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Antifungal peptides from living organisms

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In the post-COVID-19 era, people are increasingly concerned about microbial infections, including fungal infections that have risen in recent years. However, the currently available antifungal agents are rather limited. Worse still, the widespread use of the antifungal agents has caused the emergence of antifungal resistance in *Candida*, *Cryptococcus*, and *Aspergillus* species. Therefore, the development of novel antifungals is urgently needed. Antimicrobial peptides (AMPs), as components of the first-line defense of the host, are found to exhibit broad antimicrobial activity against bacteria, fungi, parasites, viruses, and protozoa. AMPs with antifungal activity are specifically referred to as antifungal peptides (AFPs). AFPs are currently regarded as the most promising alternative to conventional antifungal agents due to the fact that they are highly selective and less prone to facilitate the selection of drug resistance. In this review, we present an overview of the origin and classification of natural AFPs as well as their modes of action. Additionally, the production of natural, semisynthetic, and synthetic AFPs with a view to greater levels of exploitation is discussed. Finally, we evaluate the current and potential applications of AFPs in clinics and in the food industry.

KEYWORDS

antifungal peptide, sources, mechanisms, production, application

1 Introduction

Fungi are eukaryotic microorganisms ranging from giant mushrooms to tiny multicellular molds and unicellular yeasts. It is estimated that there are approximately 2–11 million fungi on Earth, of which only 150,600 are officially categorized (Phukhamsakda et al., 2022; Lücking et al., 2021; Baldrian et al., 2021). Fungi are widely distributed in the soil and the air, in lakes, rivers, and oceans, on plants and animals, and in food and clothing. In recent years, fungi have been found to be a part of the commensal microbiota at different sites of human bodies (e.g., oral cavity, intestine, skin, lung, and vagina), although it remains still controversial over what constitutes the standard mycobiome composition (Auchtung et al., 2018; Huffnagle and Noverr, 2013; Kapitan et al., 2018).

Fungi are beneficial to many aspects of our daily life, notably the production of bread, wine, beer, soy sauce, and certain cheeses. Fungi are also used as a source of food; for example, some mushrooms, morels, and truffles are epicurean delicacies (Campbell-Platt and Cook, 2008; Money, 2016; Mukherjee et al., 2018). However, fungi have a harmful side too. It has been reported that at least 300 species of fungi can cause infections in both human beings and animals (Gupta et al., 2017). Recently, a list of fungal priority pathogens has been presented by the World Health Organization (2022) to guide research, development, and public health action. The list includes 19 fungal pathogens that are ranked and categorized into three priority

(critical, high, and medium priority) groups based on their mortality rate, infection rate, and difficulty in diagnosis and treatment. The critical group includes *Candida albicans*, *Aspergillus fumigatus*, *Candida auris,* and *Cryptococcus neoformans*; the high group contains *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Fusarium* spp., *Histoplasma* spp., Mucorales, and eumycetoma causative agents; and the medium group comprises *Candida krusei*, *Pneumocystis jirovecii*, *Scedosporium* spp., *Cryptococcus gattii*, *Lomentospora prolificans*, *Coccidioides* spp., *Talaromyces marneffei,* and *Paracoccidioides* spp. Fungal infections have become a serious threat to human health, especially for people with weakened immune systems and potential health problems, such as diabetes mellitus, cancer, and HIV. It is estimated that fungal infections annually affect approximately 25% of the general population globally, causing high morbidity and mortality rates (Brown et al., 2012; Gamaletsou et al., 2018). Unfortunately, there are limited effective antifungal agents to treat fungal infections (Kathiravan et al., 2012). Currently, only four classes of antifungal drugs, i.e., polyenes (e.g., amphotericin B), triazoles (e.g., fluconazole), echinocandins (e.g., caspofungin), and fluorinated pyrimidines (e.g., 5-flucytosine), are available for the choice of systemic therapy of fungal diseases, and most of them, especially amphotericin B, can induce nephrotoxicity and hematotoxicity (Wang et al., 2024; Turcu et al., 2009). Worse still, the restricted spectrum and widespread use of the antifungal agents have caused the emergence of antifungal resistance in *Candida*, *Cryptococcus*, and *Aspergillus* species (Fisher et al., 2018; Lestrade et al., 2019; Pfaller et al., 2019). Furthermore, some fungal pathogens, such as *Mucorales*, *C. auris*, and some molds, are intrinsically resistant to the drugs above and difficult to treat at present. These all prompt an urgent need for the development of new antifungal agents with high efficiency and low toxicity. Of note, fungal cells are eukaryotic, and the development of selective antifungals is thus a particularly great challenge to identify pathogen-specific targets that are not present in human cells.

In addition to infection of humans and animals, fungi can also cause food spoilage, which leads to economic losses and may affect human health. Food-spoiling fungi and their mycotoxins released contaminate approximately 25% of raw materials produced by agriculture worldwide (World Health Organization (WHO), 1999). Therefore, the control and prevention of fungal pathogens and foodborne poisoning is one of the most important public health challenges that we are facing today. A number of physical, chemical, and biological methods have been applied to control fungal pathogens and mycotoxin contamination, including green and emerging technologies such as ionizing and non-ionizing radiation, ultrasound, pulsed electric field and high-pressure processing, and biological preservation. Among them, the use of antifungal compounds is regarded as an alternative environmentally friendly strategy. However, the antifungal compounds currently available for this use are quite limited (Thery et al., 2019). Antimicrobial peptides (AMPs) can really be a good candidate, given their lower likelihood of selecting resistance.

AMPs, first described by Dubos (1939) from *Bacillus brevis*, are short peptides with rapid microbicidal effects that are typically composed of <100 amino acids. Albeit highly diverse in amino acid sequence, AMPs usually possess a net positive charge and hydrophobic regions and facilitate interactions with membranes. AMPs kill microbes via several mechanisms, including binding to or inserting into microbial membranes (which has fatal depolarization of the normally polarized membrane), forming physical pores, disrupting the usual distribution of lipids between the bilayer leaflets, and damaging critical intracellular targets (Gennaro and Zanetti, 2000; Hancock, 2000; Nawrocki et al., 2014). Because of their multi-point and multi-level mechanisms of action, the likelihood of developing resistance to AMPs is relatively low.

AMPs, as components of the first-line defense of the host, are produced by all organisms, from bacteria to humans (Faruck et al., 2016; Kang et al., 2015; Shishido et al., 2015; Silva et al., 2014; Tam et al., 2015), and exhibit broad antimicrobial activity against bacteria, fungi, parasites, viruses, and protozoa (Hancock and Chapple, 1999). Currently, there are 1,479 peptides with antifungal properties documented in the Antimicrobial Peptide Database (APD3). In the majority of cases, the classification of AFPs is based on the peptide origin: natural, semisynthetic, or synthetic (De Lucca, 2000). In this study, we present an overview of the origin and classification of natural AFPs and their modes of action. In addition, the production of natural, semisynthetic, and synthetic AFPs with a view to greater levels of exploitation is discussed. Finally, we evaluate the current and potential applications of AFPs in clinics and in the food industry.

