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•Review•

Recent progress on anti-*Candida* natural products

SUN Fu-Juan, LI Min, GU Liang, WANG Ming-Ling, YANG Ming-Hua*

State Key Laboratory of Natural Medicines, Department of Natural Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

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[ABSTRACT] *Candida* is an intractable life-threatening pathogen. *Candida* infection is extremely difficult to eradicate, and thus is the major cause of morbidity and mortality in immunocompromised individuals. Morevover, the rapid spread of drug-resistant fungi has led to significant decreases in the therapeutic effects of clinical drugs. New anti-*Candida* agents are urgently needed to solve the complicated medical problem. Natural products with intricate structures have attracted great attention of researchers who make every endeavor to discover leading compounds for antifungal agents. Their novel mechanisms and diverse modes of action expand the variety of fungistatic agents and reduce the emergence of drug resistance. In recent decades, considerable effort has been devoted to finding unique antifungal agents from nature and revealing their unusual mechanisms, which results in important progress on the development of new antifungals, such as the novel cell wall inhibitors YW3548 and SCY-078 which are being tested in clinical trials. This review will present a brief summary on the landscape of anti-*Candida* natural products within the last decade. We will also discuss in-depth the research progress on diverse natural fungistatic agents along with their novel mechanisms.

[KEY WORDS] *Candida*; Natural products; Antifungal activity; Mechanisms
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Introduction

Candida is a fungal pathogen which causes a vareity of human mycoses worldwide. *Candida* species are currently the fourth leading cause of hospital-acquired bloodstream infection [1]. *Candida albicans* infection is the most common invasive human candidiasis, accounting for more than 50% [2]. Risk factors for developing this disease include the use of broad-spectrum antibiotics, the presence of central venous catheters, gastrointestinal surgery and parenteral nutrition [3]. High-risk patients include but are not limited to immunocompromised individuals, such as HIV-positive people, transplant recipients, pediatric and elderly populations, cancer patients, as well as those receiving immunosuppressive treatment for various reasons [4, 5].

There are limited types of antifungals in use, including azoles, polyenes and echinochandins. The azole agents (e.g., fluconazole) are the most widely used fungistatic durgs which inhibit cytochrome P450 enzyme 14α-demethylase to prevent the conversion of lanosterol to ergosterol, an essential component of the fungal membrane. Polyene antifungals (e.g., amphotericin B) selectively bind to ergosterol and directly disrupt fungal membrane integrity. As for the echinochandins (e.g., caspofungin), they can inhibit β-1, 3-glucan synthase which mediates an essential step in the production of glucan in cell wall. Unfortunately, the above-mentioned agents may induce severe fungal resistance, which needs urgent research attention [6, 7].

Natural products, well known for unique chemical diversity and bioactivity, have been widely used to treat various diseases for centuries [8]. According to the statistics, more than half of all new drugs approved by the FDA from 1981 to 2019 were either natural products or related to them [9]. Notably, some clinical antimycotics of the first line are typically natural products or their derivatives. The above-mentioned polyenes and echinochandins are derived from actinomycetic and fungal metabolites, respectively [10, 11]. Several antifungal molecules that are being intensively studied, such as nikkomycins and sordarins, are also derived from natural products [12, 13]. In recent years, the exploration of antifungal natural products has made significant progress. A considerable number of natural molecules have been found to possess therapeutic effects against different *Candida* species. They belong

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[*Corresponding author] E-mail: skeepjack@163.com
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to diverse types including essential oils, alkaloids, terpenoids, etc. Their anti-*Candida* mechanisms of action may be associated with anti-virulence activities, anti-biofilm properties, inhibiting cell wall or cell membrane synthesis, and inducing cell apoptosis.

There were a few reviews concerning anti-*Candida* natural products in the past several years. In 2017, Soliman *et al*. focused on the anti-*Candida* constituents of plants [14], while Zida *et al*. gave a review limited to the anti-*C. albicans* products [15]. In view of the fast-growing researches and in order to provide a more comprehensive summary, we reviewed nearly 200 references published in the last decade, hoping to give a wide collection of anti-*Candida* natural products from various sources and to provide an overview of their antifungal mechanisms.

Anti-*Candida* Activity of Natural Products

In the past decade, there were nearly 200 reported anti-*Candida* natural products isolated from different sources (Table 1, Fig. 1). Fungal metabolites were the primary source, followed by plants. Most of these compounds belong to alkaloids, polyketides, terpenoids, phenolics, macrolides, and peptides. Among them, terpenoids are the most abundant group, followed by alkaloids and polyketides. Here, we briefly outline the antifungal properties of the above three classes and illustrate with examples.

Alkaloids

There are 36 alkaloids in Table 1, which were isolated from diverse sources such as higher plants, endophytic fungi and sponges. They belong to various types including indoles, pyridines, quinolone, etc. Among them, indole alkaloids are the most abundant group, followed by quinolone alkaloids. These two types of alkaloids were reported for a relatively broad antifungal spectrum, but their fungistatic activity was generally moderate. In contrast, the reported pyridine alkaloids all showed strong antimycotic activity. For instance, penicolinate B displayed great activity against *C. albicans* with MIC_{50} of 1.45 μg·mL^{-1} [28]. In addition, piperidine and pyridone alkaloids account for the smallest proportion in which only one active compound was reported for each, namely epidihydropinidine and didymellamide A, respectively [20, 22].

Polyketides

There are 34 polyketides in Table 1, and most of them were isolated from fungal metabolites. These polyketides with different carbon skeletons were reported to have a narrow antifungal spectrum, as most of them simply presented fungistatic effects on *C. albicans* (MIC 1−50 μg·mL^{-1}). Among them, three carbamidocyclophane polyketides derived from *Nostoc* sp. exerted significant antifungal activity against *C. albicans*, especially carbamidocyclophane B (MIC 1.3 μmol·L^{-1}) [34]. A few polyketides exhibited moderate antimycotic activity against other *Candida* species like *C. glabrata*, *C. parapsilosis* and *C. tenuis* (MIC 5−25 μg·mL^{-1}).

Terpenoids

Terpenoids is the largest group of anti-*Candida* natural products in Table 1. The 52 compounds mainly are the metabolites of higher plants and endophytic fungi, and primarily belong to sesquiterpenes, diterpenes and triterpenes. Sesquiterpenes are the largest sub-group of anti-*Candida* terpenoids, which include eudesmane, laurane, and others. The eudesmane type account for the highest proportion of sesquiterpenes, with good inhibitory effects on *C. albicans* (MIC 4−8 μg·mL^{-1}). The laurane type from *Laurencia okamurai* showed notable anti-*C. glabrata* activity, such as lauokamurene C (MIC_{80} 1 μg·mL^{-1}) [92]. Furthermore, there are nine diterpenes and most of them can slightly inhibit the growth of *C. albicans*. It is worth mentioning that the triterpenes in Table 1 are basically derived from *Ganoderma gibbosum*, which effectively inhibited the vitality of *C. albicans* (MIC_{50} 3−10 μg·mL^{-1}) [88].

Others

Other anticandidal natural products are phenolics, macrolides, peptides, saponins and glycolipids. Most of the phenolics showed mediocre inhibition on *C. albicans* (MIC > 10 μg·mL^{-1}), while a few displayed relatively strong effects against *C. albicans*, for instance, latifolol with MIC value of 2 μg·mL^{-1} [63]. It is also worth noting that pinocembrin, a potential neuroprotective compound, possessed good anti-*C. albicans* activity (MIC 6.25 μg·mL^{-1}) [53]. Moreover, the macrolides and peptides are small groups in Table 1, but both have good potential anticandidal activity. For example, PF1163A is a 13-membered macrolide which showed remarkable activity against *C. albicans* (MIC 1 μg·mL^{-1}) [73]. Cavinafungin A and cavinafungin B, two linear peptides, exhibited a broad spectrum of activity against *Candida* species (MIC 0.5−4 μg·mL^{-1}), where *C. tropicalis* was the most susceptible [77].

In addition, essential oils are proved to be effective against *Candida* species, such as thyme oil, tea tree oil, peppermint and clove oil [103]. Since there are several reviews describing the antimycotic activity of essential oils [104, 105], those studies are not included in the current article.

Anti-*Candida* Mechanism of Natural Products

In this part, we summarize the representative natural products with in-depth mechanism exploration in the past ten years. They are mostly pure compounds (Fig. 2), but several unique essential oils and extracts are also introduced. Their anti-*Candida* mechanisms are primarily related to inhibition of virulence factor, suppression of biofilm formation, damage of cell wall integrity, destruction of cell membrane flexibility and induction of cell apoptosis (Table 2).

Inhibition of Candida virulence factors

The major virulence factors that mediate fungal pathogenesis are adherence, hypha formation and the secretion of aspartyl proteases (SAPs) [106]. Adherence plays a crucial role in the early stages of *Candida* colonization and invasion through a variety of mechanisms. Disrupting the adhesion

Table 1 Sources, classifications and MICs of anti-*Candida* natural compounds

Classifications	Organism	Compounds	*Candida* species	MIC/(μg·mL^{-1})	Ref.
		Alkaloids			
Bromopyrrole alkaloids	*Agelas* sp.	Nagelamide U, W	*Ca*	4 [a]	[16]
Bipyridine alkaloids	*Actinoalloteichus cyanogriseus*	Caerulomycin A, C	*Ca*	21.8, 19.3 [#]	[17]
Bisindole alkaloids	*Hyrtios* sp.	Hyrtimomine D, E	*Ca*	4, 8 [a]	[18]
Imidazole alkaloids	*Pilocarpus pennatifolius*	Pennatifoline A	*Ck*	3.12	[19]
Piperidine alkaloids	*Picea abies*	Epidihydropinidine	*Ca*, *Cg*	5.37	[20]
Monoterpene indole alkaloids	*Rhazya stricta*	16, 17-Epoxyisositsirikine; tetrahydrosecodine; rhazinaline N_b-oxide; antirhine; eburenine; strictanol	*Ca*, *Cg*, *Cl*	3.125−12.5	[21]
Pyridone alkaloids	*Stagonosporopsis cucurbitacearum*	Didymellamide A	*Ca*, *Cg*	3.1	[22]
Quinolone alkaloids	*Waltheria indica*	8-Deoxoantidesmone; waltherione E, F, G, J; antidesmone	*Ca*, *Ck*, *Cp*	2−16	[23]
Alkaloids	*Aristolochia orbicularis*	Aristoloxazine A	*Ca*	25	[24]
Cytochalasan alkaloids	*Aspergillus micronesiensis*	Cyschalasin A, B	*Ca*	43.3, 94.7 [a]	[25]
Indole alkaloids	*Asteropus* sp.	Indolo[3, 2-*a*]carbazole	*Ca*	25	[26]
Guanidine alkaloids	*Pseudaxinella reticulate*	Crambescin A2 364, 392, 406, 420	*Ca*, *Cg*, *Ck*	6.1−39 [#, a]	[27]
Pyridine alkaloids	*Penicillium* sp.	Penicolinate B, C; phenopyrrozin; gliotoxin	*Ca*	1.45−12.48 [a]	[28]
Alkaloids	*Isaria farinose*	Militarinone B	*Ca*	43.4 ± 1.2 [#, a]	[29]
Alkaloids	*Pseudallescheria boydii*	Tyroscherin; *N*-methyltyroscherin	*Ca*, *Cp*	2−32	[30]
		Polyketides			
	Alternaria alternata	Altenuene-2-acetoxy ester; altenuene-3-acetoxy ester; altenuene; alterlactone	*Ca*	13.7−25 [b]	[31]
	Cananga latifolia	Cananginone H, I	*Ca*	75.2, 37.4 [#, a]	[32]
	Penicillium sp.	Penctrimertone	*Ca*	4	[33]
	Nostoc sp.	Carbamidocyclophane F, A, B	*Ca*	2.9, 5.5, 1.3 [#]	[34]
	Biatriospora sp.	Biatriosporin D, K; anhydrofusarubin; methoxynaphthazarin	*Ca*	16−64 [b]	[35]
	Phoma sp.	Colletotric A; 3-hydroxy-5-methoxy-2, 4, 6-trimethylbenzoic acid	*Ca*	3.27, 2.62	[36]
	Janthinobacterium sp.	Janthinopolyenemycin A, B	*Ca*	15.6	[37]
	Pestalotiopsis heterocornis	Heterocornol C, G; agropyrenol; vaccinol G	*Cp*	100	[38]
	Ulocladium sp.	7-Hydroxy-3; 5-dimethyl-isochromen-1-one	*Ca*	97.93 ± 1.12 [#]	[39]
	Decaschistia parviflora	Parvifloral A, E; syriacusin A, C	*Ca*	64−198 [#, a]	[40]
	Evodia lepta	(−)-Evodialone A; (+)-evodialone A	*Cp*, *Cg*	17.1, 34.2 [#]	[41]
	Hohenbuehelia grisea	Dihydropleurotinic acid	*Ca*, *Ct*	33.3, 25	[42]
	Triadenum japonicum	(−)-Nemorosonol; trijapin D	*Ca*	32, 8 [a]	[43]
	Floricola striata	Floricolin C	*Ca*	8	[44]
	Dendrodochium sp.	Dendrodochol A, C	*Ca*, *Cg*, *Cp*	8−16 [b]	[45]
		Phenolics			
Coumarins	*Clausena excavata*	Excavarin A	*Ca*, *Ct*	78, 39	[46]
Coumarins	*Pilocarpus pennatifolius*	Dimethyl allyl xanthyletin; jaborandine	*Ck*	15.6, 1.56	[19]
Isocoumarins	*Lachnum palmae*	Palmaerone A, B, D, E	*Ca*	50−75	[47]

