Review

Structural Diversity and Biological Activities of Fungal Cyclic Peptides, Excluding Cyclodipeptides

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Abstract: Cyclic peptides are cyclic compounds formed mainly by the amide bonds between either proteinogenic or non-proteinogenic amino acids. This review highlights the occurrence, structures and biological activities of fungal cyclic peptides (excluding cyclodipeptides, and peptides containing ester bonds in the core ring) reported until August 2017. About 293 cyclic peptides belonging to the groups of cyclic tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, deca-, undeca-, dodeca-, tetradeca- and octadecapeptides as well as cyclic peptides containing ether bonds in the core ring have been isolated from fungi. They were mainly isolated from the genera Aspergillus, Penicillium, Fusarium, Acremonium and Amanita. Some of them were screened to have antimicrobial, antiviral, cytotoxic, phytotoxic, insecticidal, nematicidal, immunosuppressive and enzyme-inhibitory activities to show their potential applications. Some fungal cyclic peptides such as the echinocandins, pneumocandins and cyclosporin A have been developed as pharmaceuticals.

Keywords: cyclopeptides; fungi; biological activities; occurrence; applications

1. Introduction

Cyclic peptides (also called cyclopeptides) are cyclic compounds formed mainly by proteinogenic or non-proteinogenic amino acids joined together by amide bonds (or peptide bonds). Cyclic peptides have been isolated from plants [1], fungi [2], bacteria (including actinomycetes) [3], sponges [4], algae [5,6], and mammals [7]. Among these organisms, fungi are well-known producers of a diversity of cyclic peptides with interesting structures and biological activities [8]. Here, we focus on the cyclic peptides derived from fungi, including insect pathogenic fungi, plant pathogenic fungi, soil-derived fungi, marine-derived fungi, plant or insect endophytic fungi, and the macroscopic fungi which we usually call mushrooms. Some of the fungal cyclic peptides are mycotoxins which pose a hazard to animals and plants [2]. Interest in cyclic peptides is due to their significant biological activities, such as antimicrobial, insecticidal, cytotoxic, and anticancer activities, in addition to their important physiological and ecological functions. Therefore, they have the potential to be developed as pharmaceuticals and agrochemicals [9].

Fungal cyclic peptides mainly include cyclic di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decapeptides. Recent special reviews covering the chemical synthesis [10], biosynthesis [11,12], as well as developments and applications (i.e., echinocandins, pneumocandins and cyclosporin A) [13,14] of fungal cyclic peptides are available. In this review, we describe the occurrence, biological activities, structures, and potential applications of the fungal cyclic peptides and their analogs, with the exception of cyclodipeptides (called 2,5-diketopiperazines), which were previously reviewed [15]. Cyclic depsipeptides from organisms including fungi, which are a big group of cyclic peptides in which one or more amino acid is replaced by a hydroxy acid, resulting in the formation of at least one
ester bond in the core ring structure, have also been reviewed [16]. The cyclic peptides containing at least one ether bond in the core ring were considered as a special group and included in this review.

2. Cyclic Tripeptides

Cyclic tripeptides are composed of three amino acid residues in the core ring. They are described in the genera *Aspergillus*, *Penicillium* and *Xylaria*. Cyclic tripeptides exhibit insecticidal [17], cytotoxic [18] and antifungal activities [19]. Their origins, and biological activities are listed in Table 1, and the structures are provided in Figure 1.

Aspochracin (1) was the first cyclic tripeptide isolated from fungi in 1969. It was obtained from the culture broth of *Aspergillus ochraceus*, a pathogenic fungus causing muscardine on insects. This compound shows contact toxicity on the first instar larvae as well as the eggs of silkworm [17].

Aspochracin (1), JBIR-15 (2) and sclerotiotides A–K (12–22) were obtained from the halotolerant fungus *Aspergillus sclerotiorum* PT06-1. Only sclerotiotides A (12), B (13), F (17) and I (20), and JBIR-15 (2) show selective antifungal activity against *Candida albicans*, with minimum inhibitory concentration (MIC) values of 7.5, 3.8, 6.7, and 30 µM, respectively [19].

Psychrophilins A–H (compounds 4–11) were isolated from *Aspergillus* and *Penicillium* species [18–23]. Among them, psychrophilin D (7) from *Penicillium algidum* show cytotoxic activity [18], psychrophilin E (8) from *Aspergillus* sp. shows antiproliferative activity [22], and psychrophilin G (10) from *Aspergillus versicolor* ZLN-60 shows lipid-lowering effects [23].

Table 1. Fungal cyclic tripeptides and their biological activities.

| Name                  | Fungus and its Origin            | Biological Activity       | Ref.      |
|-----------------------|----------------------------------|---------------------------|----------|
| Aspochracin (1)       | *Aspergillus ochraceus*          | Insecticidal activity     | [17]     |
|                       | *Aspergillus sclerotiorum* PT06-1|                           |          |
| JBIR-15 (2)           | *Aspergillus sclerotiorum*       | Antifungal activity       | [19,25]  |
| Pre-sclerototide F (3)| *Aspergillus insulicola*        |                           | [26]     |
| Psychrophilin A (4)   | *Penicillium ribeum* from a soil under the tree Ribes sp. |              | [20]     |
| Psychrophilin B (5)   | *Penicillium ribeum* from a soil under the tree Ribes sp. |              | [21]     |
| Psychrophilin C (6)   | *Penicillium ribeum* from a soil under the tree Ribes sp. |              | [21]     |
| Psychrophilin D (7)   | *Penicillium algidum*           | Cytotoxic activity        | [18]     |
| Psychrophilin E (8)   | *Aspergillus versicolor* ZLN-60  | Antiproliferative activity| [22,23]  |
| Psychrophilin F (9)   | *Aspergillus versicolor* ZLN-60  |                           | [23]     |
| Psychrophilin G (10)  | *Aspergillus versicolor* ZLN-60  | Lipid-lowering effect     | [23]     |
| Psychrophilin H (11)  | *Aspergillus versicolor* ZLN-60  |                           | [23]     |
| Sclerotiotide A (12)  | *Aspergillus sclerotiorum* PT06-1| Antifungal activity       | [19]     |
| Sclerotiotide B (13)  | *Aspergillus sclerotiorum* PT06-1| Antifungal activity       | [19]     |
| Sclerotiotide C (14)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Sclerotiotide D (15)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Sclerotiotide E (16)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Sclerotiotide F (17)  | *Aspergillus insulicola*        |                           | [26]     |
| Sclerotiotide G (18)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Sclerotiotide H (19)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Sclerotiotide I (20)  | *Aspergillus sclerotiorum* PT06-1| Antifungal activity       | [19]     |
| Sclerotiotide J (21)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Sclerotiotide K (22)  | *Aspergillus sclerotiorum* PT06-1| -                         | [19]     |
| Xyloallenolide A (23) | *Xylaria* sp. No. 2508           |                           | [27]     |
Figure 1. Structures of the cyclic tripeptides isolated from fungi.
3. Cyclic Tetrapeptides

Cyclic tetrapeptides have been found in many genera such as Acremonium, Alternaria, Cylindrocladium, Fusarium, Helicoma, Penicillium, Peniophora, Phoma, Phomopsis, Pseudoxylaria, Stachylylaidum, and Verticillium. Their origins and biological activities are listed in Table 2, and the corresponding structures are shown in Figure 2.

