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MINIREVIEW

Antifungal Peptides: Novel Therapeutic Compounds against Emerging Pathogens

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INTRODUCTION

The need for safe and effective antifungal agents increases in parallel with the expanding number of immunocompromised patients at risk for invasive fungal infections. The emergence of fungal pathogens resistant to current therapies further compounds the dearth of antifungal agents. Currently available antifungal compounds act on targets also found in mammalian cells (34), which may result in toxicity or an adverse drug interaction. It is therefore imperative to find antifungal compounds that are not toxic to mammalian cells. The past decade has witnessed a dramatic growth in knowledge of natural peptides. Peptides such as the cecropins were shown to be antimicrobial but not lethal for mammalian cells (21, 141, 162, 182). Most data on antimicrobial peptides concern bacteria. This minireview presents a review of the current literature on antifungal peptides, including their in vitro and in vivo activities, mechanisms of action, and structure-function relationships, when known.

CLASSIFICATION OF PEPTIDES

Antifungal peptides are classified by their mode of action. The first group acts by lysis, which occurs via several mechanisms (158). Lytic peptides may be amphipathic, that is, molecules with two faces, with one being positively charged and the other being neutral and hydrophobic. Some amphipathic peptides bind only to the membrane surface and can disrupt the membrane structure without traversing the membrane. Others traverse membranes and interact specifically with certain molecules. Finally, other amphipathic peptides aggregate in a selective manner, forming aqueous pores of variable sizes, allowing passage of ions or other solutes. The second peptide group interferes with cell wall synthesis or the biosynthesis of essential cellular components such as glucan or chitin (34). An excellent review of lipopeptide antifungal agents affecting cell wall synthesis has been published previously (9).

MAMMALIAN PEPTIDES

Defensins. α-Defensins ("classic defensins") and β-defensins (Table 1), which are present in many organisms, are predominantly β-sheet structures stabilized by three disulfide bonds that distinguish them from other antimicrobial peptides that form amphipathic helices (185). They are small, variably cationic proteins whose three-dimensional folds form highly amphipathic molecules (55). Defensins electrostatically bond to membranes, causing the formation of multimeric pores and the leakage of essential minerals and metabolites (102, 105, 133, 185). Defensin A caused membrane depolarization, decreased cytoplasmic ATP levels, and inhibited cellular respiration (31). The entrance of defensins into cells has caused DNA damage (58, 105).

Rabbit, guinea pig, rat, and human neutrophils contained defensins within azurophilic granules (42, 55, 155–157). Rabbit granulocytes contained six α-defensins structurally homologous to human defensins (106). Three such peptides, NP-1, NP-2, and NP-3a, were highly effective against *Candida albicans* (157). Although NP-5 lacked candidacidal properties alone, at submicromolar concentrations it potentiates the anti-*Candida* effects of other rabbit defensins (106). This effect of NP-5, however, was not observed with NP-3b or NP-4. NP-1 had MICs ranging from 3.75 to 15 μg/ml for encapsulated strains of *Cryptococcus neoformans*, while the MICs for acapsular strains were much lower (0.93 μg/ml) (3). NP-1 and other rabbit defensins were also lethal for *Coccidiodes immitis*, as well as hyphae and germinating conidia, but not dormant conidia, of *Rhizopus oryzae* and *Aspergillus fumigatus* (107, 153). As measured by the yellow tetrazolium salt assay, NP-1, NP-2, and NP-3 killed all *A. fumigatus* hyphae at 25, 25, and 100 μg/ml, respectively (107). At 100 μg/ml, NP-4 killed only 11% of the hyphae, while NP-5 had no effect. Resting conidia of *A. fumigatus* were resistant to 100 μg of these peptides per ml. Purified chitin and its fragments chitobiose and chitotrose bound to NP-1 and prevented the death of *A. fumigatus*, suggesting that the lethality of NP-1 was through binding to cell wall chitin (107).

Human α-defensins, HNP-1 to HNP-3, are constituents of the microbicidal granules of neutrophils (104). At 50 μg/ml, HNP-1 and HNP-2, but not HNP-3, were lethal for *C. albicans* (103). On a concentration basis, rabbit NP-1 was 10- to 20-fold more active than HNP-1 against *C. albicans* (103). HNP-1 to HNP-3 at 50 μg/ml inhibited *C. neoformans* growth, with a reduction of $>10^3$ CFU/ml compared to the growth of the control after 4 h (56).

Bovine tracheal antimicrobial peptide, a cysteine-rich β-defensin produced by respiratory epithelial cells, was active (41) against the yeast forms of several *C. albicans* strains. The synthetic form at 400 μg/ml was active against the hyphal forms of *A. fumigatus* and *C. albicans* (98). In contrast, magainin II, α-defensin, and amphotericin B had lower MICs for *A. fumigatus* (250, 200, and 0.8 μg/ml, respectively) (98).

Protegrins and gallinacins. The protegrins, which are related to the β-defensins, are produced by porcine leukocytes.