2 Origin and classification of AFPs

The innate immunological components including endogenic peptides of organisms could rapidly respond to invading pathogens to avoid their adverse effects on the host. Natural AFPs are produced by a number of species of bacteria, archaea, and eukarya isolated from natural sources (De Lucca and Walsh, 1999). They typically adopt an α-helix structure, β-hairpin or sheet (containing two cysteine residues) structure, or mixed α-helix/β-sheet structure upon interaction with membranes. Some natural AFPs are rich in specific amino acids such as glycine, proline, arginine, histidine, and tryptophan, and accordingly, they are often classified as glycine-rich, proline-rich, arginine-rich, histidine-rich, and tryptophan-rich AFPs (Bondaryk et al., 2017).

2.1 AFPs from microorganisms

The AFPs produced by microorganisms, including bacteria and archaea (both prokaryotes) as well as fungi (eukaryotes), can be secreted into extracellular surroundings and offer a competitive advantage in ecological niches. Bacteria generate a number of different AFPs (Table 1). The first example of an archaeal antimicrobial peptide with antifungal activity is VLL-28, isolated from the archaeon *Sulfolobus islandicus*, which showed antifungal activity against 10 clinical isolates of *Candida* spp. (Roscetto et al., 2018). The well-known AFP-producing bacteria include the genera *Bacillus*, *Lactobacillus*, *Streptomyces*, and *Burkholderia*. For example, the iturin A produced by *Bacillus subtilis* exhibits a conspicuous antifungal activity against *Aspergillus* spp., *Fusarium* spp., and *Penicillium* spp. (Klich et al., 1991); the peptide mixture generated by *Lactobacillus plantarum* TE10 suppresses *Aspergillus flavus* in maize seeds, displaying a considerable potential for the development of bio-control agents (Muhialdin et al., 2020); the champacyclin, a head-to-tail cyclic octapeptide obtained from *Streptomyces champavatii*, inhibits the growth of the yeast *C. glabrata* (Pesic et al., 2013); the natamycin from

TABLE 1 Representative antifungal peptides from microorganisms and plants.

Organisms	Peptide (length)	Net charge; hydrophobic residue %	Origin	Structure	Antifungal spectrum	References
Archaea	VLL-28 (28)	+10; 35%	*Sulfolobus islandicus*	Helix	*C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei*	Roscetto et al. (2018) and Notomista et al. (2015)
Bacteria	Iturin A	–	*Bacillus subtilis*	cyclic peptidolipid	*Aspergillus* spp., *Fusarium* spp., *and Penicillium* spp.	Klich et al. (1991)
	Champacyclin	–	*Streptomyces champavatii*	cyclic octapeptide	*C. glabrata*	Pesic et al. (2013)
	Natamycin	–	*Streptomyces philanthi* RL-1-178	–	*A. flavus*	Boukaew et al. (2023)
	AFC-BC11	–	*Burkholderia cepacia*	–	Variety of soil fungi	Kang et al. (1998)
	AFP1 (87)	−3; 36%	*Streptomyces tendae* Tu901	Beta	*Aspergillus* spp.	Bormann et al. (1999)
Fungi	PeAfpC		*Penicillium expansum*		*B. spectabilis*	van der Weerden et al. (2013)
	Antifungal peptide (AgAFP) (51)	+9; 31%	*Aspergillus giganteus*	Beta	*Fusarium* spp.	Theis et al. (2005)
	PAF (55)	+5; 25%	*Penicillium chrysogenum*	Beta	Filamentous fungi *A. flavus, A. fumigatus, A. giganteus, A. niger, B. cinerea, C. carbonum, F. oxysporum, G. roseum, M. circinelloides, N. crassa, P. chrysogenum, and T. koningii*	Kaiserer et al. (2003)
	PAFB (PgAFP) (58)	+4; 27%	*Penicillium chrysogenum* RP42C/Q176	Beta	Filamentous fungi *A. fumigatus, A. niger, A. terreus, N. crassa, P. chrysogenum, T. rubrum,* yeasts *C. albicans, and S. cerevisiae*	Rodríguez-Martín et al. (2010) and Huber et al. (2018)
Plants	*Chitinases*					
	PR protein families	–	–	–	*B. cinerea*	Van Baarlen et al. (2007)
	Chitinase	–	–	–	*R. solani*	Shrestha et al. (2007)
	Defensins					
	Dm-AMP1 (50)	+1; 38%	*Dahlia merckii*	Combined Helix/Beta	*B. cinerea, C. sphaerospermum, F. culmorum, L. maculans, P. digitatum, S. tritici, and V. albo-atrum*	Osborn et al. (1995)
	Ace-AMP1		*Allium cepa*	Combined Helix/Beta	*A. solani, F. solani, and F. oxysporum*	Wu et al. (2011) and Tassin et al. (1998)
	MsDef1 (45)	+3; 33%	*Medicago sativa*	Combined Helix/Beta	*V. Dahliae, F. graminearum, A. solani*., and *F. culmorum*	Gao et al. (2000)
	MtDef4 (47)	+6; 31%	*Medicago truncatula*	Combined Helix/Beta	*F. graminearum*	Ramamoorthy et al. (2007)

(Continued)

TABLE 1 (Continued)

Organisms	Peptide (length)	Net charge; hydrophobic residue %	Origin	Structure	Antifungal spectrum	References
	RsAFP2 (51)	+6; 39%	*Raphanus sativus*	Combined Helix/ Beta	*B. cinerea, C. sphaerospermum, F. culmorum, L. maculans, P. digitatum, T. viride, S. tritici, V. albo-atrum, C. albicans, P. pastoris, C. krusei, A. flavus, F. solani, and F. graminearum*	Osborn et al. (1995) and Terras et al. (1993)
	PvD1 (21)	−1; 21%	*Phaseolus vulgaris*	Bridge	*C. albicans, C. parapsilosis, C. tropicalis, C. guilliermondii, K. marxiannus, S. cerevisiae, F. oxysporum, F. solani, F. lateritium, and R. solani*	Games et al. (2008) and Mello et al. (2011)
	Hevein-type					
	Ee-CBP (45)	+5; 28%	*Euonymus europaeus* L.	Bridge	*A. brassicicola, B. cinerea, F. culmorum, F. oxysporum* f.sp. *cubense, F. oxysporum* f.sp. *matthiolae, M. eumusae, N. crassa, P. exigua, P. cryptogea, P. ultimum, R. solani, and T. hamatum*	Van den Bergh et al. (2002)
	SmAMP3 (35)	+2; 34%	*Stellaria media* L.	Bridge	*A. niger, B. sorokiniana, B. cinerea, F. solani, and A. alternata*	Rogozhin et al. (2015)
	WAMP-1a (44)	+3; 38%	*Triticum kiharae*	Combined Helix/ Beta	*B. sorokiniana, B. cinerea, N. crassa, F. oxysporum, F. verticillioides, and F. solani*	Odintsova et al. (2009)
	Snakins					
	Snakin-1 (63)	+8; 31%	*Solanum tuberosum*	Helix	*B. cinerea, F. solani, F. culmorum, F. oxysporum* f. sp. *conglutinans, F. oxysporum* f. sp. *lycopersici, P. cucumerina, C. graminicola, C. lagenarium, B. maydis, and A. flavus*	Segura et al. (1999)
	Snakin-2 (66)	+9; 34%	*Solanum tuberosum* cv. Jaerla	Bridge	*B. cinerea, F. solani, F. culmorum, F. oxysporum* f. sp. *conglutinans, F. oxysporum* f. sp. *lycopersici, P. cucumerina, C. graminicola, C. lagenarium, B. maydis, and A. flavus*	Berrocal-Lobo et al. (2002)
	Gly-rich peptides					
	Cc-GRP (35)	−1; 0%	*Coffea canephora*	Gly-rich	*F. Oxysporum and C. lindemuthianum*	Zottich et al. (2013)