Histone deacetylases (HDACs) are important regulators of gene expression and have been implicated as key participants in a variety of diseases. HC-toxins are host-selective toxins and act as inhibitors of HDAC [28]. JM47 (65) from a marine Fusarium species belongs to the HC-toxin family, and contains a 2-amino-8-oxo-9,10-epoxydecanoic acid residue [29]. Other cyclic tetrapeptides such as 1-alanineclamydocin (24), apicidin (25), clamydocin (41), FR235222 (60), microsporins A (66) and B (67), and trapoxins A (83) and B (84) also show inhibitory activity on HDAC [30,31]. Apicidin analogs (25-35) from Fusarium species show antiprotozoal activity by inhibiting parasite HDAC [32-35]. These HDAC inhibitors were considered as the potential therapeutics for spinal muscular atrophy [36].

AS1387392 (36) from Acremonium sp. No. 27082 showed a strong inhibitory effect against mammalian HDAC and T-cell proliferation which suggested its potential as immunosuppressant [37].

Asperterrestide A (38) from the fermentation broth of the marine-derived fungus Aspergillus terreus SC5GAF0162 showed cytotoxicity against U937 and MOLT4 human carcinoma cell lines and inhibitory effects on influenza virus strains H1N1 and H3N2 [38].

Chlamydocin (41) was isolated from Dieterespora chlantydosporia [39] and Penicillium sp. BCC18034 [40], respectively. This compound showed antimalarial and cytotoxic activities. Three chlamydocin analogs cyclo[(2S,9R)-9-(acetoxy)-2-amino-8-oxodecanoyl-2-methylalanyl-L-phenylvalanyl-L-prolyl] (42), cyclo[2-methylalanyl-L-phenylalanlyl-D-prolyl-(2S)-2-amino-8-oxodecanoyl] (43), and cyclo[2-methylalanlyl-L-phenylalanlyl-D-prolyl-(2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl] (44) were isolated from the culture filtrate of the soil fungus Peniophora sp. They all showed plant growth-retarding activity by reducing the height of rice seedlings without blotch and wilting [41].

Three cyclic tetrapeptides cyclo(Gly-L-Phe-L-Pro-L-Tyr) (45), cyclo(L-Leu-trans-4-hydroxy-L-Pro-L-Leu-trans-4-hydroxy-L-Pro) (46) and cyclo(D-Pro-L-Tyr-L-Pro-L-Tyr) (47) were isolated from the co-culture broth of two mangrove fungi, Phomopsis sp. K38 and Alternaria sp. E33. These compounds all had moderate antifungal activity against Candida albicans, Gaecumannomyces graminis, Rhizoctonia cerealis, Helminthosporium sativum and Fusarium graminearum [42,43].

Three cyclic tetrapeptides cyclo(N-methyl-L-Phe-L-Val-N-methyl-L-Phe-L-Val) (48), cyclo(N-methyl-L-Phe-L-Val-N-methyl-L-Phe-L-Ile) (49), and cyclo(N-methyl-L-Phe-L-Ile-N-methyl-L-Phe-L-Ile) (50) were isolated from the crude fermentation extract of Onychocola sclerotica. They all display inhibitory activity as cardiac calcium channel blockers on wild-type HEK or C1-6-37-3 cells with IC50 values of 5.0-7.1 μM [44].

Cyl-1 (51) and Cyl-2 (52) from the plant fungal pathogen Cylindrocladium scoparium exhibited marked inhibition on the growth of rice and lettuce seedlings, especially on their root growth, which suggested that they could be used to inhibit plant growth [45,46].

Microsporins A (66) and B (67) from the marine-derived fungus Microsporum cf. gypseum CNL-692 obtained from a sample of the bryozoan Bugula sp. collected in the U.S. Virgin Islands. Both compounds showed inhibitory activity on HDAC and demonstrated cytotoxic activity against human colon adenocarcinoma (HCT-116) cells [47].

Penicopeptide A (69) was isolated from the endophytic fungus Penicillium commune from Vitis vinifera. It exhibited significant inhibitory activity against 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in vitro and showed strong binding affinity to recombinant human 11β-HSD1 by micoscale thermophoresis assay. Moreover, penicopeptide A (69) decreased the lipid droplet accumulation associate with the inhibiton of 11β-HSD1 activity of 3T3-L1 cells in vivo [48].

Pseudoxyllalamycins A–F (73-78) were isolated from the termite-associated fungus Pseudoxyllaria sp. X802. Pseudoxyllalamycins A–D (73-76) showed antibacterial activity against Gram-negative...
human-pathogenic *Pseudomonas aeruginosa* and antiproliferative activity against human umbilical vein endothelial cells and K-562 cell lines [49].

Tentoxin (81) and its derivatives dihydrotentoxin (54) and isotentoxin (64) were important mycotoxins from *Alternaria* spp. [50]. Tentoxin B (82) was isolated from the marine-derived fungus *Phoma* sp. from the giant jellyfish *Nemopilema nomurai*. This compound showed weak suppressive effect on the production of nitric oxide in murine macrophage cells [51].

Trapoxins A (83) and B (84) from *Helicoma ambiens* RF-1023 exhibited detransformation activity against *v-sis* oncogene-transformed NIH3T3 cells (*sis*/NIH3T3) [52]. In addition, trapoxin A (83) showed HDAC inhibitory activity [31]. Both compounds displayed their potential as antitumor agents.