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TABLE 1. Mammalian antifungal peptides

Peptide	Source	No. of amino acids	Mode of action	Typical target organism	In vitro MIC (μg/ml)
Defensins					
NP-1	Rabbit granulocytes	33	Lysis	*C. neoformans*	3.75–15.0[a]
NP-2	Rabbit granulocytes	33	Lysis	*A. fumigatus*	25.0
NP-3A	Rabbit granulocytes	34	Lysis	*A. fumigatus*	100.0
NP-3B	Rabbit granulocytes	33	Lysis	*A. fumigatus*	100.0
NP-4	Rabbit granulocytes	33	Lysis	*A. fumigatus*	>100.0
NP-5	Rabbit granulocytes	33	Lysis	*A. fumigatus*	Inactive alone
HNP-1	Human neutrophils	30	Lysis	*C. albicans*	50.0
HNP-2	Human neutrophils	29	Lysis	*C. albicans*	50.0
HNP-3	Human neutrophils	30	Lysis	*C. neoformans*	50.0 (LD_{50}[b])
Gallinacin-1	Chicken	39	Lysis	*C. albicans*	25.0
Lactoferricin-B	Human, bovine	18	Lysis	*C. albicans*	0.8
Protegrins 1 to 3	Human, porcine	16–18	Lysis	*C. albicans*	3.0–60.0
Tracheal antimicrobial peptide	Human, bovine	38	Lysis	*C. albicans*	6.0–12.0
Tritrptcin	Human, porcine	13	Lysis	*A. flavus*	250.0

[a] MICs based on assays with multiple isolates.
[b] LD_{50}, lethal dose for 50% of the population.

They are cationic, cysteine-rich molecules with two intermolecular, parallel, disulfide bridges which stabilize an amphipathic β-sheet structure comprising two antiparallel strands (7, 70, 89). Protegrins formed weakly selective ionic channels that anions and small cations permeated, indicating that the cysteine bridges are a prerequisite for membrane permeability alteration but not for antimicrobial activity (112). In contrast, others reported that these intramolecular disulfide bonds enhance the antimicrobial and lytic actions of protegrins (71). Zone inhibition studies showed that protegrins 1, 2, and 3 inhibited *C. albicans* growth at 60, 8, and 3 μg/ml, respectively (89). Chicken leukocytes produce the gallinacin peptide family (69). Gallinacins have three intramolecular cystine disulfide bonds, are relatively cationic, and are rich in lysine and arginine. Gallinacin-1 and -1α inhibited *C. albicans* in a radial diffusion assay (69). However, gallinacin-2 showed no activity at up to 400 μg/ml in this assay.

Tritrpticin and lactoferricin. Precursors of many antimicrobial peptides of porcine, bovine, and rabbit origin share highly conserved regions with antifungal properties (108, 163, 189). Tritrpticin corresponds to 13 amino acids of the C-terminal portion of cathelin, a putative proteinase inhibitor from porcine blood leukocytes. In vitro, it was weakly inhibitory for *Aspergillus flavus* and *C. albicans* (97). Bovine lactoferrin, an iron-binding protein, had broad antimicrobial properties (25, 143). Lactoferricin, an enzymatic product of lactoferrin, possessed greater antimicrobial properties than lactoferrin and corresponds to the 18 amino acid residues near the N terminus of lactoferrin in a region distinct from its iron-binding sites (16, 176). Lactoferricin was active against *C. albicans*; however, its antimicrobial properties were diminished by Ca^{2+}, Mg^{2+}, and Fe^{2+} (186). The optimum pH for this peptide was 6.0, and it bound to outer bacterial membranes, causing disruption of normal permeability functions of the cytoplasmic membrane and ultrastructural damage (17, 186).

BPI protein domain III analogs. The bactericidal and permeability-increasing (BPI) protein is a cationic protein stored principally in the azurophilic granules of neutrophils (43). Several potent antifungal peptides with activity against *Candida* spp., *C. neoformans*, and *A. fumigatus* were derived from BPI protein functional domain III (109). These constructs produced significant, dose-dependent reductions in the numbers of *C. albicans* CFU in the kidney and significant protection from mortality in murine candidiasis models (5). Three small synthetic peptides (XMP.284, XMP.366, and XMP.391) based on BPI protein domain III were found to be fungicidal for several *Candida* species, while subinhibitory concentrations of these peptides enhanced the anti-*Candida* activities of fluconazole (78). XMP.391 was effective against murine disseminated aspergillosis and enhanced the effectiveness of amphotericin B (4).

INSECT-DERIVED ANTIMICROBIAL PEPTIDES

Cecropins. Cecropins (Table 2), which form α-helices in solution, are linear peptides in the hemolymph of the giant silk moth (*Hyalopora cecropia*) (21, 162). They are positively charged and form time-variant and voltage-dependent ion channels in planar lipid membranes (29). Cecropins were not lethal for mammalian cells at microbicidal levels and have been administered safely to animals (21, 65, 122, 141, 162, 182). At between 25 and 100 μg/ml it is fungicidal for pathogenic *Aspergillus* species (37, 38). *Fusarium moniliforme* and *Fusarium oxysporum* were especially sensitive to cecropin A, with total killing attained at 12.4 μg/ml (37).