Continued

Classifications	Organism	Compounds	*Candida* species	MIC/(μg·mL^{-1})	Ref.
Isocoumarin derivatives	*Pestalotiopsis* sp.	Pestalactone C	*Cg*	3.49 [a]	[48]
Isocoumarins	*Saccharomonospora azurea*	Saccharonol B	*Ca*	128−248	[49]
Isocoumarins	*Penicillium minioluteum*	Peniisocoumarin H	*Ca*	30	[50]
Flavonoids	*Mimosa caesalpiniifolia*	Mimocaesalpin B, C, D, E	*Cg*	3.9 [a]	[51]
Flavonoids	*Psiadia punctulata*	Arcapillin; 5, 7, 3′, 4′ tetramethoxyflavone	*Ca*	60, 30	[52]
Flavonoids	Combretaceae species	Pinocembrin	*Ca*	6.25	[53]
Flavonoids	*Eriosema chinense*	2-Hydroxylupinifolinol	*Ca*	37.5	[54]
Flavonoids	*Derris eriocarpa*	4′-Hydroxy-5, 7-dimethoxy-6-(3-methyl-2-butenyl)-isoflavone	*Ca*, *Cu*	12.5	[55]
Flavonoids	*Dalea formosa*	Sedonan A	*Cg*	20 [#]	[56]
Polyphenols	*Sapium baccatum*	Tercatain; 1, 2, 3, 4, 6-penta-*O*-gally-*β*-D-glucopyranose	*Ca*	64	[57]
Polyphenols	*Glycyrrhiza iconica*	(3*S*)-Licoricidin; topazolin	*Ca*	31	[58]
Polyphenols	*Dimocarpus longan*	Ellagic acid	*Cp*	7.81	[59]
Polyphenols	*Limonium caspium*	5-Methylmyricetin; myricetin; myricetin-3-*O*-*β*-glucoside	*Cg*	6−16 [a]	[60]
Polyphenols	*Symphyocladia latiuscula*	Symphyocladin G	*Ca*	10	[61]
Polyphenols	*Woodfordia uniflora*	Woodfordiamycin; catechin 4′-*O*-gallate; procyanidin B3-3-*O*-gallate	*Ca*	15−60 [#]	[62]
Polyphenols	*Spirotropis longifolia*	Piceatannol; latifolol	*Cp*, *Ca*, *Ck*	1−2	[63]
Quinones	*Streptomyces* sp.	Strepoxepinmycin A, B, C, D; medermycin	*Ca*	5−10	[64]
Quinone	*Rubia yunnanensis*	2-Methoxy-1, 4-naphthoquinone	*Ca*	16.0 [#, a]	[65]
Stilbenoids	*Scirpus yagara*	Sciryagarol I, II	*Ca*	152, 79.3	[66]
Phenols	*Cadophora* sp.	Isosclerone	*Ca*	40	[67]
Xanthones	*Talaromyces funiculosus*	Funiculosone	*Ca*	35 [a]	[68]
Phenylpropanoid glycosides	*Cathaya argyrophylla*	3-*O*-*β*-D-glucopyranoside	*Ca*	10.74 ± 1.25 [#,a]	[69]
		Saponins			
Spirostanol glycosides	*Trillium kamtschaticum*	*β*-D-glucopyranoside; floribundasaponin B; pennogenin 3-*O*-*β*-chacotrioside; polyphyllin V; ophiopogonin B	*Ca*	8−22 [#]	[70]
		Glycolipids			
	Ustilago maydis	Ustilagic acid B, C	*Ca*	50−100	[71]
		Macrolides			
	Penicillium fuscum and *P. camembertii/clavigerum*	Berkeleylactone A	*Ca*, *Cg*	6−26	[72]
	Penicillium meleagrinum	PF1163A, B	*Ca*	1−2	[73]
	Streptomyces sp.	Bahamaolide A	*Ca*	12.5	[74]
	Acremonium sp.	(+)-Brefeldin A	*Ca*	32	[75]
		Peptides			
Antimicrobial peptides	*Hylaeus signatus*	HYL-3, 8	*Ca*	5−5.2 [#]	[76]
Linear lipopeptides	*Colispora cavincola*	Cavinafungin A, B	*Ca*, *Cg*, *Ck*, *Cp*, *Ct*, *Cl*	0.5−4	[77]
Hydrophilic peptides	*Satureja khuzistanica*	Skh-AMP1	*Ca*, *Ck*, *Cg*	19~22 [#]	[78]
Cyclic pentapeptides	*Xylaria* sp.	Cyclicpeptide 1	*Ca*	6.25	[79]

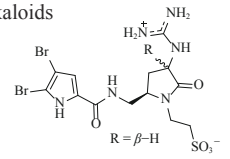
Continued

Classifications	Organism	Compounds	*Candida* species	MIC/(μg·mL^{-1})	Ref.
Glutarimide peptides	*Streptomyces* sp.	Streptoglutarimide D, I	*Ca*	8, 12	[80]
		Terpenoids			
Sesquiterpenoids	*Anvillea garcinii*	Guaiane sesquiterpene lactone 1, 2	*Ca*, *Cp*	15−45	[81]
Sesquiterpenoids	*Acremonium* sp.	Trichodermol	*Ca*	64	[75]
Sesquiterpenoids	*Penicillium minioluteum*	Purpuride E, F, G	*Ca*	6−25	[50]
Diterpenoids	*Stachybotrys chartarum*	Atranone Q	*Ca*	8	[82]
Sesquiterpenoids	*Chloranthus angustifolius*	Henriol A; spicachlorantin A; chloramultilide A; shizukaol B; tianmushanol; 8-*O*-methyltianmushanol	*Ca*	4−8	[83]
Diterpenoids	*Chloranthus henryi*	3*β*-Hydroxyabieta-8, 11, 13-trien-7-one	*Ca*	97.3 [#, a]	[84]
Sesquiterpenoids	*Chiliadenus montanus*	Chiliadenol A, D	*Ca*	6.25, 3.125	[85]
Diterpenoids	*Drechmeria* sp.	Drechmerin B	*Ca*	12.5	[86]
Meroterpenoids	*Eucalyptus robusta*	(+)-Eucalrobusone X; eucalrobusone U	*Ca*, *Cg*	10.78, 1.53 [a]	[87]
Triterpenoids	*Ganoderma gibbosum*	Gibbosicolid A, D; gibbosic acid I, L; applanoxidic acid A, B, F	*Ca*	2−10 [a]	[88]
Meroterpenoids	*Hypericum yojiroanum*	Yojironin A	*Ca*	2 [a]	[89]
Sesquiterpenoids	*Hyalis argentea*	Onoseriolide acetate	*Ca*	15.6 [a]	[90]
Diterpenoids	*Heteroscyphus coalitus*	Heteroscyphin D	*Ca*	4	[91]
Sesquiterpenoids	*Laurencia okamurai*	Laurepoxyene; 3*β*-hydroperoxyaplysin; laurokamurene C	*Cg*	1−4 [b]	[92]
Diterpenoids	*Microporus* Species	Microporenic acid D, E	*Ct*	37.5	[93]
Sesquiterpenoids	*Pogostemon cablin*	Patchouliguaiol C, F	*Ca*	500, 300 [#]	[94]
Triterpenoids	Pitcairn Island	3-Oxo-cycloart-24*E*-en-21, 26-diol-21, 26-diacetate	*Ca*	64	[95]
Sesquiterpenoids	*Plagiochila fruticosa*	Plagicosin F	*Ca*	16	[96]
Triterpenoids	*Rubia yunnanensis*	Rubiarbonol G	*Ca*	10.8 [#, a]	[65]
Diterpenoids	*Swartzia simplex*	(5*S*, 10*S*)-11, 15(*R*)-Dihydroxy, 12-methoxyswartziarboreol G; simplexene D	*Ca*	32	[97]
Sesquiterpenoids	*Streptomyces albolongus*	Bafilomycin C1; bafilomycin C1 amide; 21-deoxybafilomycin A1; dimethyloctahydronaphthalene-1, 4a(2*H*)-diol	*Cp*	1.56−3.13	[98]
Sesquiterpenoids and Diterpenoids	*Xylaria* sp.	(1*S*, 4*S*, 5*S*, 7*R*, 10*R*, 11*S*)-Guaiane-1, 10, 11, 12-tetraol; (1*R*, 4*S*, 5*S*, 7*S*, 9*R*, 10*S*, 11*R*)-guaiane-9, 10, 11, 12tetraol; 9-deoxy-hymatoxin A	*Ca*	16−32	[99]
Sesquiterpenoids	*Trichoderma brevicompactum*	Trichodermin; (4*β*)-4-(acetyloxy)-12, 13-epoxytrichothec-9-ene-9-carboxaldehyde	*Ca*	1~2	[100]
Sordarin diterpene glycosides	*Curvularia hawaiiensis*	Moriniafungin E	*Ca*	2.9 [#]	[101]
Triterpenoid saponins	*Sapindus mukorossi*	Oleanolic acid arabinopyranoside	*Ca*	8 [b]	[102]

[a] MIC_{50}: the minimum concentration of a drug that inhibits 50% fungal growth; [b] MIC_{80}: the minimum concentration of a drug that inhibits 80% fungal growth; [#] μmol·L^{-1}; *Ca*: *Candida albicans*; *Cg*: *Candida glabrata*; *Cu*: *Candida.guilliermondii*; *Ck*: *Candida krusei*; *Cp*: *Candida parapsilosis*; *Ct*: *Candida tropicalis*; *Cl*: *Candida lusitaniae*

process can prevent further colonization of host tissue, thereby controlling the infected proceedings [107]. Hypha formation is essential for candidiasis at the superficial and systemic levels. Targeted inhibition of this morphological switch may provide an attractive approach for inhibiting the infectious progression [108-110]. Besides, the SAPs have been reported to directly mediate virulence by cleaving several important proteins in host defense, such as antibodies of immunoglobulin G and A isotypes, thus damaging host tissues and promoting infection. Repression of these proteases may not

Alkaloids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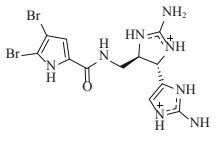
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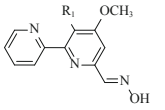
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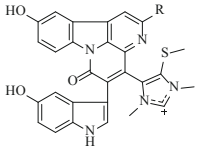
R_1 = OCH_3 Caerulomycin C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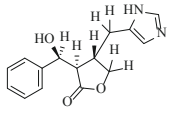
R = COOH Hyrtimomine E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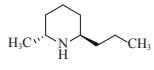
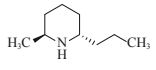
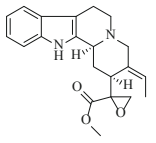
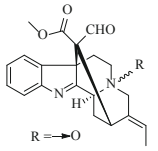
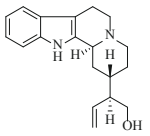
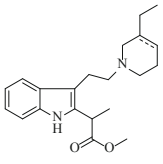

(+)−Epidihydropinidine

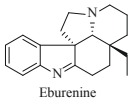

(−)−Epidihydropinidine

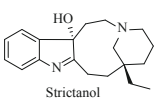

16, 17−Epoxyisositsirikine

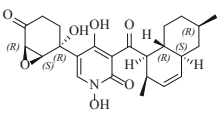

Rhazinaline N_b−oxide

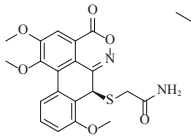

Antirhine

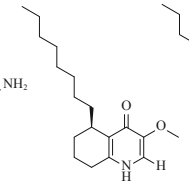

Tetrahydrosecodine

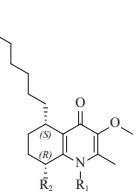

Eburenine

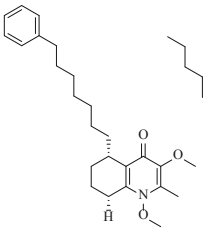

Strictanol

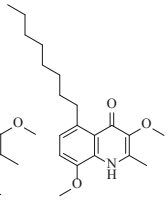

Didymellamide A

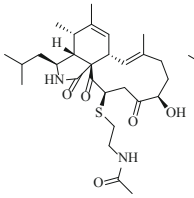

Aristoloxazine A

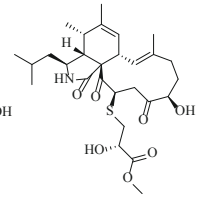

8−Deoxoantidesmone

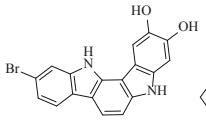

R_1 = H, R_2 = O Antidesmone
R_1 = H, R_2 = OCH_3 Waltherione E
R_1 = OCH_3, R_2 = H Waltherione J

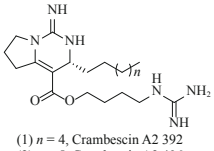

Waltherione G

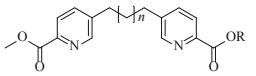

Waltherione F

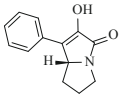

Cyschalasin A

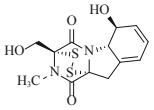

Cyschalasin B

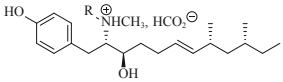

Indolo[3, 2−a]carbazole

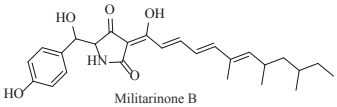

(1) *n* = 4, Crambescin A2 392
(2) *n* = 5, Crambescin A2 406
(3) *n* = 6, Crambescin A2 420
(4) *n* = 2, Crambescin A2 364


n = 8, R = H Penicolinate B
n = 6, R = CH_3 Penicolinate C

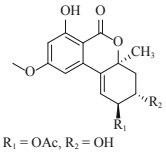

Phenopyrrozin

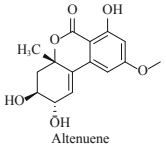

Gliotoxin

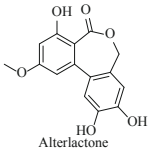

R = H Tyroscherin
R = CH_3 *N*−methyltyroscherin

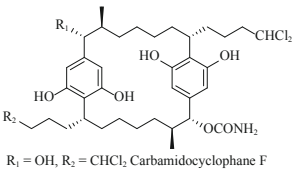

Militarinone B

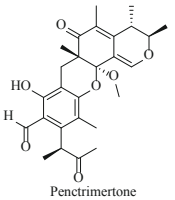
Polyketides

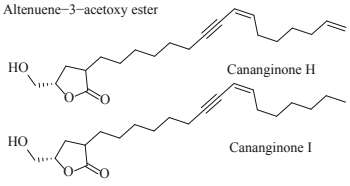

R_1 = OAc, R_2 = OH
Altenuene−2−acetoxy ester
R_1 = OH, R_2 = OAc
Altenuene−3−acetoxy ester

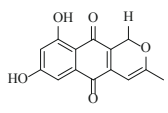

Altenuene

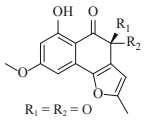

Alterlactone

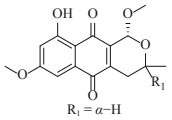

R_1 = OH, R_2 = $CHCl_2$ Carbamidocyclophane F
R_1 = $OCONH_2$, R_2 = $CHCl_2$ Carbamidocyclophane A
R_1 = $OCONH_2$, R_2 = CH_2Cl Carbamidocyclophane B