Streptomyces philanthi RL-1-178 possesses a fungicidal activity against *A. flavus* (Boukaew et al., 2023); and the AFC-BC11, a lipopeptide isolated from *Burkholderia cepacia*, exerts an antifungal activity toward a variety of soil fungi (Kang et al., 1998). Similarly, eukaryotic microorganisms such as filamentous fungi and yeasts also produce a variety of AFPs (Table 1). For instance, the peptide PeAfpC produced

by the filamentous fungus *Penicillium expansum* can effectively inhibit the growth of *Byssochlamys spectabilis*, which is capable of causing the spoilage of pasteurized juices and canned foods (van der Weerden et al., 2013). In addition, the two peptides, namely, PAF and PAFB, generated by the filamentous fungus *Penicillium chrysogenum*, are capable of exerting antifungal activity against a variety of filamentous fungi, with PAFB suppressing the growth of some toxigenic molds (Kaiserer et al., 2003; Rodríguez-Martín et al., 2010; Huber et al., 2018).

2.2 AFPs from plants

Plants have developed various mechanisms in their innate immune systems to protect themselves against fungal attacks, including soluble peptides and proteins released from plants with antifungal activities (Chiu et al., 2022). These peptides/proteins that are constitutively synthesized are able to trigger defense responses in plants. On the basis of sequence, cysteine residues, and function, the plant-sourced AFPs can be divided into different families (Table 1), including chitinases, defensins, and snakins, as well as hevein-type and gly-rich peptides (Tam et al., 2015; Yan et al., 2015). Chitinases are among the best-known and most-studied plant AFPs. They display strong antifungal activity against a wide range of phytopathogenic fungi, including *Botrytis cinerea* (Van Baarlen et al., 2007) and *Rhizoctonia solani* (Shrestha et al., 2007). Plant chitinases have been used to treat fungal infections as exogenously applied pest control agents (Karasuda et al., 2003). The Dm-AMP1 is a defensin peptide found in *Dahlia merckii* that shows inhibitory activity against a variety of fungi, such as *B. cinerea* and *Leptosphaeria maculans* in the presence of $CaCl_2$ and KCl (Osborn et al., 1995). Another defensin Ace-AMP1, a potent AFP found in onion (*Allium cepa*) seeds, has been applied to control the tomato early blight disease caused by the pathogen *Alternaria solani* (Wu et al., 2011). The peptide Ee-CBP containing five disulfide bridges obtained from the bark of spindle tree (*Euonymus europaeus*) is a hevein-type AFP, exhibiting antifungal activity against various fungi including *Alternaria brassicicola* (50% growth inhibition IC_{50} = 3 μg/mL), *Phoma exigua* (IC_{50} = 33 μg/mL), and *Fusarium oxysporum* f.sp. *cubense* (IC_{50} = 15 μg/mL) (Van den Bergh et al., 2002). The WAMP-1a, another hevein-type AFP from seeds of *Triticum kiharae*, shows high broad-spectrum inhibitory activity against a wide range of chitin-containing and non-chitin-containing pathogens including *Bipolaris sorokiniana*, *Neurospora crassa*, *Fusarium verticillioides,* and *Fusarium solani* (Odintsova et al., 2009). The snakins 1 and 2 are representative AFPs of snakin family identified from *Solanum tuberosum*, exerting antifungal activity against fungi such as *B. cinerea*, *F. solani*, *A. flavus*, *Colletotrichum graminicola*, and *Bipolaris maydis* (Segura et al., 1999; Berrocal-Lobo et al., 2002). The Cc-GRP is a gly-rich AFP identified from *Coffea canephora* that can combat fungi such as *F. oxysporum* and *Colletotrichum lindemuthianum* (Zottich et al., 2013).

2.3 AFPs from animals

Many animal-sourced AFPs have been found to be part of the innate immune responses of both invertebrates and vertebrates (Tables 2, 3). As invertebrates lack adaptive immunity, AMPs play a significant role in their immune response and comprise an essential source of AFPs (Table 2). The AFPs obtained from marine invertebrates include penaeidins, Cm-p1, and tachystatins. The penaeidin family originates from shrimp, and currently, there are nine members available for this family in the ADP3 database (Destoumieux et al., 2000; Cuthbertson et al., 2002; An et al., 2016). The members of the penaeidin family show broad-spectrum fungicidal activity. For example, both penaeidins 2 and 3a are fungicidal against filamentous fungi and shrimp pathogen *F. oxysporum* (Destoumieux et al., 2000). Cm-p1 is a 10-mer short peptide isolated from marine snails. Cm-P1 has the ability to inhibit the growth of yeasts and filamentous fungi, while it shows little toxic effects on mammalian cells (López-Abarrategui et al., 2012). The tachystatin family consists of four members: tachystatin A, tachystatin B1, tachystatin B2, and tachystatin C, all of which have been identified in horseshoe crabs. All four members of the tachystatin family contain three disulfide bridges and have sequences similar to spider neurotoxins. Since horseshoe crabs are close relatives of spiders, tachystatins and neurotoxins may have evolved from a common ancestral peptide gene. Tachystatins are capable of binding to chitin and then exert their antifungal activity against *C. albicans* and *Pichia pastoris* (Osaki et al., 1999). AFPs are also found in insects. Representative AFPs from insects include melittin and thanatin. Melittin was isolated from bee venom by Neuman et al. (1952), which existed in hemolysin phospholipase A (Habermann, 1972). Melittin shows strong antifungal activity against various strains of fungi, including *Aspergillus* sp., *Candida* sp., *Malassezia* sp., *Penicillium* sp., and *Trichoderma* sp. (Memariani and Memariani, 2020). It is found that melittin exerts inhibitory activity against fungi via a series of combined mechanisms of inhibition of (1,3)-β-D-glucan synthase, membrane permeabilization, apoptosis induction by reactive oxygen species (ROS), and alterations in gene expression (Memariani and Memariani, 2020). Thanatin, a 21-residue peptide, was first isolated from the insect *Podisus maculiventris* (Fehlbaum et al., 1996). It is highly potent in inhibiting the growth of fungi at considerably low concentrations (Fehlbaum et al., 1996; Dash and Bhattacharjya, 2021). Protonectin was originally isolated from the venom of the neotropical social wasp *Agelaia pallipes pallipes* (Mendes et al., 2004). Later, protonectin was shown to have potent antifungal and fungicidal activity against *C. glabrata*, *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* by disturbing membrane integrity and inducing ROS production in yeast cells (Wang et al., 2015). Recently, a 41-amino acid peptide called blapstin, isolated from the Chinese medicinal beetle *Blaps rhynchopetera,* was shown to possess antifungal activity against *C. albicans* and *Trichophyton rubrum*. Cryo-scanning electron microscope (Cryo-SEM) observations showed that blapstin directly resulted in disruption in the cell structure of *C. albicans* and *T. rubrum* (Zhang et al., 2023).