Drosomycin. *Drosophila melanogaster* produces drosomycin, an insect defensin with significant homology with plant antifungal peptides isolated from seeds of members of the family *Brassicaceae* (47). It was similar in structure to the radish antifungal peptide, Rs-AFP_1, and was particularly effective against *F. oxysporum* isolates (118).

Antifungal peptide, holotricin 3, and thanatin. Insect peptides which are antifungal include antifungal peptide, holotricin 3, and thanatin. Antifungal protein, a histidine-rich peptide that causes cellular leakage, was purified from the third instar larval hemolymph of *Sacrophaga peregrina*, and in vitro, it was lethal for *C. albicans* (79). Holotricin 3, a glycine- and histidine-rich peptide purified from the larval hemolymph of *Holotrichia diomphalia*, inhibited *C. albicans* growth (101). Thanatin, produced by *Podisus maculiventris*, is nonhemolytic and is active against *F. oxysporum* and *A. fumigatus* (46).

TABLE 2. Insect and amphibian antimicrobial peptides

Peptide	Source	No. of amino acids	Mode of action	Typical target organism	In vitro MIC (μg/ml)
Antifungal peptide	*S. peregrina*	67	Lysis	*C. albicans*	25.0
Cecropins					
A	*H. cecropia*	37	Lysis	*F. oxysporum*	12.0
B	*H. cecropia*	35	Lysis	*A. fumigatus*	9.5
Dermaseptins					
b	*P. sauvagii*	27	Lysis	*C. neoformans*	60.0
s	*P. sauvagii*	34	Lysis	*C. neoformans*	5.0
Drosomycin	*D. melanogaster*	44	Lysis	*F. oxysporum*	5.9–12.3[a]
Magainin 2	*X. laevis*	23	Lysis	*C. albicans*	80
Thanatin	*P. maculiventris*	21	Unknown	*A. fumigatus*	24–48[a]

[a] MICs based on assays with multiple isolates.

AMPHIBIAN-DERIVED PEPTIDES

Magainins. The African clawed frog (*Xenopus laevis*) produces the magainins, which are α-helical ionophores that dissipate ion gradients in cell membranes, causing lysis (184). Their helical, amphiphilic structure was responsible for affinity to membranes (28). An increase in the magainin concentration caused the artificial lipid bilayer thickness to decrease, suggesting adsorption within the head-group region of the lipid bilayer (111). Magainin 2 was nonhemolytic and inhibited *C. albicans* growth (190). This nonhemolytic property may result from a peptide-cholesterol interaction in mammalian membranes that inhibits the formation of peptide structures capable of lysis (179).

Dermaseptin. The South American arboreal frog (*Phyllomedusa sauvagii*) produces the dermaseptin family of nonhemolytic antifungal peptides (38, 125). Dermaseptins are linear cationic, lysine-rich peptides and are believed to lyse microorganisms by interacting with lipid bilayers, leading to alterations in membrane functions responsible for osmotic balance (67, 124, 139). Zone inhibition assays demonstrated that 10 μg/ml suppresses the growth of *A. fumigatus* (123). Dermaseptins s1 to s5 were potent antifungal agents that inhibited a wide range of fungi (124). Dermaseptin b inhibited the in vitro growth of yeasts and some filamentous fungi; however, the dermaseptin s group was more effective (123).

ANTIFUNGAL PEPTIDES PRODUCED BY BACTERIA AND FUNGI

Iturins. Various strains of *Bacillus subtilis* produce the iturin peptide family. They are small cyclic peptidolipids characterized by a lipid-soluble β-amino acid linked to a peptide containing D and L amino acids (136). Iturins affected membrane surface tension, which caused pore formation and which resulted in the leakage of K^+ and other vital ions, paralleling cell death (19, 95, 175). One family member, bacillomycin F (Table 3), inhibited the growth of fungi including *Aspergillus niger*, *C. albicans*, and *F. oxysporum* (94, 117). In a disc assay, iturin A inhibited *A. flavus* and *F. moniliforme* growth (88). Initial clinical trials involving humans and animals showed that iturin A was effective against dermatomycoses and had a wide spectrum of antifungal properties and low allergenic effects (20, 30). Unfortunately, bacillomycin L and iturin A have been found to be hemolytic, which may reduce their potential use as antifungal drugs (96).

Syringomycins and related peptides. Members of the *Pseudomonas syringae* pv. *syringae* group produce small cyclic lipodepsipeptides known as syringomycins (154), the major form being syringomycin E (SE). SE increased transmembrane K^+, H^+, and Ca^{2+} fluxes and the membrane potential in plasma membranes of plants and yeasts (142, 167, 169, 192). SE formed voltage-sensitive ion channels, altered protein phosphorylation and H^+-ATPase activity (48). Ergosterol was a binding site in yeast for the syringomycins (168). Sorenson et al. (159) published a thorough study of the potent fungicidal properties of several compounds produced by *P. syringae*, including SE, syringotoxin B, and syringostantin A. These compounds were fungicidal for *Candida*, *Cryptococcus*, and *Aspergillus* isolates (159). A 12% (wt/vol) ointment of SE was effective in controlling vaginal candidiasis in a murine model (160). *P. syringae* also produced the pseudomycins, another family of peptides with broad-spectrum antifungal activity (68).