| Name                        | Fungus and Its Origin                  | Biological Activity                                                                 | Ref. |
|-----------------------------|----------------------------------------|--------------------------------------------------------------------------------------|------|
| 1-Alaninechloramycocin (24) | *Tolypocladium* sp.                    | Inhibitory activity on histone deacetyl (HDAC) activity, antiproliferation, cytotoxicity, cell cycle arrest, and apoptosis induction | [30] |
| Apicidin (25)               | *Fusarium pallidoroseum*               | Antimalarial activity                                                                | [32] |
|                             | *Fusarium semitectum*                  | Phytotoxic activity                                                                  | [53] |
|                             | -                                      | Antiprotozoal activity by inhibiting parasite HDAC                                   | [35] |
| Apicidin A (26)             | *Fusarium pallidoroseum*               | Antimalarial activity                                                                | [32] |
|                             | *Fusarium semitectum*                  | -                                                                                    | [53] |
| Apicidin B (27)             | *Fusarium pallidoroseum*               | Antiprotozoal activity                                                               | [33] |
| Apicidin C (28)             | *Fusarium pallidoroseum*               | Antiprotozoal activity                                                               | [33] |
| Apicidin D1 (29)            | *Fusarium pallidoroseum*               | Antiprotozoal activity                                                               | [34] |
| Apicidin D2 (30)            | *Fusarium pallidoroseum*               | Antiprotozoal activity                                                               | [34] |
|                             | *Fusarium semitectum*                  | Phytotoxic activity                                                                  | [53] |
| Apicidin D3 (31)            | *Fusarium pallidoroseum*               | Antiprotozoal activity                                                               | [34] |
| Apicidin E (32)             | *Fusarium semitectum* mutant           | -                                                                                    | [54] |
| Apicidin F (33)             | *Fusarium fujikuroi*                   | Antimalarial activity                                                                | [55] |
| Apicidin G (34)             | *Fusarium semitectum*                  | -                                                                                    | [56] |
| Apicidin H (35)             | *Fusarium semitectum*                  | -                                                                                    | [56] |
| AS1387392 (36)              | *Acremonium* sp. No. 27082             | Immunosuppressive activity                                                           | [37] |
| Aspercolorin (37)           | *Aspergillus versicolor*               | -                                                                                    | [57] |
| Asperterrestide A (38)      | *Aspergillus terreus* SCSGAP0162       | Cytotoxic and antiviral activity                                                     | [38] |
| Auxarthride A (39)          | Coprophilous fungus *Auxarthron pseudoauxarthron* | -                                                                                   | [58] |
| Auxarthride B (40)          | Coprophilous fungus *Auxarthron pseudoauxarthron* | -                                                                                   | [58] |
| Chlamydocin (41)            | *Diheterospora chlantydosporia*        | Cytostatic activity                                                                 | [39] |
|                             | *Penicillium* sp. BCC18034             | Antimalarial and cytotoxic activity                                                  | [40] |
| Cyclo[25(9R)-9-((acetyloxy)-2-amino-8-oxodecanoyl-2-methylalanyl-1-phenylalanyl-D-prolyl][42] | *Peniophora* sp.                   | Plant growth-retardant activity                                                     | [41] |
| Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(25)-2-amino-8-oxodecanoyl] (43) | *Peniophora* sp.                   | Plant growth-retardant activity                                                     | [41] |
| Name                                                                 | Fungus and Its Origin                  | Biological Activity                      | Ref.                  |
|----------------------------------------------------------------------|----------------------------------------|-------------------------------------------|-----------------------|
| Cyclo[2-methylalanyl-1-phenylalanyl-1-prolyl- (2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl] (44) | *Peniophora* sp.                        | Plant growth-retardant activity            | [41]                 |
| Verticillium cocosporum                                              |                                        |                                           |                       |
| Cyclo(Gly-1-Phe-1-Pro-1-Tyr) (45)                                    | Co-culture broth of two mangrove fungi | *Phomopsis* sp. K38 and *Alternaria* sp. E33 | Antifungal activity    | [42]                 |
| Verticillium coccosporum                                              |                                        |                                           |                       |
| Cyclo([Leu-4-hydroxy-1-Pro-D-Leu-4-hydroxy-1-Pro] (46)               | Co-culture broth of two mangrove fungi | *Phomopsis* sp. K38 and *Alternaria* sp. E33 | Antifungal activity    | [43]                 |
| Cyclo([Pro-1-Tyr-1-Pro-1-Tyr) (47)                                    | Co-culture broth of two mangrove fungi | *Phomopsis* sp. K38 and *Alternaria* sp. E33 | Antifungal activity    | [42]                 |
| Cyclo(N-methyl-1-Phe-1-Val-N-methyl-Phe-1-Val) (48)                  | *Onychola sclerotica*                  | Cardiac calcium channel blocker           | [44]                 |
| Cyclo(N-methyl-1-Phe-1-Val-N-methyl-Phe-1-Ile) (49)                  | *Onychola sclerotica*                  | Cardiac calcium channel blocker           | [44]                 |
| Cyclo(N-methyl-1-Phe-1-Ile-N-methyl-1-Phe-1-Ile) (50)                | *Onychola sclerotica*                  | Cardiac calcium channel blocker           | [44]                 |
| Cyl-1 (51)                                                          | *Cylindrocladium scoparium*            | Phytotoxic activity                       | [45, 46]             |
| Cyl-2 (52)                                                          | *Cylindrocladium scoparium*            | Phytotoxic activity                       | [46, 60]             |
| Diheteropeptin (53)                                                  | *Diheterospora* sp.                    | TGF-β-like activity                       | [61]                 |
|                          | *Diheterospora chlamydiospora*         | TGF-β-like activity                       | [62]                 |
| Dihydrotentoxin (54)                                                 | *Alternaria porri*                     | -                                         | [63]                 |
|                          | *Phoma* sp.                           | -                                         | [51]                 |
| Endolide A (55)                                                     | *Stackyliadium* sp. from the sponge *Callyspongia* sp. | Affinity to the vasopressin receptor 1A with a Ki of 7.04 µM | [64] |
| Endolide B (56)                                                     | *Stackyliadium* sp. from the sponge *Callyspongia* sp. | Be selective toward the serotonin receptor 5HT2b with a Ki of 0.77 µM | [64] |
| Endolide C (57)                                                     | Marine-sponge-derived *Stackyliadium* sp. 293 K04 | -                                         | [65]                 |
| Endolide D (58)                                                     | Marine-sponge-derived *Stackyliadium* sp. 293 K04 | -                                         | [65]                 |
| 5,5’-Epoxy-MKN-349A (59)                                            | Endophytic fungus *Penicillin* sp. GD6 from the mangrove *Bruguiera gymnorrhiza* | -                                         | [66]                 |
| FR235222 (60)                                                       | *Acremonium* sp. No. 27082             | Immunosuppressant that inhibits mammalian histone deacetylase | [67–69]             |
| Fungisporin (61)                                                    | *Penicillium chrysogenum*              | -                                         | [70]                 |
| HC-toxin (62)                                                       | *Helminthosporium carbonum = Cochliobolus carbonum* | Phytotoxic activity                       | [71, 72]             |
| Hirsutide (63)                                                      | Spider-derived fungus *Hirsutella* sp. | -                                         | [73]                 |
| Isotentoxin (64)                                                    | *Alternaria porri*                     | -                                         | [63]                 |
| Name | Fungus and Its Origin | Biological Activity | Ref. |
|------|-----------------------|---------------------|-----|
| JM47 (65) | Marine-derived *Fusarium* sp. from the alga *Codium fragile* | - | [29] |
| Microsporin A (66) | *Microsporum* cf. *gypseum* CNL-692 | Inhibitory activity on histone deacetylase; cytotoxic activity | [47] |
| Microsporin B (67) | *Microsporum* cf. *gypseum* CNL-692 | Inhibitory activity on histone deacetylase; cytotoxic activity | [47] |
| Nidulanin A (68) | *Aspergillus nidulans* | - | [74] |
| Penicopeptide A (69) | Endophytic *Penicillium commune* from *Vitis vinifera* | Inhibitory activity on 11β-hydroxysteroid dehydrogenase | [48] |
| PF1070A (70) | *Calonectria ilicicola* | Phytotoxic activity | [75] |
| PF1070B (71) | *Hunincola* sp. | Antitumour activity | [76] |
| Phoenistatin (72) | *Acremonium fusigerum* | Enhancing activity on gene expression | [77] |
| Pseudoxyllalemycin A (73) | Termite-associated fungus *Pseudoxylaria* sp. X802 | Antibacterial and antiproliferative activities | [49] |
| Pseudoxyllalemycin B (74) | Termite-associated fungus *Pseudoxylaria* sp. X802 | Antibacterial and antiproliferative activities | [49] |
| Pseudoxyllalemycin C (75) | Termite-associated fungus *Pseudoxylaria* sp. X802 | Antibacterial and antiproliferative activities | [49] |
| Pseudoxyllalemycin D (76) | Termite-associated fungus *Pseudoxylaria* sp. X802 | Antibacterial and antiproliferative activities | [49] |
| Pseudoxyllalemycin E (77) | Termite-associated fungus *Pseudoxylaria* sp. X802 | - | [49] |
| Pseudoxyllalemycin F (78) | Termite-associated fungus *Pseudoxylaria* sp. X802 | - | [49] |
| Sartoryglabramide A (79) | Marine-derived *Neosartorya glabra* KUFA 0702 from the sponge *Mycale* sp. | - | [78] |
| Sartoryglabramide B (80) | Marine-derived *Neosartorya glabra* KUFA 0702 from the sponge *Mycale* sp. | - | [78] |
| Tentoxin (81) | *Alternaria linicola* | Phytotoxic activity | [79] |
| | *Alternaria porri* | - | [63] |
| | *Phoma* sp. | - | [51] |
| Tentoxin B (82) | Marine-derived fungus *Phoma* sp. from the giant jellyfish *Nemopilema nomurai* | Weak suppressive effect on the production of nitric oxide in murine macrophage cells without notable cytotoxicity | [51] |
| Trapoxin A (83) | *Helicoma ambiens* RF-1023 | Detransformation activity against v-sis oncogene-transformed NIH3T3 cells | [52] |
| | - | HDAC inhibitory activity | [31] |
| Trapoxin B (84) | *Helicoma ambiens* RF-1023 | Detransformation activity against v-sis oncogene-transformed NIH3T3 cells | [52] |
| WF-3161 (85) | *Petriella guttlata* | Antitumor activity | [80] |
Figure 2. Cont.
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Figure 2. Structures of the cyclic tetrapeptides isolated from fungi.
4. Cyclic Pentapeptides