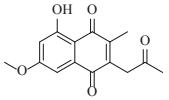

Penctrimertone

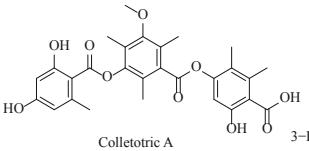

Cananginone H
Cananginone I

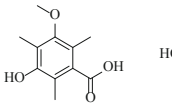

Anhydrofusarubin


R_1 = R_2 = O Biatriosporin D


R_1 = α−H Biatriosporin K


Methoxynaphthazarin


Colletotric A


3−Hydroxy−5−methoxy−2, 4, 6−trimethylbenzoic acid

Janthinopolyenemycin A

Janthinopolyenemycin B

Heterocornol C

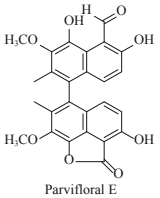
Agropyrenol

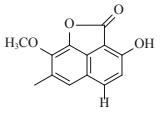
Heterocornol G

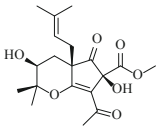
Vaccinol G

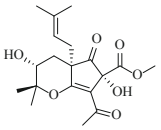
7−Hydroxy−3, 5−dimethyl−isochromen−1−one

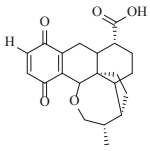
R_1 = OH, R_2 = OCH_3 Parvifloral A
R_1 = OCH_3, R_2 = OH Syriacusin A

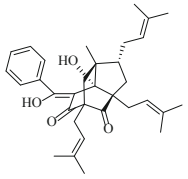

Parvifloral E

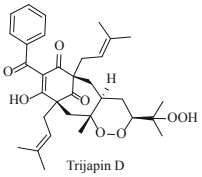

Syriacusin C

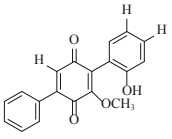

(−)−Evodialone A

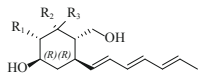

(+)−Evodialone A


Dihydropleurotinic acid

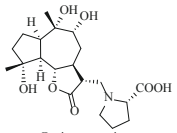

(−)−Nemorosonol

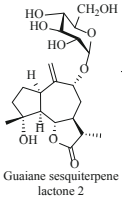

Trijapin D

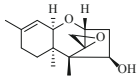

Floricolin C

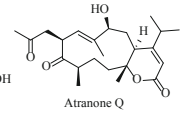

R_1 = OH, R_2, R_3 = O Dendrodochol A
R_1 = R_3 = H, R_2 = OH Dendrodochol C

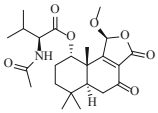
Terpenoids

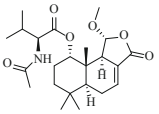

Guaiane sesquiterpene lactone 1

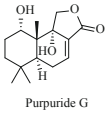

Guaiane sesquiterpene lactone 2

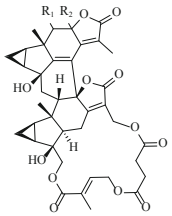

Trichodermol

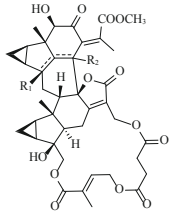

Atranone Q

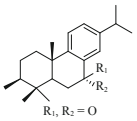

Purpuride E

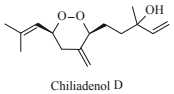

Purpuride F

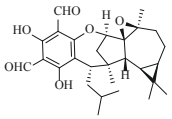

Purpuride G

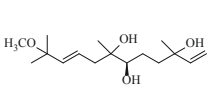

R_1 = β−OH, R_2 = α−OH Henriol A
R_1 = O, R_2 = α−OH Spicachlorantin A
R_1 = β−OH, R_2 = β−OH Tianmushano
R_1 = β−OH, R_2 = β−OCH$_3$ 8−*O*−methyltianmushanol

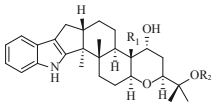

R_1 = OH, $\Delta^{5,6}$ Chloramultilide A
R_2 = H, $\Delta^{4,5}$ Shizukaol B

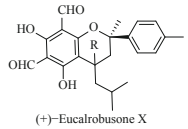

R_1, R_2 = O
3β-Hydroxy-8, 11, 13-trien-7-one

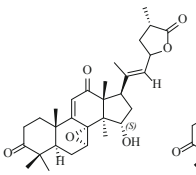

Chiliadenol D

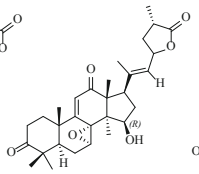

Eucalrobusone U

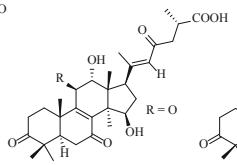

Chiliadenol A

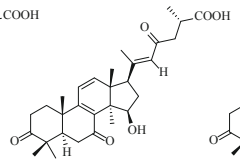

R_1 = COOH, R_2 = H
Drechmerin B

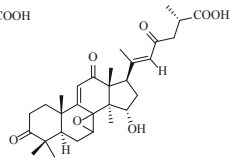

(+)−Eucalrobusone X

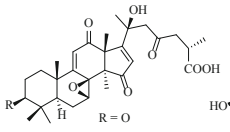

Gibbosicolid A

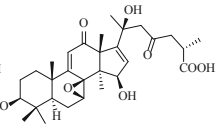

Gibbosicolid D

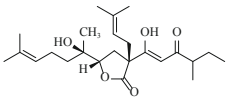

R = O
Gibbosic acid I

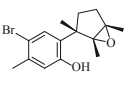

Gibbosic acid L

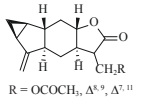

Applanoxidic acid A

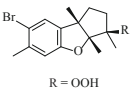

R = O
Applanoxidic acid B

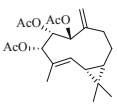

Applanoxidic acid F

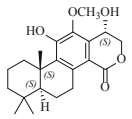

Yojironin A

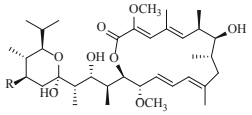

Laurepoxyene

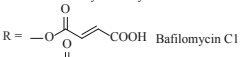

R = OCOCH$_3$, $\Delta^{8,9}$, $\Delta^{7,11}$
Onoseriolide acetate

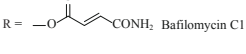

R = OOH
3β−Hydroperoxyaplysin


Plagicosin F


(5*S*, 10*S*)−11, 15(*R*)−Dihydroxy, 12−methoxyswartziarboreol G


R = H 21−Deoxybafilomycin A1


R = Bafilomycin C1


R = Bafilomycin C1 amide

Dimethyloctahydronaphthalene −1, 4α (2*H*)−diol

Rubiarbonol G

Simplexene D

Heteroscyphin D

Laurokamurene C

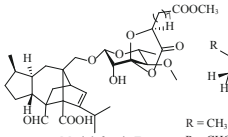
Microporenic acid D

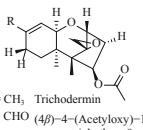
Microporenic acid E

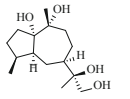
Patchouliguaiol C

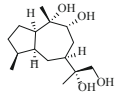
Patchouliguaiol F

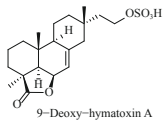
3−Oxo−cycloart−24*E*−en−21, 26−diol−21, 26−diacetate

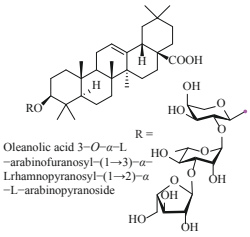

Moriniafungin E


R = CH_3 Trichodermin
R = CHO (4β)−4−(Acetyloxy)−12, 13 −epoxytrichothec−9−ene −9−carboxaldehyde

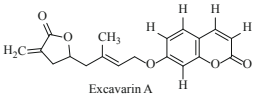

(1*S*, 4*S*, 5*S*, 7*R*, 10*R*, 11*S*)−Guaiane−1, 10, 11, 12−tetraol

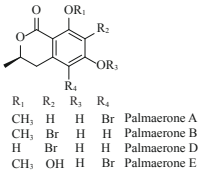

(1*R*, 4*S*, 5*S*, 7*S*, 9*R*, 10*S*, 11*R*)−Guaiane−9, 10, 11, 12tetraol

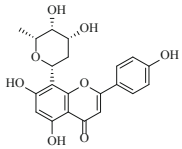

9−Deoxy−hymatoxin A

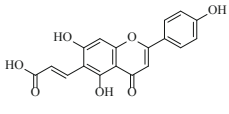

R =
Oleanolic acid 3−*O*−*α*−L −arabinofuranosyl−(1→3)−*α*− Lrhamnopyranosyl−(1→2)−*α* −L−arabinopyranoside

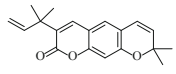
Other types

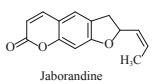

Excavarin A

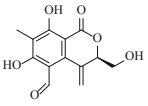

R_1	R_2	R_3	R_4	
CH_3	H	H	Br	Palmaerone A
CH_3	Br	H	H	Palmaerone B
H	Br	H	H	Palmaerone D
CH_3	OH	H	Br	Palmaerone E

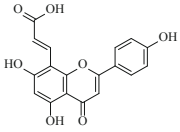

Mimocaesalpin B

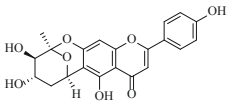

Mimocaesalpin C

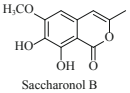

Dimethyl allyl xanthyletin

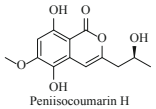

Jaborandine

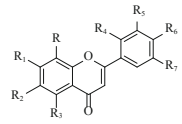

Pestalactone C

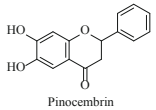

Mimocaesalpin D


Mimocaesalpin E

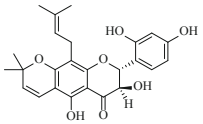

Saccharonol B

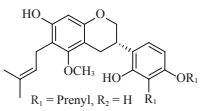

Peniisocoumarin H

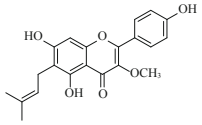

R R1 R2 R3 R4 R5 R6 R7
H OCH3 OCH3 OH OH H OH OCH3
H OCH3 H OCH3 H OCH3 OCH3 H

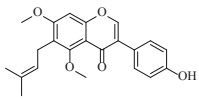

Pinocembrin

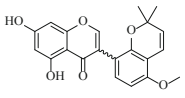
Arcapillin
5, 7, 3', 4'−Tetramethoxyflavone

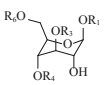

2−Hydroxylupinifolinol

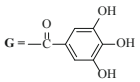

R_1 = Prenyl, R_2 = H
(3*S*)−Licoricidin

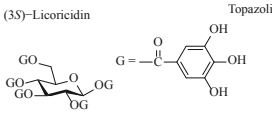

Topazolin

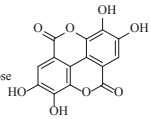

4'−Hydroxy−5, 7−dimethoxy− 6−(3−methyl−2−butenyl)− isoflavone

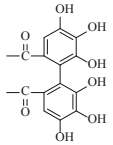

Sedonan A


R_1 = G, R_3−R_6 = HHDP, R_4 = G
Tercatain


G =


1, 2 , 3 , 4, 6−Penta−*O*−gally−*β*−D−glucopyranose


Ellagic acid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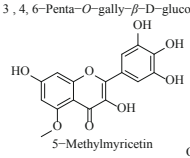
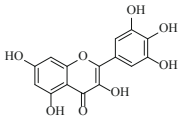
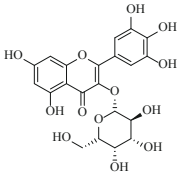
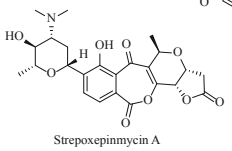
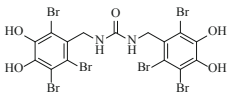
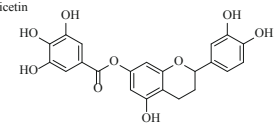

5−Methylmyricetin

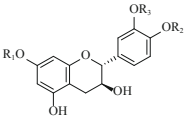

Myricetin

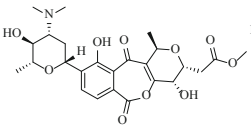

Myricetin−3−*O*−*β*−Glucoside

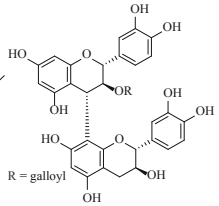

Strepoxepinmycin A

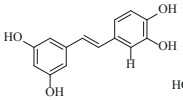

Symphyocladin G

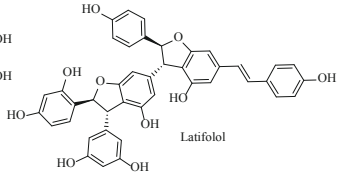

Woodfordiamycin


R_1 = H, R_2 = H, R_3 = galloyl
Catechin 4'−*O*−gallate


Strepoxepinmycin B


R = galloyl
Procyanidin B3−3−*O*−gallate


Piceatannol


Latifolol

Strepoxepinmycin C

Strepoxepinmycin D

R = H Sciryagarol I
R = OH Sciryagarol II

CH_2O−b−D−Glc
3−*O*−*β*−D−Glucopyranoside

Isosclerone

2−Methoxy−1, 4−naphthoquinone

Funiculosone

Medermycin

Ustilagic acid B

Ustilagic acid C

R_1 = S_2, R_2 = H, R_3 = H Polyphyllin V
R_1 = H, R_2 = OS_5, R_3 = H Ophiopogonin B

R_1 = S_2, R_1 = H Pennogenin 3−*O*−*α*−L−rhamnopyranosyl− (1→2)−*β*−D−glucopyranoside
R_1 = S_3, R_2 = H Floribundasaponin B
R_1 = S_5, R_2 = H Pennogenin 3−*O*−*β*−chacotrioside

S_2 = S_3 = S_4 = S_5 =

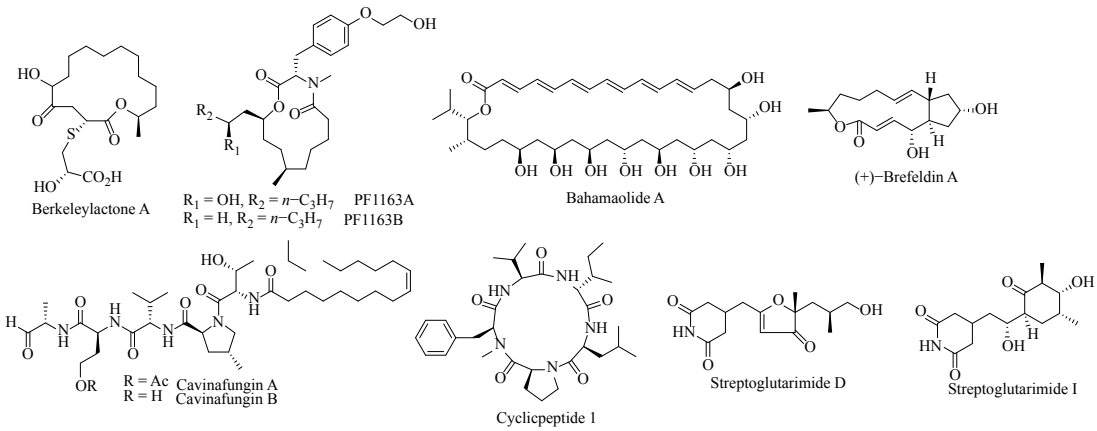


Fig. 1 The structures of anticandidal natural products in Table 1

kill *Candida* cells but cause their incapability in infection [111]. In brief, targeting virulence is an appealing method in the development of novel antifungals. Many natural products possess virulence inhibitory properties over the last decade.

