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Review

Fungal bioactive peptides: Rejuvenating the era of peptide-based therapy

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Abstract
Fungi, which are recognized as the most complex group of microorganisms, are a treasure trove of bioactive compounds, contributing significantly to drug discovery initiatives. Bioactive peptides derived from fungi show great promise as therapeutic agents for combating the global burden of diseases, including infections, cancers, and inflammatory disorders. This review delves into the multifarious landscape of fungus-derived bioactive peptides, highlighting their advantages over conventional small molecule-based drug counterparts and rendering a rationale for their use in peptide-based therapies. The review comprehensively covers various bioactive peptides derived from a wide range of fungal species found in terrestrial and marine habitats, such as endophytic fungi in plant tissues, insects, sponges, and medicinal mushrooms. In addition, the review categorizes natural fungal peptides based on their structural features, including linear peptides, cyclic peptides based on amino acid chain length, cyclic depsipeptides, lipopeptides, and peptide antibiotics, demonstrating their unique biological activities and therapeutic index. Conclusively, an in-depth classification of fungal bioactive peptides, revealing the impact of conformational attributes shaped by amino acid differences and their link to bioactivity, paves the way for advances in peptide-based drug discovery, their rational modification, and therapeutic development.

Keywords: Antimicrobial, Bioactivity, Endophyte, Lipopeptide, Marine fungi, Therapeutics

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1. Introduction

The global healthcare landscape is facing more and more challenges due to the global burden of disease (GBD) contributed by lifestyle disorders and infectious diseases, driving the ongoing epidemiological transformation (GBD 2021). The rapid uptick in the prevalence of lifestyle

disorders such as diabetes, cancer, cardiovascular disorders, and obesity has significantly contributed to increasing global mortality and morbidity rates. Additionally, communicable diseases such as multidrug-resistant (MDR) bacterial infections have further aggravated these health challenges (Sahu *et al.*, 2024). According to the World Health Organization (WHO), lifestyle disorders are accountable for nearly 74 % of all deaths worldwide, with ischemic heart disease and strokes topping the mortality charts. While antimicrobial resistance (AMR) accounts for approximately 1.27 million deaths per year, thereby exacerbating the risk caused by infectious diseases (Antimicrobial Resistance Collaborators, 2022). Conventional therapeutic regimens relied on small molecule-based drugs as a mainstay of drug development. Although small molecule-based drugs have been sourced from diverse resource setups and applications, higher toxicity, poor selectivity, numerous side effects, and limitations in long-term treatments often hinder their deployment. These challenges are further exacerbated by unwanted side effects such as the crossing of the blood-brain barrier and the generation of toxic byproducts during metabolism. In addition, small molecules often suffer from resistance development and off-target effects, underscoring the need for innovative and precise therapeutic solutions (Gurevich & Gurevich, 2014; Maurer *et al*., 2022). In this context, bioactive peptides, small protein fragments or compounds with low molecular weights, have emerged as promising alternatives, particularly for tackling AMR and chronic lifestyle diseases. By targeting specific biological pathways with precision, bioactive peptides align with the objectives of personalized medicine and hold the potential to significantly ameliorate the GBD. These peptides are small protein fragments or compounds with low molecular weights, derived from natural or synthetic sources, exhibiting various biological activities such as antimicrobial, anti-inflammatory, immunomodulatory, and antihypertensive effects (Akbarian *et al*., 2022).

Peptides play a vital role in normal physiological processes like cellular signaling and biochemical regulation and offer several advantages over traditional compounds, such as greater stability, attenuated toxicity, augmented bioavailability, and absorption *in vivo* (Rossino *et al*., 2023). The era of therapeutic peptides began with the marvelous discovery of insulin, a peptide with 51 amino acids, in the first half of the 20th century. Insulin was first isolated by Frederick Banting in 1921, who subsequently developed it with Charles Best, and it became the first commercial peptide drug in 1923, rejuvenating the diabetes treatment regimen. Although animal-derived insulin dominated the market for decades, recombinant insulin eventually replaced it, meeting growing demands and improving patient outcomes (Vecchio *et al*., 2018). Since the mid-20th century, numerous peptide hormones and receptors with therapeutic potential have been reported and characterized. Peptide-based drug development saw a huge upsurge due to advances in structural biology, recombinant DNA technology, and synthetic technologies, establishing a sophisticated framework for discovery, design, synthesis, modification, and evaluation (Anand *et al*., 2023; Martinovich & Baradzina, 2022). Besides this, peptide drugs derived from natural sources have acquired considerable market traction, with global sales surpassing $70 billion in 2019. It was reported that in 2019, the top-selling 200 drugs included 10 non-insulin peptide drugs (Njardarson, 2020). Notable examples of this include GLP-1 analogues for type-2 diabetes mellitus (T2DM), such as Trulicity (dulaglutide), Victoza (liraglutide), and Rybelsus (semaglutide), which altogether render billions in sales and are ranked among the top peptide drugs globally (Karásek, 2022). The emergence of bioactive peptide-based therapeutics has meant a transformative shift in modern therapeutics, offering innovative solutions to address unmet medical needs.

2. Benefits of Peptide Therapy

Peptide-based therapies provide recognized benefits for managing lifestyle disorders and

infectious diseases because of their high specificity, selectivity, reduced toxicity to healthy tissues, and versatility in targeting different molecular pathways involved in disease progression. Additionally, unlike proteins, peptides are fully absorbed at the intestinal level, enabling them to wield both local and systemic effects through the cardiovascular system. Small-molecule drugs, with their extended therapeutic chronicle, represent several advantages, such as low production costs, economical price, oral administration, and efficient membrane penetration (Fetse *et al*., 2023; Rossino *et al*., 2023). Both naturally derived and synthetically produced small molecules offer competitive prices as compared to peptide-based drugs and other protein-based biologics, including antibodies. Their oral bioavailability contributes to safety and patient cooperation, while their small size allows them to pinpoint intracellular molecules effectively. On the other hand, their small size restricts their ability to curb large surface interactions, such as protein-protein interactions (PPIs). In contrast, peptide drugs, with their larger size and flexible backbone, stand out as inhibitors of PPIs (Li *et al*., 2024). For example, tyrosine kinase inhibitors like sorafenib and sunitinib target the tyrosine kinase domains of vascular endothelial growth factor (VEGF) receptors, achieving anti-angiogenic effects in cancer therapy. However, these inhibitors also interact with other kinase receptors, such as serine/threonine kinase receptors, leading to cytotoxicity. Consequently, over 90 % of peptides in progressive clinical development are centered around extracellular targets like G-protein coupled receptors (GPCRs), gonadotropin-releasing hormone (GnRH) receptors, and glucagon-like peptide 1 (GLP-1) receptors. Several therapeutic peptides sourced from bacteria, fungi, plants, and animals have demonstrated a range of therapeutic attributes. For example, venom peptides, such as VEGF analogues derived from snake venom, have been modified for clinical applications. Exenatide, optimized from Gila monster venom, acts as a GLP-1 agonist, while ziconotide, derived from *Conus magus* venom, is used to manage chronic neuropathic pain (Vidya *et al*., 2021). At present, approximately 100 clinical trials are ongoing, and two peptide-drug conjugates, 177Lu-dotatate (lutathera) and Pepaxto (melphalan flufenamide/ melflufen), have received U.S. Food and Drug Administration (FDA) approval. As a first-in-class PDC, 177Lu-dotatate, a radiolabeled octreotide, is administered intravenously to treat gastrointestinal, pancreatic, and neuroendocrine tumors. These peptides displayed different pharmacological mechanisms, considering direct cell membrane lysis, organelle targeting, and anticancer immune responses, which may help overcome MDR challenges (Ladriere *et al*., 2023; Xie & Duong, 2022).

3. Rationale behind the activity of peptides

Peptides generally exhibit higher potency and selectivity in comparison to small molecules due to their chemical and biological diversity. Naturally occurring therapeutic peptides like insulin display reduced toxicity and fast clearance, thereby requiring a lower dose regimen to yield comparable therapeutic effects. Furthermore, many factors such as target selection, chemical modification approaches, conjugation for enhanced stability, and innovative delivery techniques have prioritized the peptide therapeutics over small-molecule drugs for identical conditions (Pereira *et al*., 2024). These approaches have spurred a revitalization of peptides as contending pharmaceutical agents in the therapeutic market (Rafferty *et al*., 2016).

4. Fungi as a source of bio-active peptides

Fungi are known for their ability to secrete an assorted array of linear, cyclic peptides, cyclodepsipeptides, lipopeptides, peptide antibiotics, etc. (Shahidi & Saeid, 2025; Zhou *et al*., 2023). These peptides frequently display a distinct structural diversity and a wide array of bioactivities, viz., antimicrobial, antiviral, anticancer, and immunosuppressive properties (Table 1). Their chemical diversity and bioactive potential make peptides a valuable focus of

research in drug discovery and development. In the upcoming sections, a comprehensive summary of each class, highlighting their fungal source, structural characteristics, and associated bioactivities with an emphasis on their therapeutic potential, is discussed.

Table 1: List of fungal-derived peptides with significant biological activities

S. No.	Peptide Name	Structural conformation of peptide	Source organism/Host Plant	Biological activity	IC_{50}/ MIC	Reference
Anticancer Activity						
1.	Trichoguizaibols J	Peptaibols	*Trichoderma guizhouense* (DS9-1)	Displayed cytotoxicity against MDA-MB-231, SK-Hep1, SKOV3, DU145, and HCT116 cells	IC_{50} - 0.68 to 1.4 µM	Han *et al.* (2024a)
2.	Tolypocladamides A–G	linear peptaibols	*Tolypocladium inflatum*	Demonstrated significant cytotoxicity by inhibition of Ras/Raf interactions	IC_{50} - 0.5 to 5.0 µM	Senadeera *et al.* (2022)
3.	Halovirs I and J	Planer	*Paramyrothecium roridum* NRRL 2183	Anticancer activity against A549, MCF7, and HeLa cell lines	IC_{50}- 1.3 to 3.3 µM	Xiao *et al.* (2022)
4.	Velutibol A	linear peptaibols	*Trichoderma velutinum*	Potent cytotoxicity over MDA-MB231 and human myeloid leukemia (HL-60) cell lines	IC_{50} - 7µM and 4µM	Singh *et al.* (2020)
5.	Lipovelutibols B and D	Lipopeptaibols	*Trichoderma velutinum*	Exhibited cytotoxic effect against HL-60 and MDA-MB-231	IC_{50} - 2 and 4 µM	Singh *et al.* (2018)
6.	Lipovelutibols D	Lipopeptaibols	*Trichoderma velutinum*	Exhibited cytotoxic effect against HL-60, LS180, MDA-MB-231 and A549 cancer cell lines	IC_{50} - 4, 7, 5, 4 µM	Singh *et al.* (2018)
7.	Simplicilliumtides A and G	Linear	*Simplicillium obclavatum*	Cytotoxic activity against HL-60 cells	IC_{50} - 64.7 and 100 µM	Liang *et al.* (2016)
8.	Simplicilliumtides E and H	Linear	*Simplicillium obclavatum*	Cytotoxic activity against K562 cells	IC_{50} - 39.4 and 73.5 µM	Liang *et al.* (2016)
9.	PM181110	Depsipeptide	*Phomopsis glabrae*/ *Pongamia pinnata*	Anticancer activity against a panel of 40 human cancer	IC_{50}- 0.089 µM	Verekar *et al.* (2014)

				cell lines		
Antimicrobial Activity						
10.	SK-P1	Linear peptaibols	*Stephanonectria keithii* LZD-10-1	Antibacterial activity against multidrug-resistant *S. aureus*	MIC- 2 µg/ml	Chen *et al.* (2025)
11.	Simplicpeptaibs A–K	Peptaibiotics	*Simplicillium obclavatum* EIODSF 020	Antibacterial activity against *Ralstonia solanacearum* or tilapia pathogens *Streptococcus iniae* and *Streptococcus agalactiae*	MIC_{90} - 7.7 to >64 µM	Liang *et al.* (2024)
12.	Avellanins E	Cyclic pentapeptides	*Aspergillus fumigatus* GXIM D 03099 fungus from *Acanthus ilicifolius*	Anti-insecticidal activity against larvae of *Culex quinquefasciatus*	LC_{50} - 86.6 µM	Wang et al. (2024)
13.	Avellanins G	Cyclic pentapeptides	*Aspergillus fumigatus* GXIM D 03099 from *Acanthus ilicifolius*	Antibacterial activity against *Vibrio harveyi*	MIC - 5.85 µM	Wang *et al.* (2024)
14.	Aspergilalkaloid A	Cyclic dipeptide	*Aspergillus* sp. HDN20-1401	Antibacterial activity against *Bacillus cereus*	MIC- 12.5 µM	Anjum *et al.* (2024)
15.	Simplicilliumtides N and O	Cyclic	*Simplicillium obclavatum* EIODSF 020	Antifungal activity against phytopathogenic *Alternaria solani* and *Colletotrichum asianum*	MIC- 0.195–6.250 µg/disc	Karim *et al.* (2022)
16.	Talaropeptins A and B	Tripeptide	*Talaromyces purpureogenus* CX11	Antifungal activity against *Fusarium oxysporum*	MIC- 12.5 and 25 µg/ml	Zhou *et al.* (2022)
17.	Pipecolisporin	Cyclic hexapeptide	*Nigrospora oryzae* CF-298113/*Triticum* sp.	Antimalarial (*P. falciparum*) and Antitrypanosome (*Trypanosoma cruzi*) activity	IC_{50} - 3.21 and 8.46 µM	Fernández-Pastor *et al.* (2021)
18.	Simplicilliumtides D	Linear	*Simplicillium obclavatum*	Antifouling activity against *Bugula neritina* larvae	EC_{50} - 7.8 µg/ml	Liang *et al.* (2016)
19.	Colisporifungin	cyclic depsilipopeptide	*Colispora cavincola*	Antifungal activity against *Aspergillus fumigatus* and *Candida albicans*	MIC- 8 µg/ml and 0.5-4 µg/ml	Ortíz-López *et al.* (2015)

4.1 Linear peptides

A linear tetra-peptide, hirsutellic acid, featuring the presence of a distinct anthranilic acid residue at its C-terminal, was purified from the parasitic fungus *Hirsutella* sp. BCC 1528. Under *in vitro* conditions, it displayed potent activity against *Plasmodium falciparum* K1, with an IC_{50} value of 8.0 μM, while no cytotoxicity was observed in Vero cells up to the concentration of 95 μM (Thongtan *et al*., 2006). Five new linear hybrid peptide-polyketides, curvularides A–E, were isolated from *Curvularia geniculata,* an endophytic fungus recovered from the limbs of *Catunaregam tomentosa.* Out of these five peptides, curvularide B was observed to exhibit antifungal activity against *Candida albicans* as well as synergism when administered along with the drug fluconazole (Chomcheon *et al*., 2010). Aspergillipeptide E, a linear tetrapeptide, was recovered from *Aspergillus* sp. SCSIO 41501 derived from marine gorgonian and was reported to exhibit potent antiviral activity against HSV-1 in Vero cell line with IC_{50} of 19.8 μM (Ma *et al*., 2017).