Cyclic pentapeptides have been mainly isolated from the genera of *Aspergillus*, *Fusarium*, *Hamigera*, *Penicillium*, *Pseudallescheria* and *Xylaria*. Their distributions in fungi, and biological activities are listed in Table 3, and the structures are provided in Figure 3.

Argadin (86) and argifin (87) produced by *Clonostachys* sp. FO-7314 and *Gliocladium* sp. FTD-0668, respectively, were identified in screening as chitinase inhibitors [81,82]. Chitinases play key roles in organisms, ranging from bacteria to humans. There is a need for specific, potent inhibitors to probe the function of these chitinases in different organisms. Such molecules could also provide leads for the development of chemotherapeutics with fungicidal, insecticidal, or anti-inflammatory potential. Argadin (86) and argifin (87) could be used as the leads for the development of novel chitinase inhibitors [83].

Aspergillipeptide D (88) was isolated from the marine gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501. It showed evident antiviral activity against herpes simplex virus type 1 (HSV-1) with a median inhibitory concentration (IC$_{50}$) value of 9.5 µM under their non-cytotoxic concentration against a Vero cell line, and also had antiviral activity against acyclovir-resistant clinical isolates of HSV-1 [84].

Cycloaspeptides A–F (103–108) are anthranilic acid (ABA)-containing cyclic pentapeptides. Among them, cycloaspeptides A–C (103–105) were isolated from *Aspergillus* sp. NE-45 [85], cycloaspeptide D (106) with antiplasmodial activity from *Penicillium algidum* [18] and the psychrotolerant fungus *Penicillium ribeum* [20], cycloaspeptide E (107) with insecticidal activity from several *Penicillia* species and a *Tricothecium* strain [86], and cycloaspeptides F (108) and G (109) from *Isaria farinosa* [87]. The presence of a glucose unit in cycloaspeptide F (108) was very rare in the isolated cyclic peptides.

Seven malformins (114–120) were isolated from a few *Aspergillus* species [88–91]. Malformin A1 (114) from *Aspergillus niger* and *Aspergillus tubingensis* showed malformation activity in the corn root, and cytotoxic activity, and anti-TMV activity [89,90,92,93]. Malformin C (119) from *Aspergillus niger* had potent cell growth inhibition activity [94], but its therapeutic index was too low to be an anti-cancer drug [95].

Pseudacyclins A–E (125–129) were isolated from *Pseudallescheria boydii* which is an emerging fungal pathogen causing fatal infections in both immunocompromised and immunocompetent hosts. Among them, pseudacyclin A (125) exhibited immunosuppressive activity [96].

| Name                | Fungus and Its Origin                  | Biological Activity                  | Ref.   |
|---------------------|----------------------------------------|--------------------------------------|--------|
| Argadin (86)        | Clonostachys sp. FO-7314               | Chitinase inhibitor                   | [81]   |
| Argifin (87)        | Gliocladium sp. FTD-0668               | Chitinase inhibitor                   | [82,97]|
| Aspergillipeptide D (88) | Marine gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501 | Antiviral activity                   | [84]   |
| Asperpeptide A (89) | Marine gorgonian-derived *Aspergillus* sp. XS-2009B15 | Antibacterial activity               | [98]   |
| Avellanin A (90)    | *Hamigera* sp.                         | Vasoconstriction and pressor effect   | [99]   |
| Avellanin B (91)    | *Hamigera* sp.                         | Vasoconstriction and pressor effect   | [99]   |
| Avellanin C (92)    | *Hamigera paravellanea*                | Vasoconstriction and pressor effect   | [99]   |
| Chrysosporide (93)  | *Sepedonium chrysospermum*             | Weak cytotoxic to murine leukemia cell line | [100] |
| Clavatustide C (94) | *Aspergillus clavatus* C2WU            | -                                    | [101]  |
Table 3. Cont.