The essential oil extracted from *Rosmarinus offcinalis* showed strong anti-adherent activity against *C. albicans* through significant cell disruption [112]. The extracts of *Schinus terebinthifolius* and *Croton urucurana* inhibited the adherent potency on biofilm formed by *C. albicans* [113]. Tea saponin effectively inhibited the yeast-to-hyphal transition *in vitro* by decreasing the intracellular cAMP level which is essential for filamentation [114]. Similarly, biatriosporin D (**1**) isolated from an endolichenic fungus *Biatriospora* sp. also exhibited anti-virulence activity through reducing intracellular cAMP levels [35, 115-117]. Solasodine-3-*O*-*β*-D-glucopyranoside (**2**) isolated from *Solanum. nigrum* L. constructively attenuated the virulence and biofilm formation of *C. albicans*. Further studies showed that down-regulation of genes in the Ras1-cAMP-PKA signaling pathway and reduction of cAMP content accounted for its activity [118, 119]. Plagicosin F (**3**) displayed potent anti-virulence activity by inhibiting adherence, hyphal morphogenesis and biofilm formation of *C. albicans* [98]. Curcumin (**4**), a yellow pigment extracted from the roots of *Curcuma longa*, reduced the proteolytic enzyme activities of phospholipases and the SAPs without down-regulating gene expression, thereby exhibiting slight antifungal activity against *C. albicans* [120]. Ellagic acid (**5**) from *Miconia myriantha* also inhibited the SAPs of *C. albicans* [121].

Inhibition of Candida biofilm formation

The biofilm of *Candida* has a dense three-dimensionalstructure and contains rich extracellular polymer matrix [122, 123]. It can generate highly drug-resistant persisters, and thereby protect fungal cells from external factors such as host immune system defense and antifungal drugs. With respect to biofilm formation, the fungi can adhere to different surfaces, such as intravascular catheters, prosthetic heart valves and joint replacements, or sustain in different tissues in the host, and eventually exacerbate clinical fungal infections [124]. The formation of *Candida* biofilm has important clinical repercussions, and the emergence of antifungal resistance with the development of biofilms is still an intractable problem. As there are few therapeutic options for *Candida* biofilm-related diseases, it is urgent to develop new anti-biofilm agents [125]. Some natural products exhibited anti-biofilm effects by reducing cell adhesion, inhibiting yeast-hypha morphological transformation, or acting directly on mature biofilm.

Formyl-phloroglucinol meroterpenoids (FPMs) are a unique class of secondary metabolites of the genera *Eucalyptus* and *Psidium*, which were reported for their antifungal activities against *Candida* spp. [126]. Our previous research found that an FPM from the leaves of *E. robusta*, eucarobustol E (**6**), exhibited potent inhibitory effects against *C. albicans* biofilm [127]. It inhibited the expression of hypha specific genes, which might be achieved through stimulating the farnesol production to active the negative regulatory mechanism [128]. Riccardin D (**7**) is a macrocyclic bisbibenzyl isolated from the liverwort *Dumortiera hirsute*, which interfered with the biofilm formation of *C. albicans* through downregulating the expression of hypha specific genes and inhibiting the formation of hyphae [129]. Waikialoid A and waikialide A (**8**, **9**) are obtained from the metabolites of an *Aspergillus* spp., which were found to reduce cell adherence, hyphal development, and/or biofilm assembly during the early stage of surface colonization [130]. Baicalein (**10**) is a major active component of *Scutellaria baicalensis*, and studies indicated that it reduced the cell surface hydrophobicity (CSH) of biofilm by decreasing *CSH1* expression, thus reducing adhesion, thereby inhibiting the biofilm formation of *C. albicans* [131]. Roemerine (**11**) is an aporphine alkaloid isolated from *Fibraurea recisa,* which showed anti-biofilm effects similarly through decreasing the CSH [132]. Xanthochymol and garcinol (**12**, **13**) are benzophenones isolated from *Garcinia xantuochymus*, which effectively inhibited the germination tube and induced apoptosis of early and mature biofilm cells, hence directly killing hypha and biofilm [133].

Disruption in Candida cell wall

The essential cell wall of fungi is mainly composed of chitin, glucan and glycoproteins [134, 135]. It protects fungal

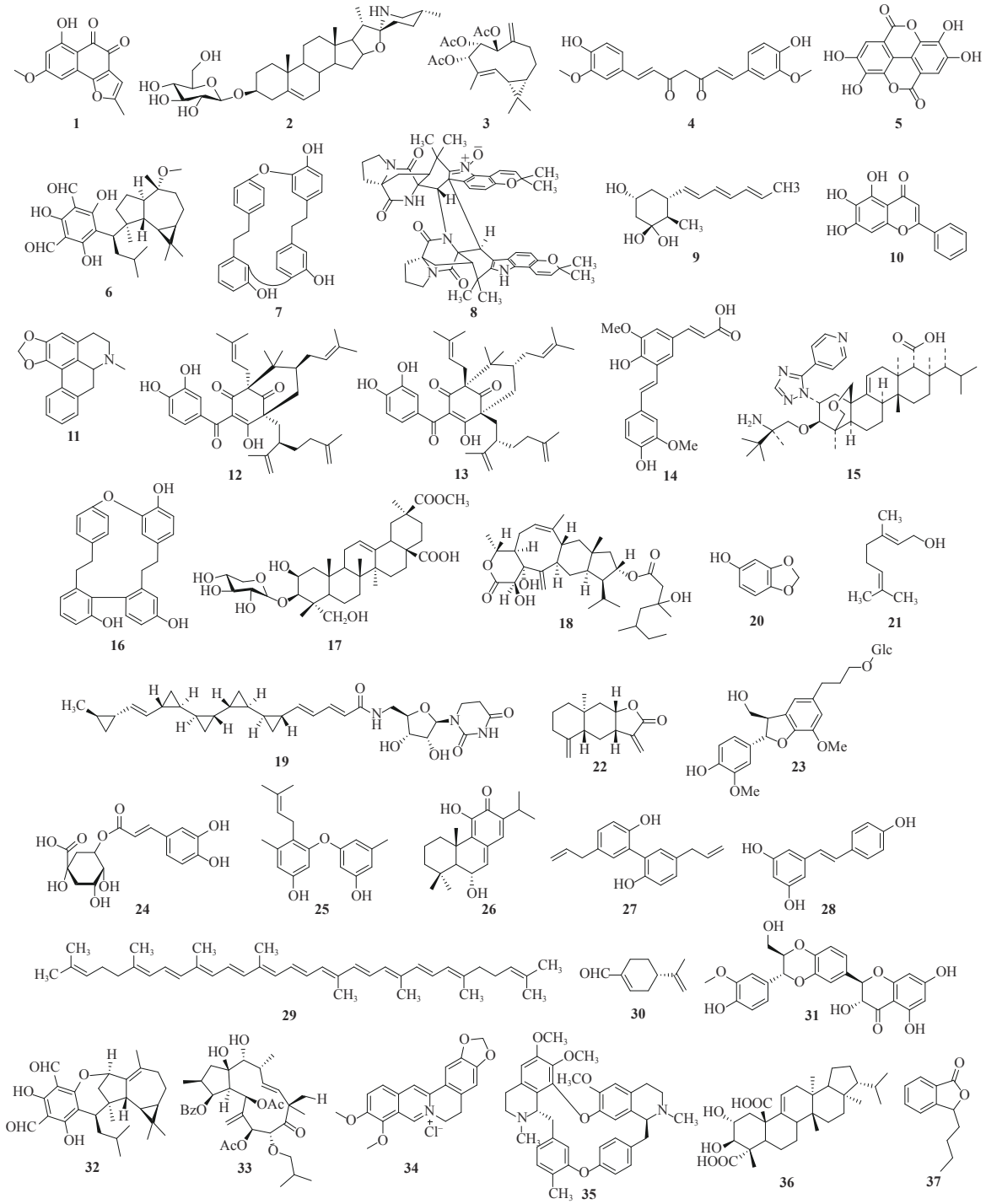


Fig. 2 Structures of anticandidal natural products 1–37

cells from changes in osmotic pressure and different environmental stress, while mediating cell interaction with the environment. Fungal cell walls are structurally unique and significantly differ from mammalian cells, which therefore are attractive targets for antifungal therapy [136]. The echinocandin is the first clinic agent that targets fungal cell wall by inhibiting the synthesis of β-1, 3-D-glucan [137]. The nikkomycin Z is currently under Phase II clinical trials, and reported to competitively inhibit chitin synthase [138]. This section describes several natural products that also act on the cell wall of *Candida*.

Poacic acid (**14**) is found in lignocellulosic hydrolysates of grasses, which inhibited the growth of numerous fungus by directly binding β-1, 3-glucan [139, 140]. Similarly, SCY-078 (**15**) is a structurally novel triterpene, which is an orally bioavailable β-1, 3-D-glucan synthase inhibitor first isolated

Table 2 The antifungal mechanisms of anti-*Candida* natural products

Organism	Compounds	No.	*Candida* species	Mechanism of action/target	Ref.
Rosmarinus offcinalis	Essential oils	--	*Ca*, *Ct*	Adherence, cell disruption	[112]
Schinus terebinthifolius/Croton urucurana	Crude extract	--	*Ca*	Adherence, biofilm formation	[113]
Camellia plants	Teasaponin	--	*Ca*	cAMP level, yeast-to-hyphal transition	[114]
Biatriospora sp.	Biatriosporin D △	**1**	*Ca*	cAMP level	[35, 115-117]
Solanum nigrum	Solasodine-3-*O*-*β*-D-glucopyranosid △	**2**	*Ca*	cAMP content, Ras1-cAMP-PKA pathway	[118, 119]
Plagiochila fruticosa	Plagicosin F	**3**	*Ca*	Adherence, hyphal morphogenesis, biofilm formation	[98]
Curcuma longa	Curcumin	**4**	*Ca*	Phospholipases, the SAPs	[120]
Miconia myriantha	Ellagic acid	**5**	*Ca*	the SAPs	[121]
Eucalyptus robusta	Eucarobustol E	**6**	*Ca*	Hypha specific genes, biofilm formation	[127, 128]
Liverwort	Riccardin D	**7**	*Ca*	Hypha specific genes, biofilm formation	[129]
Hawaiian Aspergillus	Waikialoid A; waikialide A	**8**, **9**	*Ca*	Adherence, hyphal development, biofilm assembly	[130]
Scutellaria baicalensis	Baicalein	**10**	*Ca*	*CSH1* expression, CSH reduction, biofilm formation	[131]
Fibraurea recisa	Roemerine	**11**	*Ca*	CSH reduction, biofilm formation	[132]
Garcinia xantuochymus	Xanthochymol; garcinol	**12**, **13**	*Ca*	Germination tube inhibition, apoptosis, biofilm formation	[133]
Lignocellulosic hydrolysates of grasses	Poacic acid	**14**	*Ca*, *Ct*, *Ck*, *Cg*, *Cp*	*β*-1, 3-glucan synthase	[139, 140]
Hormonema sp.	SCY-078 △	**15**	*Ca*	*β*-1, 3-D-glucan synthase	[141]
Marchantia polymorpha	Plagiochin E	**16**	*Ca*	Chitin synthesis (Chs1, Chs2 and Chs3 chitinases)	[142,143]
Phytolacca tetramera	Phytolaccoside B	**17**	*Ca*	Chitin synthesis (Chs1 chitinase)	[144]
Codinea simplex	YW3548 △	**18**	*Ca*, *Ck*, *Cg*, *Cp*, *Cl*	GPI biosynthesis (*Mcd4*)	[145, 146]
Oligocyclopropylcontainig natural product	Jawsamycin △	**19**	*Ca*	GPI biosynthesis (Gpi3 subunit)	[147, 148]
Sesamum sp.	Sesamol	**20**	*Ca*, *Ck*, *Cg*, *Cp*, *Ct*	Calcineurin pathway, ergosterol biosynthesis	[153]
Palmarosa oil	Geraniol	**21**	*Ca*, *Cg*, *Ct*	Ergosterol biosynthesis	[154]
Raphanus sativus	RsAFP2	--	*Ca*	Sphingolipid glucosylceramie	[155, 156]
Tritomaria quinquedentata	*ent*-Isoalantolactone	**22**	*Ca*	Ergosterol biosynthesis (Erg11 and Erg6)	[157]
Sambucus williamsii	Glochidioboside	**23**	*Ca*, *Cp*	Membrane depolarization and permeabilization	[158]
Several fruit and plants	Chlorogenic acid	**24**	*Ca*	Membrane potential and fluidity	[159]
Aspergillus versicolor	Diorcinol D	**25**	*Ca*, *Ck*, *Cg*, *Cp*, *Ct*	Membrane integrity, intracellular ROS production	[160]
Metasequoia Glyptostroboides	Taxodone	**26**	*Ca*, *Cg*, *Cp*, *Ct*	Membrane permeability and plasticity	[161]
Magnolia officinalis	Honokiol △	**27**	*Ca*, *Ck*, *Cg*, *Cp*, *Ct*	Mitochondrial membrane potential, accumulation of ROS	[167, 168]
Polygonum cuspidatum	Resveratrol	**28**	*Ca*, *Ck*, *Cg*, *Cp*, *Ct*, *Cd*	Mitochondrial membrane potential, accumulation of ROS	[169, 170]
Apis mellifera	Melittin	--	*Ca*	Accumulation of ROS, apoptosis	[171]
Psacothea hilaris	Psacotheasin	--	*Ca*	Accumulation of ROS, apoptosis	[172]

Continued

Organism	Compounds	No.	*Candida* species	Mechanism of action/target	Ref.
Ocimum sanctum	Essential oil	--	*Ca*	Cytochrome *c* release, apoptosis	[174, 175]
Solanum lycopersicum	Lycopene	**29**	*Ca*	Cytochrome *c* release, mitochondrial depolarization	[176, 177]
Perilla frutescens	Perillaldehyde	**30**	*Ca*	Intracellular Ca^{2+} level, apoptosis	[179]
Silybum marianum	Silibinin	**31**	*Ca*, *Cp*	Mitochondrial Ca^{2+} influx pathway, apoptosis	[180]

--: not specified; *Ca*: *Candida albicans*; *Ck*: *Candida krusei*; *Cg*: *Candida glabrata*; *Cp*: *Candida parapsilosis*; *Ct*: *Candida tropicalis*; *Cl*: *Candida lusitaniae*; *Cd*: *C. dubliniensis*; $^{\triangle}$ *in vivo* and *in vitro* experiments (no special note means that the compound has only been tested *in vitro*)

from the fungus *Hormonema* sp. [141]. Plagiochin E (**16**), an antifungal macrocyclic bis(bibenzyl) isolated from liverwort *Marchantia polymorpha* L. [142], reduced the activity of the three chitinases (Chs1, Chs2 and Chs3) in a concentration-dependent manner, resulting in the synthetic failure of chitinase and structure defect of cell wall in *C. albicans* [143]. Phytolaccoside B (**17**) is isolated from *Phytolacca tetramera* which displayed efficacious antifungal activity through altering the typical structure of cell wall. It was shown to boost the vitality of Chs1 in *Candida* to produce an abnormally thicker cell wall [144]. YW3548 (**18**) is a metabolite from *Codinea simplex*. It inhibited the biosynthesis of glycosyl phosphatidylinositol (GPI) by blocking Mcd4-mediated ethanolaminephosphate transferase activity, thereby destroying cell wall integrity [145, 146]. Jawsamycin (**19**), an oligocyclopropyl-containing compound discovered in the fermentation broth of *Streptoverticillium fervens* HP-891, disrupted the integrity of cell wall by selectively and potently targeting the catalytic subunit Gpi3 of the fungal UDP-glycosyltransferase [147, 148].