CHITIN SYNTHASE INHIBITORS

Nikkomycins. Nikkomycins, which are produced by *Streptomyces tendae*, enter target cells via dipeptide permeases and inhibit chitin biosynthesis in *C. albicans* both in vitro and in vivo (27, 75, 114, 115, 121, 172). Nikkomycins provided antifungal protection to infected kidneys, while other organs were unprotected (27). Nikkomycin Z at high dosages prolonged the survival of mice with disseminated candidiasis (15, 72). Nikkomycins X and Z were active against pathogenic dimorphic fungi but showed only modest to poor activity against yeast and filamentous fungi (73, 74). However, they were highly efficacious in murine models of coccidioidomycosis and blastomycosis, with moderate efficacy against histoplasmosis. Given orally, the nikkomycins prevented the deaths of mice infected with a 100% lethal challenge of *C. immitis*, with nikkomycin Z being more active than nikkomycin X.

Polyoxins. Polyoxins, which are produced by *Streptomyces cacaoi*, were active against isolated chitin synthases but had variable activity against intact organisms (76, 77, 84, 164). Polyoxin D was fungistatic for *C. albicans* at concentrations of 500 to 2,000 μg/ml, depending on the strain, and inhibited *C. neoformans* growth (14). Notably, polyoxin D reduced the ability of *C. albicans* to bind to buccal epithelial cells by as much as 58% compared to the binding ability of controls (61).

FR-900403. FR-900403 differs in structure from the polyoxins and nikkomycins in that its nucleoside is adenosine and the peptide is linked to the nucleoside at the C-3′ residue. It was

TABLE 3. Bacterial and fungal antifungal peptides

Peptide	Source	Structure	Mode of action	Typical target organism	In vitro MIC (μg/ml)
1901-II	*P. lilacinus*	Amino-lipopeptide	Unknown	*C. tropicalis*	12.5
1907-VIII	*P. lilacinus*	Amino-peptide	Unknown	*C. tropicalis*	50.0
A12-C	*B. licheniformis*	Peptide	Hyphal proliferation	*M. canis*	Unknown
Aculeacins	*Aspergillus aculeatus*	Lipopeptide	Glucan synthesis	*C. albicans*	0.2–6.3[a]
Aureobasidin A	*A. pullulans*	Cyclic depsipeptide	Actin assembly	*C. neoformans*	0.63
Bacillomycin F	*Bacillus subtilis*	Lipopeptide	Lysis	*Aspergillus niger*	40.0
CB-1	*B. licheniformis*	Lipopeptide	Chitin binding	*F. oxysporum*	50.0 (IC_{50}[b])
Cepacidine A_1	*B. cepacia*	Cyclic glycopeptide	Unknown	*A. niger*	0.098
Cepacidine A_2	*B. cepacia*	Cyclic glycopeptide	Unknown	*A. niger*	0.096
Echinocandin B	*A. nidulans*	Lipopeptide	Glucan synthesis	*C. albicans*	0.625
Fungicin M-4	*B. licheniformis*	Cyclic peptide	Unknown	*Mucor sp.*	8.0
FR900403	*Kernia* sp.	Lipopeptide	Chitin synthesis	*C. albicans*	0.4
Helioferin A	*M. rosea*	Lipopeptide	Unknown	*C. albicans*	5.0
Helioferin B	*M. rosea*	Lipopeptide	Unknown	*C. albicans*	5.0
Iturin A	*B. subtilis*	Lipopeptide	Lysis	*S. cerevisiae*	22.0
Leucinostatin A	*P. lilacinum*	Amino-lipopeptide	Unknown	*C. neoformans*	0.5
Leucinostatin H	*P. marquandii*	Amino-lipopeptide	Unknown	*C. albicans*	10.0
Leucinostatin K	*P. marquandii*	Amino-lipopeptide	Unknown	*C. albicans*	25.0
Mulundocandin	*A. syndowi*	Lipopeptide	Glycan synthesis	*C. albicans*, *A. niger*	0.97 31.25
Nikkomycin X	*Streptomyces tendae*	Peptide-nucleoside	Chitin synthesis	*C. immitis*	0.125
Nikkomycin Z	*S. tendae*	Peptide-nucleoside	Chitin synthesis	*C. immitis*	0.77
Pneumocandin A_0	*Z. arboricola*	Lipopeptide	Glucan synthesis	*C. albicans* isolates	0.12–2.0[a]
Polyoxin D	*S. cacaoi*	Trinucleoside peptide	Chitin synthesis	*C. immitis*	0.125
Pseudomycin A	*P. syringae*	Lipodepsinonapeptide	Lysis	*C. neoformans*	1.56
Schizotrin A	*Schizotrix* sp.	Cyclic undecapeptide	Unknown	*C. albicans*	0.02
Syringomycin E	*P. syringae*	Lipodepsipeptide	Lysis	*C. neoformans*	0.8–12.5[a]
Syringostatin A	*P. syringae*	Lipodepsipeptide	Lysis (?)	*A. fumigatus*	5.0–40.0[a]
Syringotoxin B	*P. syringae*	Lipodepsinonapeptide	Lysis (?)	*C. albicans*	3.2–50.0[a]
Trichopolyn A	*T. polysporum*	Amino-lipopeptide	Unknown	*C. neoformans*	0.78
Trichopolyn B	*T. polysporum*	Amino-lipopeptide	Unknown	*C. neoformans*	0.78
WF11899 A	*Coleophoma empetri*	Lipopeptide	Glucan synthesis	*C. albicans*	0.16
WF11899 B	*C. empetri*	Lipopeptide	Glucan synthesis	*C. albicans*	0.008 (IC_{50})
WF11899 C	*C. empetri*	Lipopeptide	Glucan synthesis	*C. albicans*	0.008 (IC_{50})