4.2 Cyclic peptides

Peptides that form stable ring-shaped structures by cyclization of amino acid residues, due to the formation of amide bonds between carboxyl and amino groups of adjacent amino acids, are known as cyclopeptides or cyclic peptides. Due to their remarkable biological activities towards infectious diseases to the leading lifestyle disorders, cyclic peptides have garnered significant attention from the research community (Buckton *et al*., 2021). In addition, the robust nature of their cyclic structure contributes to increased stability, impedance to enzymatic degradation, and improved bioavailability in comparison to their linear counterparts, notably accelerating their therapeutic relevance. Apart from this, they also contribute significantly to vital physiological and bionomical functions, making them promising candidates for development into pharmaceuticals and agrochemicals (Costa *et al*., 2023). Around 40 cyclic peptides derived from natural sources or their derivatives are being employed as therapeutic agents nowadays (Zorzi *et al*., 2017). These versatile groups of natural products have been purified from various natural sources, including plants, bacteria, actinomycetes, algae, fungi, sponges, as well as mammals. Among all the sources, fungi are recognized as potent producers of structurally and functionally diverse cyclic peptides ranging from dipeptides to dodecapeptides, thereby offering a valuable area of research in drug discovery and development. Several bio-active and structurally distinct cyclic peptides are recovered from plant and insect pathogenic fungi, terrestrial and marine fungi, mushrooms, and plant or insect endophytic fungi (Wang *et al*., 2017).

4.2.1. Dipeptide

Marine, endophytic, and terrestrial fungi have emerged as prolific sources of cyclic dipeptides with diverse structural attributes and potent biological activities. Two antibacterial cyclic dipeptides, cyclo-(Proline-Threonine) and cyclo-(Proline-Tyrosine), were purified from the fermentation broth of the endophytic *Penicillium* sp., isolated from the mangrove plant *Acrostichum aureum.* Both dipeptides demonstrated promising activity against *Staphylococcus aureus* and *Candida albicans*, further highlighting the antimicrobial potential of fungal-derived peptides (Cui *et al*., 2008). Similarly, deep-sea *Aspergillus* sp. isolate yielded a novel cyclic dipeptide, 14-hydroxy-cyclopeptine, as a unique addition to the growing library of fungal-originated peptides. This unique dipeptide efficaciously suppressed nitric oxide production in LPS and interferon-γ stimulated macrophage cell line (RAW 264.7) with an IC_{50} value of 40.3 μg/mL, with no cytotoxicity appearance up to a concentration of 100 μg/mL, establishing its potential as an anti-inflammatory agent (Zhou *et al*., 2016). Based on the above findings, further exploration of marine fungi or fungi associated with marine organisms led to the

discovery of two new dipeptides, asperopiperazines A and B, from ethyl acetate fraction of tunicate-derived *Aspergillus* sp. DY001. Based on the ID and 2D NMR data, asperopiperazine A was comprised of leucine and phenylalanine moieties substituted with N-methyl and N-acetyl groups, and asperopiperazine B was composed of proline and phenylalanine with a hydroxyl substitution at C-2 of the proline residue. Both cyclic dipeptides (A and B) exhibited potent antimicrobial activity against *Escherichia coli* (MIC- 8 & 4 μM, respectively) and *Staphylococcus aureus* (MIC- 8 & 8 μM, respectively), compared to *Candida albicans* (MIC- 16 μM). Moreover, asperopiperazine B also displayed potent cytotoxicity against HCT 116 cells with IC_{50} of 15.1 and 16.2 μM, highlighting its value as a compound of pharmaceutical relevance (Youssef *et al*., 2022). Beyond the aspect of bioactivities, fungi have proven to be instrumental in delineating the biosynthetic pathway, also serving as a mechanism of peptide production. In this regard, echinulin-related cyclic dipeptides secreting *Eurotium cristatum* NWAFU-1 fungal strain, derived from Jing-Wei Fu brick tea, were utilized to clone the *cirC* gene encoding a non-ribosomal peptide synthetase (NRPS). The gene expression of *cirC* was deciphered in heterologous host *Aspergillus oryzae*, which was confirmed by the production of a novel metabolite comprised of L-tryptophan-L-alanine cyclic backbone. This study was the first report of NRPS in fungi capable of catalyzing cyclic dipeptide formation, thereby furnishing a new platform for scalable cyclic dipeptide biosynthesis (Qi *et al*., 2022).

4.2.2 Tripeptides

Cyclic tripeptides are a group of peptides with three amino acids linked by amide bonds to form a stable cyclic structure. This unique set of peptides was isolated from various fungal genera, namely, *Aspergillus, Xylaria*, and *Penicillium,* and was found to exhibit promising cytotoxicity, antifungal, and insecticidal properties. The very first cyclic tripeptide, Aspochracin, was purified from the muscardine disease-causing pathogenic *Aspergillus ochraceus* in 1969. The purified tripeptide displayed contact toxicity on the first instar larvae and the eggs of the silkworm (Myokei *et al*., 1969). Further research on the biological activities of aspochracin and its derivatives has expanded our understanding of their therapeutic significance. In a chemical screening and advanced NMR-MS characterization program, JBIR-15, an N-demethyl derivative of aspochracin, was purified from the sponge-derived *Aspergillus sclerotiorum.* The compound did not display cytotoxic potential against HeLa cells and malignant pleural mesothelioma ACC-MESO-1 cells, even at the concentration of 50 μg/ml (Motohashi *et al*., 2009). Along the same lines, sclerotiotides A-K, which are eleven new aspochracin-type cyclic tripeptides, along with three known compounds - JBIR-15, aspochracin, and penicillic acid - were obtained from a halotolerant *Aspergillus sclerotiorum* grown in a hypersaline medium. All 13 cyclic peptides were subjected to antimicrobial and cytotoxicity assays. Among them, sclerotiotides A, B, F, and I, along with JBIR-15, exhibited exclusive antimycotic activity against *Candida albicans* with MIC values ranging between 3.8 to 30 μM, highlighting their therapeutic potential (Zheng *et al*., 2010). Considering the previous studies, another four distinct cyclic tripeptides, psychrophilins E-H, characterized by unique amide linkages involving anthranilic acid and indole moieties, were purified from a marine-derived *Aspergillus versicolor*. Among these four peptides, only psychrophilins G demonstrated lipid-lowering effects, pointing to potential applications in treating metabolic disorders (Peng *et al*., 2014). Furthermore, psychrophilins E, belonging to the psychrophilins class of compounds, have also been purified from the mixed culture of two marine alga-derived *Aspergillus* strains*,* along with two oxepin-containing pyrimidine alkaloids and three mycotoxins. Psychrophilins E exhibited selective *in vitro* anti-proliferative activity against colon (HCT116) and ovary (A2780) cancer cell lines with IC_{50} of 28.5 and 27.3 μM, respectively (Ebada *et al*., 2014). Similarly, Sun *et al*. (2020) reported the isolation of three

new aspochracin-type cyclic tripeptides- *sclerotiotides M, N, O* - along with three known analogues, *sclerotiotide L*, *sclerotiotide F,* and *sclerotiotide B*, from *Aspergillus insulicola* HDN151418, a fungus derived from an Antarctic sponge. Out of the three new aspocharacin tripeptides, *sclerotiotides M* and *N* displayed broad-spectrum antimicrobial activity against *Bacillus cereus*, *Proteus* sp., *Mycobacterium phlei*, *Bacillus subtilis*, *Vibrio parahaemolyticus*, *Edwardsiella tarda,* and MRSA, with MIC values ranging from 1.56 to 25.0 µM. Cumulatively, the above findings emphasize the significant bioactive potential of marine fungi, particularly *Aspergillus* and *Penicillium*, as sources of structurally diverse cyclic tripeptides.

4.2.3. Cyclic Tetrapeptides

Numerous bioactive cyclic tetrapeptides have also been reported from fungal species isolated from diverse natural settings, revealing an exemplary array of bioactive attributes and emphasizing their importance in both therapeutic and biological research. A cyclic tetrapeptide antitumor antibiotic, WF-3161, consisting of phenylalanine, leucine, pipecolinic acid, and 2-amino-8-oxo-9,10-epoxydecanoic acid, was isolated from *Petriella guttulata*. The purified tetrapeptide exhibited prominent growth and inhibitory activity against *Trichophyton asteroides* along with notable efficacy in prolonging survival in mice bearing leukemia P-388, depicting a high therapeutic index (Umehara *et al*., 1983). After a few years, Itazaki and his group reported antitumor tetrapeptides, trapoxins A and B, purified from *Helicoma ambiens RF-1023*. The structural composition of these tetrapeptides was slightly different from earlier reported peptide WF-3161 in terms of the presence of two phenylalanine residues and a proline residue instead of pipecolinic acid, especially in the case of trapoxins B. Both compounds exhibited de-transformation activity towards sis/NIH3T3 cells, indicating their antitumor potential (Itazaki *et al*., 1990). Further, in the domain of anti-parasitic agents, such as cyclo-(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) derived from *Fusarium pallidoroseum*, emerged as a potent inhibitor of apicomplexan histone deacetylase (HDAC) with an IC_{50} of 1-2 nM. This HDAC inhibitory tetrapeptide exhibited promising broad-spectrum antiparasitic activity both *in vitro* and *in vivo* against *Plasmodium berghei* (Singh *et al*., 1996). Similarly, another HDAC inhibitory peptide, FR235222 against mammalian form of HDAC enzyme was purified from *Acremonium* sp. No. *27082* and was observed to exhibit strong immunosuppressive attributes by restricting T-cell proliferation and lymphokine production (Mori *et al*., 2003). Continuing in the realm of discovery of HDAC inhibitory agents, Gu *et al*. (2007) reported the purification of two cyclic tetrapeptides, namely, microsporins A and B, from *Microsporum* cf. *gypseum* associated with the bryozoan *Bugula* sp. Both peptides demonstrated promising HDAC inhibition and cytotoxicity against human colon cancer cell line (HCT-116) along with a 60-cancer-cell panel from National Cancer Institute, thereby highlighting their potential in cancer therapy. Further studies in this domain underpin the discovery of a novel cyclic tetrapeptide isolated from *Phoma* sp. recovered from the giant jellyfish *Nemopilema nomurai*. The peptide did not exert any cytotoxicity but did show sparse repression on the nitric oxide production in murine macrophage cell line (RAW264.7) (Kim *et al*., 2012). Moreover, in line with the work of Singh *et al*. (1996), an apicidin-like compound, apicidin F, was isolated from *Fusarium fujikuroi b*y overexpressing the pathway-specific transcription factor pertaining to an apicidin-like gene cluster. The newly isolated apicidin F also demonstrated significant *in vitro* activity against *Plasmodium falciparum* with an IC_{50} of 0.67 µM (Von Bargen *et al*., 2013).

Further studies documented the discovery of 1-alaninechlamydocin isolated from *Tolypocladium* sp. recovered from the Great Lakes region with incredible antiproliferative activity against pancreatic cancer cells (MIA PaCa-2). The peptide was found to induce G2/M

cell cycle arrest and apoptosis through HDAC inhibition with LC_{50} of 22nM (Du *et al*., 2014). Another engrossing discovery includes pseudoxylallemycins A-F, a series of six cyclic tetrapeptides isolated from *Pseudoxylaria* sp. *X802*, a termite associated with fungus. Unusually, three of these tetrapeptides, pseudoxylallemycins B-D, displayed an occurrence of rare, chemically modifiable allene moieties, which may open-up way to new avenues for chemical modifications and therapeutic exploration. Further, pseudoxylallemycins A-D exhibited promising antimicrobial activity against *Pseudomonas aeruginosa* and antiproliferative effects towards human umbilical vein endothelial cells and K-562 cell lines (Guo *et al*., 2016). Furthermore, two peculiar N-methylated tetrapeptides, endolide A and B, containing a rare 3-(3-furyl)-alanine amino acid, were discovered from the *Callyspongia* sponge-derived *Stachylidium* sp. cultured in sea salt-supplemented biomalt medium. Endolide A demonstrated an affinity for the vasopressin receptor 1A (K_i = 7.04 μM) while endolide B selectively targeted the serotonin receptor 5HT2b (K_i = 0.77 μM) only, suggesting their relevance in receptor-based therapies (Almeida *et al*., 2016). Another study documented the reports of two antifungal peptides, auxarthrides A and B, from coprophilous *Auxarthron pseudauxarthro.* Both peptides displayed intermediate antifungal activity against *Cryptococcus neoformans* and *Candida albicans* without any cytotoxic effect toward human cancer cell lines (Li *et al*., 2017). Cyclic tetrapeptides were also reported to display their efficiency towards inflammation-associated maladies via reports of cyclic tetrapeptides from the ethyl acetate fraction of a sponge-derived *Aspergillus violaceofuscus.* The peptide demonstrated significant anti-inflammatory potential by down-regulating the expression of IL-10 in LPS-stimulated THP-1 cells with 84.3 %, highlighting their potential application in inflammation-related disorders (Liu *et al*., 2018). In addition, an antibacterial peptide called 14,31-dimethoxy-enicopeptide A was isolated from the endophytic *Aspergillus versicolor* of *Paris polyohylla* var. *yunnanensis* (Franch) Hand-Mazz cultured on rice perlite. 14,31-dimethoxy-enicopeptide A was found to display strong antibacterial activity against *Bacillus subtilis* with an IC_{50} of 31.89 μM, further extending the repertoire of bioactive cyclic tetrapeptides (Li *et al*., 2022). More recently, a unique aureobasidin analogue, persephacin, differentiated due to both phenylalanine residues and the presence of a novel amino acid, persephanine, was produced by *Elsinoë* sp. Persephacin exhibited the promising antifungal activity against various pathogenic yeasts, i.e., several clinical strains of *Candida auris* as well as diverse filamentous fungi such as *Aspergillus fumigatus.* The compound also demonstrated extraordinary effects in an *ex vivo* eye infection model by subduing the fluconazole-resistant *Candida albicans* and *A. fumigatus* at a concentration of 0.1 %, significantly lower than the clinically recommended levels for fluconazole (2 %) and natamycin (5 %). Moreover, no toxicity or irritation episodes occurred in 3D tissue models for acute dermal and ocular safety at threshold concentrations recommended for antifungal treatments (Du *et al*., 2023). Cyclic tetrapeptides are an assorted and promising class of bioactive natural products with extraordinary therapeutic potential. Their broad-spectrum activities, encompassing antitumor, antifungal, antibacterial, anti-inflammatory, and antiparasitic properties, in conjunction with their diverse origins ranging from terrestrial, endophytic to marine fungi, offer ample possibilities for further chemical alterations to intensify their efficacy and applicability in modern medicine.