Alteration in Candida cell membrane

The fungal cell membrane is primarily composed of sterols, glycerophospholipids and sphingolipids. It provides the material basis for various functional proteins and maintains structural integrity of the membrane [149]. Ergosterol is an abundant sterol, which is responsible for the permeability and fluidity of cell membrane [150]. Most antifungal drugs disturb the function of ergosterol by interfering with different steps of ergosterol biosynthesis (e.g., allylamines, azoles and morpholines) or directly combining with ergosterol (e.g., polyenes), thus leaking intracellular contents and causing cell death [151]. Glycerophospholipids and sphingolipids act to regulate cellular functions and signal transduction pathways. Several compounds have been reported to inhibit fungal glycerophospholipid and sphingolipid biosynthesis, which exerted antimycotic effects by inhibiting various enzymes in the pathway [152]. Therefore, targeting fungal cell membrane is a common approach to explore and develop antifungals. Meanwhile, a large number of natural products presented prominent fungistatic effects by impairing cell membrane.

According to recent studies, sesamol (**20**) devastated the calcineurin pathway of *C. albicans*, which led to a significant decrease in ergosterol content, thus damaging the integrity of cell membrane [153]. Similarly, geraniol (**21**), a common component of various essential oils, strikingly reduced ergosterol content at sub-MIC concentrations [154]. RsAFP2, a plant defensin isolated from *Raphanus sativus*, exhibited potent antifungal effects at micromolar concentrations [155]. Reports have demonstrated that the special interaction of RsAFP2 with fungal sphingolipid glucosylceramide led to subsequent permeabilization, Ca^{2+} influx and growth arrest [156]. Several eudesmane sesquiterpenes from *Tritomaria quinquedentata* were found active against efflux pump-deficient *C. albicans* strains. For instance, *ent*-isoalantolacton (**22**) interfered with sterol synthesis by targeting Erg6 and Erg11 of *C. albicans* to exert antimicrobial activity [157]. Natural products can also destroy the structure of cell membrane by affecting its physicochemical properties. Glochidioboside (**23**), obtained from *Sambucus williamsii*, played fungistatic activity by inducing membrane depolarization and permeabilization [158]. Chlorogenic acid (**24**) disrupted membrane potential and changed the fluidity of cell membrane [159]. Diorcinol D (**25**), isolated from *Aspergillus versicolor*, caused loss of cell membrane integrity and increased intracellular ROS production [160]. Similarly, taxodone (**26**) increased cell permeability and disrupted the membrane plasticity of tested *Candida* isolates [161].

Induction of Candida apoptosis

Apoptosis is a programmed cell death process in eukaryotes, which involves a series of enzymes under the control of specific genes [162, 163]. For fungal cells, apoptosis is a key regulatory factor of their occurrence and development, and it is possible to find new ways to control fungal infection through regulating apoptosis [164]. In recent years, many natural products have been revealed to induce the apoptosis of *Candida*, and the underlying mechanisms are mainly reactive oxygen species (ROS) dependent pathway, cytochrome *c* pathway and Ca^{2+} pumping pathway.

Mitochondrial respiration plays a critical role in the survival of *Candida* cells, while the accumulation of ROS can inactivate mitochondrial enzymes and lose membrane potential, thus leading to mitochondrial dysfunction and ultimately inducing early apoptosis of *Candida* [165, 166]. Honokiol (**27**) is isolated from the bark of the *Magnolia officinalis*, which disrupted mitochondrial membrane potential through inducing

the overproduction of ROS [167, 168]. Similarly, resveratrol (**28**) played a role in the early to late stages in *C. albicans* apoptosis by inducing ROS and further damaging mitochondrial membrane potential [169, 170]. Some antimicrobial peptides such as RsAFP2 [156], melittin [171] and psacotheasin [172], also induced apoptosis in *C. albicans* through intracellular ROS accumulation.

Cytochrome *c* (Cyt *c*) is an important component of the mitochondrial respiratory chain. Normally, Cyt *c* exists in the mitochondrial intermembrane and binds to the mitochondrial inner membrane. In the early stage of cell apoptosis, Cyt *c* is released from the mitochondrial inner membrane and interacts with apoptotic protease activators in the cytoplasm to induce a cascade of apoptosis [173]. Cyt *c* is undoubtedly one of the most important factors in cell apoptosis. Therefore, its regulation is significant. *Ocimum sanctum* essential oil and its two major constituents (methyl chavicol and linalool) were proved to induce the release of Cyt *c*, leading to the apoptosis of *C. albicans* [174, 175]. Similarly, a well-known carotenoid pigment, lycopene (**29**) also induced apoptosis by triggering the release of Cyt *c* and inducing mitochondrial depolarization [176, 177].

The Ca^{2+} pump on the cell membrane of *C. albicans* pumps intracellular Ca^{2+} outside through the hydrolysis of ATP to maintain intracellular homeostasis and ensure the normal development of cell function [178]. The intracellular Ca^{2+} overload may cause apoptosis of *C. albicans* cells. Perillaldehyde (**30**) is a natural monoterpenoid compound derived from *Perilla frutescens*. It exerted antifungal activity by elevating intracellular Ca^{2+} level thus inducing cell apoptosis [179]. Silibinin (**31**), an effective ingredient isolated from *Silybum marianum*, prompted *C. albicans* apoptosis mediated by mitochondrial Ca^{2+} influx pathway [180].

Synergistic mechanisms

Combination therapy is a beneficial avenue to combat drug-resistant fungal infections, which has the advantages of enhancing therapeutic effect, improving drug safety and reducing fungal resistance [181]. In recent years, numerous studies have found that various natural products can exert a synergistic role with clinical antifungals and the coordination mechanisms primarily involve inhibition on the overexpression of genes related to cell membrane efflux pump and changes in ergosterol biosynthesis pathway (Table 3) [182, 183].

The up-regulation of drug efflux is a conservative evolutionary mechanism which is the major cause of resistance to antifungal drugs. The inhibition of drug efflux thus can improve the sensitivity of drug-resistant fungi to clinical drugs [184, 185]. Eucalyptal D (**32**), an FPM from *Eucalyptus* genera, showed weak activity to FLC-resistant strains, but its MICs decreased by 4-64 times when combined with FLC [186]. Further research found that it reduced the efflux of FLC mainly through affecting *CDR1* and *CDR2* expression. Similarly, curcumin showed the synergistic effects with FLC which was potentially due to that curcumin significantly promoted FLC uptake by inhibiting the overexpression of the CaMdr1p [187]. Jatrophane ester (**33**) from *Euphorbia* spp. act as a modulator of *C. albicans* multidrug transporters, and then exerting synergistic effects when combined with FLC [188]. Besides, the above-mentioned biatriosporin D [115], plagiochin E [189] as well as several other natural products such as berberine (**34**) [190], baicalein [191], tetrandrine (**35**) [192], retigeric acid B (**36**) [193], and *n*-butylphthalide (**37**) [194] were known to have antifungal properties in combination with FLC, and their synergistic mechanisms were all associated with inhibiting the activity of efflux pump.

In addition to the above efflux pump mechanism, there

Table 3 The synergistic mechanisms of natural products and clinical drugs

Organism	Compounds	No.	Clinical drug	*Candida* species	Mechanism of action/target	Ref.
Eucalyptus/Psidium genera	Eucalyptal D	**32**	FLC	*Ca*	*CDR1*/*CDR2*, efflux pump	[186]
Curcuma longa	Curcumin	**4**	FLC	*Ca*	*MDR1*, efflux pump	[187]
Euphorbia spp.	Jatrophane ester 8	**33**	FLC	*Ca*	*CDR1*/*CDR2*/*MDR1*, efflux Pump	[188]
Biatriospora sp.	Biatriosporin D	**1**	FLC	*Ca*	*CDR1*/*CDR2*, efflux pump	[115]
Marchantia polymorpha	Plagiochin E	**16**	FLC	*Ca*	*CDR1*, efflux pump	[189]
Coptis chinensis	Berberine	**34**	FLC	*Ca*	*CDR2*, efflux pump	[190]
Scutellaria baicalensis	Baicalein	**10**	FLC	*Ca*	Efflux pump	[191]
Stephania tetrandra	Tetrandrine	**35**	FLC	*Ca*	Efflux pump, ATP supply	[192]
Lobaria kurokawae	Retigeric acid B	**36**	FLC, TCZ, ICZ	*Ca*	Efflux pump, ergosterol synthesis	[193]
Apium graveolens	*n*-Butylphthalide $^{\triangle}$	**37**	FLC	*Ca*, *Ct*, *Ck*, *Cg*	Accumulation of ROS, efflux pump	[194]
Aspergillus versicolor	Diorcinol D	**25**	FLC	*Ca*	Efflux pump, ergosterol synthesis	[195]

FLC: Fluconazole; TCZ: Ketoconazole; ICZ: Itraconazole; *Ca*: *Candida albicans*; *Ck*: *Candida krusei*; *Cg*: *Candida glabrata*; *Ct*: *Candida tropicalis*; $^{\triangle}$*In vivo* and *in vitro* experiments

are a few other synergistic mechanisms. Diorcinol D, isolated from *Aspergillus versicolor*, reversed drug resistance by diminishing the intracellular ergosterol of *C. albicans*, which facilitated the antifungal action of FLC [195]. Retigeric acid B synergized with azoles against *C. albicans* by depleting ergosterol on the cellular membrane [193]. Similarly, berberine damaged ergosterol biosynthesis, thereby exerting synergistic effects with FLC [190].

Conclusion and Prospect

The demand for new anti-*Candida* agents is increasing, especially with the emergence of drug-resistant *Candida* strains. According to the above review, various natural products have preferable antifungal effects. Some nature products also show attractive synergistic effects when combined with clinical drugs, even though they were weak or invalid when used alone. Meanwhile, the novel antifungal mechanisms of some compounds are explained, and related studies provide precursor structures for the development of unprecedented and efficient antifungals.

However, only a few studies were conducted on the cytotoxic activity, while the safety of most natural products with antimycotic activity is unrevealed. Although some compounds have fungistatic effects when used alone or in combination with positive drugs *in vitro*, there are few *in vivo* experiment data. Hence, further studies are strongly needed in the future.

Based on the structure and chemical properties of some natural products, safe and effective fungistatic agents will be obtained through modification in medicinal chemistry. On the one hand, it is convenient to further investigate the mechanisms of action or related targets. On the other hand, it provides more drug sources for combination therapy. So far, no small molecular compounds have been screened out which can overcome fungal resistance. However, the studies concerning natural compound synergy therapy provide new thoughts to deal with the problem of fungal resistance. Further researches on combination drugs are necessary to provide evidence for the development of new antifungal drugs. To sum up, natural products are of scientific importance and clinical value in the treatment of various *Candida* infections.

References

[1] Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem [J]. *Clin Microbiol Rev*, 2007, **20**(1): 133-163.

[2] Moran C, Grussemeyer CA, Spalding JR, *et al*. Comparison of costs, length of stay, and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream infections [J]. *Am J Infect Control*, 2010, **38**(1): 78-80.

[3] Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America [J]. *Crit Rev Microbiol*, 2010, **36**(1): 1-53.

[4] Andes D. *In vivo* pharmacodynamics of antifungal drugs in treatment of candidiasis [J]. *Antimicrob Agents Chemother*, 2003, **47**(4): 1179-1186.

[5] Lee Y, Puumala E, Robbins N, *et al*. Antifungal drug resistance: molecular mechanisms in *Candida albicans* and beyond [J]. *Chem Rev*, 2021, **121**(6): 3390-3411.

[6] McLellan CA, Whitesell L, King OD, *et al*. Inhibiting GPI anchor biosynthesis in fungi stresses the endoplasmic reticulum and enhances immunogenicity [J]. *ACS Chem Biol*, 2012, **7**(9): 1520-1528.

[7] Monk BC, Goffeau A. Outwitting multidrug resistance to antifungals [J]. *Science*, 2008, **321**(5887): 367-369.

[8] Arif T, Bhosale JD, Kumar N, *et al*. Natural products: antifungal agents derived from plants [J]. *J Asian Nat Prod Res*, 2009, **11**(7): 621-638.

[9] Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019 [J]. *J Nat Prod*, 2020, **83**(3): 770-803.

[10] Jansook P, Fülöp Z, Ritthidej GC. Amphotericin B loaded solid lipid nanoparticles (SLNs) and nanostructured lipid carrier (NLCs): physicochemical and solid-solution state characterizations [J]. *Drug Dev Ind Pharm*, 2019, **45**(4): 560-567.

[11] Chen L, Yue Q, Zhang X, *et al*. Genomics-driven discovery of the pneumocandin biosynthetic gene cluster in the fungus *Glarea lozoyensis* [J]. *BMC Genomics*, 2013, **14**: 339.

