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Antifungal peptides: Biosynthesis, production and applications

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ABSTRACT

Fungal infections in animal, plants and fungal contamination of food for humans and livestock result in substantial worldwide economic losses. In the last few years, fungal infection has increased strikingly by a rise in the number of deaths of acquired immunodeficiency syndrome (AIDS) cancer patients, transplant patients owing to fungal infections. The growth rate of fungi is very slow as compared to bacteria and very difficult to identify. Approximately 100 peptides have been investigated to date for their antifungal properties, which can be of great importance to overcome the human diseases. Insects secrete such compounds, which can be peptides, as a part of their immune defense reactions. Antifungal peptides are excellent models for drug discovery exhibiting unique characteristics such as high specificity, broad spectrum, low level of resistance reaching and unique mode of action. The aim of this review is to provide information on research on these important peptides.

KEY WORDS: ANTIFUNGAL; PEPTIDES; MODE OF ACTION; FUNGAL INFECTION; FUNGI CIDAL

INTRODUCTION

Many research advances have been made in medicine at present. Be it in the treatment of HIV-AIDS, cancer, or organ transplantation, the success rates have increased drastically over past 50 years. Even though success rates have been increased, many patients are left with compromised immune systems (Wisplinghoff *et al.*, 2004). The Patients, receiving chemotherapy, organ transplantation, use of prosthetic Devices and vascular catheters, dialysis etc., are easily susceptible to manybacterial, viral and fungal infections (Spellberg *et al.*, 2008). Even though fungal species are serious pathogens, they get lesser attention when compared to bacterial and viral infec-

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tions as, the frequency of occurrence of fungal infections has been comparatively less to bacterial and viral infections (Georgopapadakou *et al*., 1996; Wisplinghoff *et al*., 2004; Porto *et al*., 2012). Human fungal infections, caused by *Aspergillus fumigatus*, *Cryptococcusneoformans*, *Candida albicans*, are increasing in a number ofimmune-compromised patients (Blanco *et al*., 2008). Fungal pathogens such as *Candida* species and *Aspergillus* species are more common and account up to 19% of cases (Schelenz *et al*., 2009). *C. albicans* is known as major fungal pathogen and is 4th most common cause of nosocomial infections (Banerjee *et al*., 1991; Beck-Sague *et al*., 1993; Wisplinghoff *et al*., 2004; Xiao *et al*., 2013; Chen *et al*., 2016; Ageitos *et al*., 2017; Bondaryk *et al*., 2017).

Only a limited number of antifungal drugs are available such as echinocandins, polyenes etc., (Gupte *et al*., 2002). Amphotericin B, which was discovered in 1956, is still used for treatment many fungal infections. Just like bacterial resistance, fungal pathogens have also developed resistance in past 20 years. (Gold *et al*., 2002; Georgopapadakou *et al*., 1996). The fact that fungal and bacterial infections are different and bacterial infections are treated more easily is because, fungal cells are eukaryotic and bacterial cells are prokaryotic. The main concern in treating fungal infections is that any chemical substance that is successful in damaging the eukaryotic cell wall of fungi may also cause possible damage to human cells, unlike antibiotics, which won't have any effect on humans. Any chemical substance that is toxic to fungus may also be toxic to humans (Mohammad *et al*., 2015). Therefore, there is need to discover new biochemical targets in fungi. Antifungal peptides are treatment alternatives, derived from natural sources and are effective against fungal infections, thus, safe for immune compromised patients (Gold *et al*., 2002; Ravi *et al*., 2011; Thakur *et al*., 2012; Jia *et al*., 2016; Wang *et al*., 2016; Veltri *et al*., 2017).

Antifungal peptides from natural sources are much cheaper than commercial antifungal drugs and are also better alternative to combat resistance. Antifungal peptides are cationic biomolecules with weight around 1.3 kDa to 30 kDa (Mohammad *et al*., 2015). Antifungal peptides are classified into two types based on their mode of action. First group are, lytic peptides, (Rees *et al*., 1997; Shai *et al*., 1995). These peptides are amphipathic in nature (contain a positive and a neutral charge) and disrupt the membrane structure by fixing onto its surface (Leuschner *et al*., 2004; Shai *et al*., 1995). The second group of peptides act by inhibiting the synthesis of cell wall or essential cell wall components such as glucan, chitin (Fernández *et al*., 2004; Lata *et al*., 2010; Joseph *et al*., 2012; Liu *et al*., 2016; Bondaryk *et al*., 2017).