Spiders and centipedes are also known to produce AFPs, such as juruin, gomesin, and lactoferricin B-like peptide (LBLP), especially in venoms. Juruin isolated from the venom of the Amazonian pink toe spider *Avicularia juruensis* has antifungal activity against filamentous fungi and yeasts, including *Aspergillus niger*, *Beauveria bassiana*, *C. albicans*, *C. krusei*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis,* and *Candida guilliermondii* (Ayroza et al., 2012). Gomesin, an 18-amino acid AMP isolated from the hemolymph of the tarantula spider *Acanthoscurria gomesiana*, inhibits the development of filamentous fungus and yeast (Silva et al., 2000). LBLP, a 23-mer AMP derived

TABLE 2 Representative antifungal peptides from invertebrates.

	Peptide (length)	Net charge; hydrophobic residue %	Origin	Structure	Antifungal spectrum	References
Marine invertebrate	Penaeidins family	–	*Penaeus vannamei*	Helix/random coil	Filamentous fungi; shrimp pathogen *F. oxysporum*	Destoumieux et al. (2000)
	Cm-p1 (10)	+1; 30%	*Cenchritis muricatus*	Helix	*A. niger, C. albicans* 01 U, *C. albicans* 38 U, *C. parapsilosis, C. neoformans*, and *T. rubrum*	López-Abarrategui et al. (2012)
	Polyphemusin I, II (18)	+8; 44%	*Limulus polyphemus*	Beta	*C. albicans* M9	Miyata et al. (1989)
	Tachyplesin II (17)	+7; 47%	*Tachypleus tridentatus*	Beta	*C. albicans* M9	
	Big defensin (79)	+6; 45%		Combined Helix/ Beta	Fungi such as *C. albicans*	Saito et al. (1995)
	Tachystatins family	–	*Tachypleus tridentatus; Limulus polyphemus*	Beta	*C. albicans and P. pastoris*	Osaki et al. (1999)
	Arenicin-1 (21)	+6; 52%	*Arenicola marina*	Beta	*C. albicans* 820	Ovchinnikova et al. (2004)
Insect	Lasiocepsin (27)	+9; 48%	*Lasioglossum laticeps*	Helix	*C. albicans*	Monincová et al. (2012)
	Melittin (26)	+6; 46%	*Apis mellifera*	Helix	*C. albicans*, *T. beigelii*, and *M. furfur*	Fennell et al. (1967) and Sung et al. (2008)
	Papiliocin (37)	+8; 48%	*Papilio xuthus*	Helix	Yeast	Kim et al. (2010)
	Polybia-CP (12)	+2; 58%	*Polybia paulista*	Helix	Yeast	Souza et al. (2005)
	Protonectin (12)	+2; 58%	*Agelaia pallipes pallipes*	Helix	*Candida* spp.	Mendes et al. (2004)
	Spinigerin (25)	+5; 52%	*Pseudacanthotermes spiniger*	Helix	Various filamentous fungi and yeast strains	Lamberty et al. (2001b)
	Termicin (36)	+6; 50%	*Pseudocanthothermes spiniger, Reticulitermes flavipes*	Combined Helix/ Beta	*F. Culmorum, F. oxysporum, N. crassa, N. haematococca, and T. viride*	Lamberty et al. (2001b)
	Heliomicin (44)	+2; 36%	*Heliothis virescens*	Combine Helix/ Beta	*C. albicans and P. pastoris*	Lamberty et al. (2001a)
	Thanatin (21)	+6; 28%	*Podisus maculiventris*	Beta	*N. crassa, N. crassa, N. haematococca, T. viride, A. brassicicola, F. culmorum, A. pisi, and F. oxysporum*	Fehlbaum et al. (1996) and Dash and Bhattacharjya (2021)
	Alo-3 (36)	+5; 27%	*Acrocinus longimanus*	Beta	*C. albicans and C. glabrata*	Barbault et al. (2003)
	Psacotheasin (34)	+2; 35%	*Psacothea hilaris*	Knottin-type	*C. albicans*	Hwang et al. (2010)
	ARD1 (41)	+3; 39%	*Archeoprepona demophoon*	Combined Helix/ Beta	*Fumigatus and C. albicans*	Landon et al. (2004)
	Coprisin (43)	+3; 51%	*Copris tripartitus*	Combined Helix/ Beta	*A. flavus, A. fumigatus, A. parasiticus, C. albicans, C. parapsilosis, M. furfur, T. beigelii, and T. rubrum*	Hwang et al. (2009) and Lee et al. (2012)
	Drosomycin (44)	+1; 34%	*Drosophila melanogaster*	Combined Helix/ Beta	Filamentous fungi: *A. fumigatus*, *A. ustus*, *F. solani*, and *F. oxysporum*	Fehlbaum et al. (1994) and Simon et al. (2008)
	Gambicin (61)	+4; 39%	*Anopheles gambiae*	Beta	Filamentous fungus *N. crassa*	Vizioli et al. (2001)
	Es-termicin (35)	+1; 45%	*Eupolyphaga sinensis*	Combined Helix/ Beta	*C. albicans*	Liu et al. (2016)
	Blapstin (41)	+4; 27%	*Blaps rhynchopetera*	Bridge	*C. albicans and T. rubrum*	Zhang et al. (2023)

(Continued)

TABLE 2 (Continued)

	Peptide (length)	Net charge; hydrophobic residue %	Origin	Structure	Antifungal spectrum	References
Other Arthropoda	Juruin (38)	+5; 42%	*Avicularia juruensis*	Cystine-knot	*C. albicans, C. krusei, C. glabrata, C. parapsilosis, C. tropicalis, C. guilliermondii, and A. niger*	Ayroza et al. (2012)
	Gomesin (18)	+6; 33%	*Acanthoscurria gomesiana*	Beta	Fungi *A. brassicicola, A. fumigatus, F. culmorum, F. oxysporum, N. crassa, N. haematococca, T. viride, T. mentagrophytes*; yeasts *C. albicans, C. tropicalis, C. neoformans, S. cerevisiae, C. glabrata*, and *B. bassiana*	Silva et al. (2000)
	LBLP (23)	+8; 17%	*Scolopendra subspinipes mutilans*	Helix/random coil	*C. albicans, C. parapsilosis, M. furfur, and T. beigelii*	Choi et al. (2013)

from the centipede *Scolopendra subspinipes mutilans*, has been found to have antifungal and fungicidal activity against *C. albicans*, *C. parapsilosis*, *Malassezia furfur*, and *Trichosporon beigelii* by forming pores in the membrane, eventually leading to fungal cell death (Choi et al., 2013). Recently, LBLP has been reported to trigger mitochondrial disruption-mediated apoptosis by inhibiting respiration under nitric oxide accumulation in *C. albicans* (Kim et al., 2020).