[12] Li RK, Rinaldi MG. *In vitro* antifungal activity of nikkomycin Z in combination with fluconazole or itraconazole [J]. *Antimicrob Agents Chemother*, 1999, **43**(6): 1401-1405.

[13] Hanadate T, Tomishima M, Shiraishi N, *et al*. FR290581, a novel sordarin derivative: synthesis and antifungal activity [J]. *Bioorg Med Chem Lett*, 2009, **19**(5): 1465-1468.

[14] Soliman S, Alnajdy D, El-Keblawy AA, *et al*. Plants' natural products as alternative promising anti-*Candida* drugs [J]. *Pharmacogn Rev*, 2017, **11**(22): 104-122.

[15] Zida A, Bamba S, Yacouba A, *et al*. Anti-*Candida albicans* natural products, sources of new antifungal drugs: a review [J]. *J Mycol Med*, 2017, **27**(1): 1-19.

[16] Tanaka N, Kusama T, Takahashi-Nakaguchi A, *et al*. Nagelamides U–W, bromopyrrole alkaloids from a marine sponge *Agelas* sp. [J]. *Tetrahedron Lett*, 2013, **54**(29): 3794-3796.

[17] Fu P, Wang S, Hong K, *et al*. Cytotoxic bipyridines from the marine-derived actinomycete *Actinoalloteichus cyanogriseus* WH1-2216-6 [J]. *J Nat Prod*, 2011, **74**(8): 1751-1756.

[18] Tanaka N, Momose R, Takahashi Y, *et al*. Hyrtimomines D and E, bisindole alkaloids from a marine sponge *Hyrtios* sp. [J]. *Tetrahedron Lett*, 2013, **54**(31): 4038-4040.

[19] do Carmo G, Fernandes TS, Pedroso M, *et al*. Phytochemical and antimicrobial study of *Pilocarpus pennatifolius* Lemaire [J]. *Fitoterapia*, 2018, **131**: 1-8.

[20] Fyhrquist P, Virjamo V, Hiltunen E, *et al*. Epidihydropinidine, the main piperidine alkaloid compound of Norway spruce (*Picea abies*) shows promising antibacterial and anti-*Candida* activity [J]. *Fitoterapia*, 2017, **117**: 138-146.

[21] Ahmed A, Li W, Chen FF, *et al*. Monoterpene indole alkaloids from *Rhazya stricta* [J]. *Fitoterapia*, 2018, **128**: 1-6.

[22] Haga A, Tamoto H, Ishino M, *et al*. Pyridone alkaloids from a marine-derived fungus, *Stagonosporopsis cucurbitacearum*, and their activities against azole-resistant *Candida albicans* [J]. *J Nat Prod*, 2013, **76**(4): 750-754.

[23] Cretton S, Dorsaz S, Azzollini A, *et al*. Antifungal quinoline alkaloids from *Waltheria indica* [J]. *J Nat Prod*, 2016, **79**(2): 300-307.

[24] Rios MY, Navarro V, Ramírez-Cisneros M, *et al*. Sulfur-containing aristoloxazines and other constituents of the roots of *Aristolochia orbicularis* [J]. *J Nat Prod*, 2017, **80**(12): 3112-3119.

[25] Wu Z, Zhang X, Anbari WHA, *et al*. Cysteine residue containing merocytochalasans and 17, 18-*seco*-aspochalasins from *Aspergillus micronesiensis* [J]. *J Nat Prod*, 2019, **82**(9):

2653-2658.
[26] Russell F, Harmody D, McCarthy PJ, *et al*. Indolo [3, 2-*a*] carbazoles from a deep-water sponge of the genus *Asteropus* [J]. *J Nat Prod*, 2013, **76**(10): 1989-1992.
[27] Jamison MT, Molinski TF. Antipodal crambescin A2 homologues from the marine sponge *Pseudaxinella reticulata*. antifungal structure-activity relationships [J]. *J Nat Prod*, 2015, **78**(3): 557-561.
[28] Intaraudom C, Boonyuen N, Suvannakad R, *et al*. Penicolinates A–E from endophytic *Penicillium* sp. BCC16054 [J]. *Tetrahedron Lett*, 2013, **54**(8): 744-748.
[29] Ma C, Li Y, Niu S, *et al*. *N*-Hydroxypyridones, phenylhydrazones, and a quinazolinone from *Isaria farinosa* [J]. *J Nat Prod*, 2011, **74**(1): 32-37.
[30] Nirma C, Eparvier V, Stien D. Antifungal agents from *Pseudallescheria boydii* SNB-CN73 isolated from a *Nasutitermes* sp. termite [J]. *J Nat Prod*, 2013, **76**(5): 988-991.
[31] Wang Y, Yang MH, Wang XB, *et al*. Bioactive metabolites from the endophytic fungus *Alternaria alternata* [J]. *Fitoterapia*, 2014, **99**: 153-158.
[32] Wongsa N, Kanokmedhakul S, Kanokmedhakul K. Cananginones A–I, linear acetogenins from the stem bark of *Miliusa velutina* [corrected] [J]. *Phytochemistry*, 2011, **72**(14-15): 1859-1864.
[33] Li HT, Duan RT, Liu T, *et al*. Penctrimertone, a bioactive citrinin dimer from the endophytic fungus *Penicillium* sp. T2-11 [J]. *Fitoterapia*, 2020, **146**: 104711.
[34] Luo S, Kang HS, Krunic A, *et al*. Carbamidocyclophanes F and G with anti-*Mycobacterium tuberculosis* activity from the cultured freshwater cyanobacterium *Nostoc* sp. [J]. *Tetrahedron Lett*, 2014, **55**(3): 686-689.
[35] Zhou YH, Zhang M, Zhu RX, *et al*. Heptaketides from an endolichenic fungus *Biatriospora* sp. and their antifungal activity [J]. *J Nat Prod*, 2016, **79**(9): 2149-2157.
[36] Chen Y, Yang W, Zou G, *et al*. Bioactive polyketides from the mangrove endophytic fungi *Phoma* sp. SYSU-SK-7 [J]. *Fitoterapia*, 2019, **139**: 104369.
[37] Anjum K, Sadiq I, Chen L, *et al*. Novel antifungal janthinopolyenemycins A and B from a co-culture of marine-associated *Janthinobacterium* spp. ZZ145 and ZZ148 [J]. *Tetrahedron Lett*, 2018, **59**(38): 3490-3494.
[38] Lei H, Lin X, Han L, *et al*. Polyketide derivatives from a marine-sponge-associated fungus *Pestalotiopsis heterocornis* [J]. *Phytochemistry*, 2017, **142**: 51-59.
[39] Wang QX, Bao L, Yang XL, *et al*. Polyketides with antimicrobial activity from the solid culture of an endolichenic fungus *Ulocladium* sp. [J]. *Fitoterapia*, 2012, **83**(1): 209-214.
[40] Wongsa N, Kanokmedhakul S, Kanokmedhakul K, *et al*. Parviflorals A−F, trinorcadalenes and bis-trinorcadalenes from the roots of *Decaschistia parviflora* [J]. *Phytochemistry*, 2013, **95**: 368-374.
[41] Tang YQ, Li YQ, Xie YB, *et al*. Evodialones A and B: polyprenylated acylcyclopentanone racemates with a 3-Ethyl-1, 1-diisopentyl-4-methylcyclopentane skeleton from *Evodia lepta* [J]. *J Nat Prod*, 2018, **81**(6): 1483-1487.
[42] Sandargo B, Thongbai B, Stadler M, *et al*. Cysteine-derived pleurotin congeners from the nematode-trapping basidiomycete *Hohenbuehelia grisea* [J]. *J Nat Prod*, 2018, **81**(2): 286-291.
[43] Oya A, Tanaka N, Kusama T, *et al*. Prenylated benzophenones from *Triadenum japonicum* [J]. *J Nat Prod*, 2015, **78**(2): 258-264.
[44] Li W, Gao W, Zhang M, *et al*. *p*-Terphenyl derivatives from the endolichenic fungus *Floricola striata* [J]. *J Nat Prod*, 2016, **79**(9): 2188-2194.
[45] Xu DX, Sun P, Kurtán T, *et al*. Polyhydroxy cyclohexanols from a *Dendrodochium* sp. fungus associated with the sea cucumber *Holothuria nobilis* Selenka [J]. *J Nat Prod*, 2014, **77**(5): 1179-1184.
[46] Kumar R, Saha A, Saha D. A new antifungal coumarin from *Clausena excavata* [J]. *Fitoterapia*, 2012, **83**(1): 230-233.
[47] Zhao M, Yuan LY, Guo DL, *et al*. Bioactive halogenated dihydroisocoumarins produced by the endophytic fungus *Lachnum palmae* isolated from *Przewalskia tangutica* [J]. *Phytochemistry*, 2018, **148**: 97-103.
[48] Song RY, Wang XB, Yin GP, *et al*. Isocoumarin derivatives from the endophytic fungus, *Pestalotiopsis* sp. [J]. *Fitoterapia*, 2017, **122**: 115-118.
[49] Singh B, Parshad R, Khajuria RK, *et al*. Saccharonol B, a new cytotoxic methylated isocoumarin from *Saccharomonospora azurea* [J]. *Tetrahedron Lett*, 2013, **54**(49): 6695-6699.
[50] Ma M, Ge H, Yi W, *et al*. Bioactive drimane sesquiterpenoids and isocoumarins from the marine-derived fungus *Penicillium minioluteum* ZZ1657 [J]. *Tetrahedron Lett*, 2020, **61**(7): 151504.
[51] Dias SM, Simonet AM, Silva NC, *et al*. Bioassay-guided isolation of fungistatic compounds from *Mimosa caesalpiniifolia* leaves [J]. *J Nat Prod*, 2019, **82**: 1496-1502.
[52] Dal Piaz F, Bader A, Malafronte N, *et al*. Phytochemistry of compounds isolated from the leaf-surface extract of *Psiadia punctulata* (DC.) Vatke growing in Saudi Arabia [J]. *Phytochemistry*, 2018, **155**: 191-202.
[53] Katerere DR, Gray AI, Nash RJ, *et al*. Phytochemical and antimicrobial investigations of stilbenoids and flavonoids isolated from three species of Combretaceae [J]. *Fitoterapia*, 2012, **83**(5): 932-940.
[54] Thongnest S, Lhinhatrakool T, Wetprasit N, *et al*. *Eriosema chinense*: a rich source of antimicrobial and antioxidant flavonoids [J]. *Phytochemistry*, 2013, **96**: 353-359.
[55] Zhang HX, Lunga PK, Li ZJ, *et al*. Flavonoids and stilbenoids from *Derris eriocarpa* [J]. *Fitoterapia*, 2014, **95**: 147-153.
[56] Belofsky G, Kolaczkowski M, Adams E, *et al*. Fungal ABC transporter-associated activity of isoflavonoids from the root extract of *Dalea formosa* [J]. *J Nat Prod*, 2013, **76**(5): 915-925.
[57] Li T, Wang S, Fan P, *et al*. New coumarins and monoterpene galloylglycoside from the stem bark of *Sapium baccatum* [J]. *Fitoterapia*, 2019, **134**: 435-442.
[58] Kırmızıbekmez H, Uysal GB, Masullo M, *et al*. Prenylated polyphenolic compounds from *Glycyrrhiza iconica* and their antimicrobial and antioxidant activities [J]. *Fitoterapia*, 2015, **103**: 289-293.
[59] Rangkadilok N, Tongchusak S, Boonhok R, *et al*. *In vitro* antifungal activities of longan (*Dimocarpus longan* Lour.) seed extract [J]. *Fitoterapia*, 2012, **83**(3): 545-553.
[60] Gadetskaya AV, Tarawneh AH, Zhusupova GE, *et al*. Sulfated phenolic compounds from *Limonium caspium*: isolation, structural elucidation, and biological evaluation [J]. *Fitoterapia*, 2015, **104**: 80-85.
[61] Xu X, Piggott AM, Yin L, *et al*. Symphyocladins A–G: bromophenol adducts from a Chinese marine red alga, *Symphyocladia latiuscula* [J]. *Tetrahedron Lett*, 2012, **53**(16): 2103-2106.
[62] Yu JS, Park M, Pang C, *et al*. Antifungal phenols from *Woodfordia uniflora* collected in Oman [J]. *J Nat Prod*, 2020, **83**(7): 2261-2268.
[63] Basset C, Rodrigues AM, Eparvier V, *et al*. Secondary metabolites from *Spirotropis longifolia* (DC) Baill and their antifungal activity against human pathogenic fungi [J]. *Phyto-*