SOURCES OF ANTIFUNGAL PEPTIDES

Bacterial Peptides Iturins

Iturin was one of first antifungal peptides, ever isolated. It is produced by different strains of *Bacillus subtilis* (Georgopapadakou *et al*., 1996). They are cyclic lipopeptides and act by disrupting the cell membrane of fungi, hence leaking its vital ions (XinZhao *et al*., 2013; Lemaitre *et al*., 1997). Iturin A, of iturin family, was observed to inhibit *A. flavus* and *F. moniliforme* growth and had Minimal inhibitory concentration (MIC) of 22.0 µg/ml against *Saccharomyces cerevisiae*. It was found to be effective against dermatomycoses. (De Lucca *et al*., 1999). But iturin A was also observed to be hemolytic. Bacillomycin F, another family member of iturin, is known to inhibit strains such as *Byssochlamys fulva*, *A.niger*, *C.albicans*, and *F.oxysporum*and had MIC of 40.0µg/ml for *A.niger* (De Lucca *et al*., 1999). Bacillomycin D produced by *Bacillus amyloliquefaciens* was found to be effective against a plant pathogenic fungi *Fusarium graminearum and Candida* species. MIC of (12.5-25) µg/ml was observed against various *Candida* species (Tabbene *et al*., 2015; Qin Gu *et al*., 2017).

Syringomycins: Syringomycins are produced by *Pseudomonas syringae* are small cyclic lipodepsipeptides with ergosterol as a binding site in yeast. The most prevalent of Syringomycinsis syringomycin-E (SE) which was found to be lethal to many strains such as *A. flavus, A. fumigatus, A.niger, F. moniliforme and F. oxysporum* showing LD95 of 1.9 µg/ml. it showed MIC of (0.8–12.5) µg/ml against *C. neoformans* (De Lucca et al., 1999). Syringotoxin B, syringostantin A which were lipodepsinonapeptides were found to be effective against *Candida, Cryptococcus*, and *Aspergillus* species. Syringostantin A had MIC of 5.0µg/ml against *A. fumigatus*. Syringotoxin B had MIC of 3.2µg/ml against *C. albicans* (Sorensen et al., 1996; Zhao et al., 2013; Chereddy et al., 2014; Deslouches et al., 2015; Gao et al., 2016; Kubicek-Sutherland et al., 2017).

Pseudomycins: Pseudomycins, another family, structurally related to syringomycins also have antifungal activity against wide ranges of species. Existing as pseudomycins (A, B, and C), these have shown antifungal activity against *Ceratocystis ulmi, C. Albicans, Rynchosporium secalis,Rhizoctonia solani,Sclerotiniasclerotiorum Verticillium albo-atrum, Verticillium dahliae, Thielaviopis basicola, F. oxysporum, F. culmorum. The MIC of pseudomycin A, against C. neoformans* was 1.56 µg/ml whereas 3.12 µg/ml was observed against *C. albicans* (De Lucca *et al*., 1999).

Plant Peptides: Large number of antifungal peptides are identified from plant sources, but only few were tested and found to be effective.

Table 1. Antifungal peptides from bacterial sources

Peptide name	Family/group	Structure	source	Fungal species effected	Typical target organism	Mode of action	In vitro MIC (µg/ml)	Reference
Bacillomycin F	Iturins	lipopeptide	*B. subtilis.*	*Byssochlamys fulva, A. niger, C.albicans, and F.oxysporum*	*A. niger*	lysis	40	(De Lucca et al., 1999; Bionda et al., 2016)
iturin A	Iturins	lipopeptide	*Bacillus amyloliquefaciens*	*A. flavus, F. moniliforme, S. cerevisiae*	*S. cerevisiae*	lysis	22.0	(Georgopapadakou et al., 1996; De Lucca et al., 1999; Brandenburg et al., 2015)
bacillomycin D	Iturins	lipopeptide	*Bacillus amyloliquefaciens*	*F. graminearum and Candida species.*	*Candida species*	*lysis*	12.50-25.0	*(*Tabbene et al., 2015; Qin Gu et al., 2017,*)*
syringomycin-E (SE)	Syringomycins	lipodepsipeptide	*Pseudomonas syringae*	*A. flavus, A. fumigatus, A.niger, F. moniliforme and F. oxysporum*	*C. neoformans*	lysis	0.8–12.5	(De Lucca et al., 1999; Falciani et al., 2014)
syringostantin A	Syringomycins	lipodepsinonapeptides	*Pseudomonas syringae*	*Candida, Cryptococcus, and Aspergillus species*	*A. fumigatus*	lysis	5.0	(Sorensen et al., 1996; Falciani et al., 2014)
Syringotoxin B	Syringomycins	Lipodepsinonapeptide	*Pseudomonas syringae*	*Candida, Cryptococcus, and Aspergillus species.*	*C. albicans*	lysis	3.2	(Sorensen et al., 1996; Lyu et al., 2016)
pseudomycin A	Pseudomycins	lipodepsinonapeptides	*Pseudomonas syringae*	*C. albicans, F. oxysporum , F. culmorum, C. neoformans*	*C. albicans*	lysis	3.12	(De Lucca et al., 1999; Brunetti et al., 2016)