4.2.4 Cyclic Pentapeptide

Argadin, a novel chitinase inhibitor, isolated from the fermented broth of *Clonostachys* sp. FO-7314 exhibited inhibitory activity against *Lucilia cuprina* (blowfly) chitinase with an IC_{50} value of 150 nM at 37 °C and 3.4 nM at 20 °C. The structural characteristics of argadin were found to be cyclo(Nω-acetyl-L-arginyl-D-prolyl-homoseryl-histidyl-L-2-aminoadipyl), with the homoseryl γ-methylene moiety covalently joined to the histidyl α-amino group. Furthermore,

it was observed to cease the molting process in cockroach larvae following injection into the ventral abdominal region (Arai *et al*., 2000b). Another chitinase inhibitor, argifin, was purified from the fermented broth of *Gliocladium* sp. strain FTD-0668. Structural elucidation using NMR spectroscopy revealed its composition as cyclo(Nω-(N-methylcarbamoyl)-L-arginyl-N-methyl-L-phenylalanyl-β-L-aspartyl-β-L-aspartyl-D-alanyl) (Arai *et al*., 2000a). Further studies in the realm of discovery of bioactive cyclic pentapeptides by Li and colleagues led to the isolation of two new cyclic pentapeptides: cyclo-(L-Phe-L-Leu1-L-Leu2-L-Leu3-L-Ile) and cyclo-(Phe-Val-Leu-Leu-Leu) purified from the endophytic fungal strain (No. 2524), isolated from *Avicennia marina* seeds in a Hong Kong mangrove. Among these, cyclo-(L-Phe-L-Leu1-L-Leu2-L-Leu3-L-Ile) demonstrated cytotoxic activity against the human cancer cell line Bel-7402, by suppressing the cell viability to 67 % at 15 µg/mL (Li *et al*., 2004). Another study documenting the purification of chrysosporide from pathogenic *Sepedonium chrysospermum* obtained from a degraded basidiomycete sporophore collected in a podocarp forest in the Bay of Plenty, New Zealand, displayed very low cytotoxicity towards P388 murine leukemia cell line with an IC_{50} of 33.4 µM (Mitova *et al*., 2006). In a similar pattern, weak cytotoxic activity was exhibited by two cyclopentapeptides, cotteslosins A and B, isolated from an Australian marine-derived *Aspergillus versicolor* MST-MF495 (Fremlin *et al*., 2009). Furthermore, a novel cyclo-pentapeptide, asperpeptide A, was purified from a gorgonian-derived *Aspergillus* sp. XS-20090B15, which was reported to demonstrate prominent antibacterial activity against *Bacillus cereus* and *Staphylococcus epidermidis* with a minimum inhibitory concentration (MIC) of 12.5 µM (Chen *et al*., 2014). Another study documenting the inhibitory activity against Tobacco Mosaic Virus (TMV) infection and replication by novel cyclic pentapeptide malformin A1 recovered from an endophytic *Aspergillus tubingensis* FJBJ11, exhibited IC_{50} of 19.7 µg/mL and 45.4 µg/mL (Tan *et al*., 2015). Similarly, cysteine residue containing malformin E, an analogue of malformin A1, was isolated from the fermented broth of *Aspergillus tamarii* FR02, an endophytic fungus from the roots of *Ficus carica.* Malformin E exhibited strong cytotoxic activity against human breast cancer (MCF-7) and lung cancer (A-549) cell lines with IC_{50} values of 0.65 and 2.42 µM, respectively. It also exhibited significant antimicrobial activities against a panel of gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus),* gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli*), and fungal species such as *Penicillium chrysogenum, Candida albicans, and Fusarium solani* with MIC values spanning between 0.45–7.24 µM (Ma *et al*., 2016). Further, aspergillipeptide D, an antiviral cyclic pentapeptide, was purified from the gorgonian-derived *Aspergillus* sp. SCSIO 41501. The peptide was found to exhibit a potent antiviral effect against HSV-1 in Vero cell line with an IC_{50} of 9.5 µM under their non-cytotoxic concentrations and with 50 % inhibition rate at a concentration of 12.5 µM against acyclovir-resistant clinical isolates of HSV-1-106 and HSV-1-153 (Ma *et al.*, 2017). In the following years, Luo *et al*. (2020) recovered basidiosins A from the mycelial extracts of *Basidiobolus meristosporus* RCEF 4516 isolated from forest soil of the Anhui region of China. The peptide displayed moderate growth inhibitory activity against *Candida albicans* at a higher concentration of 200 µg/ml, thereby indicating their role in providing protection to hosts against fungal infections. Likewise, nine basidiosins - Basidiosins D-L were isolated from the mycelia of *B. meristosporus* RCEF4516, displaying a significant decrease in nitric oxide production among LPS-activated RAW264.7 cells in a dose-dependent fashion. However, Basidiosin J demonstrated more inhibitory effects on α-glucosidase than acarbose (Zhao *et al*., 2023a). In the same year, Pseudoviridinutans A−F (1−7), novel cyclic pentapeptides, were purified from the marine-derived *Aspergillus pseudoviridinutans* TW585, featuring the presence of a rare amino acid, O, β-dimethyltyrosine, by molecular networking-guided isolation. Among these, pseudoviridinutans F modulated NLRP3 and iNOS expression and suppressed LPS-induced NO production (Ding *et al*., 2023).

4.2.5 Cyclic Hexapeptides

Many cyclic hexapeptides with interesting biological activities have garnered significant attention in the past three decades from scientists across the globe. Cycloaspeptide A and pseurotin A are notable examples of cyclic hexapeptides derived from fungal sources. Cycloaspeptide A was first isolated by Kobayashi *et al*. (1987) from an *Aspergillus* species and later delineated from the psychrotolerant *Penicillium ribeum* (Dalsgaard *et al*., 2004). Further research led to the reports of cycloaspeptide A from *Penicillium algidum* recovered from soil under a *Ribes* sp. from the East of Oksestien, Zackenberg, Greenland, with moderate activity against *Plasmodium falciparum* and an IC_{50} of 3.5 µg/ml (Dalsgaard *et al*., 2005). As a continuation of this, two cyclic hexapeptides, cycloaspeptide A and pseurotin A, were purified from *Penicillium janczewskii*, an endophytic fungus associated with the phloem of the Chilean gymnosperm *Prumnopitys andina*. Both peptides displayed low cytotoxicity towards human lung fibroblasts with an $IC_{50} \geq 1000$ µM and intermediate antimicrobial effects, with pseurotin A exhibiting activity against *Erwinia carotovora* and *Pseudomonas syringae* (Schmeda-Hirschmann *et al*., 2008). However, cyclic hexapeptide pseurotin A was previously reported from *Pseudeurotium ovalis* (Bloch & Tamm, 1981) and *Aspergillus fumigatus* as well as from *Pochonia chlamydosporia* var. *catenulata* (Hellwig *et al*., 2003).

The repertoire of cyclic hexapeptides from fungal species was further expanded by the recent discovery of two novel cyclic peptides, guaspertide A and guaspertide B, from mangrove endophytic *Aspergillus* sp. GXNU-4QQY1. Both peptides exhibited promising insecticidal activity against *Citrus psyllid*s, highlighting their potential as an insecticide for agricultural applications (Tan *et al*., 2023). Similarly, recent investigations have unveiled the discovery of six new cyclic hexapeptides, futrines (1–6), purified from the ethyl acetate extract of the wheat pathogen *Fusarium tricinctum* HM76, which was observed to display significant insecticidal activity. However, futrines 2 and 6 exhibited potent insecticidal activities against *Tetranychus cinnabarinus* and *Aphis citricola*, with LC_{50} and LD_{50} values of 0.212 mg/mL and 2.230 ng/nymph, respectively. Moreover, the biosynthetic gene flock, which accounts for the production of futrines was identified through gene knockout studies, rendering valuable insights into their biosynthetic pathways and intensifying their potency for new insecticide development (Ren *et al*., 2024).

4.2.6. Cyclic Heptapeptide and Octapeptide

Three new cyclic heptapeptides, cordyheptapeptides C–E, were isolated from the culture filtrate of marine-derived *Acremonium persicinum* SCSIO 115. Out of these three peptides, cordyheptapeptides C and E demonstrated cytotoxicity against SF-268, MCF-7, and NCI-H460 tumor cell lines with IC_{50} values ranging from 2.5 to 12.1 µM (Chen *et al*., 2012). Furthermore, two cyclic heptapeptides, scytalidamides A and B, were purified from marine *Scytalidium* sp. collected from the Bahamas. Both peptides exhibited moderate cytotoxicity against HCT-116 human colon adenocarcinoma cells, with IC_{50} values of 2.7 µM and 11.0 µM, respectively (Tan *et al*., 2003). Cyclic octapeptides represent a diverse class of fungal metabolites with evident biological activities. Fungisporin was the first cyclic octapeptide secreted by various species of *Penicillium* and *Aspergillus* and was categorized as mycotoxin (Miyao, 1960). Further, shearamide A, another addition to the cyclic octapeptide family, purified from the stromata of *Eupenicillium shearii* exhibited strong insecticidal potential against *Helicoverpa zea* larvae, highlighting its potency for pest control applications (Belofsky *et al*., 1998). In subsequent years, another octapeptide - epichlicin - purified from *Epichloe typhina*, an endophytic fungus of *Phleum pretense* (timothy plant), exhibited potent inhibitory activity against the spore germination of a timothy plant pathogen, *Cladosporium phlei*, with an IC_{50} value of 22 nM

(Seto *et al*., 2007). Another report of octapeptides includes the discovery of two novel compounds, mariannamides A and B, recovered from *Pinus densiflora*-derived *Mariannaea elegans* NBRC102301. However, only mariannamide A was observed to up-regulate the mRNA expression of sirtuin 1 in mouse skeletal muscle myoblast cell line (C2C12 cells) and showed potent antimicrobial activity against *Escherichia coli* and *Cryptococcus neoformans* (Ishiuchi *et al*., 2020). Similarly, broomeanamide A, a novel cyclic octapeptide from fungicolous *Sphaerostilbella broomeana*, exhibited antifungal activity against *Cryptococcus neoformans* and *Candida albicans*, with MIC of 8.0 and 64 µg/mL, respectively (Ekanayake *et al*., 2021). Together, these cyclic hepta and octapeptides underscore the potential of fungal metabolites as indispensable sources for developing bioactive agents with applications ranging from antimicrobial and antifungal therapies to insect pest management.

4.2.7 Decapeptides

In the past decade, several studies have provided strong evidence pertaining to the discovery and characterization of new cyclic peptides from various fungal sources. The group of Grunwald and colleagues reported the discovery of four cyclic decapeptides, auyuittuqamides A–D, purified from *Sesquicillium microsporum* RKAG 186, derived from marine sediments collected in the intertidal zone of Frobisher Bay, Nunavut, Canada. All the peptides demonstrated cytotoxic activity against MCF-7 and HEK cell lines (Grunwald *et al*., 2021). In subsequent years, auyuittuqamides E-H (1-4) were obtained from a soil-derived *Sesquicillium* sp. These peptides contained both d- and l- isomers of N-methylleucine, and a bioinformatics-based analysis disclosed a putative biosynthetic gene cluster (auy), with these peptides showing *in vitro* growth inhibition of *vancomycin-resistant Enterococcus faecium* with MIC values of 8 µg/mL (Xiao *et al*., 2023). In another study, Zhao *et al*. (2023b) reported three new cyclic peptides, meristosporins A–C, from the opportunistic pathogen *Basidiobolus meristosporus*. The biosynthesis of meristosporin A (a hexapeptide) was linked to nonribosomal peptide synthetase gene clusters. Both peptides demonstrated strong cytotoxicity against RAW264.7 and 293T cells, respectively, potentially contributing to fungal pathogenicity in humans. With an aim of boosting the process of discovery of novel and unique bioactive peptides, a targeted genomics and metabolomics approach was used to harness additional cyclopeptides from fungi. Seven cyclopeptides, six of which were new, namely isaridins I–N, were purified from the *Beauveria felina* SYSU-MS7908, a marine-derived fungus. However, out of these seven peptides, only isaridin K displayed the presence of a rare amino acid N-methyl-2-aminobutyric acid residue, and isaridin J was reported to exert a growth inhibitory effect on *Geotrichum citri-aurantii* via destabilizing its cell membrane, thereby emerging as a promising agrochemical fungicide (Jiang *et al*., 2023).