In vertebrates (Table 3), the immune system is divided into innate immunity and adaptive immunity. Adaptive immunity provides an effective and specific immune response against pathogens, while innate immunity consisting of the first line of defense is much quicker to respond to initial attacks. AMPs produced in response to pathogenic attacks form part of the first line of defense and are a source of AFPs. AFPs derived from vertebrates are usually produced on the skin, mucous membranes, and other areas that are easily exposed to microbial environments (López-Meza et al., 2011). It has been shown that the piscidins synthesized in the epithelia of gills, skin, stomach, and gut of a variety of teleost species exhibit antifungal activity against *C. albicans*, *M. furfur,* and *T. beigelii* through membrane disruption mode (Asensio-Calavia et al., 2023; Rakers et al., 2013). In addition, pleurocidin secreted by the skin of winter flounder inhibits the growth of *Alternaria* spp., *C. albicans*, *F. Oxysporum*, and *A. niger* (Cole et al., 1997; Souza et al., 2013). Recently, we have shown that AP10W, a short peptide derived from AP-2 complex subunit mu-A of zebrafish, displays conspicuous antifungal activities against the main fungal pathogens of human infections *C. albicans* and *A. fumigatus*. We also show that AP10W inhibits fungal biofilm formation and decrease pre-established fungal biofilms (Gong et al., 2022).

Similarly, the skin and secretory glands of amphibian frogs are also a rich source of AFPs, such as magainins and peptide glycine-leucine-amide (PGLa) identified in the clawed frog *Xenopus laevis* (Zasloff, 1987; Soravia et al., 1988), and temporins A, B, and L identified in the red frog *Rana temporaria* (Simmaco et al., 1996; Marcocci et al., 2018; Roscetto et al., 2021). Temporin G, recently isolated from the skin of *Rana temporaria*, is demonstrated to exert fungicidal ability against *C. neoformans, Candida* spp., and *Aspergillus* spp. In addition, temporin G reduces the metabolic activity of *C. albicans* cells, induces moderate membrane perturbation, and is effective against virulence factors of *C. albicans* (D'Auria et al., 2022).

In mammals, both neutrophils and epithelial cells are known to produce AFPs, including defensins, cathelicidins, histatins, and lactoferricins. Defensins are widely present in eukaryotes (fungi, plants, and animals), with four types of human defensins, known as HNP-1, HNP-2, HNP − 3, and HNP-4. All human defensins have been shown to possess candidacidal ability and are capable of influencing the ionic environment and the metabolic state of *C. albicans* cells (Selsted et al., 1985; Lehrer et al., 1988; Wilde et al., 1989). Cathelicidins have been identified in both humans and chimpanzees. LL-37, a 37-mer peptide derived from the N-terminal 37 residues of human cathelicidins, inhibits the growth of fungi including *Aspergillus*, *Candida*, *Colletotrichum*, *Fusarium*, *Malassezia*, *Pythium*, and *Trichophyton*. LL-37 exerts its fungal inhibition through several mechanisms, including cell wall integrity disruption, membrane permeabilization, and intracellular effects such as formation of autophagy-like structures, disturbance of endoplasmic reticulum homeostasis, induction of oxidative stress, inhibition of cell cycle progression, and alterations in gene expression (Memariani and Memariani, 2023). Histatins are histidine-rich peptides abundantly present in human saliva and the oral cavity (Oppenheim et al., 1988). Histatins exhibit a broad spectrum of antifungal activities and play an important role in controlling periodontal and oral fungal infections (Kavanagh and Dowd, 2004; Pólvora et al., 2018). Human histatins are composed of nine classes (human histatins 1–9), and histatin 5 is found to have strong fungicidal activity against *C. albicans*, *C. glabrata*, *C. krusei*, *C. neoformans,* and *Saccharomyces cerevisiae* (Sharma et al., 2021). Lactoferrin is a glycoprotein with AMP activity, found in saliva, milk, vaginal secretions, tears, and other exocrine secretions of mammals (cows, pigs, mice, and humans) (Moreno-Expósito et al., 2018; Rascón-Cruz et al., 2021; Drago-Serrano et al., 2018). Lactoferricin is found to have antifungal activity against a variety of fungi including *Clavispora lusitaniae*, *Pichia kudriavzevii*, *Kluyveromyces marxianus*, *Meyerozyma guilliermondii*, *S. cerevisiae*, *Candida* spp., and *Cryptococcus* spp.(Fernandes et al., 2020). Moreover, lactoferricin also shows inhibitory activity against the fungal biofilm

TABLE 3 Representative antifungal peptides from vertebrates.

	Peptide (length)	Net charge; hydrophobic residue %	Origin	Structure	Antifungal spectrum	References
Fish and Amphibian	Piscidins family	–	Various fish taxa	Helix	*C. albicans, M. furfur, and T. beigelii*	Asensio-Calavia et al. (2023) and Rakers et al. (2013)
	Pleurocidin (25)	+4; 44%	*Pleuronectes americanus*	Helix	*C. albicans, F. oxysporum, A. niger, and Alternaria* spp.	Cole et al. (1997) and Souza et al. (2013)
	Misgurin (21)	+7; 28%	*Misgurnus anguillicaudatus*	Helix	*C. albicans, C. neoformans, and S. cerevisiae*	Park et al. (1997)
	Magainin 2 (23)	+3; 43%	*Xenopus laevis*	Helix	*C. albicans and S. cerevisiae*	Zasloff (1987)
	PGLa (21)	+5; 61%	*Xenopus laevis*	Helix	*C. albicans and S. cerevisiae*	Soravia et al. (1988)
	Temporins G (13)	+2; 61%	*Rana temporaria*	–	*Candida* spp., *C. neoformans*, and *Aspergillus* spp.	Simmaco et al. (1996) and D'Auria et al. (2022)
	Andricin B (10)	+2; 50%	*Andrias davidianus*	Random coil	*A. niger, C. albicans, and S. cerevisiae*	Pei et al. (2018)
Mammal	Defensins					
	HNP-1, HNP-2, HNP-3, HNP-4	–	*Homo sapiens*	Beta	*C. albicans*	Selsted et al. (1985), Lehrer et al. (1988), and Wilde et al. (1989)
	NP-1 (33)	+9; 51%	*Oryctolagus cuniculus*	Bridge	*C. neoformans*	Alcouloumre et al. (1993)
	hBD2 (41)	+7; 36%	*Homo sapiens*	Combined Helix/ Beta	*Candida* spp.	Joly et al. (2004)
	RTD-1 (18)	+5; 55%	*Rhesus Macaque*	Beta	*C. albicans and C. neoformans*	Tran et al. (2002)
	Cathelicidins					
	SMAP-29 (29)	+10; 37%	*Ovis aries*	Helix	*C. albicans, C. neoformans, and R. rubra*	Skerlavaj et al. (1999)
	Indolicidin (13)	+4; 53%	*Bos taurus*	Extended boat-shaped structure	*C. albicans, S. cerevisiae, and T. beigelii*	Lee et al. (2003)
	LL-37 (37)	+6; 35%	*Homo sapiens; Pan troglodytes*	Helix	*Candida* spp.	Scarsini et al. (2015)
	Histatins					
	Human Histatins 1–9	–	*Homo sapiens*	His-rich classic	Histatin 5: *C. albicans, C. glabrata, C. krusei, C. neoformans, and S. cerevisiae*	Sharma et al. (2021)
	Mfa-hst5 (30)	+10; 3%	*Macaca fascicularis*	Helix	*C. albicans, C. neoformans, C. lusitaniae, and C. tropicalis*	Padovan et al. (2010)
	Lactoferricins					
	Lactoferricin B (25)	+8; 48%	*Bos taurus*	Beta	*A. fumigatus, F. solani, and C. albicans*	Sengupta et al. (2012)

formed by keratitis-associated fungal pathogens, such as *A. fumigatus*, *F. solani*, and *C. albicans* (Sengupta et al., 2012).