chemistry, 2012, **74**: 166-172.
[64] Jiang YJ, Zhang DS, Zhang HJ, *et al*. Medermycin-type naphthoquinones from the marine-derived *Streptomyces* sp. XMA39 [J]. *J Nat Prod*, 2018, **81**(9): 2120-2124.
[65] Fan JT, Kuang B, Zeng GZ, *et al*. Biologically active arborinane-type triterpenoids and anthraquinones from *Rubia yunnanensis* [J]. *J Nat Prod*, 2011, **74**(10): 2069-2080.
[66] Liang QL, Lei LL, Cui X, *et al*. Bioactive *cis*-stilbenoids from the tubers of *Scirpus yagara* [J]. *Fitoterapia*, 2013, **84**: 170-173.
[67] Rusman Y, Held BW, Blanchette RA, *et al*. Soudanones A−G: antifungal isochromanones from the ascomycetous fungus *Cadophora* sp. isolated from an iron mine [J]. *J Nat Prod*, 2015, **78**(6): 1456-1460.
[68] Padhi S, Masi M, Cimmino A, *et al*. Funiculosone, a substituted dihydroxanthene-1, 9-dione with two of its analogues produced by an endolichenic fungus *Talaromyces funiculosus* and their antimicrobial activity [J]. *Phytochemistry*, 2019, **157**: 175-183.
[69] He WJ, Fu ZH, Zeng GZ, *et al*. Terpene and lignan glycosides from the twigs and leaves of an endangered conifer, *Cathaya argyrophylla* [J]. *Phytochemistry*, 2012, **83**: 63-69.
[70] Chen Y, Ni W, Yan H, *et al*. Spirostanol glycosides with hemostatic and antimicrobial activities from *Trillium kamtschaticum* [J]. *Phytochemistry*, 2016, **131**: 165-173.
[71] Yang XL, Awakawa T, Wakimoto T, *et al*. Induced production of the novel glycolipid ustilagic acid C in the plant pathogen *Ustilago maydis* [J]. *Tetrahedron Lett*, 2013, **54**(28): 3655-3657.
[72] Stierle AA, Stierle DB, Decato D, *et al*. The berkeleylactones, antibiotic macrolides from fungal coculture [J]. *J Nat Prod*, 2017, **80**(4): 1150-1160.
[73] Okabe M, Sugita T, Kinoshita K, *et al*. Macrolides from a marine-derived fungus, *Penicillium meleagrinum* var. viridiflavum, showing synergistic effects with fluconazole against azole-resistant *Candida albicans* [J]. *J Nat Prod*, 2016, **79**(4): 1208-1212.
[74] Kim DG, Moon K, Kim SH, *et al*. Bahamaolides A and B, antifungal polyene polyol macrolides from the marine actinomycete *Streptomyces* sp. [J]. *J Nat Prod*, 2012, **75**(5): 959-967.
[75] Rukachaisirikul V, Rodglin A, Sukpondma Y, *et al*. Phthalide and isocoumarin derivatives produced by an *Acremonium* sp. isolated from a mangrove *Rhizophora apiculata* [J]. *J Nat Prod*, 2012, **75**(5): 853-858.
[76] Nešuta O, Hexnerová R, Buděšínský M, *et al*. Antimicrobial peptide from the wild bee *Hylaeus signatus* Venom and its analogues: structure-activity study and synergistic effect with antibiotics [J]. *J Nat Prod*, 2016, **79**(4): 1073-1083.
[77] Ortíz-López FJ, Monteiro MC, González-Menéndez V, *et al*. Cyclic colisporifungin and linear cavinafungins, antifungal lipopeptides isolated from *Colispora cavincola* [J]. *J Nat Prod*, 2015, **78**(3): 468-475.
[78] Khani S, Seyedjavadi SS, Zare-Zardini H, *et al*. Isolation and functional characterization of an antifungal hydrophilic peptide, Skh-AMP1, derived from *Satureja khuzistanica* leaves [J]. *Phytochemistry*, 2019, **164**: 136-143.
[79] Wu W, Dai H, Bao L, *et al*. Isolation and structural elucidation of proline-containing cyclopentapeptides from an endolichenic *Xylaria* sp. [J]. *J Nat Prod*, 2011, **74**(5): 1303-1308.
[80] Zhang D, Yi W, Ge H, *et al*. Bioactive streptoglutarimides A−J from the marine-derived *Streptomyces* sp. ZZ741 [J]. *J Nat Prod*, 2019, **82**(10): 2800-2808.
[81] Perveen S, Alqahtani J, Orfali R, *et al*. Antimicrobial guaianolide sesquiterpenoids from leaves of the Saudi Arabian plant *Anvillea garcinii* [J]. *Fitoterapia*, 2019, **134**: 129-134.
[82] Yang B, He Y, Lin S, *et al*. Antimicrobial dolabellanes and atranones from a marine-derived strain of the toxigenic fungus *Stachybotrys chartarum* [J]. *J Nat Prod*, 2019, **82**(7): 1923-1929.
[83] Yang X, Wang C, Yang J, *et al*. Antimicrobial sesquiterpenes from the Chinese medicinal plant, *Chloranthus angustifolius* [J]. *Tetrahedron Lett*, 2014, **55**(41): 5632-5634.
[84] Xie C, Sun L, Liao K, *et al*. Bioactive *ent*-pimarane and *ent*-abietane diterpenoids from the whole plants of *Chloranthus henryi* [J]. *J Nat Prod*, 2015, **78**(11): 2800-2807.
[85] Hegazy MF, Matsuda H, Nakamura S, *et al*. Chemical constituents and their antibacterial and antifungal activity from the egyptian herbal medicine *Chiliadenus montanus* [J]. *Phytochemistry*, 2014, **103**: 154-161.
[86] Zhao JC, Wang YL, Zhang TY, *et al*. Indole diterpenoids from the endophytic fungus *Drechmeria* sp. as natural antimicrobial agents [J]. *Phytochemistry*, 2018, **148**: 21-28.
[87] Shang ZC, Han C, Xu JL, *et al*. Twelve formyl phloroglucinol meroterpenoids from the leaves of *Eucalyptus robusta* [J]. *Phytochemistry*, 2019, **163**: 111-117.
[88] Pu D, Li X, Lin J, *et al*. Triterpenoids from *Ganoderma gibbosum*: a class of sensitizers of FLC-resistant *Candida albicans* to fluconazole [J]. *J Nat Prod*, 2019, **82**(8): 2067-2077.
[89] Mamemura T, Tanaka N, Shibazaki A, *et al*. Yojironins A−D, meroterpenoids and prenylated acylphloroglucinols from *Hypericum yojiroanum* [J]. *Tetrahedron Lett*, 2011, **52**(28): 3575-3578.
[90] Fernández LR, Butassi E, Svetaz L, *et al*. Antifungal terpenoids from *Hyalis argentea* var. latisquama [J]. *J Nat Prod*, 2014, **77**(7): 1579-1585.
[91] Wang X, Jin XY, Zhou JC, *et al*. Terpenoids from the Chinese liverwort *Heteroscyphus coalitus* and their anti-virulence activity against *Candida albicans* [J]. *Phytochemistry*, 2020, **174**: 112324.
[92] Yu XQ, He WF, Liu DQ, *et al*. A *seco*-laurane sesquiterpene and related laurane derivatives from the red alga *Laurencia okamurai* Yamada [J]. *Phytochemistry*, 2014, **103**: 162-170.
[93] Chepkirui C, Yuyama KT, Wanga LA, *et al*. Microporenic acids A−G, biofilm inhibitors, and antimicrobial agents from the *Basidiomycete Microporus* species [J]. *J Nat Prod*, 2018, **81**(4): 778-784.
[94] Zhou QM, Chen MH, Li XH, *et al*. Absolute configurations and bioactivities of guaiane-type sesquiterpenoids isolated from *Pogostemon cablin* [J]. *J Nat Prod*, 2018, **81**(9): 1919-1927.
[95] Georgieva K, Trusheva B, Uzunova V, *et al*. New cycloartane triterpenes from bioactive extract of propolis from Pitcairn island [J]. *Fitoterapia*, 2018, **128**: 233-241.
[96] Qiao YN, Jin XY, Zhou JC, *et al*. Terpenoids from the liverwort *Plagiochila fruticosa* and their antivirulence activity against *Candida albicans* [J]. *J Nat Prod*, 2020, **83**(6): 1766-1777.
[97] Favre-Godal Q, Dorsaz S, Queiroz EF, *et al*. Anti-*Candida* cassane-type diterpenoids from the root bark of *Swartzia simplex* [J]. *J Nat Prod*, 2015, **78**(12): 2994-3004.
[98] Ding N, Jiang Y, Han L, *et al*. Bafilomycins and odoriferous sesquiterpenoids from *Streptomyces albolongus* isolated from *Elephas maximus* Feces [J]. *J Nat Prod*, 2016, **79**(4): 799-805.
[99] Wu SH, He J, Li XN, *et al*. Guaiane sesquiterpenes and isopimarane diterpenes from an endophytic fungus *Xylaria* sp. [J]. *Phytochemistry*, 2014, **105**: 197-204.
[100] Klaiklay S, Rukachaisirikul V, Saithong S, *et al*. Trichothecenes from a soil-derived *Trichoderma brevicompactum* [J]. *J Nat Prod*, 2019, **82**(4): 687-693.
[101] Zhang MQ, Xu KX, Xue Y, *et al*. Sordarin diterpene glycos-

ides with an unusual 1, 3-dioxolan-4-one ring from the zoanthid-derived fungus *Curvularia hawaiiensis* TA26-15 [J]. *J Nat Prod*, 2019, **82**(9): 2477-2482.
[102] Hu Q, Chen YY, Jiao QY, *et al*. Triterpenoid saponins from the pulp of *Sapindus mukorossi* and their antifungal activities [J]. *Phytochemistry*, 2018, **147**: 1-8.
[103] Rajkowska K, Otlewska A, Kunicka-Styczyńska A, *et al*. *Candida albicans* impairments induced by peppermint and clove oils at sub-inhibitory concentrations [J]. *Int J Mol Sci*, 2017, **18**(6): 1307.
[104] Tariq S, Wani S, Rasool W, *et al*. A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens [J]. *Microb Pathog*, 2019, **134**: 103580.
[105] Donato R, Sacco C, Pini G, *et al*. Antifungal activity of different essential oils against *Malassezia* pathogenic species [J]. *J Ethnopharmacol*, 2020, **249**: 112376.
[106] Staniszewska M, Bondaryk M, Piłat J, *et al*. Virulence factors of *Candida albicans* [J]. *Przegl Epidemiol*, 2012, **66**(4): 629-633.
[107] Cotter G, Kavanagh K. Adherence mechanisms of *Candida albicans* [J]. *Br J Biomed Sci*, 2000, **57**(3): 241-249.
[108] Lu Y, Su C, Liu H. *Candida albicans* hyphal initiation and elongation [J]. *Trends Microbiol*, 2014, **22**(12): 707-714.
[109] Azadmanesh J, Gowen AM, Creger PE, *et al*. Filamentation involves two overlapping, but distinct, programs of filamentation in the pathogenic fungus *Candida albicans* [J]. *G3 (Bethesda)*, 2017, **7**(11): 3797-3808.
[110] Vila T, Romo JA, Pierce CG, *et al*. Targeting *Candida albicans* filamentation for antifungal drug development [J]. *Virulence*, 2017, **8**(2): 150-158.
[111] Rüchel R. Cleavage of immunoglobulins by pathogenic yeasts of the genus *Candida* [J]. *Microbiol Sci*, 1986, **3**(10): 316-319.
[112] Cavalcanti YW, Almeida LdFDd, Padilha WWN. Anti-adherent activity of *Rosmarinus officinalis* essential oil on *Candida albicans*: an SEM analysis [J]. *Revista Odonto Ciência*, 2011, **26**(2): 139-144.
[113] Barbieri DS, Tonial F, Lopez PV, *et al*. Antiadherent activity of *Schinus terebinthifolius* and *Croton urucurana* extracts on *in vitro* biofilm formation of *Candida albicans* and *Streptococcus mutans* [J]. *Arch Oral Biol*, 2014, **59**(9): 887-896.
[114] Ribeiro BD, Alviano DS, Barreto DW, *et al*. Functional properties of saponins from sisal (*Agave sisalana*) and juá (*Ziziphus joazeiro*): critical micellar concentration, antioxidant and antimicrobial activities [J]. *Colloids Surf A Physicochem Eng Asp*, 2013, **436**: 736-743.
[115] Lindsay AK, Deveau A, Piispanen AE, *et al*. Farnesol and cyclic AMP signaling effects on the hypha-to-yeast transition in *Candida albicans* [J]. *Eukaryot Cell*, 2012, **11**(10): 1219-1225.
[116] Zhang M, Chang W, Shi H, *et al*. Biatriosporin D displays antivirulence activity through decreasing the intracellular cAMP levels [J]. *Toxicol Appl Pharmacol*, 2017, **322**: 104-112.
[117] Li Y, Shan M, Li S, *et al*. Teasaponin suppresses *Candida albicans* filamentation by reducing the level of intracellular cAMP [J]. *Ann Transl Med*, 2020, **8**(5): 175.
[118] Chang W, Li Y, Zhang M, *et al*. Solasodine-3-*O*-*β*-D-glucopyranoside kills *Candida albicans* by disrupting the intracellular vacuole [J]. *Food Chem Toxicol*, 2017, **106**(Pt A): 139-146.
[119] Li Y, Chang W, Zhang M, *et al*. Natural product solasodine-3-*O*-*β*-D-glucopyranoside inhibits the virulence factors of *Candida albicans* [J]. *FEMS Yeast Res*, 2015, **15**(6): 1-8.
[120] Chen E, Benso B, Seleem D, *et al*. Fungal-host interaction: curcumin modulates proteolytic enzyme activity of *Candida albicans* and inflammatory host response *in vitro* [J]. *Int J Dent*, 2018, **2018**: 2393146.
[121] Li XC, Jacob MR, Pasco DS, *et al*. Phenolic compounds from *Miconia myriantha* inhibiting *Candida* aspartic proteases [J]. *J Nat Prod*, 2001, **64**(10): 1282-1285.
[122] Zhang Z, ElSohly HN, Jacob MR, *et al*. Natural products inhibiting *Candida albicans* secreted aspartic proteases from *Lycopodium cernuum* [J]. *J Nat Prod*, 2002, **65**(7): 979-985.
[123] Odds FC. Molecular phylogenetics and epidemiology of *Candida albicans* [J]. *Future Microbiol*, 2010, **5**(1): 67-79.
[124] Lee CH, Chen YC, Chen IL, *et al*. Impact of biofilm production by *Candida* species and antifungal therapy on mortality of patients with candidemia [J]. *Mycoses*, 2020, **63**(12): 1382-1391.
[125] Chang W, Zhang M, Li Y, *et al*. Flow cytometry-based method to detect persisters in *Candida albicans* [J]. *Antimicrob Agents Chemother*, 2015, **59**(8): 5044-5048.
[126] Cavalheiro M, Teixeira MC. *Candida* biofilms: threats, challenges, and promising strategies [J]. *Front Med (Lausanne)*, 2018, **5**: 28.
[127] Musyimi DM, Ogur JA. Comparative assessment of antifungal activity of extracts from *Eucalyptus globulus* and *Eucalyptus citriodora* [J]. *Res J Phytochem*, 2008, **2**(1): 35-43.
[128] Liu RH, Shang ZC, Li TX, *et al*. *In vitro* antibiofilm activity of eucarobustol E against *Candida albicans* [J]. *Antimicrob Agents Chemother*, 2017, **61**(8): e02707-e02716.
[129] Cheng A, Sun L, Wu X, *et al*. The inhibitory effect of a macrocyclic bisbibenzyl riccardin D on the biofilms of *Candida albicans* [J]. *Biol Pharm Bull*, 2009, **32**(8): 1417-1421.
[130] Wang X, You J, King JB, *et al*. Waikialoid A suppresses hyphal morphogenesis and inhibits biofilm development in pathogenic *Candida albicans* [J]. *J Nat Prod*, 2012, **75**(4): 707-715.
[131] Cao Y, Dai B, Wang Y, *et al*. *In vitro* activity of baicalein against *Candida albicans* biofilms [J]. *Int J Antimicrob Agents*, 2008, **32**(1): 73-77.
[132] Ma C, Du F, Yan L, *et al*. Potent activities of roemerine against *Candida albicans* and the underlying mechanisms [J]. *Molecules*, 2015, **20**(10): 17913-17928.
[133] Jackson DN, Yang L, Wu S, *et al*. Garcinia xanthochymus benzophenones promote hyphal apoptosis and potentiate activity of fluconazole against *Candida albicans* biofilms [J]. *Antimicrob Agents Chemother*, 2015, **59**(10): 6032-6038.
[134] Bowman SM, Free SJ. The structure and synthesis of the fungal cell wall [J]. *Bioessays*, 2006, **28**(8): 799-808.
[135] Garcia-Rubio R, de Oliveira HC, Rivera J, *et al*. The fungal cell wall: *Candida*, *Cryptococcus*, and *Aspergillus* species [J]. *Front Microbiol*, 2019, **10**: 2993.
[136] Georgopapadakou NH, Tkacz JS. The fungal cell wall as a drug target [J]. *Trends Microbiol*, 1995, **3**(3): 98-104.
[137] Perlin DS. Current perspectives on echinocandin class drugs [J]. *Future Microbiol*, 2011, **6**(4): 441-457.
[138] Hector RF, Zimmer BL, Pappagianis D. Evaluation of nikkomycins X and Z in murine models of coccidioidomycosis, histoplasmosis, and blastomycosis [J]. *Antimicrob Agents Chemother*, 1990, **34**(4): 587-593.
[139] Piotrowski JS, Okada H, Lu F, *et al*. Plant-derived antifungal agent poacic acid targets *β*-1, 3-glucan [J]. *Proc Natl Acad Sci USA*, 2015, **112**(12): E1490-1497.
[140] Lee KK, Kubo K, Abdelaziz JA, *et al*. Yeast species-specific, differential inhibition of *β*-1, 3-glucan synthesis by poacic acid and caspofungin [J]. *Cell Surf*, 2018, **3**: 12-25.
[141] Butler MS, Robertson AA, Cooper MA. Natural product and natural product derived drugs in clinical trials [J]. *Nat Prod*