[a] MICs based on assays with multiple isolates.
[b] IC_{50}, inhibitory concentration for 50% of the population.

active against *C. albicans* but not against filamentous fungi (86).

PEPTIDES AFFECTING GLUCAN SYNTHESIS

Echinocandins. Echinocandins, which consist of a diverse family of lipopeptides, are noncompetitive inhibitors of (1,3)-β-D-glucan synthase (13, 119, 134, 150). Their mode of action is similar to that of the papulacandins, naturally occurring antifungal glycolipids (8, 11, 64). The name echinocandin was originally applied to a small family of cyclic lipopeptide antifungal natural products with the same cyclic peptide nucleus but different fatty acid side chains (178). However, the echinocandin peptide family now includes the echinocandins, cilofungin, pneumocandins, aculeacins, mulundocandin, and WF11899 (Table 3). Three excellent reviews describe this peptide family (57, 93, 178). Of the three types of echinocandins (types B, C, and D), type B is the major species produced by some members of the *Aspergillus nidulans* and *Aspergillus rugulosus* groups (18, 87, 177). Echinocandins possessed antimicrobial activity against *Pneumocystis carnii* and *C. albicans* (10, 152, 178). Since echinocandin B is hemolytic due to the acyl side chain, it has not been used clinically (32, 33, 178).

Echinocandin analogs. The hemolytic property of the native echinocandins was greatly reduced by enzymatically creating analogs (designated LY compounds) of echinocandin B, listed in Table 4 (50). Cilofungin (LY121019), an analog of echinocandin B, was greater than 10-fold less lytic for erythrocytes

TABLE 4. Synthetic and semisynthetic antifungal peptides

Peptide	Structure	Mode of action	Typical target organism	In vitro MIC (μg/ml)
Cilofungin (LY121019)	Lipopeptide	Glucan synthesis	*C. albicans*	0.62
D4E1	Linear peptide	Lysis (?)	*A. flavus*	26.25
L731,373	Lipopeptide	Glucan synthesis	*C. albicans*	≤0.06
L733,560	Lipopeptide	Glucan synthesis	*C. albicans*	0.06
L743,872 (MK-0991)	Lipopeptide	Glucan synthesis	*A. flavus*	0.09–3.12
L773,560	Lipopeptide	Glucan synthesis	*C. albicans*	0.5
LY303366	Lipopeptide	Glucan synthesis	*Candida krusei*	0.5

than the parent compound and retained potent fungicidal activity (13, 59, 60, 165). Cilofungin also showed excellent in vitro and in vivo activities against *Candida* spp. and *A. fumigatus* (13, 40, 137, 146, 161, 165, 183, 187) but displayed only limited activity (151) against *P. carinii* pneumonia (PCP).

LY303366, a semisynthetic derivative that has potent in vitro candidacidal properties on the basis of its selective inhibition of β-(1,3)-glucan synthase, is effective against *Candida* species clinical isolates, with MICs at which 90% of isolates are inhibited (MIC_{90}s) ranging from 0.5 to 4.0 μg/ml in RPMI 1640 (34, 138, 180). MIC_{90}s were considerably lower in antibiotic medium 3, ranging from 0.003 to 2.0 μg/ml. In antibiotic medium 3, LY303366 was 16- to >2,000-fold more active than itraconazole, fluconazole, amphotericin B, and flucytosine against all *Candida* species except *Candida parapsilosis* (138). However, in RPMI 1640, the activity of LY303366 was comparable to those of amphotericin B and itraconazole, but it was more active than fluconazole and flucytosine. Against *Aspergillus* species, LY303366 had a minimum effective concentrations for 90% of isolates tested and an MIC_{90} of 0.02 and 10.24 μg/ml, respectively (191). It was inactive against *C. neoformans* and *Blastomyces dermatitidis*. In contrast, amphotericin B and itraconazole were more potent than LY303366 against *Aspergillus* isolates. Amphotericin B, flucytosine, fluconazole, and ketoconazole were also more effective against *C. neoformans* and *B. dermatitidis* than LY303366. Ernst et al. (45) indicated that the use of the current interpretive endpoint MIC in RPMI 1640 may underestimate the antifungal activity of LY303366 and suggested that alternative media be used to obtain a more accurate MIC endpoint for this peptide. This may also hold true for other antimicrobial peptides. For example, the fungicidal properties of cecropin B and dermaseptin were reduced by increasing the pH of the bioassay media from 6 to 7 (38). A pH increase may neutralize the positive charges on some amino acids near the C terminus, which, in turn, could reduce the ability of the C termini of these peptides to insert into the negatively charged outer membrane, thereby preventing lysis. LY303366 is being studied in phase II clinical trials.