Table 2. Antifungal peptides from plant sources

Peptide name	Family/group	No. of amino acids	source	Target organism	In vitro MIC (µg/ml)	Reference
Ib-AMP3	Plant defensins	20	*Impatiens balsamina*	*F. moniliforme*	50.0	(De Lucca et al., 1999; Asano et al., 2013)
Frangufoline	Cyclopeptides	*534	*Rhamnus frangula*	*A. niger*	5.0	(Gournelis et al., 1997; De Lucca 2000; Tan et al., 2006; Choe et al., 2015)
Rugosanine A	Cyclopeptides	*585	*Ziziphus rugosa*	*A. niger*	5.0	(Gournelis et al., 1997; De Lucca 2000; Tan et al., 2006; Cole et al., 2016)
Nummularine	Cyclopeptides	*587	*Ziziphus nummularia*	*A. niger*	5.0	(Gournelis et al., 1997; De Lucca 2000; Tan et al., 2006; Dobson et al., 2014)
ACE-AMP1	Lipid transfer proteins	93	*Allium cepa L*	*F. oxysporum*	10.0	(De Lucca 2000; Dutta et al., 2015)

Plant defensins

Plant defensins are eight disulfide-linked cysteines with a single helix and triple-stranded b-sheet (Bruix *et al.*, 1995). Ib-AMP$_3$, isolated from *Impatiens balsamina,* was observed to be lethal against germinated conidia of *A. flavus* by 42%, where as it was non-lethal against non-germinated conidia.It had MIC of 50.0µg/ml against *F. moniliforme* (De Lucca *et al.*, 1999; Asano *et al.*, 2013).

Table 3. Antifungal peptides from fungal sources

Peptide name	Structure	source	Typical target organism	Mode of action	In vitro MIC (µg/ml)	Reference
Caspofungin	lipopeptide	*G.lozoyensis*	*Candida spp*	*glucan synthesis*	8 - 64	(Bartizalet al., 1997;Groll et al., 1999; Kuhn et al., 2002; *Deresinski* et al., *2003*; Porto et al., 2012)
Anidulafungin (LY303366)	Lipopeptide	*A. nidulans*	*Candida spp*	*glucan synthesis*	0.5 - 4.0	*(Lucca et al., 1999; Denning et al., 1997;* Ghannoum et al., 2005; De *Lei* et al., *2013)*
Cilofungin (LY121019)	Lipopeptide	*A. nidulans*	*C. albicans*	*Glucan synthesis*	0.62	(De Lucca 2000; Joseph et al., 2012)
Echinocandin B	Lipopeptide	*A. nidulans*	*C. albicans*	*Glucan synthesis*	0.625	(De Lucca 2000; Veltri et al., 2017)
Aculeacin	Lipopeptide	*A. aculeatus*	*C. albicans*	*Glucan synthesis*	0.2	(De Lucca et al., 1999; Chen et al., 2016)
Trichopolyn	Amino-lipopeptide	*Trichoderma polysporum*	*C. albicans*	*Unknown*	0.8	(De Lucca 2000; Liu et al., 2016)
Leucinostatin	Amino-lipopeptide	*Penicillium lilacinum*	*C. neoformans*	*Unknown*	0.5	(De Lucca 2000; Zhao et al., 2013)