Rep, 2014, **31**(11): 1612-1661.
[142] Niu C, Qu JB, Lou HX. Antifungal bis [bibenzyls] from the Chinese liverwort *Marchantia polymorpha* L. [J]. *Chem Biodivers*, 2006, **3**(1): 34-40.
[143] Wu XZ, Cheng AX, Sun LM, *et al*. Effect of plagiochin E, an antifungal macrocyclic bis (bibenzyl), on cell wall chitin synthesis in *Candida albicans* [J]. *Acta Pharmacol Sin*, 2008, **29**(12): 1478-1485.
[144] Escalante A, Gattuso M, Pérez P, *et al*. Evidence for the mechanism of action of the antifungal phytolaccoside B isolated from *Phytolacca tetramera* Hauman [J]. *J Nat Prod*, 2008, **71**(10): 1720-1725.
[145] Sütterlin C, Horvath A, Gerold P, *et al*. Identification of a species-specific inhibitor of glycosylphosphatidylinositol synthesis [J]. *EMBO j*, 1997, **16**(21): 6374-6383.
[146] Mann PA, McLellan CA, Koseoglu S, *et al*. Chemical genomics-based antifungal drug discovery: targeting glycosylphosphatidylinositol (GPI) precursor biosynthesis [J]. *ACS Infect Dis*, 2015, **1**(1): 59-72.
[147] Yoshida M, Ezaki M, Hashimoto M, *et al*. A novel antifungal antibiotic, FR-900848. I. Production, isolation, physico-chemical and biological properties [J]. *J Antibiot (Tokyo)*, 1990, **43**(7): 748-754.
[148] Fu Y, Estoppey D, Roggo S, *et al*. Jawsamycin exhibits *in vivo* antifungal properties by inhibiting Spt14/Gpi3-mediated biosynthesis of glycosylphosphatidylinositol [J]. *Nat Commun*, 2020, **11**(1): 3387.
[149] Sant DG, Tupe SG, Ramana CV, *et al*. Fungal cell membrane-promising drug target for antifungal therapy [J]. *J Appl Microbiol*, 2016, **121**(6): 1498-1510.
[150] Song J, Zhai P, Zhang Y, *et al*. The *Aspergillus fumigatus* damage resistance protein family coordinately regulates ergosterol biosynthesis and azole susceptibility [J]. *mBio*, 2016, **7**(1): e01919-01915.
[151] Jordá T, Puig S. Regulation of ergosterol biosynthesis in *Saccharomyces cerevisiae* [J]. *Genes*, 2020, **11**(7): 795.
[152] Scorzoni L, de Paula ESAC, Marcos CM, *et al*. Antifungal therapy: new advances in the understanding and treatment of mycosis [J]. *Front Microbiol*, 2017, **8**: 36.
[153] Ansari MA, Fatima Z, Hameed S. Sesamol: a natural phenolic compound with promising anticandidal potential [J]. *J Pathog*, 2014, **2014**: 895193.
[154] Sharma Y, Khan LA, Manzoor N. Anti-*Candida* activity of geraniol involves disruption of cell membrane integrity and function [J]. *J Mycol Med*, 2016, **26**(3): 244-254.
[155] Thevissen K, Warnecke DC, François IE, *et al*. Defensins from insects and plants interact with fungal glucosylceramides [J]. *J Biol Chem*, 2004, **279**(6): 3900-3905.
[156] Aerts AM, Carmona-Gutierrez D, Lefevre S, *et al*. The antifungal plant defensin RsAFP2 from radish induces apoptosis in a metacaspase independent way in *Candida albicans* [J]. *FEBS Lett*, 2009, **583**(15): 2513-2516.
[157] Li S, Shi H, Chang W, *et al*. Eudesmane sesquiterpenes from Chinese liverwort are substrates of Cdrs and display antifungal activity by targeting Erg6 and Erg11 of *Candida albicans* [J]. *Bioorg Med Chem*, 2017, **25**(20): 5764-5771.
[158] Lee H, Choi H, Ko HJ, *et al*. Antifungal effect and mode of action of glochidioboside against *Candida albicans* membranes [J]. *Biochem Biophys Res Commun*, 2014, **444**(1): 30-35.
[159] Sung WS, Lee DG. Antifungal action of chlorogenic acid against pathogenic fungi, mediated by membrane disruption [J]. *Pure Appl Chem*, 2010, **82**(1): 219-226.
[160] Li Y, Chang W, Zhang M, *et al*. Diorcinol D exerts fungicidal action against *Candida albicans* through cytoplasm membrane destruction and ROS accumulation [J]. *PLoS One*, 2015, **10**(6): e0128693.
[161] Bajpai VK, Park YH, Kang SC. A diterpenoid taxodone from *Metasequoia glyptostroboides* with antimycotic potential against clinical isolates of *Candida* species [J]. *J Mycol Med*, 2015, **25**(1): e31-38.
[162] Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics [J]. *Br J Cancer*, 1972, **26**(4): 239-257.
[163] Wyllie AH, Kerr JF, Currie AR. Cell death: the significance of apoptosis [J]. *Int Rev Cytol*, 1980, **68**: 251-306.
[164] Sharon A, Finkelstein A, Shlezinger N, *et al*. Fungal apoptosis: function, genes and gene function [J]. *FEMS Microbiol Rev*, 2009, **33**(5): 833-854.
[165] Murphy MP. How mitochondria produce reactive oxygen species [J]. *Biochem J*, 2009, **417**(1): 1-13.
[166] Seong M, Lee DG. Reactive oxygen species-independent apoptotic pathway by gold nanoparticles in *Candida albicans* [J]. *Microbiol Res*, 2018, **207**: 33-40.
[167] Sun L, Liao K, Wang D. Effects of magnolol and honokiol on adhesion, yeast-hyphal transition, and formation of biofilm by *Candida albicans* [J]. *PLoS One*, 2015, **10**(2): e0117695.
[168] Sun L, Liao K, Hang C, *et al*. Honokiol induces reactive oxygen species-mediated apoptosis in *Candida albicans* through mitochondrial dysfunction [J]. *PLoS ONE*, 2017, **12**(2): e0172228.
[169] Weber K, Schulz B, Ruhnke M. Resveratrol and its antifungal activity against *Candida* species [J]. *Mycoses*, 2011, **54**(1): 30-33.
[170] Lee J, Lee DG. Novel antifungal mechanism of resveratrol: apoptosis inducer in *Candida albicans* [J]. *Curr Microbiol*, 2015, **70**(3): 383-389.
[171] Park C, Lee DG. Melittin induces apoptotic features in *Candida albicans* [J]. *Biochem Biophys Res Commun*, 2010, **394**(1): 170-172.
[172] Hwang B, Hwang JS, Lee J, *et al*. The antimicrobial peptide, psacotheasin induces reactive oxygen species and triggers apoptosis in *Candida albicans* [J]. *Biochem Biophys Res Commun*, 2011, **405**(2): 267-271.
[173] Garrido C, Galluzzi L, Brunet M, *et al*. Mechanisms of cytochrome *c* release from mitochondria [J]. *Cell Death Differ*, 2006, **13**(9): 1423-1433.
[174] Shin S, Kang CA. Antifungal activity of the essential oil of *Agastache rugosa* Kuntze and its synergism with ketoconazole [J]. *Lett Appl Microbiol*, 2003, **36**(2): 111-115.
[175] Khan A, Ahmad A, Khan LA, *et al*. *Ocimum sanctum* (L.) essential oil and its lead molecules induce apoptosis in *Candida albicans* [J]. *Res Microbiol*, 2014, **165**(6): 411-419.
[176] Sung WS, Lee IS, Lee DG. Damage to the cytoplasmic membrane and cell death caused by lycopene in *Candida albicans* [J]. *J Microbiol Biotechnol*, 2007, **17**(11): 1797-1804.
[177] Choi H, Lee DG. Lycopene induces apoptosis in *Candida albicans* through reactive oxygen species production and mitochondrial dysfunction [J]. *Biochimie*, 2015, **115**: 108-115.
[178] Luna-Tapia A, DeJarnette C, Sansevere E, *et al*. The vacuolar Ca^{2+} ATPase pump Pmc1p is required for *Candida albicans* pathogenesis [J]. *mSphere*, 2019, **4**(1): e00715-00718.
[179] Tian H, Qu S, Wang Y, *et al*. Calcium and oxidative stress mediate perillaldehyde-induced apoptosis in *Candida albicans* [J]. *Appl Microbiol Biotechnol*, 2017, **101**(8): 3335-3345.
[180] Yun DG, Lee DG. Silibinin triggers yeast apoptosis related to mitochondrial Ca^{2+} influx in *Candida albicans* [J]. *Int J Biochem Cell Biol*, 2016, **80**: 1-9.
[181] Lewis RE, Kontoyiannis DP. Rationale for combination anti-

fungal therapy [J]. *Pharmacotherapy*, 2001, **21**(8 Pt 2): 149s-164s.
[182] Shrestha SK, Fosso MY, Garneau-Tsodikova S. A combination approach to treating fungal infections [J]. *Sci Rep*, 2015, **5**: 17070.
[183] Lu M, Li T, Wan J, *et al*. Antifungal effects of phytocompounds on *Candida* species alone and in combination with fluconazole [J]. *Int J Antimicrob Agents*, 2017, **49**(2): 125-136.
[184] Sharma M, Manoharlal R, Shukla S, *et al*. Curcumin modulates efflux mediated by yeast ABC multidrug transporters and is synergistic with antifungals [J]. *Antimicrob Agents Chemother*, 2009, **53**(8): 3256-3265.
[185] Holmes AR, Cardno TS, Strouse JJ, *et al*. Targeting efflux pumps to overcome antifungal drug resistance [J]. *Future Med Chem*, 2016, **8**(12): 1485-1501.
[186] Xu J, Liu R, Sun F, *et al*. Eucalyptal D enhances the antifungal effect of fluconazole on fluconazole-resistant *Candida albicans* by competitively inhibiting efflux pump [J]. *Front Cell Infect Microbiol*, 2019, **9**: 211.
[187] Garcia-Gomes AS, Curvelo JA, Soares RM, *et al*. Curcumin acts synergistically with fluconazole to sensitize a clinical isolate of *Candida albicans* showing a MDR phenotype [J]. *Med Mycol*, 2012, **50**(1): 26-32.
[188] Esposito M, Nim S, Nothias LF, *et al*. Evaluation of jatrophane esters from *Euphorbia* spp. as modulators of *Candida albicans* multidrug transporters [J]. *J Nat Prod*, 2017, **80**(2): 479-487.
[189] Guo XL, Leng P, Yang Y, *et al*. Plagiochin E, a botanic-derived phenolic compound, reverses fungal resistance to fluconazole relating to the efflux pump [J]. *J Appl Microbiol*, 2008, **104**(3): 831-838.
[190] Li DD, Xu Y, Zhang DZ, *et al*. Fluconazole assists berberine to kill fluconazole-resistant *Candida albicans* [J]. *Antimicrob Agents Chemother*, 2013, **57**(12): 6016-6027.
[191] Huang S, Cao YY, Dai BD, *et al*. *In vitro* synergism of fluconazole and baicalein against clinical isolates of *Candida albicans* resistant to fluconazole [J]. *Biol Pharm Bull*, 2008, **31**(12): 2234-2236.
[192] Zhang X, Guo H, Gao L, *et al*. Molecular mechanisms underlying the tetrandrine-mediated reversal of the fluconazole resistance of *Candida albicans* [J]. *Pharm Biol*, 2013, **51**(6): 749-752.
[193] Sun LM, Cheng AX, Wu XZ, *et al*. Synergistic mechanisms of retigeric acid B and azoles against *Candida albicans* [J]. *J Appl Microbiol*, 2010, **108**(1): 341-348.
[194] Gong Y, Liu W, Huang X, *et al*. Antifungal activity and potential mechanism of *n*-butylphthalide alone and in combination with fluconazole against *Candida albicans* [J]. *Front Microbiol*, 2019, **10**: 1461.
[195] Li Y, Chang W, Zhang M, *et al*. Synergistic and drug-resistant reversing effects of diorcinol D combined with fluconazole against *Candida albicans* [J]. *FEMS Yeast Res*, 2015, **15**(2): 1-10.

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Prof. YANG Ming-Hua obtained his Ph.D. degree in Science of Chinese Materia Medica from China Pharmaceutical University in 2010, and has been working there as a full professor (2020) and doctoral supervisor (2016). His researches cover the fields of chemistry of Chinese Materia Medica and the chemistry of natural medicinal products, with most research work done in antifungal components from Traditional Chinese Medicines (TCMs) and fungal metabolites. Dr. YANG has been the director for many research projects at the state and ministerial/provincial levels, such as the National Natural Science Foundation of China. He has published more than 50 research papers in such well-known domestic and international journals, such as "*Organic Letters*", "*Journal of Natural Products*", "*Organic Chemistry Frontiers*", and "*Chemistry-A European Journal*". And he has been conferred serveal awards and honors academically, including the second prize of National Prize for Progress in Science and Technology (2015) and the first prize recipient of Jiangsu Provincial Science and Technology Awards (2013 and 2019).