Candida and anti-candidal plant compounds

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Definition

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.

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]
	EO: eugenol (77.22%),	C. albicans	1000	150		
		C. dubliniensis	1000	200		
		C. tropicalis	1000	350		

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.
Cinnamomum verum J. Presl (Lauraceae)	benzyl benzoate (4.53%), trans-caryophyllene (3.39%), acetyl eugenol (2.75%), linalool 2.11%				Biofilm adhesion; XTT	[31]
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]

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.
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		
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		
		C. albicans	7500	15,000		
		C. krusei	7500	37,500		
Laserpitium zernyi Hayek = L. siler subsp. zernyi (Hayek)	Extract: isomontanolide,				Mature biofilm;	[42]

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Tutin (Apiaceae)	montanolide, tarolide				luminescence	
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]
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]

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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]
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]

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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]

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.
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]
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]

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.
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		
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]

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.
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]
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]

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-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]
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		
		C. parapsilosis	100–20,000	300–1250		

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.
					Mature biofilm; XTT	[61]
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]
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]

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.
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]
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]

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.
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]
			250	250	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	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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Keywords

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