Pneumocandins. *Zalerion arboricola* produces the pneumocandins, which were effective against *P. carinii* infections in rats and which had greater potency and spectra of activity than the echinocandins (50, 152). Pneumocandin A_0, the most important member of this group, has potent anti-*Candida* activity and was more active than echinocandin against experimental murine infections (50). Pneumocandin A_0 was generally more active than the echinocandin derivatives tretrahydroechinocandin B and cilofungin (11). However, pneumocandin A_0 has no activity against *A. flavus*, *A. fumigatus*, *C. neoformans*, or *Candida guilliermondii* (50). Pneumocandin A_0 was hemolytic at a level (6.25 μg/ml) much higher than that required for activity (50).

Pneumocandin analogs. L-693,989, a phosphate ester of pneumocandin A, had a 90% minimum effective dose of 0.15 mg/kg of body weight and a 99% minimum effective dose of 3.0 mg/kg in animal models of PCP and candidiasis, respectively (10). In contrast, cilofungin was at least 15 times less potent than L-693,989 in a PCP model. Importantly, L-693,989 produced hemolysis only at levels greater than 400 μg/ml, which was considerably greater than the concentration that inhibited fungal growth.

L-773,560, L-731,373, L-733,560, and L-743,872 are water-soluble, semisynthetic derivatives of pneumocandin B_0 and are significantly more potent than the narrow-spectrum parent compound (12, 113). The MICs of these compounds were 0.06 to 4.0 μg/ml for clinical isolates of *Candida* species, 8 to 64 μg/ml for *C. neoformans*, and >128 μg/ml for *A. flavus* and *A. fumigatus*. These peptides were relatively nonhemolytic for human and mouse erythrocytes. In contrast, amphotericin B was much more hemolytic (12). They were effective against disseminated aspergillosis and candidiasis but not cryptococcosis in murine models and delayed mortality due to pulmonary aspergillosis at an effective dose (administered intraperitoneally) of 5 mg/kg in a rat model (1, 92). Against *Candida* isolates, the tricationic analogs of pneumocandin, L-731,373 and L-733,560, were more potent than the dicationic analogs, which, in turn, were more potent than the monocationic analogs (188).

The highly soluble compound L-743,872 (MK-0991) was effective against clinically important fungal isolates and was well tolerated by rodents (35, 116). The MICs of L-743,872 were between 0.06 and 4.0 μg/ml for *A. flavus* and *A. fumigatus*. It appeared to lack significant in vitro activity against *F. oxysporum*, *Fusarium solani*, *Rhizopus arrhizus*, and *Paecilomyces lilacinus* but enhanced the efficacies of fluconazole and amphotericin B against *C. neoformans* (49). It significantly reduced the *C. albicans* numbers in the mouse kidney compared to the numbers in the kidneys of the controls and enhanced the activities of amphotericin B and fluconazole in vitro against *C. neoformans* (2, 49). The administration route affected L-743,872, with administration by the oral route being 300-fold less active than administration by the parental route. It was efficacious in mouse target organ assays against *Candida tropicalis* and other *Candida* species. This peptide significantly prolonged the survival of DBA/2N mice with disseminated aspergillosis, with 50 and 90% effective doses of 0.03 and 0.12 mg/kg/dose, respectively, at 28 days postchallenge but was ineffective against disseminated *C. neoformans* infections (2). In animals, the pharmacokinetics of L-743,872 featured a long half-life, ranging from 5.2 to 7.6 h, and the compound slowly accumulated in tissues (66). No significant differences in the in vitro antifungal activity of either LY-303366 or L-743,872 was observed (90). L-743,872 is being investigated in phase II studies.

Aculeacins. Aculeacins (A through G) are produced by *Aspergillus aculeatus* (120, 149). The inhibitory concentrations for 50% of the cultures (IC_{50}s) for aculeacin A were 0.008 to 0.62 μg/ml for *Candida* species and 2.5 μg/ml for *A. niger* and *A. fumigatus* (85). Aculeacins A through D, F, and G have good in vitro activity against *C. albicans* and *Saccharomyces cerevisiae* but reduced the growth of only a few filamentous fungi (119, 120, 149).

Mulundocandins. *Aspergillus syndowi* var. *mulundenis* produces the mulundocandins, whose structures differ from those of the echinocandins by the replacement of one of the threonines with a serine residue, and the lipophilic side chain is 12-methylmyristoyl rather than lineoyl (127, 147). Mulundocandin and the related compound deoxymulundocandin were found to be active against *C. albicans* and *A. niger* (128).

WF11899 group. *Cleophoma empetri* F-11899 produces the water-soluble lipopeptides WF11899 A, B, and C. The IC_{50} for *C. albicans* ranged from 0.0004 to 0.03 μg/ml (85). These peptides demonstrated potent in vivo anti-*Candida* activities in a murine model of systemic infection and were superior to cliofungin and fluconazole (85). However, WF11899 A, B, and C lysed mouse erythrocytes in vitro at 62 μg/ml (85).