| Name | Fungus and Its Origin | Biological Activity | Ref. |
|------|-----------------------|---------------------|------|
| Cotteslosin A (95) | *Aspergillus versicolor* | Weak cytotoxic to human cancer cell lines | [102] |
| Cotteslosin B (96) | *Aspergillus versicolor* | Weak cytotoxic to human cancer cell lines | [102] |
| Cyclo(l-Ile-l-Leu-l-Leu-l-Leu-l-Leu) (97) | Endophytic fungus *Cryptosporiopsis* sp. of *Zanthoxylum leptocarpum* | Motility inhibitory and lytic activities against zoospores; Antifungal activity; weak cytotoxic activity on brine shrimp larvae | [103] |
| Cyclo(l-Leu-l-Leu-d-Leu-l-Leu-l-l-Leu) (98) | Endophytic fungus *Fusarium decempertitale* LG53 from Chinese medicinal plant *Mahonia fortunei* | Antagonistic effect on fungus | [104] |
| Cyclo(l-Leu-l-Leu-d-Leu-l-Leu-l-Leu) (99) | Endophytic fungus *Fusarium decempertitale* LG53 from Chinese medicinal plant *Mahonia fortunei* | Antagonistic effect on fungus | [104] |
| Cyclo(l-Leu-l-Leu-d-Leu-l-Leu-l-leu) (100) | Endophytic fungus *Fusarium decempertitale* LG53 from Chinese medicinal plant *Mahonia fortunei* | Antagonistic effect on fungus | [104] |
| Cyclo(l-Phe-l-Leu-l-Leu-l-Leu-l-Leu-l-Ile) (101) | Unidentified endophytic fungus No. 2524 from the mangrove *Avicennia marina* | - | [105] |
| Cyclo(l-Phe-l-Leu-l-Leu-l-Leu-l-Leu-l-leu) (102) | Endophytic fungus *Cryptosporiopsis* sp. of *Zanthoxylum leptocarpum* | Motility inhibitory and lytic activities against zoospores; Antifungal activity; Weak cytotoxic activity on brine shrimp larvae | [103] |
| Cyclosaspeptide A (103) | *Aspergillus sp. NE-45* | - | [85] |
| | *Penicillium algidum* | Antiplasmodial activity | [18] |
| | *Penicillium jamesonlandense* | - | [106] |
| | *Penicillium janczewskii* | - | [107] |
| | *Penicillium lanosum* | - | [106] |
| | *Penicillium ribiun* | - | [106] |
| | *Penicillium rubeculum* from a soil under the tree *Ribes sp.* | - | [20] |
| Cyclosaspeptide B (104) | *Aspergillus sp. NE-45* | - | [85] |
| Cyclosaspeptide C (105) | *Aspergillus sp. NE-45* | - | [85] |
| Cyclosaspeptide D (106) | *Penicillium algidum* | Antiplasmodial activity | [18] |
| | *Penicillium rubeculum* from a soil under the tree *Ribes sp.* | - | [20] |
Table 3. Cont.

| Name                       | Fungus and Its Origin                  | Biological Activity                                      | Ref.         |
|---------------------------|----------------------------------------|----------------------------------------------------------|--------------|
| Cycloaspeptide E (107)    | *Penicillia sp.*                       | Insecticidal activity                                   | [86]         |
|                           | *Tricothecium sp.*                     |                                                          |              |
| Cycloaspeptide F (108)    | *Isaria farinosa*                      | Cytotoxic activity                                       | [87]         |
| Cycloaspeptide G (109)    | *Isaria farinosa*                      | Cytotoxic activity                                       | [87]         |
| Cyclochlorotine (110)     | *Penicillium islandicum*               | Liver fibrosis, liver injuries                          | [108–110]    |
| Hydroxycyclochlorotin (111)| *Penicillium islandicum*               |                                                          | [108]        |
| Islanditoxin (112)       | *Penicillium islandicum*               |                                                          | [111]        |
| Lajollamide A (113)       | Marine-derived fungus *Asteromyces cruciatus* | Weak antibacterial on Gram-positive bacteria         | [112]        |
| Malformin A1 (114)        | *Aspergillus niger*                    | Malformation activity in the corn root; Cytotoxic activity | [92,93]      |
|                           | *Aspergillus tubingensis*              | Cytotoxic activity; Anti-TMV activity                   | [89,90]      |
| Malformin A2 (115)        | *Aspergillus niger*                    |                                                          | [92]         |
| Malformin B1a (116)       | *Aspergillus niger*                    | Curvature activity in the corn root test                | [88]         |
| Malformin B1b (117)       | *Aspergillus niger*                    |                                                          | [88]         |
| Malformin B2 (118)        | *Aspergillus niger*                    |                                                          | [88]         |
| Malformin C (119)         | *Aspergillus niger*                    | Anticancer activity                                     | [94,95]      |
| Malformin E (120)         | Endophytic fungus *Aspergillus tamari* from *Ficus carica* | Cytotoxic and antibiotic activity                      | [91]         |
| MBJ-0174 (121)            | *Mortierella alpina* $f28740$ from a soil sample collected in Ise, Japan | Stimulators of cellular fibrinolytic activity          | [113]        |
| PF1171B (122)             | *Hamigera sp.*                         |                                                          | [99]         |
| PF1171D (123)             | *Hamigera sp.*                         |                                                          | [99]         |
| PF1171E (124)             | *Hamigera sp.*                         |                                                          | [99]         |
| Pseudacyclin A (125)      | Animal fungal pathogen *Pseudallescheria boydii* | Immunosuppressive activity                              | [96]         |
| Pseudacyclin B (126)      | Animal fungal pathogen *Pseudallescheria boydii* |                                                          | [96]         |
| Pseudacyclin C (127)      | Animal fungal pathogen *Pseudallescheria boydii* |                                                          | [96]         |
| Pseudacyclin D (128)      | Animal fungal pathogen *Pseudallescheria boydii* |                                                          | [96]         |
| Pseudacyclin E (129)      | Animal fungal pathogen *Pseudallescheria boydii* |                                                          | [96]         |
| Versicoloritide A (130)   | *Aspergillus versicolor* LCJ-5-4       |                                                          | [114]        |
| Versicoloritide B (131)   | *Aspergillus versicolor* LCJ-5-4       |                                                          | [114]        |
| Versicoloritide C (132)   | *Aspergillus versicolor* LCJ-5-4       |                                                          | [114]        |
| Versicotide A (133)       | *Aspergillus versicolor* ZLN-60 from the sediment of the Yellow Sea |                                                          | [115]        |
Table 3. Cont.

| Name               | Fungus and Its Origin                          | Biological Activity | Ref. |
|--------------------|------------------------------------------------|---------------------|------|
| Versicotide B (134)| *Aspergillus versicolor* ZLN-60 from the sediment of the Yellow Sea | -                   | [115]|
| Xylarotide A (135) | *Xylaria* sp. 101                              | -                   | [116]|
| Xylarotide B (136) | *Xylaria* sp. 101                              | -                   | [116]|

**Figure 3. Cont.**
Figure 3. Cont.
Figure 3. Structures of the cyclic pentapeptides isolated from fungi.

5. Cyclic Hexapeptides

About 40 cyclic hexapeptides have been isolated from fungi. Their distributions in fungi, and biological activities are shown in Table 4, and the structures are provided in Figure 4.

Aculeacin A (137) was isolated from Aspergillus aculeatus M-4214. This compound showed marked antifungal activity by inhibiting synthesis of β-1,3-glucan [117,118].