5. Cyclic depsipeptides

Cyclic depsipeptides are a unique class of cyclopeptides where additional ester bonds are present in the peptides along with the usual amide bonds. Numerous cyclodepsipeptides with diverse biological activities, such as antibacterial, antiviral, insecticidal, cytotoxic, and anthelmintic activities, have been recovered from *Aspergillus, Trichoderma, Fusarium* and *Penicillium* (Wang *et al*., 2018). Some classical examples include commercialized cyclic depsipeptides like fusafungine, comprising a blend of enniatins to treat rhinosinusitis (Sy-cordero *et al*., 2012) and emodepside, a semisynthetic derivative of PF1022A, being used as an anthelmintic agent (Sasaki *et al.*, 1992). Two depsipeptides, namely 1962A and B, were purified from the culture filtrate of an endophytic fungus 1962 inhabiting the leaves of *Kandelia candel* from Hong Kong. Both depsipeptides shared a structural similarity in terms of having at least one D-amino acid. However, of the two, only 1962A was observed to

demonstrate weak cytotoxicity against MCF-7 human breast cancer cell line in the *in vitro* MTT assay (Huang *et al*., 2007). Further studies in this domain revealed the discovery of a novel CDP, cordycommunin, from the insect-pathogenic *Ophiocordyceps communis* BCC 16475 with strong growth inhibitory effects on *Mycobacterium tuberculosis* H37Ra (MIC-15 µM) and weak cytotoxic activity, with IC_{50} of 45 µM in KB cells (Haritakun *et al*., 2010). Studies documenting the antibacterial potential of already reported CDPs, halobacillin and PF1022F from *Trichoderma asperellum,* an endophytic fungus of *Panax notoginseng* (Ding *et al*., 2012) and immuosupperssive effects of trichomides A and B, purified from *Trichothecium roseum,* by modulating the Bcl-2 and Bax expression profiling (Zhang *et al*., 2013), spurred the research sector in its exploration of fungi for bioactive peptides or their derivatives. A molecular networking strategy led to the discovery of xylaroamide A from an endolichenic *Xylaria* sp. with promising cytotoxic activity against BT-549 and RKO cancer cell lines with IC_{50} values of 2.5 and 9.5 µM, respectively (Luo *et al*., 2022). Apart from the cyclic depsipeptides, several reports on cyclic tridepsipeptides, pentadepsipeptides, and hexadepsipeptides state that they account for approximately 350 CDPs from fungi only. Cyclic tridepsipeptides, such as colletopeptides A–D, a group of hybrid peptide-polyketide, were purified from *Colletotrichum* sp. S8 isolated from a stem of *Rubia podantha.* All four hybrid peptides exhibited potent anti-inflammatory potential by downregulating the LPS-induced nitric oxide production in RAW264.7 macrophages with IC_{50} values ranging between 8.3 and 38.7 µM (Feng *et al*., 2019). Furthermore, aspertides A–E, which are cyclic pentadepsipeptides, were isolated from marine-derived *Aspergillus tamarii* and *Aspergillus insuetus*. Among these five peptides, only aspertide D and E demonstrated activity against aquatic pathogens like *Edwardsiella tarda* and *Vibrio* sp., with MIC values of 8–32 µg/mL (Chi *et al*., 2023). Similarly, there were a few reports documenting the bioactivity of hexadepsipeptides from fungal species inhabiting diverse natural habitats. Two antimalarial cyclohexadepsipeptides, Hirsutatins A and B, isolated from *Hirsutella nivea* BCC 2594, restricted the growth of malarial parasite *Plasmodium falciparum K1* with an IC_{50} value of 5.8 µg/mL, by deploying hirsutatin B (Isaka *et al*., 2005). Similarly, paecilodepsipeptide A from *Paecilomyces cinnamomeus* exhibited better antimalarial activity against *P. falciparum* K1 with IC_{50} of 4.9 µM as compared to hirsutatin B, along with cytotoxic activity against KB and BC cancer cell lines (Isaka *et al*., 2007). Another important hexadepsipeptide includes pullularins E from *Bionectria ochroleuca,* recovered from the leaf part of *Sonneratia caseolaris* (Sonneratiaceae) found on Hainan Island (China). Pullularin E exhibited cytotoxic effects against mouse lymphoma cells with IC_{50} of 0.1-6.7 µg/ml (Ebrahim *et al*., 2012). Lastly, ethyl acetate extract of *Aspergillus japonicus,* a marine sponge-derived fungus, led to the purification of japonamides A and B with potent synergistic antifungal effects when combined with fluconazole, ketoconazole, or rapamycin, significantly lowering their MIC values (Wang *et al*., 2022). These findings highlight the therapeutic potential of CDPs in combating fungal infections and other diseases.

6. Cyclic Lipopeptides

Cyclic lipopeptides are a unique class of compounds in which amino acids are linked with one or more fatty acid chains in the stable cyclic form. These lipopeptides, demonstrating a range of biological activities, are reported to come from numerous microorganisms, especially fungi. Cyclic lipopeptides and related compounds isolated from fungal species have been observed to display diverse biological activities and ecological roles. The lipopeptide echinocandin A was purified from *Cryptosporiopsis* sp. and *Pezicula* sp., endophytic fungi from *Pinus sylvestris* and *Fagus sylvatica*, respectively. The lipopeptide was observed to display antimicrobial potential against certain yeasts (Noble *et al*., 1991). Two cyclic lipopeptides, namely, fusaristatins A and B, purified from rice cultures of *Fusarium* sp. YG-45 were reported to

demonstrate moderate inhibition of topoisomerases I and II with IC_{50} values of 73 µM and 98 µM, respectively. In addition, both of these lipopeptides also inhibit the growth of LU 65 lung cancer cells with IC_{50} values of 23 µM and 7 µM, respectively (Shiono *et al*., 2007). Similarly, a study reported the isolation of fusaristatin A was also reported from *Fusarium decemcellulare* LG53, an endophyte inhabiting *Mahonia fortunei*. Interestingly, fusaristatin A was observed to exert allelopathic effects on another endophyte, *Glomerella acutata* LG52, pointing towards the mechanism of balanced antagonism between co-inhabiting endophytes (Li *et al*., 2016). Another study reported the isolation of three antimicrobial peptides from *Emericellopsis alkalina* strain A118, which were classified as nonribosomal membrane-active peptaibols. Among these peptaibols, A118-37 displayed significant antifungal activity against *Candida albicans, Aspergillus niger,* and clinical fungal isolates of *mycosis* pathogens, including multidrug-resistant strains (Baranova *et al*., 2019).

7. Peptide Antibiotics

Fungi are also considered to be a prolific source of peptide antibiotics with bio-active attributes, immunomodulatory, anticancer, and antimicrobial, etc. Alamethicin is the first antibiotic peptide isolated from *Trichoderma viride,* containing 20 amino acid residues (Meyer & Reusser, 1967). Afterwards, leucinostatins, another class of peptide antibiotics, were isolated from endophytic *Acremonium* sp. inhabiting *Taxus baccata*, and they demonstrated clear antifungal-anticancer properties. Among these, leucinostatin A was found to display significant antifungal activity against *Pythium ultimum* with $IC_{50} < 1$ µM and potent cytotoxicity against human cancer cell lines, such as BT-20 breast cancer cells with $IC_{50} = 2.3$ nM (Strobel *et al*., 1997). The first defensin isolated from fungi was plectasin, a defensin protein isolated from *Pseudoplectania nigrella* recovered from the Northern-Europe Pine Forest area (Mygind *et al*., 2005), which was found to exhibit a promising antibacterial activity profile comparable to that of penicillin and vancomycin against *Streptococcus pneumoniae* (Schneider *et al*., 2010). Similarly, 17 fungal defensin-like peptides were also purified from *Microsporum canis.* These were observed to demonstrate antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (Zhu *et al*., 2012). A novel cyclic nonapeptide, amanexitide, was isolated from *Amanita exitialis,* a toxic mushroom endemic to China. The structural characteristics of amanexitide were found to display close resemblance with antamanide, a cyclic decapeptide with antidotal activity against amatoxins, indicating its potential protective role against toxin-induced damage (Xue *et al*., 2011). Furthermore, leucinostatin A, a linear nonapeptide also known as Antibiotic P168, exhibits reasonable activity against *Candida albicans* and *Cryptococcus neoformans.* Liposome-encapsulated leucinostatin A formulations have also been explored to intensify therapeutic efficacy and less toxicity, achieving a 15-fold reduction in LD_{50} in mice (Ricci *et al*., 2015). Similarly, a related compound, leucinostatin Y, was purified from *Purpureocillium lilacinum*. It has exhibited preferential cytotoxicity towards cancer cells in the absence of glucose and repressed mitochondrial function in pancreatic cancer cells, highlighting the importance of its C-terminal structure (Momose *et al*., 2019). Furthermore, Emericellipsin A, a novel peptide antibiotic recovered from the alkalophilic *Emericellopsis alkalina,* displays potent antifungal activity against *Candida albicans, Aspergillus niger* and multidrug-resistant fungal pathogens. It has also exhibited selective cytotoxicity against tumor cell lines such as Hep G2 and HeLa cells (Rogozhin *et al*., 2018). Further studies led to the discovery of additional homologs, emericellipsins B–E, from specialized alkaline culture conditions, which displayed exclusive anticancer properties, validating them as promising candidates for treating invasive mycoses and drug-resistant fungal infections (Kuvarina *et al*., 2021). Collutellin A, an antifungal peptide from *Colletotrichum dematium,* inhibits plant pathogens such as *Botrytis cinerea* and

Sclerotinia sclerotiorum with a MIC value of 3.6 µg/mL. It also suppressed CD4+ T-cell activation and interleukin-2 production (Ren *et al*., 2008).

8. Linear Peptaibols

Two novel lipopeptaibols, tolypocaibols A and B, were purified from *Tolypocladium* sp. a marine algal endophyte. The purified lipopeptaibols were found to be comprised of 11 amino acid residues with a valinol C-terminus and an N-terminal decanoyl chain. Both lipopeptaibols demonstrated selective activity against gram-positive and acid-fast bacteria (Morehouse *et al*., 2023). Along the same lines, seven 18-residue peptaibols, trichorzins A–G, isolated from *Trichoderma* sp. derived from sponges, exhibited potent cytotoxic effects on human carcinoma cell lines with IC_{50} value of 0.46–4.7 µM (Lin *et al*., 2023).

9. Amino acid composition analysis of linear and cyclic peptides

A comparative amino acid composition analysis between linear and cyclic peptides was done based on the predominance and ratio of hydrophobic versus hydrophilic residues, the existence of unusual or modified residues, and the occurrence of non-proteinogenic or rare amino acids. This compositional analysis elucidated both shared and unique structural characteristics between linear and cyclic peptides of fungal origin. Cyclic peptides such as futrines, pullularins, auyuittuqamides, argadin, pseudoviridinutans, and asperopiperazine displayed rich predominance of hydrophobic residues—notably leucine, isoleucine, phenylalanine, valine, and alanine—in contrast to their linear counterparts. The higher hydrophobic content and under-representation of hydrophillic residues such as serine, arginine, and asparagine are significantly contributing to membrane permeability, target interaction, bioavailability, and metabolic stability, attributes frequently reinforced by the rigid cyclic backbone (Biron *et al.,* 2008; Hoang *et al.,* 2021). Interestingly, many cyclic peptides also comprise unique or chemically modified amino acid residues such as N-methylated residue, for example, N-methylleucine in auyuittuqamides, α-aminoisobutyric acid, hydroxylated proline in asperopiperazine B and D-amino acids, for example in argifin, which augment resistance to proteolysis and target selectivity (Lucana *et al.*, 2021; Feng and Xu, 2016). However, a few peptides, such as argadin and colletopeptides, incorporate rare amino acids like anthranilic acid and homoserine, being responsible for their unique folding and bioactivity. The abundance of cyclic conformations among natural bioactive peptides, particularly hexapeptides and octapeptides, affirms nature's preference for conformational constraint as a strategy for bioactivity optimization. In contrast, linear peptides such as penilumamides, aspergillipeptides, and leucinostatins also incorporate hydrophobic amino acid residue; nonetheless, they typically display a more balanced composition, diversified with mixture of polar and charged amino acids such as serine, threonine, glutamine, asparagine. This variegated arrangement may obstruct membrane diffusion alongside enhancing aqueous solubility and alleviating engagement with intracellular signaling molecules (Hitchner *et al*., 2021; Schifano & Caputo, 2022). While linear peptides also encompass N-methylations and D-amino acid residues, for example, in penilumamides and leucinostatins, to improve their pharmacological profiles, such attributes are more sporadic and less structurally integrated as compared to cyclic analogs. Henceforth, the strong correlation between cyclic backbone, high hydrophobicity, and the presence of atypical and rare amino acid residues suggests an evolutionary adaptation of fungal biosynthetic pathways towards chemically stable and diverse peptide frameworks (Jwad *et al*., 2020; D'Amato, 2022).

Apart from these bioactive classes, numerous inactive peptides belonging to different categories have also been reported from fungal sources (Table 2). Although these peptides may

not display proximate bioactivity, they possess immense potential for further drug development through peptide modification strategies. By employing sophisticated peptide engineering techniques such as site-directed mutagenesis, incorporation of unusual/rare amino acids, or cyclization, chemical conjugation leading to the formation of peptidomimetics offers opportunities for the transformation of inactive peptides into bioactive entities with enhanced stability, specificity, and pharmacokinetic properties (Lee & Poh, 2023). Therefore, peptidomimetics, acting as intermediaries, bridge the gap between peptides and small molecules, showcasing the immense potential of optimizing peptides to develop novel therapeutics (Han *et al*., 2024b). This development has been majorly exemplified by milestones such as captopril, an ACE inhibitor, initially derived from snake venom teprotide, which became the first example of peptide modification into a clinically successful small molecule (Smith & Vane, 2003). Similarly, Pfizer developed Parecoxib, initially a peptide-based COX-2 inhibitor, via a similar peptide modification approach, thereby further highlighting this strategy's ability to enhance pharmacokinetics and bioavailability and ushering peptide-derived small molecules into the therapeutic mainstream (Dalpiaz & Peterson, 2004; Han *et al*., 2024b). Harnessing the potential of these peptides will not only expand the compendium of chemical diversity of therapeutic agents but will also fortify the importance of fungal biodiversity in contributing to novel peptide-based solutions for modern medicine.