3 Modes of action of AFPs

Exploration of the modes of action of AFPs is a significant aspect of AFP research as the understanding of antifungal mechanisms can be a great help for researchers to further develop and design novel AFPs. In general, AFPs are known to function via three modes of action (Figure 1), i.e., inhibition of biosynthesis of cell wall components, interaction with membrane components, and interference with intracellular targets (Zhang et al., 2021). It is notable that some AFPs often function via multiple modes of action. For example, the fish-sourced peptide AP10W has been shown to exert its fungicidal activity through modes of combined actions, including interaction with the fungal cell walls via laminarin, mannan, and chitin, enhancement of cell wall permeabilization, induction of membrane depolarization, and increase in intracellular ROS generation (Gong et al., 2022).

3.1 Inhibition of biosynthesis of cell wall components

The fungal cell wall, the first barrier of the cell to effectively resist the influence of the external environment, is mainly composed of chitin, mannans, glycoproteins, and glucans ($\beta-1,3$-glucan, $\beta-1,6$-glucan, α-1,3-glucan, α-1,4-glucan, and mixed β-1,3−/β-1,4-glucan) (Bowman and Free, 2006). It protects the fungal cell from the pressure of the external environment and maintains normal cell metabolism, ion exchange, and osmotic pressure (Cabib and Arroyo, 2013).

Chitin and β-1,3-glucan are both the major structural components of the cell walls of many fungi and play a key role in maintaining the structural integrity of fungal cell walls (Bowman and Free, 2006; Lenardon et al., 2010; Fleet, 1991). Some AFPs are inhibitors of chitin synthase or (1–3)-β-D-glucan synthase, capable of blocking the synthesis of cell wall components, which then disrupts the normal cell morphology and diminishes the cell's capacity to regulate osmotic pressure. For example, the fungus-sourced AgAFP suppresses the activity of chitin synthases III and V, which are important for chitin biosynthesis (Hagen et al., 2007). The echinocandin, a cyclic hexapeptide isolated from several species of *Aspergillus*, inhibits β-1,3-D-glucan synthase necessary for glucan biosynthesis (Ciociola et al., 2016; Thorn et al., 2024). Neopeptins have been reported against some plant pathogenic fungi by inhibiting proteoheteroglycan and β-1,3-glucan synthesis, which could affect cell wall biosynthesis (Ubukata et al., 1984). The nikkomycins (a complex of nucleoside-peptides), an analog of chitin synthase natural substrate N-acetylglucosamine, also block the synthesis of chitin in *C. albicans* (McCarthy et al., 1985). Analogously, the aureobasidin A, a cyclic depsipeptide produced by *Aureobasidium pullulans*, interferes with fungal cell wall integrity by affecting actin assembly, chitin delocalization, and synthesis of sphingolipids (Endo et al., 1997; Nagiec et al., 1997).

3.2 Interaction with membrane components

AFPs, as part of AMPs, are usually small (< 100 amino acids) cationic polypeptides, with amphiphilic structures with hydrophobic domains capable of binding to lipids and positively charged hydrophilic domains capable of binding to water or negatively charged residues (Hollmann et al., 2018). This property of AFPs renders them

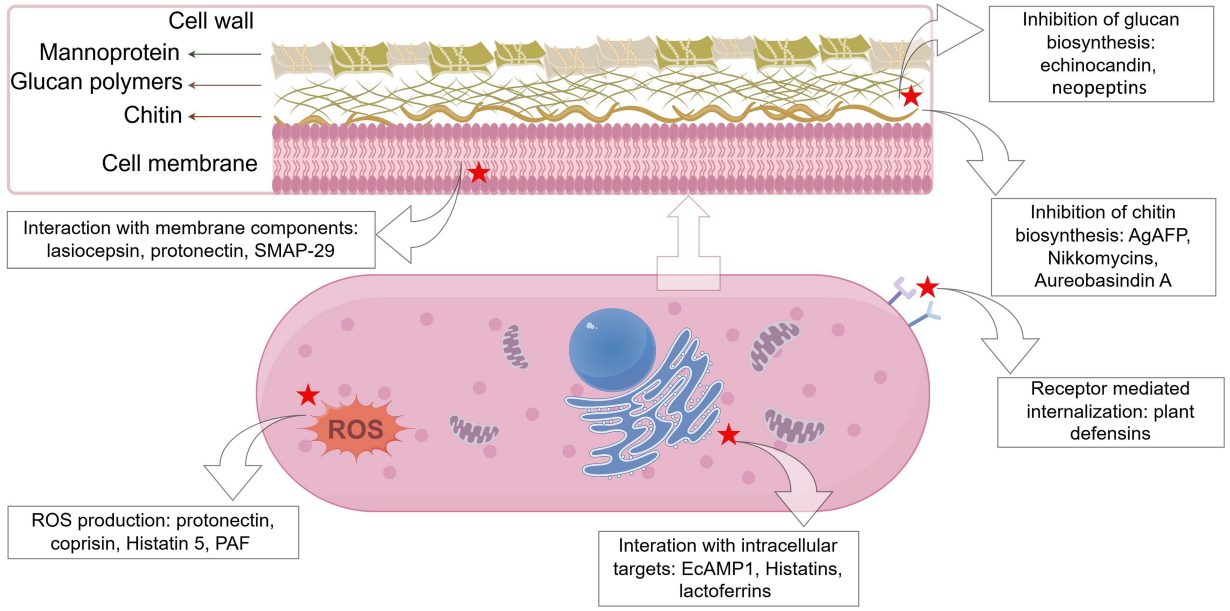

FIGURE 1
Schematic representation of the targets of some representative antifungal peptides. The red star marks the targets of AFPs (created by figdraw).