The echinocandins have emerged as first-line antifungal agents for many Candida and Aspergillus infections. They have a unique mechanism of action by inhibiting the synthesis of β-1,3-D-glucan, a key component of the fungal cell wall. Caspofungin was the first echinocandin antifungal agent to become licensed for treatment of invasive fungal infections [119]. Caspofungin has been used in immunocompromised children and neonates with invasive fungal infections [120]. The second
commercial antifungal agent in the echinocandin series was micafungin which has been used worldwide in chemotherapy for life-threatening fungal infections [121].

Mulundocandin (159) and deoxymulundocandin (143) were isolated from Aspergillus sydowii [122] and Aspergillus mulundensis [123], respectively. Both compounds showed antifungal activity against yeasts and filamentous fungi.

PF1171A (161) and PF1171C (162) were isolated from an unidentified ascomycete OK-128. Both compounds showed paralytic activity against silkworms [124]. PF1171C (162) was reisolated as similanamide (162) from the marine sponge-associated fungus Aspergillus similanensis KUFA 0013. It showed weak cytotoxic activity against the cancer cell lines [125,126].

Pneumocandin analogues (165–172) were isolated from Zalerion arboricola. They all showed anticandial activity by inhibiting 1,3-β-D-glucan synthesis [127,128].

Sclerotides A (173) and B (174) were isolated from Aspergillus sclerotiorum PT06-1. They all showed moderate antifungal activity against Candida albicans. In addition, sclerotide B (174) exhibited antibacterial and cytotoxic activities [129].

### Table 4. Fungal cyclic hexapeptides and their biological activities.

| Name                  | Fungus and Its Origin                                      | Biological Activity                                              | Ref.     |
|-----------------------|------------------------------------------------------------|------------------------------------------------------------------|----------|
| Aculeacin A (137)     | Aspergillus aculeatus M-4214                                | Antifungal activity by inhibiting synthesis of β-1,3-glucan      | [117,118]|
| Anthracine (138)      | Acremonium sp. A29-2004                                    |                                                                  | [130]    |
| ASP2397 (139)         | Acremonium persicinum MF-347833 from Malaysian leaf litter | Antifungal activity                                              | [131]    |
| AS2524371 (140)       | Acremonium persicinum MF-347833 from Malaysian leaf litter |                                                                  | [131]    |
| Deoxymulundocandin (143) | Aspergillus sydowii                                      | Antifungal activity                                              | [133]    |
| Cryptocandin (142)    | Cryptosporiopsis cf. quercina                               | Antifungal activity                                              | [132]    |
| Echinocandin B (144)  | Aspergillus nidulans var. roseus ATCC 58397                | Antifungal activity                                              | [134]    |
|                       | Aspergillus mulundensis                                    |                                                                  | [123]    |
| Echinocandin C (145)  | Aspergillus sp.                                            | Antifungal activity                                              | [135]    |
|                       | Aspergillus mulundensis                                    | Antifungal activity                                              | [123]    |
| Echinocandin D (146)  | Aspergillus sp.                                            | Antifungal activity                                              | [135]    |
| Ferrichrome (147)     | Ustilago maydis                                            |                                                                  | [136]    |
| Ferrichrome A (148)   | Ustilago maydis                                            |                                                                  | [136]    |
| Ferricrocin (149)     | Colletotrichum gloeosporioides                             | Phytotoxic activity                                              | [137]    |
| Ferrirhodin (150)     | Botrytis cinerea                                           |                                                                  | [138]    |
| FR190295 (151)        | Tolypocladium parasiticum No. 16616                       | Antifungal activity                                              | [139]    |
| FR209602 (152)        | Coleophoma crateriformis No. 738                          | Antifungal activity                                              | [140]    |
| FR209603 (153)        | Coleophoma crateriformis No. 738                          | Antifungal activity                                              | [140]    |
| FR209604 (154)        | Coleophoma crateriformis No. 738                          | Antifungal activity                                              | [140]    |
| FR220897 (155)        | Coleophoma empetri No. 14573                              | Antifungal activity                                              | [141]    |
| FR220899 (156)        | Coleophoma empetri No. 14573                              | Antifungal activity                                              | [141]    |
| FR227673 (157)        | Chalara sp. No. 22210                                      | Antifungal activity                                              | [139]    |
| FR901379 (158)        | Coleophoma empetri F-11899                                | Antifungal activity                                              | [142]    |
| Mulundocandin (159)   | Aspergillus sydowii                                       | Antifungal activity                                              | [122]    |
|                       | Aspergillus mulundensis                                    | Antifungal activity                                              | [123]    |
| Penitropeptide (160)  | Endophytic fungus Penicilium tropicum isolated from leaves of Sapium ellipticum |                                                                  | [143]    |
| PF1171A (161)         | Unidentified ascomycete OK-128                            | Paralytic activity against silkworms                             | [124]    |
Table 4. Cont.

| Name                                      | Fungus and Its Origin                  | Biological Activity                                                                 | Ref. |
|-------------------------------------------|----------------------------------------|-------------------------------------------------------------------------------------|------|
| PFI171C = Similanamide (162)              | Marine sponge-associated fungus        | Antipneumocystis, anticandida and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
|                                           | Aspergillus similanensis KUFA 0013     | Weak cytotoxic activity against the cancer cell lines                                 | [125,126] |
|                                           | Hamigera sp.                           | -                                                                                   | [99] |
| PFI171F (163)                             | Unidentified ascomyete OK-128          | Paralytic activity against silkworms                                                | [124] |
| PFI171G (164)                             | Unidentified ascomyete OK-128          | Paralytic activity against silkworms                                                | [144] |
| Pneumocandin A0 = L-671,329 (165)         | Zalerion arboricola                    | Antifungal activity                                                                  | [145] |
|                                           |                                       | Antipneumocystis, anticandida and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin A1 (166)                     | Zalerion arboricola                    | Anticandida activity and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin A2 (167)                     | Zalerion arboricola                    | Anticandida activity and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin A3 (168)                     | Zalerion arboricola                    | Anticandida activity and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin A4 (169)                     | Zalerion arboricola                    | Anticandida activity and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin B0 (170)                     | Zalerion arboricola                    | Antipneumocystis, anticandida and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin B2 (171)                     | Zalerion arboricola                    | Antipneumocystis, anticandida and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Pneumocandin C0 (172)                     | Zalerion arboricola                    | Antipneumocystis, anticandida and Candida albicans 1,3-β-D-glucan synthesis inhibition activity | [127,128] |
| Sclerotide A (173)                        | Aspergillus sclerotiorum PT06-1        | Antifungal activity                                                                  | [129] |
| Sclerotide B (174)                        | Aspergillus sclerotiorum PT06-1        | Antifungal, antibacterial and cytotoxic activity                                     | [129] |
| Simplicilliumtide M (175)                 | Deep-sea derived Simplicillium obclavatum EIODSF 020 | -                                                                                  | [146] |
| Versicotide C (176)                       | Aspergillus versicolor ZLN-60          | -                                                                                  | [23] |

Figure 4. Cont.
Figure 4. Cont.
Figure 4. Cont.
6. Cyclic Heptapeptides

There are 37 cyclic heptapeptides isolated from fungi. Their distributions in fungi, and biological activities are listed in Table 5, and the structures are shown in Figure 5.