Table 2: List of fungal-derived inactive peptides, their classification along with source with potential for bioactivity through peptide modification

S. No.	Peptide Name	Peptide chain length	Source organism	Host Plant/Source	Reference
Linear Peptides					
1.	Penilumamides (B-D)	-	*Aspergillus* sp. XS-20090B15	Gorgonia	Chen *et al*. (2014)
2.	Pullularin F	-	*Bionectria ochroleuca*	*Sonneratia caseolaris*	Ebrahim *et al*. (2012)
3.	Aspergillipeptides F	Tetrapeptide	*Aspergillus* sp. SCSIO 41501	Marine gorgonian	Ma *et al*. (2017)
4.	Aspergillipeptides G	Tetrapeptide	*Aspergillus* sp. SCSIO 41501	Marine gorgonian	Ma *et al*. (2017)
5.	Coniosulfide E	Linear	*Aspergillus unguis IV17-109*	Deep-sea shrimp	Anh et al. (2022)
Cyclic peptides					
6.	Versicotide C	Hexapeptide	*Aspergillus versicolor* ZLN-60	Marine	Peng *et al*. (2014)
7.	Hirsutide	Tetrapeptide	*Hirsutella* sp.	Infected spider	Lang *et al*. (2005)
8.	cyclo-(L-Val-L-Leu-L-Val-L-Leu)	Tetrapeptide	Endophytic fungus #2221	*Castaniopsis fissa*	Yin et al. (2005)

9.	cyclo-(L-Leu-L-Ala-L-Leu-L-Ala)	Tetrapeptide	Endophytic fungus #2221	*Castaniopsis fissa*	Yin *et al*. (2005)
10.	Cyclo-(l-Leu-l-Leu-d-Leu-l-Leu-l-Ile)	Pentapeptide	*Fusarium decemcellulare* LG53	*Mahonia fortunei*	Li *et al*. (2016)
11.	Cyclo-(l-Leu-l-Leu-d-Leu-l-Leu-l-Val)	Pentapeptide	*Fusarium decemcellulare* LG53	*Mahonia fortunei*	Li *et al*. (2016)
12.	Cyclo-(l-Leu-l-Leu-d-Leu-l-Leu-l-Leu)	Pentapeptide	*Fusarium decemcellulare* LG53	*Mahonia fortunei*	Li *et al*. (2016)
13.	MBJ-0173	Pentapeptide	*Mortierella alpina* f28740	soil sample, Japan	Kawahara *et al*. (2017)
14.	MBJ-0174	Pentapeptide	*Mortierella alpina* f28740	soil sample, Japan	Kawahara *et al*. (2017)
15.	Basidiosin A	Pentapeptide	*Basidiobolus meristosporus* RCEF 4516	forest soil in Anhui Province (China)	Luo *et al*. (2020)
16.	Cyclo(Hyp-XleXle-Ala-Thr-Xle) (1–4)	Hexapeptide	*Fusarium solani* N06	*Narcissus tazetta*	Wang *et al*. (2015)
17.	cyclo(Dhp-Xle-Xle-Ala-ThrXle) (5)	Hexapeptide	*Fusarium solani* N06	*Narcissus tazetta*	Wang *et al*. (2015)
18.	cyclo(Hyp-Xle-Xle-Val-Thr-Xle) (6–8)	Hexapeptide	*Fusarium solani* N06	*Narcissus tazetta*	Wang *et al*. (2015)
19.	cyclo(Dhp-Xle-Xle-Val-Thr-Xle)	Hexapeptide	*Fusarium solani* N06	*Narcissus tazetta*	Wang *et al*. (2015)
20.	Unguisin E and F	Heptapeptide	Endophytic *Mucor irregularis*	*Moringa stenopetala*	Akone *et al*. (2016)
21.	Unguisin C	Heptapeptide	*Emericella unguis* M90A-2	Marine (Paria Bay, Venezuela)	Malmstrom *et al*. (2002)
22.	Unguisin J	Heptapeptide	*Aspergillus heteromorphus* CBS 117.55	Purchased from ARS Culture Collection	Neupane *et al*. (2024)
23.	Unguisins A and B	Heptapeptide	*Aspergillus violaceofuscus* CBS 115571	-	Wei *et al*. (2023)
24.	Sinulariapeptide F	Cylic	*Simplicillium* sp. SCSIO 41222	*Sinularia* sp., a soft coral from Yongxing Island, South China Sea	He *et al.,* (2025)

25.	Asperigimycin B	Ribosomally synthesized and post-translationally modified peptides (RiPPs)-Cyclic heptapeptide	*Aspergillus* sp.		Nie *et al.,* (2025)

10. Conclusion

Fungi are highly adaptive and complex microorganisms and represent a rich source of diverse bioactive peptides with tremendous potential for pharmaceutical and biotechnological applications. These peptides, viz. linear, cyclic, lipopeptides, peptide antibiotics, with their unique structural and functional attributes, demonstrated significant antimicrobial, anticancer, immunosuppressive, and antifungal properties, among other therapeutic activities. This diversity validates the importance of fungi as a sustainable and versatile source for natural product discovery. Future prospects in this field encompass investigating the enormous, mostly untapped fungal biodiversity to identify novel peptide scaffolds. Deployment of advanced technologies such as genomics, metabolomics, and machine learning-based drug discovery may play a crucial role in unraveling and optimizing fungal peptides. Furthermore, chemical and synthetic biology approaches for transforming peptides into small-molecule drugs can enable the fine-tuning of fungal peptides in order to meet specific therapeutic needs.

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Declaration on conflict of interest

There is no conflict of interest.

References

Akbarian, M., Khani, A., Eghbalpour, S., & Uversky, V. N. (2022). Bioactive peptides: Synthesis, sources, applications, and proposed mechanisms of action. *International Journal of Molecular Sciences, 23*(3), 1445. https://doi.org/10.3390/ijms23031445

Akone, S. H., Daletos, G., Lin, W., & Proksch, P. (2016). Unguisin F, a new cyclic peptide from the endophytic fungus *Mucor irregularis*. *Zeitschrift für Naturforschung C: Journal of Biosciences, 71*(1–2), 15–19. https://doi.org/10.1515/znc-2015-0137

Almeida, C., El Maddah, F., Kehraus, S., Schnakenburg, G., & König, G. M. (2016). Endolides A and B, vasopressin and serotonin-receptor interacting N-methylated peptides from the sponge-derived fungus *Stachylidium* sp. *Organic Letters, 18*(3), 528–531. https://doi.org/10.1021/acs.orglett.5b03553

Anand, U., Bandyopadhyay, A., Jha, N. K., Pérez de la Lastra, J. M., & Dey, A. (2023). Translational aspect in peptide drug discovery and development: An emerging therapeutic candidate. *BioFactors (Oxford, England), 49*(2), 251–269. https://doi.org/10.1002/biof.1913

Anh, C. V., Yoon, Y. D., Kang, J. S., Lee, H.-S., Heo, C.-S., & Shin, H. J. (2022). Nitrogen-containing secondary metabolites from a deep-sea fungus *Aspergillus unguis* and their anti-inflammatory activity. *Marine Drugs, 20*(3), 217. https://doi.org/10.3390/md20030217

Anjum, K., Huang, X., Zhou, L., Zhu, T., Che, Q., Zhang, G., & Li, D. (2024). New cyclic dipeptide discovered from deep-sea derived *Aspergillus* sp. HDN20-1401. *Natural Product Research, 38*(18), 3231–3236. https://doi.org/10.1080/14786419.2023.2227754

Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet, 399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0

Arai, N., Shiomi, K., Iwai, Y., & Omura, S. (2000a). Argifin, a new chitinase inhibitor, produced by *Gliocladium* sp. FTD-0668. II. Isolation, physico-chemical properties, and structure elucidation. *The Journal of Antibiotics, 53*(6), 609–614. https://doi.org/10.7164/antibiotics.53.609

Arai, N., Shiomi, K., Yamaguchi, Y., Masuma, R., Iwai, Y., Turberg, A., Kölbl, H., & Omura, S. (2000b). Argadin, a new chitinase inhibitor, produced by *Clonostachys* sp. FO-7314. *Chemical & Pharmaceutical Bulletin, 48*(10), 1442–1446. https://doi.org/10.1248/cpb.48.1442

Baranova, A. A., Rogozhin, E. A., Georgieva, M. L., Bilanenko, E. N., Kul'ko, A. B., Yakushev, A. V., Alferova, V. A., & Sadykova, V. S. (2019). Antimicrobial peptides produced by alkaliphilic fungi *Emericellopsis alkalina*: Biosynthesis and biological activity against pathogenic multidrug-resistant fungi. *Applied Biochemistry and Microbiology, 55*, 145–151.

Belofsky, G. N., Gloer, J. B., Wicklow, D. T., & Dowd, P. F. (1998). Shearamide A: A new cyclic peptide from the ascostromata of *Eupenicillium shearii*. *Tetrahedron Letters, 39*(31), 5497–5500. https://doi.org/10.1016/S0040-4039(98)01161-7

Biron, E., Chatterjee, J., Ovadia, O., Langenegger, D., Brueggen, J., Hoyer, D., Schmid, H. A., Jelinek, R., Gilon, C., Hoffman, A., & Kessler, H. (2008). Improving oral bioavailability of peptides by multiple N-methylation: somatostatin analogues. *Angewandte Chemie (International ed. in English)*, 47(14), 2595–2599. https://doi.org/10.1002/anie.200705797

Bloch, P., & Tamm, C. (1981). Isolation and structure of pseurotin A, a microbial metabolite of *Pseudeurotium ovalis* STOLK with an unusual heterospirocyclic system. *Helvetica Chimica Acta, 64*(2), 304–315. https://doi.org/10.1002/hlca.19810640131

Buckton, L. K., Rahimi, M. N., & McAlpine, S. R. (2021). Cyclic Peptides as Drugs for Intracellular Targets: The Next Frontier in Peptide Therapeutic Development. *Chemistry (Weinheim an der Bergstrasse, Germany)*, 27(5), 1487–1513. https://doi.org/10.1002/chem.201905385

Chen, M., Shao, C. L., Fu, X. M., Kong, C. J., She, Z. G., & Wang, C. Y. (2014). Lumazine peptides penilumamides B-D and the cyclic pentapeptide asperpeptide A from a gorgonian-derived *Aspergillus* sp. fungus. *Journal of Natural Products, 77*(7), 1601–1606. https://doi.org/10.1021/np5001686

Chen, S., Liu, D., Wang, L., Fan, A., Wu, M., Xu, N., Zhu, K., & Lin, W. (2025). Marine-derived new peptaibols with antibacterial activities by targeting bacterial membrane phospholipids. *Acta Pharmaceutica Sinica B, 15*(5), 2764–2777. https://doi.org/10.1016/j.apsb.2025.02.036

Chen, Z., Song, Y., Chen, Y., Huang, H., Zhang, W., & Ju, J. (2012). Cyclic heptapeptides, cordyheptapeptides C-E, from the marine-derived fungus *Acremonium persicinum* SCSIO 115 and their cytotoxic activities. *Journal of Natural Products, 75*(6), 1215–1219. https://doi.org/10.1021/np300152d

Chi, L. P., Liu, D., Li, X. M., Wan, Y., Wang, B. G., & Li, X. (2023). Aspertides A–E: Antimicrobial pentadepsipeptides with a unique p-methoxycinnamoyl amide group

from the marine isolates *Aspergillus tamarii* MA-21 and *Aspergillus insuetus* SD-512. *Journal of Agricultural and Food Chemistry, 71*(36), 13316–13324. https://doi.org/10.1021/acs.jafc.3c02610

Chomcheon, P., Wiyakrutta, S., Aree, T., Sriubolmas, N., Ngamrojanavanich, N., Mahidol, C., Ruchirawat, S., & Kittakoop, P. (2010). Curvularides A–E: Antifungal hybrid peptide–polyketides from the endophytic fungus *Curvularia geniculata*. *Chemistry – A European Journal, 16*(37), 11178–11185. https://doi.org/10.1002/chem.201000652

Costa, L., Sousa, E., & Fernandes, C. (2023). Cyclic Peptides in Pipeline: What Future for These Great Molecules?. *Pharmaceuticals* (Basel, Switzerland), 16(7), 996. https://doi.org/10.3390/ph16070996

Cui, H. B., Mei, W. L., Miao, C. D., Lin, H. P., Hong, K., & Dai, H. F. (2008). Antibacterial constituents from the endophytic fungus *Penicillium* sp. 0935030 of mangrove plant *Acrostichum aureurm*. *Chinese Journal of Antibiotics, 33*(7), 407–410.