able to form strong binding to the amphiphilic part of the cell membrane, which lays the structural basis for the interaction of AFPs with fungal cell membranes. Several models have been proposed to explain the action of membrane disruption caused by AFPs, such as the barrel-stave, toroidal pore, and carpet models (Zhang et al., 2021; Yeaman and Yount, 2003). According to the barrel-stave model, AFPs bind to lipid membranes and recognize each other to form a transmembrane pore (Theis and Stahl, 2004; Soltani et al., 2007). Ultimately, the cell membrane components are penetrated by AFPs, resulting in cell collapse and death. The toroidal model suggests that AFPs insert into the hydrophobic center of the cell membrane (Soltani et al., 2007; Le et al., 2017), triggering the phospholipid molecular layer to curve inward and form a mixed cavity randomly (Yang et al., 2001). As a consequence, the membrane structures are disordered, eventually leading to cell death. In the carpet model, AFPs interact only with the lipid head groups and are oriented parallel to the surface, forming a carpet-like pattern. Once AFPs on the membrane surface accumulate to a certain concentration threshold, they act as detergents by distorting the phospholipid bilayer, reducing the stability of the cell membrane and causing cell membrane disintegration and cell lysis (Lohner and Prenner, 1999; Zhang et al., 2020). For example, plant defensins Dm-AMP1 from dahlia (*Dahlia merckii*), RsAFP2 from radish (*Raphanus sativus*), and HsAFP1 from coral bells (*Heuchera sanguinea*) target specific binding sites on fungal cells (e.g., mannosyl diinositolphosphoryl ceramide from *S. cerevisiae* for Dm-AMP1 and glucosylceramide from *P. pastoris* for RsAFP2), leading to membrane permeabilization and eventually decreasing viability (Thevissen et al., 2003; Thevissen et al., 2004; Aerts et al., 2008). Similarly, protonectin, isolated from the venom of the neotropical social wasp *Agelaia pallipes pallipes*, exerts antifungal/fungicidal activities against the tested fungal cells via interaction with lipid membranes, disruption of the membrane integrity, and induction of the production of intracellular ROS (Wang et al., 2015). MAF-1A, a linear 26-amino acid peptide, is derived from the carboxy-terminal functional domain of the antifungal peptide-1 (MAF-1) isolated from the hemolymph of *Musca domestica* larvae (Zhou et al., 2016). It has been shown that MAF-1A disrupts the cell membrane of *C. albicans* and then enters the cell where it binds and interacts with nucleic acids (Cheng et al., 2021). However, it must be pointed out that although the interaction of AMPs (including AFPs) with biological membranes plays an important role in the entire process of their antimicrobial actions, membrane disruption is a rather complex and dynamic process, which still needs detailed study to refine the specific mechanisms (Haney et al., 2019).

3.3 Interference with intracellular targets

AFPs can also interact with fungal intracellular targets, including nucleotides (DNA and RNA), proteins, and organelles. For example, CGA-N9, an antifungal peptide derived from human chromogranin A (CGA), has been found to exert antifungal activity toward *C. tropicalis* by attenuating mitochondrial function (Li et al., 2019). Psd1 defensin from pea (*Pisum sativum*) has been found to enter *N. crassa* cells, localize to the nuclei, and interfere with the cell cycle, probably via interacting with cyclin F (Lobo et al., 2007). Similarly, histatin 5 binds to mitochondria after crossing fungal membranes via transmembrane potentials or receptors (without damaging the plasma membrane) and then induces non-lytic release of adenosine triphosphate (ATP) into the cytoplasm. The released ATP binds to purinergic receptors on the cell surface, leading to the inhibition of mitochondrial respiration and the generation of ROS, which then causes damage to nucleic acids and organelles (Kavanagh and Dowd, 2004; Helmerhorst et al., 2001). The antifungal peptide EcAMP1 isolated from barnyard grass shows strong antifungal action toward species of the *Fusarium* genus. It has been found that EcAMP1 first binds to one or several abundant components of the fungal cell surface and is then internalized by the fungal cell and accumulates in a vesicular structure in the cytoplasm without disturbing the integrity of the membrane (Nolde et al., 2011).

4 Production of AFPs

To effectively explore the structure–activity relationships, efficacy, and safety, especially in clinical treatments, it is necessary to produce sufficient amounts of highly pure AFPs. There are currently three major approaches to achieving this goal, i.e., direct isolation from various organisms, recombinant expression, and chemical synthesis (Fernández de Ullivarri et al., 2020).

4.1 Natural production

AFPs are naturally isolated from different species of organisms. Currently, only a limited number of AFPs are obtained from their natural sources for clinical use as the isolation of these natural peptides is time-consuming and expensive due to their relatively low abundance (Vriens et al., 2014). The methods commonly used now for industrial-scale AFP production from natural sources are microbial fermentation and proteolysis.

The natural echinocandins, echinocandin B, pneumocandin B0, and FR901379, are produced for commercial purposes from *Aspergillus rugulosus*, *Glarea lozoyensis,* and *Coleophoma empetri*, respectively. The production of echinocandins is an exceptional example of AFPs produced by microbial fermentation and further chemical modification in the case of the semisynthetic variants. The fermentation process is critical to obtain a competitive product and thus needs optimizing to increase the amount of natural echinocandins and control their purification costs. Temperature is a key factor in fermentation production and influences the overall production costs of AFPs (Emri et al., 2013). The optimal temperatures for the production of echinocandin B, pneumocandin B 0, and FR901379 are similar, all below 30°C. However, the optimal growth temperatures of the strains of *A. rugulosus*, *G. lozoyensis*, and *C. empetri* exhibited considerable variation. The optimal growth temperatures of *G. lozoyensis* and *C. empetri* were observed to be lower than 30°C, whereas the optimal growth temperatures of *A. rugulosus* were found to be higher than 30°C, reaching 37°C; it exhibited poor growth at the temperatures utilized for the production of echinocandin B. The addition of complex nitrogen sources and plant oils also influences the generation of echinocandins (Emri et al., 2013).

Production of pharmaceutical-grade AFPs can be achieved through enzymatic hydrolysis of proteins, resulting in the release of encrypted peptides. The process generally involves three steps, i.e.,

acquisition of raw materials, protein hydrolysis, and fractionation and isolation. By-products from dairy, fish, and meat industries are all suitable sources of proteins (Sibel Akalin, 2014; Ryder et al., 2016). For proteolysis, the utilization of immobilized enzymes possesses several advantages over the conventional soluble enzymes, such as milder and controlled conditions and recycling of enzymes used (Sewczyk et al., 2018). The final step of fractionation and isolation of AFPs includes ultrafiltration, precipitation with solvents, and liquid chromatography techniques, which are usually expensive (Brady et al., 2008). Fortunately, an alternative and cost-effective method, electro-membrane filtration, which combines electrophoresis with conventional membrane filtration, has been established (Bazinet and Firdaous, 2013) and is increasingly being applied for the fractionation and isolation of AFPs.

4.2 Recombinant production

Recombinant expression presents a solid option for producing AFPs at low cost and high efficiency. In addition, sequencing technologies have generated a vast amount of genomic and transcriptomic data, providing valuable resources for discovering and designing new and more active AFPs (Amaral et al., 2012; Porto et al., 2012; Tracanna et al., 2017). Bacteria (mainly *Escherichia coli*), yeasts (mainly *P. pastoris*), and plants (e.g., tobacco plant *Nicotiana tabacum*) are the most common expression platforms for recombinant proteins.

E. coli BL21 (DE3), deficient in proteases that may lead to protein degradation, is by far the most commonly used bacterial species as a host for recombinant production of proteins (Li, 2011). Many *E. coli* strains are unable to export proteins across their outer membrane. As a result, in the majority of cases, proteins are secreted into the cytoplasm or periplasm, leading to the formation of inclusion bodies (Singh et al., 2015). Examples of AFPs produced in *E. coli* include lactoferricin B, nikkomycin, magainin-2, and cecropin (Fernández de Ullivarri et al., 2020).

In contrast to prokaryotic *E. coli*, eukaryotic yeasts are capable of implementing certain post-translational modifications to heterologous recombinant proteins. Yeasts commonly used as hosts for recombinant proteins include *S. cerevisiae*, *P. pastoris*, *Kluyveromyces lactis*, *Yarrowia lipolytica*, *Schizosaccharomyces pombe*, and *Hansenula polymorpha*. For example, the recombinant antifungal proteins serum albumin and hen lysozyme were produced by *K. lactis* and *S. cerevisiae*, respectively (Vieira Gomes et al., 2018). In addition, filamentous fungi such as *A. pullulans*, *P. Chrysogenum*, and *P. digitatum* have also been used to generate AFPs. Some examples of AFPs produced by yeasts or filamentous fungi are protegrin-1, porcine lactoferrin, aureobasidin A, and NFAP2 (Fernández de Ullivarri et al., 2020; Slightom et al., 2009).