Cordyheptapeptides A (179) and B (180) were isolated from Cordyceps sp. which is an insect fungal pathogen [147,148]. Cordyheptapeptides C (181), D (182) and E (183) were isolated from the marine-derived fungus Acremonium persicinum SCSIO 115 [149]. Cordyheptapeptides A (179), B (180), C (181) and E (183) all showed cytotoxic activity [148,149].

Phallotoxins (191–197) were bicyclic heptapeptides cross-linked by the 2'-bound sulfur group from the poisonous mushroom Amanita phalloides. Seven phallotoxins: phallacidin (191), phallacin (192), phallisacine (193), phallisin (194), phallolidin (195), phalloin (196), and prophallin (197), have been identified so far [150]. Phallotoxins were shown to be ribosomally synthesized and posttranslationally modified peptides (RiPPs) [151].

Scytalediamides A (198) and B (199) were isolated from Acremonium sp. [152] and Scytaledium sp. [153], respectively. Both compounds showed cytotoxic activity toward HCT-116 human colon adenocarcinoma with IC50 values of 2.7 and 11.0 µM, respectively [153].

Unguisins A–D (206–209) were isolated from Emericella unguis [154,155], unguisin E (210) from Aspergillus sp. AF119 [156] and Mucor irregularis [157], and unguisin F (211) from Mucor irregularis [157]. Only unguisins A (206) and B (207) were screened to display moderate antibacterial activity [154,155]. Further investigation showed that unguisin A (206) was an anion receptor with high affinity for phosphate and pyrophosphate [158].

Virotoxins (177,178,184,185,212,213) are mono-cyclic heptapeptides containing a tryptophan residue substituted at position 2 of the indol ring by a sulfur atom. A series of virotoxins such as aladesoxiviroidin (177), alaviroidin (178), deoxoviroidin (184), deoxyviroisin (185), viroidin (212), and viroisin (213) have been identified from the mushrooms Amanita phalloides and Amanita virosa so far. They were toxic to animals [150,159].

Table 5. Fungal cyclic heptapeptides and their biological activities.

| Name                  | Fungus and Its Origin | Biological Activity                  | Ref.   |
|-----------------------|-----------------------|--------------------------------------|--------|
| Aladesoxiviroidin (177) | Amanita phalloides     | Toxic to some animal species          | [150]  |
| Alaviroidin (178)     | Amanita phalloides     | Toxic to some animal species          | [150]  |
| Cordyheptapeptide A (179) | Cordyceps sp. BCC1788 | Antimalarial activity against Plasmodium falciparum K1 | [147]  |
| Cordyheptapeptide B (180) | Cordyceps sp. BCC 16176 | Cytotoxic activity                   | [148]  |
| Cordyheptapeptide C (181) | Acremonium persicinum SCSIO 115 | Cytotoxic activity                   | [149]  |
| Cordyheptapeptide D (182) | Acremonium persicinum SCSIO 115 | -                                   | [149]  |
| Cordyheptapeptide E (183) | Acremonium persicinum SCSIO 115 | Cytotoxic activity                   | [149]  |
**Table 5. Cont.**

| Name                           | Fungus and Its Origin | Biological Activity                  | Ref.   |
|--------------------------------|-----------------------|--------------------------------------|--------|
| Deoxoxvirodin (184)            | Mushroom Amanita caesarea | Hepatotoxicity                      | [159]  |
| Deoxoxvirosin (185)            | Mushroom Amanita caesarea | Hepatotoxicity                      | [159]  |
| Epichloeo1en B (186)           | *Epichloë festucae*    | -                                    | [160]  |
| Mortiamide A (187)             | Marine-derived Mortierella sp. | -                                    | [161]  |
| Mortiamide B (188)             | Marine-derived Mortierella sp. | -                                    | [161]  |
| Mortiamide C (189)             | Marine-derived Mortierella sp. | -                                    | [161]  |
| Phallacidin (191)              | Amanita phalloides      | Toxic to some animal species         | [150]  |
| Phallacin (192)                | Amanita phalloides      | Toxic to some animal species         | [150]  |
| Phallacin (193)                | Amanita phalloides      | Toxic to some animal species         | [150]  |
| Phallisin (194)                | Amanita phalloides      | Toxic to some animal species         | [150]  |
| Phalloin (196)                 | Amanita phalloides      | Toxic to some animal species         | [150]  |
| Prophallin (197)               | Amanita phalloides      | Toxic to some animal species         | [150]  |

| Scytalidamide A (198)          | *Acremonium* sp.        | -                                    | [152]  |
| Scytalidamide B (199)          | *Acremonium* sp.        | -                                    | [152]  |

| Serinocyclin A (200)           | *Metarhizium anisopliae* | Insecticidal activity on mosquito larvae | [162]  |
| Serinocyclin B (201)           | *Metarhizium anisopliae* | -                                    | [162]  |
| Talarodiode A (202)            | Marine tunicte-associated fungus *Talaromyces* sp. CMB-TU011 | -                                    | [163]  |
| Talaromin A (203)              | *Talaromyces wortmannii* | -                                    | [164]  |
| Talaromin B (204)              | *Talaromyces wortmannii* | -                                    | [164]  |
| Ternatin (205)                 | *Cladobotryum* sp.      | Cytotoxic activity; antifungal activity | [165]  |

| Unguisin A (206)               | Marine-derived *Emericella unguis* | Moderate antibacterial activity | [154], [155] |
| Unguisin B (207)               | Marine-derived *Emericella unguis* | Moderate antibacterial activity | [154], [155] |
| Unguisin C (208)               | Marine-derived *Emericella unguis* | -                                    | [155]  |
| Unguisin D (209)               | Marine-derived *Emericella unguis* | -                                    | [155]  |
| Unguisin E (210)               | *Aspergillus* sp. AF119 | -                                    | [156]  |
| Unguisin F (211)               | Endophytic fungus *Mucor irregularis* from the medicinal plant *Moringa stenopetala* | -                                    | [157]  |
| Viroisin (212)                 | Mushroom Amanita caesarea | -                                    | [159]  |
| Viroisin (213)                 | Mushroom Amanita caesarea | Toxic to some animal species         | [159]  |

![Figure 5. Cont.](image-url)
Figure 5. Cont.
7. Cyclic Octapeptides

The distributions and biological activities of fungal cyclic octapeptides are listed in Table 6, and the structures are shown in Figure 6.

Fungal cyclic octapeptides mainly include the amatoxins, which are bicyclic octapeptides distributed in the poisonous mushroom *Amanita phalloides*. Nine amatoxin analogs amanin (214), amanin amide (215), amanullin (216), amanullinic acid (217), α-amanitin (218), β-amanitin (219), γ-amanitin (220), ε-amanitin (221), and proamanullin (225) have been identified [150]. The most important biochemical effect of amatoxins is the inhibition of RNA polymerases (especially polymerase II). This interaction leads to a tight complex, and the inhibition is of a non-competitive type. Non-mammalian polymerases show little sensitivity to amanitins. The amatoxins cause necrosis of the liver, also partly in the kidney, with the cellular changes causing the fragmentation and segregation of all nuclear components. Various groups of somatic cells of emanation resistance have been isolated, including from a mutant of *Drosophila melanogaster* [150].