Dalpiaz, A. S., & Peterson, D. (2004). Parecoxib: A shift in pain management? *Expert Review of Neurotherapeutics, 4*(2), 165–177. https://doi.org/10.1586/14737175.4.2.165

Dalsgaard, P. W., Larsen, T. O., Frydenvang, K., & Christophersen, C. (2004). Psychrophilin A and cycloaspeptide D, novel cyclic peptides from the psychrotolerant fungus *Penicillium ribeum*. *Journal of Natural Products, 67*(5), 878–881. https://doi.org/10.1021/np0303714

Dalsgaard, P. W., Larsen, T. O., & Christophersen, C. (2005). Bioactive cyclic peptides from the psychrotolerant fungus *Penicillium algidum*. *The Journal of Antibiotics, 58*(2), 141–144. https://doi.org/10.1038/ja.2005.16

D'Amato, A. (2022). Structure–bioactivity relationship in cyclic peptoids: An overview. *European Journal of Organic Chemistry*, 2022(21), e202200665. https://doi.org/10.1002/ejoc.202200665

Ding, G., Chen, A. J., Lan, J., Zhang, H., Chen, X., Liu, X., & Zou, Z. (2012). Sesquiterpenes and cyclopeptides from the endophytic fungus *Trichoderma asperellum* Samuels, Lieckf. & Nirenberg. *Chemistry & Biodiversity, 9*(6), 1205–1212. https://doi.org/10.1002/cbdv.201100185

Ding, W., Tian, D., Chen, M., Xia, Z., Tang, X., Zhang, S., Wei, J., Li, X., Yao, X., Wu, B., & Tang, J. (2023). Molecular networking-guided isolation of cyclopentapeptides from the hydrothermal vent sediment derived fungus *Aspergillus pseudoviridinutans* TW58-5 and their anti-inflammatory effects. *Journal of Natural Products, 86*(8), 1919–1930. https://doi.org/10.1021/acs.jnatprod.3c00287

Du, L., Haldar, S., King, J. B., Mattes, A. O., Srivastava, S., Wendt, K. L., You, J., Cunningham, C., & Cichewicz, R. H. (2023). Persephacin is a broad-spectrum antifungal aureobasidin metabolite that overcomes intrinsic resistance in *Aspergillus fumigatus*. *Journal of Natural Products, 86*(8), 1980–1993. https://doi.org/10.1021/acs.jnatprod.3c00382

Du, L., Risinger, A. L., King, J. B., Powell, D. R., & Cichewicz, R. H. (2014). A potent HDAC inhibitor, 1-alaninechlamydocin, from a *Tolypocladium* sp. induces G2/M cell cycle arrest and apoptosis in MIA PaCa-2 cells. *Journal of Natural Products, 77*(7), 1753–1757. https://doi.org/10.1021/np500387h

Ebada, S. S., Fischer, T., Hamacher, A., Du, F. Y., Roth, Y. O., Kassack, M. U., Wang, B. G., & Roth, E. H. (2014). Psychrophilin E, a new cyclotripeptide, from co-fermentation of two marine alga-derived fungi of the genus *Aspergillus*. *Natural Product Research, 28*(11), 776–781. https://doi.org/10.1080/14786419.2014.880911

Ebrahim, W., Kjer, J., El Amrani, M., Wray, V., Lin, W., Ebel, R., Lai, D., & Proksch, P. (2012). Pullularins E and F, two new peptides from the endophytic fungus *Bionectria*

ochroleuca isolated from the mangrove plant *Sonneratia caseolaris*. *Marine Drugs, 10*(5), 1081–1091. https://doi.org/10.3390/md10051081

Ekanayake, D. I., Perlatti, B., Swenson, D. C., Põldmaa, K., Bills, G. F., & Gloer, J. B. (2021). Broomeanamides: Cyclic octapeptides from an isolate of the fungicolous ascomycete *Sphaerostilbella broomeana* from India. *Journal of Natural Products, 84*(7), 2028–2034. https://doi.org/10.1021/acs.jnatprod.1c00414

Feng, Z., & Xu, B. (2016). Inspiration from the mirror: D-amino acid containing peptides in biomedical approaches. *Biomolecular concepts,* 7(3), 179–187. https://doi.org/10.1515/bmc-2015-0035

Feng, L., Wang, J., Liu, S., Zhang, X. J., Bi, Q. R., Hu, Y. Y., Wang, Z., & Tan, N. H. (2019). Colletopeptides A–D, anti-inflammatory cyclic tridepsipeptides from the plant endophytic fungus *Colletotrichum* sp. S8. *Journal of Natural Products, 82*(6), 1434–1441. https://doi.org/10.1021/acs.jnatprod.8b00829

Fernández-Pastor, I., González-Menéndez, V., Annang, F., Toro, C., Mackenzie, T. A., Bosch-Navarrete, C., Genilloud, O., & Reyes, F. (2021). Pipecolisporin, a novel cyclic peptide with antimalarial and antitrypanosome activities from a wheat endophytic *Nigrospora oryzae*. *Pharmaceuticals, 14*(3), 268. https://doi.org/10.3390/ph14030268

Fetse, J., Kandel, S., Mamani, U. F., & Cheng, K. (2023). Recent advances in the development of therapeutic peptides. *Trends in Pharmacological Sciences, 44*(7), 425–441. https://doi.org/10.1016/j.tips.2023.04.003

Fremlin, L. J., Piggott, A. M., Lacey, E., & Capon, R. J. (2009). Cottoquinazoline A and cotteslosins A and B, metabolites from an Australian marine-derived strain of *Aspergillus versicolor*. *Journal of Natural Products, 72*(4), 666–670. https://doi.org/10.1021/np800777f

GBD (2021). Institute for Health Metrics and Evaluation (IHME). *Global Burden of Disease 2021: Findings from the GBD 2021 Study*. Seattle, WA: IHME, 2024.

Grunwald, A. L., Cartmell, C., & Kerr, R. G. (2021). Auyuittuqamides A-D, cyclic decapeptides from *Sesquicillium microsporum* RKAG 186 isolated from Frobisher Bay sediment. *Journal of Natural Products, 84*(1), 56–60. https://doi.org/10.1021/acs.jnatprod.0c00966

Gu, W., Cueto, M., Jensen, P. R., Fenical, W., & Silverman, R. B. (2007). Microsporins A and B: New histone deacetylase inhibitors from the marine-derived fungus *Microsporum* cf. *gypseum* and the solid-phase synthesis of microsporin A. *Tetrahedron, 63*, 6535–6541.

Guo, H., Kreuzenbeck, N. B., Otani, S., Garcia-Altares, M., Dahse, H. M., Weigel, C., Aanen, D. K., Hertweck, C., Poulsen, M., & Beemelmanns, C. (2016). Pseudoxylallemycins A-F, cyclic tetrapeptides with rare allenyl modifications isolated from *Pseudoxylaria* sp. X802: A competitor of fungus-growing termite cultivars. *Organic Letters, 18*(14), 3338–3341. https://doi.org/10.1021/acs.orglett.6b01437

Gurevich, E. V., & Gurevich, V. V. (2014). Therapeutic potential of small molecules and engineered proteins. *Handbook of Experimental Pharmacology, 219*, 1–12. https://doi.org/10.1007/978-3-642-41199-1_1

Han, J. S., Kim, E.-S., Cho, Y. B., Kim, S. Y., Lee, M. K., Hwang, B. Y., & Lee, J. W. (2024a). Cytotoxic peptaibols from *Trichoderma guizhouense*, a fungus isolated from an urban soil sample. *Journal of Natural Products, 87*(8), 1994–2003. https://doi.org/10.1021/acs.jnatprod.4c00438

Han, Z., Shen, Z., Pei, J., You, Q., Zhang, Q., & Wang, L. (2024b). Transformation of peptides to small molecules in medicinal chemistry: Challenges and opportunities. *Acta Pharmaceutica Sinica B, 14*(10), 4243–4265. https://doi.org/10.1016/j.apsb.2024.06.019

Haritakun, R., Sappan, M., Suvannakad, R., Tasanathai, K., & Isaka, M. (2010). An antimycobacterial cyclodepsipeptide from the entomopathogenic fungus *Ophiocordyceps communis* BCC 16475. *Journal of Natural Products, 73*(1), 75–78. https://doi.org/10.1021/np900520b

He, Y. C., Wang, M. Q., Tie, Q. Q., et al. (2025). Sinulariapeptide F, a new peptide from culture broth of marine-derived fungus *Simplicillium* sp. SCSIO 41222. *Journal of Antibiotics, 78*, 64–67. https://doi.org/10.1038/s41429-024-00780-w

Hellwig, V., Mayer-Bartschmid, A., Müller, H., Greif, G., Kleymann, G., Zitzmann, W., Tichy, H.-V., & Stadler, M. (2003). Pochonins A−F, new antiviral and antiparasitic resorcylic acid lactones from *Pochonia chlamydosporia* var. *catenulata*. *Journal of Natural Products, 66*(6), 829–837. https://doi.org/10.1021/np020556v

Hitchner, M.A., Necelis, M.R., Shirley, D. et al. Effect of Non-natural Hydrophobic Amino Acids on the Efficacy and Properties of the Antimicrobial Peptide C18G. *Probiotics & Antimicro. Prot.* 13, 527–541 (2021). https://doi.org/10.1007/s12602-020-09701-3

Hoang, H. N., Hill, T. A., & Fairlie, D. P. (2021). Connecting hydrophobic surfaces in cyclic peptides increases membrane permeability. *Angewandte Chemie International Edition, 60*(15), 8385–8390. https://doi.org/10.1002/anie.202012643

Huang, H., She, Z., Lin, Y., Vrijmoed, L. L., & Lin, W. (2007). Cyclic peptides from an endophytic fungus obtained from a mangrove leaf (*Kandelia candel*). *Journal of Natural Products, 70*(11), 1696–1699. https://doi.org/10.1021/np0605891

Isaka, M., Palasarn, S., Lapanun, S., & Sriklung, K. (2007). Paecilodepsipeptide A, an antimalarial and antitumor cyclohexadepsipeptide from the insect pathogenic fungus *Paecilomyces cinnamomeus* BCC 9616. *Journal of Natural Products, 70*(4), 675–678. https://doi.org/10.1021/np060602h

Isaka, M., Palasarn, S., Sriklung, K., & Kocharin, K. (2005). Cyclohexadepsipeptides from the insect pathogenic fungus *Hirsutella nivea* BCC 2594. *Journal of Natural Products, 68*(11), 1680–1682. https://doi.org/10.1021/np050246n

Ishiuchi, K., Hirose, D., Kondo, T., Watanabe, K., Terasaka, K., & Makino, T. (2020). Mariannamides A and B, new cyclic octapeptides isolated from *Mariannaea elegans* NBRC102301. *Bioorganic and Medicinal Chemistry Letters, 30*(4), Article 126946. https://doi.org/10.1016/j.bmcl.2019.126946

Itazaki, H., Nagashima, K., Sugita, K., Yoshida, H., Kawamura, Y., Yasuda, Y., Matsumoto, K., Ishii, K., Uotani, N., & Nakai, H. (1990). Isolation and structural elucidation of new cyclotetrapeptides, trapoxins A and B, having detransformation activities as antitumor agents. *The Journal of Antibiotics, 43*(12), 1524–1532. https://doi.org/10.7164/antibiotics.43.1524

Jiang, M., Chen, S., Lu, X., Guo, H., Chen, S., Yin, X., Li, H., Dai, G., & Liu, L. (2023). Integrating genomics and metabolomics for the targeted discovery of new cyclopeptides with antifungal activity from a marine-derived fungus *Beauveria felina*. *Journal of Agricultural and Food Chemistry, 71*(25), 9782–9795. https://doi.org/10.1021/acs.jafc.3c02415

Jwad, R., Weissberger, D., & Hunter, L. (2020). Strategies for fine-tuning the conformations of cyclic peptides. *Chemical Reviews*, 120(17), 9743–9789. https://doi.org/10.1021/acs.chemrev.0c00013

Karásek, D. (2022). Orální semaglutid - Rybelsus®, první agonista GLP-1 receptoru pro perorální použití v klinické praxi [Oral semaglutide - Rybelsus®, the first GLP-1 receptor agonist for oral use in clinical practice]. *Vnitrni Lekarstvi, 68*(2), 89–95.

Karim, F., Liang, X., & Qi, S.-H. (2022). Bioassay-guided isolation of antifungal cyclopeptides from the deep-sea-derived fungus *Simplicillium obclavatum* EIODSF 020. *Phytochemistry Letters, 48*, 68–71.

Kawahara, T., Itoh, M., Izumikawa, M., et al. (2017). Novel arginine-containing peptides MBJ-0173 and MBJ-0174 from *Mortierella alpina* f28740. *Journal of Antibiotics, 70*, 226–229. https://doi.org/10.1038/ja.2016.116

Kim, E. L., Li, J. L., Xiao, B., Hong, J., Yoo, E. S., Yoon, W. D., & Jung, J. H. (2012). A new cyclic tetrapeptide from the jellyfish-derived fungus *Phoma* sp. *Chemical & Pharmaceutical Bulletin, 60*(12), 1590–1593.

Kobayashi, R., Samejima, Y., Nakajima, S., Kawai, K., Udagawa, S. (1987). Studies on fungal products. XI. Isolation and structures of novel cyclic pentapeptides from *Aspergillus* sp. NE-45. *Chemical & Pharmaceutical Bulletin* 35(4),1347–1352. doi: 10.1248/cpb.35.1347.

Kuvarina, A. E., Gavryushina, I. A., Kulko, A. B., Ivanov, I. A., Rogozhin, E. A., Georgieva, M. L., & Sadykova, V. S. (2021). The emericellipsins A–E from an alkalophilic fungus *Emericellopsis alkalina* show potent activity against multidrug-resistant pathogenic fungi. *Journal of Fungi, 7*(2), 153. https://doi.org/10.3390/jof7020153

Ladriere, T., Faudemer, J., Levigoureux, E., Peyronnet, D., Desmonts, C., & Vigne, J. (2023). Safety and therapeutic optimization of Lutetium-177 based radiopharmaceuticals. *Pharmaceutics, 15*(4), 1240. https://doi.org/10.3390/pharmaceutics15041240

Lang, G., Blunt, J. W., Cummings, N. J., Cole, A. L., & Munro, M. H. (2005). Hirsutide, a cyclic tetrapeptide from a spider-derived entomopathogenic fungus, *Hirsutella* sp. *Journal of Natural Products, 68*(8), 1303–1305. https://doi.org/10.1021/np0501536

Lee, M. F., & Poh, C. L. (2023). Strategies to improve the physicochemical properties of peptide-based drugs. *Pharmaceutical Research, 40*, 617–632. https://doi.org/10.1007/s11095-023-03486-0

Li, G., Kusari, S., Golz, C., Strohmann, C., & Spiteller, M. (2016). Three cyclic pentapeptides and a cyclic lipopeptide produced by endophytic *Fusarium decemcellulare* LG53. *RSC Advances, 6*(59), 54092–54098. https://doi.org/10.1039/c6ra10905e

Li, H. J., Lin, Y. C., Yao, J. H., Vrijmoed, L. L., & Jones, G. E. (2004). Two new metabolites from the mangrove endophytic fungus no. 2524. *Journal of Asian Natural Products Research, 6*(3), 185–191. https://doi.org/10.1080/102860201653237

Li, Y., Sheng, S., Feng, J., Wang, Y., Guo, J., Jiang, Y.& Wang, W. (2022). New cyclic peptides from the endophytic *Aspergillus versicolor* 0312 with their antimicrobial activity. *Records of Natural Products, 16*(6), 585–591. http://doi.org/10.25135/rnp.315.2112.2296

Li, Y., Yue, Q., Jayanetti, D.R., Swenson, D.C., Bartholomeusz, G.A., An, Z., Gloer, J.B. & Bills, G.F. (2017). Anti-cryptococcus phenalenones and cyclic tetrapeptides from *Auxarthron pseudauxarthron*. *Journal of natural products*, *80*(7), 2101-2109. https://doi.org/10.1021/acs.jnatprod.7b00341