Plants have been explored as hosts for recombinant expression of AFPs due to their capacity for large-scale production and their cost-effectiveness. The advantages of plants as expression systems are their capability to perform appropriate glycosylation, folding, and disulfide bond formation of recombinant AFPs. Different genetic approaches have been employed to produce AMPs in plants including using whole plants, tissue-specific expression, tissue culture, or transient expression (Holaskova et al., 2015). Whole tobacco plants have been utilized to produce lactoferrin and dermaseptin with a higher yield (Chahardoli et al., 2018; Shams et al., 2019).

4.3 Chemical synthesis

The chemical synthesis of peptides allows scientists to design and produce specific sequences of AFPs on demand. Ideally, an AFP should be short. *De novo* peptide design may help reduce production costs, potential toxicity, and lability and increase bioactivity *in vivo* (Steckbeck et al., 2014). Peptide chemical synthesis is divided into two types: solid- (SPPS) or liquid (solution)-phase peptide synthesis (LPPS). Currently, fluorenylmethyloxycarbonyl (Fmoc) SPPS is the preferred method for chemical synthesis of AFPs due to the versatility and low cost of very high-quality building blocks. We have recently designed and synthesized a peptide named AP10W that shows increased antifungal activity (Gong et al., 2022).

5 Applications and prospects

A primary focus of natural AFP research is the development of novel specific antifungal drugs against fungal infections (Matejuk et al., 2010). A number of AFPs, such as human lactoferricin-based hLF1-11, novexatin, and pexiganan, are in preclinical development, but few of them reach the clinical stage (Ciociola et al., 2016; Duncan and O'Neil, 2013; Koo and Seo, 2019). The hLF1-11 is proposed for intravenous usage in immunocompromised recipients of stem cell transplants for treating both bacterial and fungal infections; novexatin, a cationic peptide generated from defensins, is suggested for treating fungal toe infections; and pexiganan, an analog of peptide magainin (extracted from the skin of *Xenopus laevis*) with 22 amino acid residues, shows robust antimicrobial activity against bacterial and fungal pathogens. In addition, human histatin-based PAC-113 is also under clinical trials as a mouth rinse for oral candidiasis in patients with human immunodeficiency virus (HIV). AFPs undergoing clinical trials are generally designed for topical use because topical administration of peptides can overcome the inherent limitation related to poor stability in physiological fluids, due to their susceptibility to proteases. In addition, in certain areas of the body, such as skin, oral cavity, and vagina, where fungal infections may occur, physiological pH values and salt concentrations are compatible with the optimum activity of AFPs (Duncan and O'Neil, 2013; Wei et al., 2007; Lombardi et al., 2015).

Emerging resistance to conventional antifungals and serious side effects of drugs currently available demand urgent development of novel strategies for protection against fungal pathogens. This goal can be achieved with combination therapy, in which conventional antifungals are used together with other antifungal drugs or AFPs to increase the treatment efficacy compared to single-drug therapy. For instance, lactoferrin-derived peptides Lf (1–11) and bLfcin both exhibit synergy with azole and amphotericin B, which reduce the minimal inhibitory concentrations against *Candida* spp. (Wakabayashi et al., 1996; Lupetti et al., 2003; Fernandes and Carter, 2017). AFPs may also be conjugated with virus-like particles, such as rotavirus VP6 inner capsid protein, to deliver the peptides at the site of infection (Bugli et al., 2014). Likewise, nanoparticles consisting of self-assembled amphiphilic peptides can be generated. Nanotechnology can offer a better delivery system for targeted therapy (Kovalainen et al., 2015). For example, the histatin 5-conjugated polymer-based AmB-delivery carrier system, which is redox-sensitive and

pH-responsive, acts both as a synergistic molecule and as a targeting ligand against *C. albicans* (Park et al., 2017).

Fungal growth and consequent mycotoxin release in food and feed pose a serious risk to human health, which may lead to death in acute cases. Therefore, control and prevention of fungal pathogens and foodborne poisoning are among the main tasks of public health we face today. AFPs have been shown to possess both antifungal and anti-mycotoxin biosynthesis activities and thus meet the desired requirements to fight fungal contaminations. Several AFPs have been approved for applications in the food industry as preservatives, such as lactoferrin certified by the European Food Safety Authority (EFSA) since 2012 (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2012). Mycotoxins commonly found in the food industry include aflatoxins (AFs), deoxynivalenol (DON), ochratoxin A (OTA), zearalenone (ZEA), fumonisins (FUM), patulin (PAT), and citrinin (CIT) (Marin et al., 2013). A few AFPs have been shown to inhibit mycotoxin biosynthesis. For example, peptide cyclo-L-leucyl-L-prolyl from *Achromobacter xylosoxidans* inhibits AF production by suppressing the expression of the AF biosynthesis regulatory gene *aflR* (Yan et al., 2004). Similarly, peptides cyclo-L-Val-L-Pro and cyclo-L-Ala-L-Pro both can inhibit AF biosynthesis of *Aspergillus parasiticus* and *A. flavus* by reducing the mRNA level of *aflR* and blocking the production of norsorolinic acid, a biosynthetic intermediate involved in an early step of AF biosynthetic pathway (Jermnak et al., 2013). In addition, iturin A from *B. subtilis* has been shown to inhibit OTA production by *Aspergillus carbonarius* (Jiang et al., 2020), and AgAFP peptide produced by *Aspergillus giganteus* has been shown to decrease DON production by the genus *Fusarium* (Barakat et al., 2010). Lipopeptides, such as surfactins and fengycins from *Bacillus* species, also have the capacity to inhibit mycotoxin synthesis (Martínez-Culebras et al., 2021).

Given the huge clinical and market needs, the development of novel AFPs and detailed studies on existing AFPs are necessary and urgent. Computer-aided drug design has become an integral part of AFP discovery and development efforts in the pharmaceutical and biotechnology fields. Sequencing has produced a large number of databases including genomic, transcriptomic, proteomic, and functional information. Progresses in the field of molecular biology, analysis of whole genomes, and high-throughput screening of natural and synthetic compounds have resulted in the identification and characterization of new targets, novel scaffolds, and leading structures for potential AFP candidates. Definitely, modern *in silico* molecular modeling techniques will make the screening and discovery of new AFPs more efficient and faster. At the same time, continuing efforts are required to develop and improve natural/modified AFPs, or their analogs/mimics, with high efficiency and a low risk of resistant pathogen emergence. In addition, more efforts should focus on combination therapy, where the synergy between AFPs and conventional antifungal drugs is the main objective. This approach can promote their effectiveness while reducing their toxicity to the host. Last but not least, the modes of action of AFPs still demand further investigation, especially in combination with animal models (Capilla et al., 2007; Hohl, 2014; Van Dijck et al., 2018).

Author contributions

YG: Conceptualization, Writing – original draft, Writing – review & editing. QX: Writing – original draft. JL: Writing – original draft. SZ: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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