Aureobasidins. Aureobasidins are produced by *Aureobasidium pullulans* (170). This group has 18 members whose structures have eight lipophilic amino acid residues and an α-hydroxyacid (80, 81). Their modes of action and structures differ from those of the echinocandins in that they are believed to alter actin assembly and delocalize chitin in cell walls, resulting in lysis by disruption of cell membranes (44). Another study

TABLE 5. Plant antifungal peptides

Peptide	Source	No. of amino acids	Mode of action	Typical target organism	In vitro MIC (μg/ml)
ACE-AMP_1	*A. cepa*	84	Unknown	*F. oxysporum*	0.3 (IC_{50}[a])
Hs-AFP_1	*H. sanginea*	54	Unknown	*F. moniliforme*	125.0
Ib-AMP_3	*I. balsamina*	20	Unknown	*F. moniliforme*	50.0
Rs-AFP_2	*R. sativus*	51	Unknown	*F. moniliforme*	125.0
Zeamatin	*Z. mays*	27	Lysis (?)	*C. albicans*	0.5

[a] IC_{50}, inhibitory concentration for 50% of the population.

indicated that sphingolipid synthesis is the target of aureobasidin A (129). Aureobasidins A, B, C, E, S_{2b}, S_3, and S_4 were potent and had MICs of 0.05 to 3.12 μg/ml for *Candida* species and *C. neoformans* isolates. The MICs for *Histoplasma capsulatum* and *Blastomyces dermatitidis* were less than 0.63 μg/ml. Aureobasidin A at ≤2.5 μg/ml was also effective against dematiaceous fungi but was inactive against *A. fumigatus*, *A. niger*, and *A. flavus* (91, 171). Its activity was superior to those of fluconazole and amphotericin B against murine candidiasis (171). Synthetic aureobasidin A was highly fungicidal, with MICs of 0.01 to 1.6 μg/ml for *Candida* species and *C. neoformans* (91). Aureobasidin showed several desirable properties, including lethality for growing *C. albicans* cells, a low level of acute toxicity, and improved survival and sterilization of kidneys in a murine model. It was one of the few peptides that had appreciable oral bioavailability (171).

OTHER ANTIFUNGAL PEPTIDES DERIVED FROM BACTERIA AND FUNGI

***Bacillus licheniformis* peptides.** CB-1 is a chitin-binding peptide containing fatty acids bound to amino acids and has an IC_{50} for *F. oxysporum* of 50 μg/ml (130). A *B. licheniformis* isolate, M-4, produces fungicin M-4 (99). It is a hydrophilic, narrow-spectrum antifungal peptide that is resistant to proteolytic enzymes and lipase and that inhibited the growth of *Microsporum canis*, *Mucor* species, and *Sporothrix schenckii*. However, fungicin M-4 was ineffective against *C. albicans*, *C. neoformans*, *A. niger*, and *Trichophyton mentagrophytes. B. licheniformis* also produces A12-C, a fungal cell growth and hyphal proliferation inhibitor. A12-C inhibited *S. schenckii*, *T. mentagrophytes*, and *M. canis* growth, as observed in zone-of-inhibition studies (54).

Schizotrin A. A cyanobacterium, *Schizotrix* (TAU strain IL-89-2), produces schizotrin A, a cyclic undecapeptide (135). Zone-of-inhibition assays demonstrated that it has activity against *C. albicans* and *C. tropicalis*. It also inhibited the radial growth of *F. oxysporum* at 0.05 μg/ml.

Cepacidines. Cepacidines A_1 and A_2 are glycopeptides that have similar structures and that are produced by *Burkholderia cepacia* (100, 110). Together, they displayed potent antifungal properties superior to those of amphotericin B (100). In vitro, the MICs of cepacidine A ranged from 0.049 to 0.391 μg/ml for *Candida* species, *C. neoformans*, *A. niger*, *T. mentagrophytes*, *Trichophyton rubrum*, *M. canis*, and *F. oxysporum* (100). Its activity was diminished significantly against *C. albicans* and *C. neoformans* in the presence of 50% human serum, which may limit its clinical potential.

1907-II and 1907-VIII. *P. lilacinus* produces two antifungal peptides, 1907-II and 1907-VIII, consisting of several amino acids, a methylamine, and a fatty acid (148). In vitro, both peptides have a MIC of 6.25 μg/ml for *C. albicans*, while *C. neoformans* was very susceptible (MICs, 0.78 and 1.56 μg/ml for 1907-II and 1907-VIII, respectively).

Leucinostatin-trichopolyn group. The leucinostatin-trichopolyn group is structurally related to 1907-II and 1907-VIII. Leucinostatins A and B are produced by submerged cultures of *Penicillium lilacinum* (6, 53). Leucinostatin A and 1907-VIII have the same molecular weight (1,217), while leucinostatin B and 1907-II have a molecular weight of 1,203 (82, 83). Leucinostatin A and B acted as uncouplers on rat mitochondria (126). Leucinostatins D, H, and K were isolated from *Paecilomyces marquandii* (Massee) Hughes and had a wide spectrum of antimicrobial properties against *Candida* species, *C. neoformans*, and other clinically important fungi (140, 145). Unfortunately, it is rather cytotoxic, with the following 50% inhibitory doses: 850 ng/ml for HeLa cells, 0.95 ng/ml for KB cells, and 1.00 ng/ml for P388/S cells. Trichopolyns A and B are produced by *Trichoderma polysporum* (51, 52). The MICs of trichopolyns A and B for *C. albicans*, *C. neoformans*, *A. niger*, *A. fumigatus*, and *T. mentagrophytes* were 0.78 to 6.25 μg/ml.