Table 4. Antifungal peptides from insect sources

Peptide name	Family/group	No. of amino acids	source	Typical Target organism	Mode of action	In vitro MIC (µg/ml)	Reference
Cecropin A	Cecropins	37	*Hyalopora cecropia*	*F. oxysporum,*	lysis	12.4	(De Lucca et al.,1998; Joseph et al., 2012)
Cecropin B	Cecropins	35	*Hyalopora cecropia*	*A. fumigatus*	lysis	9.5	(Nappi et al., 2001; Xiao et al., 2013)
Drosomycin	Cysteine-rich peptides	44	*Drosophila melanogaster and Podisus maculiveris*	*F.oxysporum*	lysis	5.9	(De Lucca, 2000; Veltri et al., 2017)
Thanatin	Cysteine-rich peptides	21	*Podisus maculiveris*	*F. oxysporum*	Unknown	5.0	(Bulet et al., 2005; Wang et al., 2015)
Heliomicins	Insect Defensins	44	*Heliothis virescens*	*C. neoformans*	Unknown	12.0	Nappi et al., 2001; De Lucca 2000; Zhao et al., 2013; Ageitos et al., 2017)

Cyclopeptides: Cyclopeptides from different species of *Rhamnaceae* family were observed to have antifungal activities. Frangufoline, from barks of *Rhamnus frangula* were observed to have anti-bacterial and anti-fungal properties. It showed MIC of 5.0 µg/ml for *A. niger*. Nummularine (B, K, R, and S), from stem barks of *Ziziphus nummularia*, Rugosanine (A and B) from stem barks of *Ziziphus rugosa* and abyssenine-C from stem barks of Ziziphus abyssinica, were all observed to have antifungal properties against *A. niger* with MIC of 5 µg/ml. However, they were observed to be well effective against *A. niger* but not against *C. albicans* and their mechanism of action was also unknown (Gournelis *et al*., 1997; De Lucca 2000; Tan *et al*., 2006).

Lipid transfer proteins and other peptides: ACE-AMP1 is a lipid transfer protein, produced by seeds of *Allium cepa* which was observed to be effective against *F. oxysporum* with MIC of 10.0 µg/ml (Cammue *et al*., 1995; De Lucca 2000). Apart from the above antifungal peptides, some other peptides include, Chitinases and glucanases, which hydrolyze chitin, glucan, and

Table 5. Antifungal peptides from amphibian sources

Peptide name	No. of amino acids	source	Typical Target organism	Mode of action	In vitro MIC (µg/ml)	Reference
Magainin 2	23	*Xenopus laevis*	*C. albicans*	Lysis	80.0	(Zasloff et al., 2002; Bondaryk et al., 2017)
Dermaseptin b	27	*Phyllomedusa sauvagii*	*C. neoformans*	Lysis	60.0	(Landon et al., 1997; Brandenburg et al., 2015)
Dermaseptin s	34	*P. sauvagii*	*C. neoformans*	Lysis	5.0	(Landon et al., 1997; Brunetti et al., 2016)
Skin-PYY (SPYY)	36	*P. bicolor*	*A. fumigatus*	Membrane permiation	80.0	(Vouldoukis et al., 1996; Brunetti et al., 2016)
Brevinin-2R	24	*Rana ridibunda*	*C. albicans*	–	3.0	(Conlon et al., 2003; Anunthawan et al., 2015)

the essential cell wall components of fungi. Prematins, members of PR-5 protein family, act by permeabilizing fungal membranes. Similarly, Thionins inhibit by permeabilizing fungal membranes and were found to be effective against *F. graminearum and F. sporotrichioides* (Velazhahan *et al*., 2001; Asano *et al*., 2013).

Fungal Peptides: Antifungal peptides from fungi are more active than those compared to bacteria and plants. Echinocandins are lipopeptides which inhibit 1,3-β-glucan synthase (Gregory et al., 2007). Glucan is the major component of cell wall of fungi and inhibition of glucan may result in osmotic instability and in cell lysis. (Lee et al., 1995; Gregory et al., 2007; Osorio et al., 2015; Liu et al., 2016). The MIC90 value of echinocandins was found to be ≤2 µg/mL against *Candida* spp (Zaas et al., 2005). A-192411.29 had anti- fungicidal activity against *C. albicans, C. tropicalis* and *C. glabrata* (Vazquez et al., 2005; Kaconis et al., 2011; Chu et al., 2013). But, the echinocandins do not show any antifungal activity against *Cryptococcus* spp, *Trichosporon* spp, *Fusarium spp*, zygomycetes (Zaas et al., 2005; Kazemzadeh-Narbat et al., 2010). They also, do not affect human cells, as human cells do not contain 1,3-β-D-glucan. However, echinocandins are labeled category C and are toxic to embryos (Gregory et al., 2007; Lakshmaiah Narayana et al., 2014).