Li, Y., Wu, M., Fu, Y., Xue, J., Yuan, F., Qu, T., Rissanou, A. N., Wang, Y., Li, X., & Hu, H. (2024). Therapeutic stapled peptides: Efficacy and molecular targets. *Pharmacological Research, 203*, 107137. https://doi.org/10.1016/j.phrs.2024.107137

Liang, X., Yang, J. F., Huang, Z. H., Ma, X., Yan, Y., & Qi, S. H. (2024). New antibacterial peptaibiotics against plant and fish pathogens from the deep-sea-derived fungus *Simplicillium obclavatum* EIODSF 020. *Journal of Agricultural and Food Chemistry, 72*(12), 6402–6413. https://doi.org/10.1021/acs.jafc.4c00493

Liang, X., Zhang, X.-Y., Nong, X.-H., Wang, J., Huang, Z.-H., & Qi, S.-H. (2016). Eight linear peptides from the deep-sea-derived fungus *Simplicillium obclavatum* EIODSF 020. *Tetrahedron, 72*(22), 3092–3097. https://doi.org/10.1016/j.tet.2016.04.032

Lin, X., Tang, Z., Gan, Y., Li, Z., Luo, X., Gao, C., Zhao, L., Chai, L., & Liu, Y. (2023). 18-residue peptaibols produced by the sponge-derived *Trichoderma* sp. GXIMD 01001. *Journal of Natural Products, 86*(4), 994–1002. https://doi.org/10.1021/acs.jnatprod.3c00014

Liu, J., Gu, B., Yang, L., Yang, F., & Lin, H. (2018). New anti-inflammatory cyclopeptides from a sponge-derived fungus *Aspergillus violaceofuscus*. *Frontiers in Chemistry, 6*, 226. https://doi.org/10.3389/fchem.2018.00226

Lucana, M. C., Arruga, Y., Petrachi, E., Roig, A., Lucchi, R., & Oller-Salvia, B. (2021). Protease-Resistant Peptides for Targeting and Intracellular Delivery of Therapeutics. *Pharmaceutics,* 13(12), 2065. https://doi.org/10.3390/pharmaceutics13122065

Luo, F., He, Y., Wei, J., Zhao, C., Zhou, X., Hu, F., Lu, R., Bao, G., & Huang, B. (2020). Basidiosins A and B: Cyclopentapeptides from the entomophthoralean fungus *Basidiobolus meristosporus*. *Fitoterapia, 146*, 104671. https://doi.org/10.1016/j.fitote.2020.104671

Luo, M., Chang, S., Li, Y., Xi, X., Chen, M., He, N., Wang, M., Zhao, W., & Xie, Y. (2022). Molecular networking-based screening led to the discovery of a cyclic heptadepsipeptide from an endolichenic *Xylaria* sp. *Journal of Natural Products, 85*(4), 972–979. https://doi.org/10.1021/acs.jnatprod.1c01108

Ma, Y. M., Liang, X. A., Zhang, H. C., & Liu, R. (2016). Cytotoxic and antibiotic cyclic pentapeptide from an endophytic *Aspergillus tamarii* of *Ficus carica*. *Journal of Agricultural and Food Chemistry, 64*(19), 3789–3793. https://doi.org/10.1021/acs.jafc.6b01051

Ma, X., Nong, X.H., Ren, Z., Wang, J., Liang, X., Wang, L., Qi, S.H. (2017). Antiviral peptides from marine gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501. Tetrahedron Letters. 58,1151–1155. https://doi.org/10.1016/j.tetlet.2017.02.005

Malmstrom, J., Ryager, A., Anthoni, U., & Nielsen, P. H. (2002). Unguisin C, a GABA-containing cyclic peptide from the fungus *Emericella unguis*. *Phytochemistry, 60*(8), 869–872. https://doi.org/10.1016/s0031-9422(02)00150-4

Martinovich, V. P., & Baradzina, K. U. (2022). Peptide hormones in medicine: A 100-year history. *Russian Journal of Bioorganic Chemistry, 48*(2), 221–232. https://doi.org/10.1134/S1068162022020157

Maurer, T. S., Edwards, M., Hepworth, D., Verhoest, P. R., & Allerton, C. (2022). Designing small molecules for therapeutic success: A contemporary perspective. *Drug Discovery Today, 27*(2), 538–546. https://doi.org/10.1016/j.drudis.2021.09.017

Meyer, C. E., & Reusser, F. (1967). A polypeptide antibacterial agent isolated from *Trichoderma viride*. *Experientia, 23*, 85–86.

Mitova, M. I., Stuart, B. G., Cao, G. H., Blunt, J. W., Cole, A. L., & Munro, M. H. (2006). Chrysosporide, a cyclic pentapeptide from a New Zealand sample of the fungus *Sepedonium chrysospermum*. *Journal of Natural Products, 69*(10), 1481–1484. https://doi.org/10.1021/np060137o

Miyao, K. (1960). The structure of fungisporin. *Journal of the Agricultural Chemical Society of Japan, 24*(1), 23–30. https://doi.org/10.1080/03758397.1960.10857626

Momose, I., Onodera, T., Doi, H., Adachi, H., Iijima, M., Yamazaki, Y., Sawa, R., Kubota, Y., Igarashi, M., & Kawada, M. (2019). Leucinostatin Y: A Peptaibiotic Produced by the Entomoparasitic Fungus *Purpureocillium lilacinum* 40-H-28. *Journal of natural products*, 82(5), 1120–1127. https://doi.org/10.1021/acs.jnatprod.8b00839

Morehouse, N. J., Flewelling, A. J., Liu, D. Y., Cavanagh, H., Linington, R. G., Johnson, J. A., & Gray, C. A. (2023). Tolypocaibols: Antibacterial lipopeptaibols from a *Tolypocladium* sp. endophyte of the marine macroalga *Spongomorpha arcta*. *Journal of Natural Products, 86*(6), 1529–1535. https://doi.org/10.1021/acs.jnatprod.3c00233

Mori, H., Urano, Y., Abe, F., Furukawa, S., Furukawa, S., Tsurumi, Y., Sakamoto, K., Hashimoto, M., Takase, S., Hino, M., & Fujii, T. (2003). FR235222, a fungal metabolite, is a novel immunosuppressant that inhibits mammalian histone deacetylase (HDAC). I. Taxonomy, fermentation, isolation and biological activities. *The Journal of Antibiotics, 56*(2), 72–79.

Motohashi, K., Inaba, S., Takagi, M., & Shin-ya, K. (2009). JBIR-15, a new aspochracin derivative, isolated from a sponge-derived fungus, *Aspergillus sclerotiorum* Huber Sp080903f04. *Bioscience, Biotechnology, and Biochemistry, 73*(8), 1898–1900. https://doi.org/10.1271/bbb.90228

Mygind, P. H., Fischer, R. L., Schnorr, K. M., Hansen, M. T., Sönksen, C. P., Ludvigsen, S., Raventós, D., Buskov, S., Christensen, B., De Maria, L., Taboureau, O., Yaver, D., Elvig-Jørgensen, S. G., Sørensen, M. V., Christensen, B. E., Kjaerulff, S., Frimodt-Moller, N., Lehrer, R. I., Zasloff, M., & Kristensen, H. H. (2005). Plectasin is a peptide antibiotic with therapeutic potential from a saprophytic fungus. *Nature,* 437(7061), 975–980. https://doi.org/10.1038/nature04051

Myokei, R., Sakurai, A., Chang, C. F., Kodaira, Y., Takahashi, N., & Tamura, S. (1969). Structure of aspochracin, an insecticidal metabolite of *Aspergillus ochraceus*. *Tetrahedron Letters, 9*, 695–698. https://doi.org/10.1016/s0040-4039(01)87785-6

Neupane, S., Rodrigues de Amorim, M., & Skellam, E. (2024). Discovery of unguisin J, a new cyclic peptide from *Aspergillus heteromorphus* CBS 117.55, and phylogeny-based bioinformatic analysis of UngA NRPS domains. *Beilstein Journal of Organic Chemistry, 20*, 321–330. https://doi.org/10.3762/bjoc.20.32

Nie, Q., Zhao, F., Yu, X., Wang, Y., Li, J., Chen, Z., Zhang, H., Liu, Y., & Zhang, M. (2025). A class of benzofuranoindoline-bearing heptacyclic fungal RiPPs with anticancer activities. *Nature Chemical Biology*. Advance online publication. https://doi.org/10.1038/s41589-025-01946-9

Njardarson, Group. (2020). Top 200 pharmaceuticals by retail sales in 2019. University of Arizona.Noble, H. M., Langley, D., Sidebottom, P. J., Lane, S. J., & Fisher, P. J. (1991). An echinocandin from an endophytic *Cryptosporiopsis* sp. and *Pezicula* sp. in *Pinus sylvestris* and *Fagus sylvatica*. *Mycological Research, 95*(12), 1439–1440. https://doi.org/10.1016/s0953-7562(09)80401-2

Ortíz-López, F. J., Monteiro, M. C., González-Menéndez, V., Tormo, J. R., Genilloud, O., Bills, G. F., Vicente, F., Zhang, C., Roemer, T., Singh, S. B., & Reyes, F. (2015). Cyclic colisporifungin and linear cavinafungins, antifungal lipopeptides isolated from *Colispora cavincola*. *Journal of Natural Products, 78*(3), 468–475. https://doi.org/10.1021/np500854j

Peng, J., Gao, H., Zhang, X., Wang, S., Wu, C., Gu, Q., Guo, P., Zhu, T., & Li, D. (2014). Psychrophilins E–H and versicotide C, cyclic peptides from the marine-derived fungus *Aspergillus versicolor* ZLN-60. *Journal of Natural Products, 77*(10), 2218–2223. https://doi.org/10.1021/np500469b

Pereira, A.J., de Campos, L.J., Xing, H. et al. (2024). Peptide-based therapeutics: challenges and solutions. *Medicinal Chemistry Research* 33, 1275–1280. https://doi.org/10.1007/s00044-024-03269-1

Qi, J., Han, H., Sui, D., Tan, S., Liu, C., Wang, P., Xie, C., Xia, X., Gao, J. M., & Liu, C. (2022). Efficient production of a cyclic dipeptide (cyclo-TA) using heterologous

expression system of filamentous fungus *Aspergillus oryzae*. *Microbial Cell Factories, 21*(1), 146. https://doi.org/10.1186/s12934-022-01872-8

Rafferty, J., Nagaraj, H., McCloskey, A. P., Huwaitat, R., Porter, S., Albadr, A., & Laverty, G. (2016). Peptide Therapeutics and the Pharmaceutical Industry: Barriers Encountered Translating from the Laboratory to Patients. *Current medicinal chemistry*, 23(37), 4231–4259. https://doi.org/10.2174/0929867323666160909155222

Ren, M., Huo, R., Han, W., Wang, Z., Wang, Y., Song, J., Wang, J., Su, L., Cao, T., Zhang, J., & Luo, D. (2024). Discovery of new insecticidal cyclic hexapeptides from *Fusarium tricinctum* HM76 and their biosynthesis. *Industrial Crops and Products, 222*(15), 120111. https://doi.org/10.1016/j.indcrop.2024.120111

Ren, Y., Strobel, G. A., Graff, J. C., Jutila, M., Park, S. G., Gosh, S., Teplow, D., Condron, M., Pang, E., Hess, W. M., & Moore, E. (2008). Colutellin A, an immunosuppressive peptide from *Colletotrichum dematium*. *Microbiology (Reading, England), 154*(Pt 7), 1973–1979. https://doi.org/10.1099/mic.0.2008/017954-0

Ricci, M., Sassi, P., Nastruzzi, C., Caputo, O., & Maggi, F. (2000). Liposome-based formulations for the antibiotic nonapeptide leucinostatin A: Fourier transform infrared spectroscopy characterization and in vivo toxicologic study. *AAPS PharmSciTech, 1*(2), Article 2. https://doi.org/10.1208/pt010102

Rogozhin, E. A., Sadykova, V. S., Baranova, A. A., Vasilchenko, A. S., Lushpa, V. A., Mineev, K. S., Georgieva, M. L., Kul'ko, A. B., Krasheninnikov, M. E., Lyundup, A. V., Vasilchenko, A. V., & Andreev, Y. A. (2018). A novel lipopeptaibol emericellipsin A with antimicrobial and antitumor activity produced by the extremophilic fungus *Emericellopsis alkalina*. *Molecules (Basel, Switzerland), 23*(11), 2785. https://doi.org/10.3390/molecules23112785

Rossino, G., Marchese, E., Galli, G., Verde, F., Finizio, M., Serra, M., Linciano, P., & Collina, S. (2023). Peptides as therapeutic agents: Challenges and opportunities in the green transition era. *Molecules (Basel, Switzerland), 28*(20), 7165. https://doi.org/10.3390/molecules28207165

Sahu, S., Kumar, S., Nagtode, N. R., & Sahu, M. (2024). The burden of lifestyle diseases and their impact on health service in India: A narrative review. *Journal of Family Medicine and Primary Care, 13*(5), 1612–1619. https://doi.org/10.4103/jfmpc. jfmpc_693_23

Sasaki, T., Takagi, M., Yaguchi, T., Miyadoh, S., Okada, T., & Koyama, M. (1992). A new anthelmintic cyclodepsipeptide, PF1022A. *The Journal of Antibiotics, 45*(5), 692–697. https://doi.org/10.7164/antibiotics.45.692

Schmeda-Hirschmann, G., Hormazabal, E., Rodriguez, J. A., & Theoduloz, C. (2008). Cycloaspeptide A and pseurotin A from the endophytic fungus *Penicillium janczewskii*. *Zeitschrift für Naturforschung C: Journal of Biosciences, 63*(5–6), 383–388. https://doi.org/10.1515/znc-2008-5-612

Schneider, T., Kruse, T., Wimmer, R., Wiedemann, I., Sass, V., Pag, U., Jansen, A., Nielsen, A. K., Mygind, P. H., Raventós, D. S., Neve, S., Ravn, B., Bonvin, A. M., De Maria, L., Andersen, A. S., Gammelgaard, L. K., Sahl, H. G., & Kristensen, H. H. (2010). Plectasin, a fungal defensin, targets the bacterial cell wall precursor Lipid II. *Science (New York, N.Y.), 328*(5982), 1168–1172. https://doi.org/10.1126/science.1185723

Senadeera, S. P. D., Wang, D., Kim, C. K., Smith, E. A., Durrant, D. E., Alexander, P. A., Wendt, K. L., Stephen, A. G., Morrison, D. K., Cichewicz, R. H., Henrich, C. J., & Beutler, J. A. (2022). Tolypocladamides A–G: Cytotoxic peptaibols from *Tolypocladium inflatum*. *Journal of Natural Products, 85*(6), 1603–1616. https://doi.org/10.1021/acs.jnatprod.2c00240

Seto, Y., Takahashi, K., Matsuura, H., Kogami, Y., Yada, H., Yoshihara, T., & Nabeta, K. (2007). Novel cyclic peptide, epichlicin, from the endophytic fungus *Epichloë typhina*. *Bioscience, Biotechnology, and Biochemistry, 71*(6), 1470–1475. https://doi.org/10.1271/bbb.60700

Schifano, N. P., & Caputo, G. A. (2022). Investigation of the role of hydrophobic amino acids on the structure–activity relationship in the antimicrobial venom peptide ponericin L1. *Journal of Membrane Biology,* 255, 537–551. https://doi.org/10.1007/s00232-021-00204-y

Shahidi, F., & Saeid, A. (2025). Bioactivity of marine-derived peptides and proteins: A review. *Marine Drugs, 23*(4), 157. https://doi.org/10.3390/md23040157

Shiono, Y., Tsuchinari, M., Shimanuki, K., Miyajima, T., Murayama, T., Koseki, T., Laatsch, H., Funakoshi, T., Takanami, K., & Suzuki, K. (2007). Fusaristatins A and B, two new cyclic lipopeptides from an endophytic *Fusarium* sp. *The Journal of Antibiotics, 60*(5), 309–316. https://doi.org/10.1038/ja.2007.39

Singh, S., Zink, D. L., Polishook, J. D., Dombrowski, A. W., Darkin-Rattray, S. J., Schmatz, D. M., & Goetz, M. A. (1996). Apicidins: Novel cyclic tetrapeptides as coccidiostats and antimalarial agents from *Fusarium pallidoroseum*. *Tetrahedron Letters, 37*, 8077–8080.