Helioferins. *Mycogone rosea* produces helioferins A and B, which are members of the leucinostatin-trichopolyn group that also may not have clinical utility (63). They inhibited *C. albicans* (MIC, 5.0 μg/ml) but were toxic to chicken embryos at levels greater than 0.5 mg/kg and caused hemolysis at concentrations greater than 100 μg/ml. They also displayed cytotoxic activities, with IC_{50}s for the L-1210 leukemia cell line and the L0929 mouse fibroblast cell line of 0.01 to 0.4 μg/ml.

PLANT ANTIFUNGAL PEPTIDES

Plant defensins. Plant defensins (Table 5), which are not related to either the mammalian or the insect defensins, have eight disulfide-linked cysteines comprising a triple-stranded antiparallel β-sheet structure with only one α helix (23, 24). Their mechanisms of action have not yet been elucidated, although the possibility of permeabilization through direct protein-lipid interactions has been eliminated (174). They reduced hyphal elongation without marked morphological distortions (23, 24). Hs-AFP_1 and Rs-AFP_2 were isolated from *Heuchera sanginea* and *Raphanus sativus* seeds, respectively (131, 173). They possess poor lethality for the clinical fungi studied to date. Hs-AFP_1 and Rs-AFP_2 at a concentration of 125 μg/ml reduced the viability of germinated conidia of *A. flavus* by only 20 and 35%, respectively (39). In contrast, Hs-AFP_1 at 125 μg/ml reduced the viabilities of nongerminated and germinating conidia of *F. moniliforme* by 42 and 85%, respectively, while Rs-AFP_2 reduced the viabilities of these conidial types by 25 and 95%, respectively. Hs-AFP_1 and Rs-AFP_2 bound at different rates to mannan, chitin, cholesterol, ergosterol, galactocerebrosides, and sphingomyelin (39).

Impatiens balsamina produces a highly basic peptide, Ib-AMP_3, with four cysteine residues that form two intramolecular disulfide bridges (166). Ib-AMP_3 at 50 μg/ml reduced the viability of germinated conidia of *A. flavus* by 42%, but it did not affect the viability of nongerminated conidia (39). At 50.0 μg/ml it was highly effective against the nongerminated and

germinated conidia of *F. moniliforme*, reducing their viabilities by 95 and 99.5%, respectively, and had a very high affinity for chitin (39).

Lipid transfer proteins. Some plants produce lipid transfer proteins, a family of homologous peptides having eight disulfide-linked cysteines. Onion seeds (*Allium cepa* L.) produce the lipid transfer peptide ACE-AMP_1, which inhibited *F. oxysporum* (26).

Zeamatin. *Zea mays* seeds produce the peptide zeamatin, which belongs to a third class of plant antifungal compounds (144). Peptides in the zeamatin family are also present in *Avena sativa*, *Sorghum bicolor*, and *Triticum aestivum* seeds (181). Zeamatin caused the release of cytoplasmic material from *C. albicans* and *Neurospora crassa*, resulting in hyphal rupture. It appears to permeabilize the fungal plasma membrane and inhibited *C. albicans*. Zeamatin activity was reduced by increasing concentrations of NaCl. A flax seed antifungal peptide similar to zeamatin, in synergy with nikkomycin Z, inhibits *C. albicans* (22).

Cyclopeptides. Members of the family *Rhamnaceae* and other plant families produce the basic cyclopeptides in which a 10- or 12-membered peptide-type bridge spans the 1,3 or 1,4 positions of a benzene ring (62). The antifungal properties of many family members have not yet been determined. Frangufoline, amphibine H, rugosanines A and B, and nummularines B, K, R, and S showed significant activity against *A. niger* but not *C. albicans* in zonal inhibition studies (132).

SYNTHETIC PEPTIDES

D4E1. D4E1 is a synthetic peptide that is active against germinated conidia of *Aspergillus* species, producing 50% lethal doses of between 2.1 and 16.8 μg/ml for several *Aspergillus* species and a 50% lethal dose of 1.1 μg/ml for *F. moniliforme* and *F. oxysporum* (36). Since D4E1 complexes with ergosterol, its mode of action may be lytic. D4E1 was more resistant in vitro to degradation by *A. flavus* proteases than the insect peptide cecropin A.

CONCLUSIONS

In conclusion, there has been a marked expansion of our knowledge of new antifungal peptides. Some of these agents have reached clinical trials, while others are undergoing detailed preclinical testing. Discovery and elucidation of antimicrobial peptides expand our understanding of intrinsic host defenses and provide new approaches to antifungal chemotherapy. The membership of this group will expand as additional natural peptides are isolated and identified and analogs of natural peptides or totally synthetic ones are produced.

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