT	[61]
			1000	750–1500	Biofilm formation; MTT	[62]
		C. glabrata	100–20,000	300–1250	Mature biofilm; XTT	[61]
		C. parapsilosis	100–20,000	300–1250		
Carvene/Limonene (monotherpene)	*Citrus × aurantium*, *Citrus limon*	*C. albicans*	1000	4000	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
Carvone/Carvol (monotherpene)	*Carum carvi*, *Mentha spicata*	*C. albicans*	>4000	250	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
β-Caryophyllene (sesquiterpene)	*Helichrysum italicum*, *Caryophyllusaromaticus*	*C. albicans*	No data	100–500	Biofilm formation; confocal laser microscopy	[35]
1,4-Cineole (monotherpene)	*Rosmarinus officinalis* , *Thymus vulgaris*	*C. albicans*	>4000	4000	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
1,8-Cineole/Eucalyptol (monotherpene)	*Eucalyptus globulus*, *Salvia officinalis*, *Pinus sylvestris*	*C. albicans*	4000	4000	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
			8	4	Mature biofilm; luminescence	[39]
			3000–23,000	Not or 3000–23,000	Biofilm formation; crystal violet and absorbance	[59]
		C. glabrata	2000	Not		
		C. krusei	4000	2000–4000		
		C. parapsilosis	2000	1000–2000		
		C. tropicalis	4000	2000–4000		

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.
Cinnamaldehyde (aldehyde)	***Cinnamomum* sp., *Apium graveolens***	***C. albicans***	**62**	**125**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[56]
			50–400	**25–200**	**Mature biofilm; XTT**	[63]
Cinnamic acid (phenolic acid)	***Cinnamomum* sp.**	***C. albicans***	**2000**	**4000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[56]
Citral (monotherpene)	***Melissa officinalis*, *Backhousia citriodora***	***C. albicans***	**500**	**1000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
Citronellal (monotherpene)	***Cymbopogon citratus* , *Melissa officinalis***	***C. albicans***	**500**	**1000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
β-Citronellol (monotherpene)	***Melissa officinalis*, *Pelargonium roseum***	***C. albicans***	**500**	**1000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
Cuminaldehyde (monotherpene)	***Carum carvi* , *Cinnamomum verum***	***C. albicans***	**1000 to >4000**	**6000–7000**	**Biofilm formation; MTT**	[62]
p-Cymene (monotherpene)	***Thymus vulgaris*, *Eucalyptus* sp.**	***C. albicans***	**2000**	**4000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
8-Deoxoantidesmone (alkaloid)	***Waltheria indica***	***C. albicans***	**16**	**32**	**Mature biofilm; XTT**	[55]
		C. glabrata	**>32**	**32**		
		C. krusei	**32**	**32**		
		C. parapsilosis	**32**	**32**		
		C. tropicalis	**>32**	**32**		
2′,4′-Dihydroxy-3′-methoxychalcone (chalcone)	***Zuccagnia punctata*, *Oxytropis falcata***	***C. albicans***	**100**	**25**	**Biofilm formation and mature biofilm; XTT and crystal violet**	[52]
Dioscin (steroidal saponin)	***Dioscorea* sp., *Chamaecostus***	***C. albicans***	**3.9–15.62**	**3.9–31.25**	**Biofilm formation and mature biofilm; MTT**	[30]

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.
Ellagic acid (polyphenol)	*Punica granatum* L.	*C. albicans*	75–100	25–40	Biofilm formation and mature biofilm; crystal violet	[48]
Emodin (anthraquinone)	*Rheum palmatum*, *Frangula alnus*	*C. albicans*	12.5–50	Not or 100–400	Biofilm adhesion; MTT	[64]
4α,5α-Epoxy-10α,14H-1-epi-inuviscolide (sesquiterpene lactone)	*Carpesium macrocephalum*	*C. albicans*	>128	38	Biofilm formation and mature biofilm; XTT	[65]
Eugenol (phenol)	*Syzygium aromaticum* , *Cinnamomum* sp.	*C. albicans*	50–400	12.5–200	Mature biofilm; XTT	[63]
			250	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
			500	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[56]
			1200	10,000–80,000	Mature biofilm; XTT	[66]
Farnesol (sesquiterpene)	*Tilia* sp., *Cymbopogon* sp.	*C. albicans*	1000	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[56]
			1000	500	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
Gallic acid (phenolic acid)	*Polygonum* sp., *Buchenavia tomentosa*	*C. albicans*	5000	2500	Biofilm formation and mature biofilm; culture	[29]