Singh, V. P., Pathania, A. S., Kushwaha, M., Singh, S., Sharma, V., Malik, F. A., Khan, I. A., Kumar, A., Singh, D., & Vishwakarma, R. A. (2020). 14-Residue peptaibol velutibol A from *Trichoderma velutinum*: Its structural and cytotoxic evaluation. *RSC Advances, 10*(52), 31233–31242. https://doi.org/10.1039/d0ra05780k

Singh, V. P., Yedukondalu, N., Sharma, V., Kushwaha, M., Sharma, R., Chaubey, A., Kumar, A., Singh, D., & Vishwakarma, R. A. (2018). Lipovelutibols A–D: Cytotoxic lipopeptaibols from the Himalayan cold habitat fungus *Trichoderma velutinum*. *Journal of Natural Products, 81*(2), 219–226. https://doi.org/10.1021/acs.jnatprod.6b00873

Smith, C. G., & Vane, J. R. (2003). The discovery of captopril. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 17*(8), 788–789. https://doi.org/10.1096/fj.03-0093life

Strobel, G. A., Torczynski, R., & Bollon, A. (1997). *Acremonium* sp.—A leucinostatin A producing endophyte of European yew (*Taxus baccata*). *Plant Science, 128*(1), 97–108. https://doi.org/10.1016/s0168-9452(97)00131-3

Sun, C., Zhang, Z., Ren, Z., Yu, L., Zhou, H., Han, Y., Shah, M., Che, Q., Zhang, G., Li, D., & Zhu, T. (2020). Antibacterial cyclic tripeptides from Antarctica-sponge-derived fungus *Aspergillus insulicola* HDN151418. *Marine Drugs, 18*(11), 532. https://doi.org/10.3390/md18110532

Sy-Cordero, A. A., Pearce, C. J., & Oberlies, N. H. (2012). Revisiting the enniatins: A review of their isolation, biosynthesis, structure determination and biological activities. *The Journal of Antibiotics, 65*(11), 541–549. https://doi.org/10.1038/ja.2012.71

Tan, L. T., Cheng, X. C., Jensen, P. R., & Fenical, W. (2003). Scytalidamides A and B, new cytotoxic cyclic heptapeptides from a marine fungus of the genus *Scytalidium*. *The Journal of Organic Chemistry, 68*(23), 8767–8773. https://doi.org/10.1021/jo030191z

Tan, M., Xu, X., Zhang, W., Wu, F., Bo, X., Qin, F., Ju, S., Song, Z., Yang, T., Li, J., & Huang, X. (2023). Isolation and insecticidal activities of new cyclic peptides from mangrove endophytic fungus *Aspergillus* sp. GXNU-4QQY1a. *Fitoterapia, 171*, 105693. https://doi.org/10.1016/j.fitote.2023.105693

Tan, Q. W., Gao, F. L., Wang, F. R., & Chen, Q. J. (2015). Anti-TMV activity of malformin A1, a cyclic penta-peptide produced by an endophytic fungus *Aspergillus tubingensis*

FJBJ11. *International Journal of Molecular Sciences, 16*(3), 5750–5761. https://doi.org/10.3390/ijms16035750

Thongtan, J., Saenboonrueng, J., Rachtawee, P., & Isaka, M. (2006). An antimalarial tetrapeptide from the entomopathogenic fungus *Hirsutella* sp. BCC 1528. *Journal of Natural Products, 69*(4), 713–714. https://doi.org/10.1021/np050549h

Umehara, K., Nakahara, K., Kiyoto, S., Iwami, M., Okamoto, M., Tanaka, H., Kohsaka, M., Aoki, H., & Imanaka, H. (1983). Studies on WF-3161, a new antitumor antibiotic. *The Journal of Antibiotics, 36*(5), 478–483. https://doi.org/10.7164/antibiotics.36.478

Vecchio, I., Tornali, C., Bragazzi, N. L., & Martini, M. (2018). The discovery of insulin: An important milestone in the history of medicine. *Frontiers in Endocrinology, 9*, 613. https://doi.org/10.3389/fendo.2018.00613

Verekar, S., Mishra, P., Sreekumar, E., Deshmukh, S. K., & Kulkarni-Almeida, A. A. (2014). Anticancer activity of a new depsipeptide compound isolated from an endophytic fungus. *The Journal of Antibiotics, 67*, 697–701. https://doi.org/10.1038/ja.2014.58

Vidya, V., Achar, R. R., M U, H., N, A., T, Y. S., Kameshwar, V. H., Byrappa, K., & Ramadas, D. (2021). Venom peptides – A comprehensive translational perspective in pain management. *Current Research in Toxicology, 2*, 329–340. https://doi.org/10.1016/j.crtox.2021.09.001

Von Bargen, K. W., Niehaus, E. M., Bergander, K., Brun, R., Tudzynski, B., & Humpf, H. U. (2013). Structure elucidation and antimalarial activity of apicidin F: An apicidin-like compound produced by *Fusarium fujikuroi*. *Journal of Natural Products, 76*(11), 2136–2140. https://doi.org/10.1021/np4006053

Wang, H., Zhang, R., Ma, B., Wang, W., Yu, C., Han, J., Zhu, L., Zhang, X., Dai, H., Liu, H., & Chen, B. (2022). Japonamides A and B, two new cyclohexadepsipeptides from the marine-sponge-derived fungus *Aspergillus japonicus* and their synergistic antifungal activities. *Journal of Fungi (Basel, Switzerland), 8*(10), 1058. https://doi.org/10.3390/jof8101058

Wang, W. X., Kusari, S., Sezgin, S., Lamshöft, M., Kusari, P., Kayser, O., & Spiteller, M. (2015). Hexacyclopeptides secreted by an endophytic fungus *Fusarium solani* N06 act as crosstalk molecules in *Narcissus tazetta*. *Applied Microbiology and Biotechnology, 99*(18), 7651–7662. https://doi.org/10.1007/s00253-015-6653-7

Wang, X., Lin, M., Xu, D., Lai, D., & Zhou, L. (2017). Structural Diversity and Biological Activities of Fungal Cyclic Peptides, Excluding Cyclodipeptides. Molecules (Basel, Switzerland), 22(12), 2069. https://doi.org/10.3390/molecules22122069

Wang, X., Gong, X., Li, P., Lai, D., & Zhou, L. (2018). Structural diversity and biological activities of cyclic depsipeptides from fungi. *Molecules, 23*(1), 169. https://doi.org/10.3390/molecules23010169

Wang, Y., Cao, G., Gan, Y., Lin, X., Yi, X., Zhao, L., Liu, Y., Gao, C., & Bai, M. (2024). New cyclic pentapeptides from the mangrove-derived *Aspergillus fumigatus* GXIMD 03099. *Marine Drugs, 22*(6), 282. https://doi.org/10.3390/md22060282

Wei, X., Chan, T. K., Kong, C. T. D., & Matsuda, Y. (2023). Biosynthetic characterization, heterologous production, and genomics-guided discovery of GABA-containing fungal heptapeptides. *Journal of Natural Products, 86*(2), 416–422. https://doi.org/10.1021/acs.jnatprod.2c01065

Xiao, D., Li, W., Li, T., Zhou, J., Zhang, M., Chen, X., Zhang, L., Yue, Q., Dun, B., Wang, C., & Xu, Y. (2023). Mass spectrometry-guided discovery of multi-*N*-methylated cyclodecapeptides Auyuittuqamides E–H from *Sesquicillium* sp. QL0466. *Journal of Natural Products, 86*(5), 1240–1250. https://doi.org/10.1021/acs.jnatprod.2c01168

Xiao, D., Zhang, M., Wu, P., Zhang, T., Zhan, J., Zhang, Y., Zhang, W., & Liu, J. (2022). Halovirs I–K, antibacterial and cytotoxic lipopeptaibols from the plant pathogenic fungus *Paramyrothecium roridum* NRRL 2183. *The Journal of Antibiotics, 75*, 247–257. https://doi.org/10.1038/s41429-022-00517-7

Xie, B., and Duong, V. (2022). Therapeutic peptides: market and manufacturing. In N. Qvit & S. J. S. Rubin (Eds.), Peptide and Peptidomimetic Therapeutics: From Bench to Bedside (pp. 689-698). Elsevier. https://doi.org/10.1016/B978-0-12-820141-1.00030-3

Xue, J. H., Wu, P., Chi, Y. L., Huang, S. X., & Liu, J. K. (2011). Cyclopeptides from *Amanita exitialis*. *Natural Products and Bioprospecting, 1*, 52–56. https://doi.org/10.1007/s13659-011-0013-9

Yin, W., Zou, J., She, Z., Vrijmoed, L. L., Jones, E. G., & Lin, Y. (2005). Two cyclic peptides produced by the endophytic fungus #2221 from *Castanopsis fissa* on the South China Sea coast. *Chinese Chemical Letters, 16*, 219–222.

Youssef, D. T. A., Shaala, L. A., & Genta-Jouve, G. (2022). Asperopiperazines A and B: Antimicrobial and cytotoxic dipeptides from a tunicate-derived fungus *Aspergillus* sp. DY001. *Marine Drugs, 20*(7), 451. https://doi.org/10.3390/md20070451

Zhang, A. H., Wang, X. Q., Han, W. B., Sun, Y., Guo, Y., Wu, Q., Ge, H. M., Song, Y. C., Ng, S. W., Xu, Q., & Tan, R. X. (2013). Discovery of a new class of immunosuppressants from *Trichothecium roseum* co-inspired by cross-kingdom similarity in innate immunity and pharmacophore motif. *Chemistry – An Asian Journal, 8*(12), 3101–3107. https://doi.org/10.1002/asia.201300734

Zhao, C., Qu, J., Lu, R., Chen, R., Dong, Q., Huang, B., Bao, G., & Hu, F. (2023b). Cyclic pentapeptides with anti-inflammatory, cytotoxic or α-glucosidase inhibitory activities from *Basidiobolus meristosporus*. *Phytochemistry, 209*, 113636. https://doi.org/10.1016/j.phytochem.2023.113636

Zhao, C., Qu, J., Peng, F., Lu, R., Bao, G. H., Huang, B., & Hu, F. (2023b). Cyclic peptides from the opportunistic pathogen *Basidiobolus meristosporus*. *Journal of Natural Products, 86*(8), 1885–1890. https://doi.org/10.1021/acs.jnatprod.2c01097

Zheng, J., Xu, Z., Wang, Y., Hong, K., Liu, P., & Zhu, W. (2010). Cyclic tripeptides from the halotolerant fungus *Aspergillus sclerotiorum* PT06-1. *Journal of Natural Products, 73*(6), 1133–1137. https://doi.org/10.1021/np100198h

Zhou, C., Cao, X., Ge, Y., Wu, X., Zhang, Z., Ma, Y., Dickschat, J. S., & Wu, B. (2022a). Talaropeptins A and B, tripeptides with an *N*-trans-cinnamoyl moiety from the marine-derived fungus *Talaromyces purpureogenus* CX11. *Journal of Natural Products, 85*(11), 2620–2625. https://doi.org/10.1021/acs.jnatprod.2c00638

Zhou, T., Li, Q., Zhao, M., Pan, Y., & Kong, X. (2023). A review on edible fungi-derived bioactive peptides: Preparation, purification and bioactivities. *International Journal of Medicinal Mushrooms, 25*(7), 1–11. https://doi.org/10.1615/IntJMedMushrooms.2023048464

Zhou, X., Fang, P., Tang, J., Wu, Z., Li, X., Li, S., Wang, Y., Liu, G., He, Z., Gou, D., Yao, X., & Wang, L. (2016). A novel cyclic dipeptide from deep marine-derived fungus *Aspergillus* sp. SCSIOW2. *Natural Product Research, 30*(1), 52–57. https://doi.org/10.1080/14786419.2015.1033623

Zhu, S., Gao, B., Harvey, P. J., & Craik, D. J. (2012). Dermatophytic defensin with anti-infective potential. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(22), 8495–8500. https://doi.org/10.1073/pnas.1201263109

Zorzi, A., Deyle, K., & Heinis, C. (2017). Cyclic peptide therapeutics: Past, present and future. *Current Opinion in Chemical Biology, 38*, 24–29. https://doi.org/10.1016/j.cbpa.2017.02.006