Micafungin from *Coleophoma empedra*, caspofungin from *Glarea lozoyensis* and anidulafungin from *A. nidulans* of echinocandin family have been approved so far (Murdoch et al., 2004; Montgomery et al., 2013). Of these, anidulafungin displays least MIC values followed by micafungin and caspofungin being most. This was observed against *Candida* spp. (Zaas et al., 2005; Mojsoska et al., 2015). Caspofungin, also known as (MK-0991) is a second generation pneumocandin from Glarea lozoyensis (Abruzzo et al., 1997; Groll et al., 1999; López-Garcia et al. 2005; Popovic et al., 2012). It was fungicidal against *C.albicans* and *C. parapsilosis* (Bartizal et al., 1997; Kuhn et al., 2002; Deresinski et al., 2003; Ordonez et al., 2014). It was observed be effective against hyphal tips *A. fumigatus* although not completely lethal (Krishnan et al., 2005). It was also lethal against several molds such as *Alternaria* sp., *Curvularia* sp., *Acremonium* sp., *Bipolaris* sp., and Trichodermasp (Kahn et al., 2006). Micafungin also known as FK463 had antifungal activity against disseminated candidiasis and aspergillosis (Petraitiset al., 2000; Lakshmaiah Narayana et al., 2015).

The optimal concentration of FR463 at single infusion was observed to be 2.5-25 mg (Azuma et al., 1998; Pettengell et al., 1999; Kasetty et al., 2015; Kang et al., 2017). Anidulafungin (V-echinocandin), previously known as LY303366 is a semisynthetic echinocandin currently used as antifungal drug (*Krause* et al., *2004;* Harder et al., 2013; Kang et al., 2017).It is a lipopeptide produced by A. nidulans, (*Lei* et al., *2013*) and acts by inhibiting glucan synthase (*Denning* et al., *1997;* Anunthawan et al., 2015). It was observed to be effective against Candidemia and other Candida infections and esophageal candidiasis. MIC of (0.5 to 4.0) µg/ml was observed in *Candida* spp. However, Anidulafungin displays low MICs against strains of *C. parapsilosis* and is not effective inactive against *C. neoformans* and Blastomyces dermatitidis *(*De Lucca et al., 1999; Ghannoum et al., 2005; Ben Lagha et al., 2017*)*.

Echinocandin B from *A. nidulans* and *A. rugulosus* was effective against *C. albicans* with MIC of 0.625 µg/ml. Cilofungin (LY121019), isolated from Aspergillus spp. had MIC of 0.62 µg/ml. Amino-lipopeptides such as Trichopolyns from Trichoderma polysporum have MIC of (0.78 - 6.25) µg/ml for *C. albicans*. Other families of potent antifungal peptides include the leucinostatins and helioferins families also consist of antifungal poperties, but, where toxic, hemolytic to mammalian cells in vitro (De Lucca 2000; *Lei* et al., *2013;* Osorio et al., 2015; Chen et al., 2016; Ageitos et al., 2017).

Insect Peptides: Cecropins

Cecropins (A and B) are linear lytic peptides, made up of an 11- amino acid sequence, produced in hemolymph giant silk moth, *Hyalopora cecropia*. Cecropin B was observed lethal against F. oxysporum (approximately 95%), A. fumigatus 9.5 µg/ml (De Lucca *et al*., 1998; Nappi *et al*., 2001). cecropin A was observed to be more fungicidal at neutral pH and was more affective against Fusarium moniliforme and Fusarium oxysporum with total killing of 12.4 µg/ml (De Lucca *et al*.,1998).

Drosomycin: Drosomycin is a Cysteine-rich peptide containing 44 amino acid with a twisted three-stranded sheet structure steadied by disulfide bonds. It is isolated from Drosophila melanogaster and *Podisus maculiveris* and was found to be effective against F.oxysporum with MIC value of 5.9 µg/ml (De Lucca, 2000).