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.
Geraniol (monotherpene)	***Pelargonium graveolens*, *Rosa* sp.**	***C. albicans***	**1000**	**1000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
		C. albicans	**100–20,000**	**300–1250**	**Mature biofilm; XTT**	[61]
		C. albicans	**No data**	**1000–8000**	**Mature biofilm; XTT**	[46]
		C. glabrata	**100–20,000**	**300–1250**	**Mature biofilm; XTT**	[61]
		C. parapsilosis	**100–20,000**	**300–1250**		
Guaiacol (phenol)	***Guaiacum officinale* , *Apium graveolens***	***C. albicans***	**500**	**1000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[56]
Hydroxychavicol (phenol)	***Piper betle***	***C. albicans***	**125–500**	**125–1000**	**Biofilm formation and mature biofilm; XTT**	[67]
β-Ionone (carotenoid)	***Lawsonia inermis* , *Camellia sinensis***	***C. albicans***	**250**	**250**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
Isomontanolide (sesquiterpenic lactone)	***Laserpitium ochridanum*, *L. zernyi***	***C. albicans***	**50**	**250**	**Mature biofilm; luminescence**	[42]
		C. krusei	**200**	**250**		
Isopulegol (monotherpene)	***Mentha rotundifolia*, *Melissa officinalis***	***C. albicans***	**>4000**	**250**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
Ivalin (sesquiterpene lactone)	***Geigeria aspera*, *Carpesium macrocephalum***	***C. albicans***	**>128**	**15.4**	**Biofilm formation and mature biofilm; XTT**	[65]
Laserpitine (sesquiterpene lactone)	***Laserpitium latifolium*, *Laserpitiumhalleri***	***C. albicans***	**200**	**400**	**Mature biofilm; luminescence**	[42]
		C. krusei	**200**	**400**		
Lichochalcone A (chalconoid)	***Glycyrrhiza* sp.**	***C. albicans***	**6.25–12.5**	**0.2–20**	**Biofilm formation; crystal violet**	[68]

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.
Linalool (monotherpene)	***Lavandula officinalis*, *Pelargonium graveolens***	***C. albicans***	**No data**	**100–500**	**Biofilm formation; confocal laser microscopy**	[35]
			2000	**1000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
			No data	**1000–8000**	**Mature biofilm; XTT**	[46]
α-Longipinene (sesquiterpene)	***Croton eluteria*, *Helichrysum italicum***	***C. albicans***	**No data**	**100–500**	**Biofilm formation; confocal laser microscopy**	[35]
Menthol (monotherpene)	***Mentha* spp.**	***C. albicans***	**>4000**	**2000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
			2500	**10,000–80,000**	**Mature biofilm; XTT**	[66]
Montanolide (sesquiterpene lactone)	***Laserpitium ochridanum*, *L. zernyi***	***C. albicans***	**200**	**400**	**Mature biofilm; luminescence**	[42]
		C. krusei	**200**	**400**		
Morin (flavonoid)	***Prunus dulcis* , *Morus alba***	***C. albicans***	**150**	**37.5–600**	**Biofilm formation; crystal violet**	[69]
Myrcene (monotherpene)	***Humulus lupulus*, *Cannabis sativa***	***C. albicans***	**1000**	**2000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
Nerol (monotherpene)	***Citrus × aurantium*, *Humulus lupulus***	***C. albicans***	**2000**	**500**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
Nerolidols (sesquiterpene)	***Citrus × aurantium*, *Piper claussenianum***	***C. albicans***	**18,600–62,500**	**2500–10,000**	**Mature biofilm; MTT**	[47]
α-Pinene (monotherpene)	***Pinus sylvestris*, *Picea abies***	***C. albicans***	**3125**	**3125**	**Biofilm formation; XTT**	[70]
β-Pinene (monotherpene)	***Pinus sylvestris*, *Picea abies***	***C. albicans***	**2000**	**4000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
			187	**187**	**Biofilm formation; XTT**	[70]

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.
Polygodial (sesquiterpene)	***Warburgia ugandensis*, *Polygonum hydropiper***	***C. albicans***	**4.1**	**10.8**	**Biofilm formation and mature biofilm; XTT and confocal laser microscopy**	[51]
		C. glabrata	**94.1**	**50.6–61.9**		
Pterostilbene (polyphenol)	***Pterocarpus marsupium*, *Pterocarpus santalinus*, *Vitis vinifera***	***C. albicans***	**No data**	**8–32**	**Biofilm formation and mature biofilm; XTT**	[71]
Riccardin D (macrocyclic bisbibenzyl)	***Dumortiera hirsuta***	***C. albicans***	**16**	**8–64**	**Mature biofilm; XTT**	[72]
Salicylaldehyde (phenolic aldehyde)	***Filipendula ulmaria*, *Fagopyrum esculentum***	***C. albicans***	**31**	**125**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[56]
Salicylic acid (phenolic acid)	***Salix* sp., *Filipendula ulmaria***	***C. albicans***	**4000**	**2000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[56]
Scopoletin (cumarin)	***Mitracarpus frigidus*, *Scopolia carniola***	***C. tropicalis***	**50**	**50**	**Biofilm adhesion, formation, and mature biofilm; absorbance and digital scanning**	[73]
6-Shogaol (phenylalkane)	***Zingiber officinale***	***C. auris***	**32–64**	**16–64**	**Mature biofilm; crystal violet**	[74]
Tarolide (sesquiterpene lactone)	***Laserpitium ochridanum*, *L. zernyi***	***C. albicans***	**400**	**1000**	**Mature biofilm; luminescence**	[42]
		C. krusei	**400**	**1000**		
Telekin (sesquiterpene lactone)	***Carpesium macrocephalum*, *Telekia speciose***	***C. albicans***	**>128**	**36**	**Biofilm formation and mature biofilm; XTT**	[65]
Terpinolene (terpene)	***Cannabis sativa*, *Citrus limon***	***C. albicans***	**2000**	**4000**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]
5,7,3′,4′-Tetramethoxyflavone (flavonoid)	***Psiadia punctulate*, *Kaempferia parviflora***	***C. albicans***	**100**	**40**	**Biofilm formation; crystal violet**	[75]
α-Thujone (monotherpene)	***Artemisia absinthium*, *Tanacetum vulgare***	***C. albicans***	**>4000**	**500**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[58]