Glycin-rich peptides

Antifungal peptides, such as holotricin-3, and tenecin-3 are glycine-rich peptides isolated from insects (Nappi *et al*., 2001). Tenecin-3 was studied to be effective against *C. albicans* (Ganz, 2003). Holotricin-3, was isolated from larval hemolymph of Holotrichia diomphalia, and was observed to inhibit *C. albicans* growth (Lee *et al*., 1995).

Thanatin: Thanatin is another non-hemolytic Cysteine-rich peptide containing 21 amino acid residues and is smaller compared to drosomycin. It was affective against many strains such as *Trichoderma viride, Alternaria brassicola, Neurospora crassa, Botrytis cinerea, and Fusarium culmorum, A. fumigatusT.* mentagro-

phytes and F. *oxysporum* (Fehlbaum *et al*., 1996; Bulet *et al*., 2005). MIC of 5.0 µg/ml was observed against *F. oxysporum*. However Thanatin was not effective against yeast (Mandard *et al*., 1998).

Heliomicin: Heliomicin from *Heliothis virescens* (tobacco budworm), was observed to have antifungal activity against *C. neoformans*, with MIC of 12.0 µg/ml (De Lucca 2000; Nappi *et al*., 2001).

Amphibian Peptides: Magainins: Magainins was the first among the antifungal peptides from amphibian sources. They are amphiphilic, non-hemolytic and are produced by *Xenopus laevis* (African clawed frog). Magainin 2 inhibited *C. albicans* growth and had MIC of 80.0 µg/ml (De Lucca *et al*., 1999; Zasloff *et al*., 2002).

Dermaseptins: Dermaseptins are linear, lytic,peptides produced by *Phyllomedusa sauvagii* (South American arboreal frog). Dermaseptin was lethal towards for *A. flavus, A. fumigatus*, and *F. oxysporum*, with LD50 values observed as 3 µM, 0.5 µM, and 0.8 µM, respectively (Landon *et al*., 1997). Dermaseptin b was effective against yeasts and some filamentous fungi such as *C. neoformans*and had MIC value of 60.0µg/ml. Dermaseptin s had MIC of 5.0µg/mlfor *C. neoformans*. (De Lucca *et al*., 1999).

Skin-PYY (SPYY): Skin-PYY (SPYY), is an antifungal compound produced by *Phyllomedusa bicolor* (South American tree frog). It was observed to inhibit *C. neoformans*, *C. albicans*, and *A. fumigatus* and had MIC values of 20 µg/ml, 15 µg/ml, and 80 µg/ml, respectively (Vouldoukis *et al*., 1996).

Brevinin: Brevinin-2R isolated from skin of Rana ridibunda (red frog). It is non-hemolytic, 24 amino acid peptide with α-helical conformation. It was observed to have MIC of 3.0 µg/ml against *C. albicans* (Conlon *et al.,* 2003).

FUTURE PROSPECTS

Emerging fungal resistance to conventional therapies necessitates the development of novel antifungal strategies. In this context, Anti-fungal peptides draw the attention as alternative potential antifungal agents (Brunetti et al., 2016). These peptides are relatively safe, tolerated and highly effective. As per the information available in the literatures, only few antifungal peptides are used in antifungal therapy (Brandenburg et al., 2015). There are various problems addressed which is limiting the uses of these peptides, such as low bioavailability, hemolytic activity, instability, high cost of production, possible aggregation, loss of activity in high salt concentrations, poor ability to cross physiological barriers (Chen et al., 2016; Ageitos et al., 2017).

Due to these effects, the therapeutic use of antifungal peptides is significantly decreased now a day. However, the utilization of these peptides could be enhanced by chemical optimization and new delivery strategies. With the advancement of new research strategies, the wide variety of natural antimicrobial peptides should be characterized both structurally and functionally for making them extremely promising source of ideas in design the novel antifungal peptides. In particular, application of dendrimers as scaffolds for assembling well defined macromolecular polyvalent molecules or synthesis de novo of per se active linear and branched peptide mimics makes them extremely promising for use as new generation antifungal peptides.As found in several studies, the modes of antifungal action must be well understood (Deslouches et al., 2015; Gao et al., 2016; Kubicek-Sutherland et al., 2017). Hopefully, all these efforts will result in the development of a novel class of antifungal agents to their full potential.

CONCLUSION

Antifungal peptides are excellent models for drug discovery exhibiting unique characteristics such as low level of resistance reaching the absent, high specificity, broad spectrum, and unique mode of action. Despite the distinctiveness, only few examples of antifungal peptides have successfully reached the market.

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