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.
Thymol (phenol)	*Thymus vulgaris*, *Trachyspermum copticum*	*C. albicans*	250	250	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[58]
			1.56–50	3.12	Biofilm formation; absorbance, crystal violet, and scanning electron microscopy	[25]
			32–128	128	Biofilm adhesion and mature biofilm; XTT	[76]
			100–20,000	300–1250	Mature biofilm; XTT	[61]
			125	125–250	Biofilm formation and mature biofilm; XTT	[77]
			1200	5000–80,000	Mature biofilm; XTT	[66]
		C. tropicalis	1.56–50	12.5	Biofilm formation; absorbance, crystal violet, and scanning electron microscopy	[25]
		C. glabrata	100–20,000	300–1250	Mature biofilm; XTT	[61]
		C. parapsilosis	100–20,000	300–1250		
Tn-AFP1 (protein)	*Trapa natans*	*C. tropicalis*	32	16	Mature biofilm; XTT	[78]
5,6,8-Trihydroxy-7,4′ dimethoxy flavone (flavonoid)	*Thymus membranaceus* subsp. *membranaceus*, *Dodonaea viscosa* var. *angustifolia*	*C. albicans*	390	390	Biofilm formation and mature biofilm; MTT	[79]
5(R)-Vanessine (alkaloid)	*Waltheria indica*	*C. albicans*	32	16	Mature biofilm; XTT	[55]
		C. glabrata	>32	16		
		C. krusei	32	16		
		C. parapsilosis	>32	16		
		C. tropicalis	>32	16		
Vanillic acid (phenolic acid)	*Angelica sinensis* , *Solanum tuberosum*	*C. albicans*	>4000	4000	Mature biofilm; XTT, crystal violet, and inverted light microscopy	[56]

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.
Vanillin (phenol)	***Vanilla planifolia***	***C. albicans***	**1000**	**500**	**Mature biofilm; XTT, crystal violet, and inverted light microscopy**	[56]
Waltheriones (alkaloid)	***Waltheria indica*, *W.viscosissima***	***C. albicans***	**4–32**	**8–32**	**Mature biofilm; XTT**	[55]
		C. glabrata	**32 or >32**	**8–32**		
		C. krusei	**16–32 or >32**	**8–32**		
		C. parapsilosis	**2–32 or >32**	**8–32**		
		C. tropicalis	**32 or >32**	**8–32**		
Warburganal (sesquiterpene)	***Warburgia* sp.**	***C. albicans***	**4**	**4.5**	**Biofilm formation and mature biofilm; XTT and confocal laser microscopy**	[51]
		C. glabrata	**72–72.6**	**49.1–55.9**		

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 [53][54].

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 [63] and 1.56 mg/L for thymol [25]), and in other studies, the activity was very poor (up to 80,000 for both [66]). 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 [80].

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the antifungal clinical breakpoints are between 0.001 mg/L and 16 mg/L [81]. Using EUCAST guidelines in this review, the most active compounds that inhibit (>50%) *Candida* biofilm formation are lichochalcone A (from 0.2 mg/L) [68], thymol (from 3.12 mg/L) [25], dioscin (from 3.9 mg/L) [30], baicalein (from 4 mg/L) [57], warburganal (4.5 mg/L) [51], pterostilbene, waltheriones and riccardin D (both from 8 mg/L) [55][72][71], polygodial (10.8 mg/L) [51], cannabidiol and eugenol (both from 12.5 mg/L) [63][60], and ivalin (15.4 mg/L) [65]. It is interesting that monotherpenes, 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 cannabinoids (cannabidiol). Most of the compounds presented in Table 2 acted on biofilm formation and/or mature biofilm.

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