Amatoxins are synthesized as proproteins on ribosomes, and are considered as ribosomally synthesized and post-translationally modified peptides (RiPPs). The proproteins are 34–35 amino acids in length and do not have predicted signal peptides [151].

Epichlicin (222) was isolated from the endophytic fungus *Epichloe typhina* from the timothy plant (*Pheum pretense*). This compound exhibited inhibitory activity toward the spore germination of *Cladosporium phleii*, a fungal pathogen of the timothy plant at an IC50 value of 22 nM [166].

Both epichloeamide (223) and epichloenin A (224) were identified from the endophytic fungus *Epichloe festucae* and endophyte-infected *Lolium perenne* [160].

Shearamide A (226) was isolated from the ascostromata of *Eupenicillium shearii*. This compound showed insecticidal effect against *Helicoverpa zea* larvae [167].

Table 6. Fungal cyclic octapeptides and their biological activities.

| Name               | Fungus and Its Origin | Biological Activity            | Ref.   |
|--------------------|------------------------|---------------------------------|--------|
| Amanin (214)       | *Amanita phalloides*   | Toxic to some animal species    | [150]  |
| Amanin amide (215) | *Amanita phalloides*   | Toxic to some animal species    | [150]  |
| Amanullin (216)    | *Amanita phalloides*   | Toxic to some animal species    | [150]  |
| Amanullinic acid (217) | *Amanita phalloides*   | Toxic to some animal species    | [150]  |
|                    | *Amanita exitialis*    |                                 |        |
| α-Amanitin (218)   | *Amanita subjunquillea* | Cytotoxic activity              | [169]  |
|                    | *Amanita phalloides*   | Toxic to some animal species    | [150]  |

Figure 5. Structures of the cyclic heptapeptides isolated from fungi.
### Table 6. Cont.

| Name          | Fungus and Its Origin | Biological Activity               | Ref.   |
|---------------|-----------------------|-----------------------------------|--------|
| β-Amanitin (219) | Amanita exitialis | Cytotoxic activity                | [168]  |
| γ-Amanitin (220) | Amanita phalloides | Toxic to some animal species      | [150]  |
| ε-Amanitin (221) | Amanita phalloides | Toxic to some animal species      | [150]  |
| Epichlicin (222) | Endophyte Epichloe typhina from Phleum pratense | Inhibitory activity on the spore germination of Cladosporium phlei | [166]  |
| Epichloeamide (223) | Epichloe festucae | -                                 | [160]  |
| Epichloenin A (224) | Epichloe festucae | -                                 | [160]  |
| Proamanullin (225) | Amanita phalloides | Toxic to some animal species      | [150]  |
| Shearamide A (226) | Eupenicillium shearii | Insecticidal effect              | [167]  |

![Figure 6. Structures of the cyclic octapeptides isolated from fungi.](image)

#### 8. Cyclic Nonapeptides

Only four cyclic nonapeptides have been identified in fungi, with their occurrence, biological activities and structures shown in Table 7 and Figure 7, respectively. Amanexitide (227) was isolated from the fruiting bodies of *Amanita exitialis*, a poisonous mushroom endemic in China [168]. Both clonostachysins A (228) and B (229) were obtained from a marine sponge-derived fungus *Clonostachys rogersoniana* strain HJK9. They exhibited a selectively inhibitory activity on the dinoflagellate *Prorocentrum micans* at 30 µM [170]. Cylindrocyclin A (230) from *Cylindrocarpon* sp. exhibited cytotoxic activity against six cell lines with IC₅₀ values ranging from 11 to 53 µM [171].
Table 7. Fungal cyclic nonapeptides and their biological activities.

| Name               | Fungus and Its Origin                  | Biological Activity          | Ref. |
|--------------------|----------------------------------------|------------------------------|------|
| Amanexitide (227)  | Amanita exitialis                      | -                            | [168]|
| Clonostachysin A (228) | Marine-derived fungus Clonostachys rogersoniana HJK9 from sponge | Anti-dinoflagellate activity | [170]|
| Clonostachysin B (229) | Marine-derived fungus Clonostachys rogersoniana HJK9 from sponge | Anti-dinoflagellate activity | [170]|
| Cylindrocyclin A (230) | Cylindrocarpon sp.                 | Cytotoxic activity           | [171]|

Figure 7. Structures of the cyclic nonapeptides isolated from fungi.

9. Cyclic Decapeptides

A total of seven cyclic decapeptides were identified in fungi. Their distributions, biological activities and structures are shown in Table 8 and Figure 8.

Antamanide (231) derived from the fungus Amanita phalloides inhibited the mitochondrial permeability transition pore, a central effector of apoptosis induction, by targeting the pore regulator cyclophillin D [172].

Arborcandins A–F (232–237) were isolated from the culture broth of an unidentified filamentous fungus SANK 17397. They possessed potent 1,3-β-glucan synthase inhibitory activity [173,174].

Figure 8. Cont.
This compound showed antifungal activity, and was capable of prolonging the survival time of skin swelling and protected against delayed neuronal cell death [185]. Stachybotrys chartarum inhibition of calcineurin, and production of IL-2 and other cytokines [176].

It has a variety of biological activities including immunosuppressive, anti-inflammatory, antifungal and antiparasitic properties. The mechanism of action has been considered as the phosphatase activity.

It was mainly produced by various types of fermentation techniques using fungi such as Trichoderma polysporum [180], Aspergillus fumigatus [177], Aspergillus terreus [178], Beauveria nivea [179], Fusarium oxysporum [180], Trichoderma polysporum [181], Tolypocladium inflatum [182], and Tolypocladium sp. [183]. It was mainly produced by various types of fermentation techniques using Tolypocladium inflatum. It has a variety of biological activities including immunosuppressive, anti-inflammatory, antifungal and antiparasitic properties. The mechanism of action has been considered as the phosphatase activity inhibition of calcineurin, and production of IL-2 and other cytokines [176].

FR901459 (263), a derivative of cyclosporin A (238), was discovered in the fermentation broth of Stachybotrys chartarum No. 19392 (isolated from soil collected in Tokyo Prefecture, Japan). This compound showed antifungal activity, and was capable of prolonging the survival time of skin allografts in rats with one-third the potency of cyclosporin A [184]. It also prevented mitochondrial swelling and protected against delayed neuronal cell death [185].

### Table 8. Fungal cyclic decapeptides and their biological activities.

| Name                | Fungus and Its Origin | Biological Activity                                                                 | Ref.   |
|---------------------|-----------------------|-------------------------------------------------------------------------------------|--------|
| Antamanide (231)    | Amanita phalloides    | Inhibition of the mitochondrial permeability transition pore, antidote activity against phallotoxins and amatoxins, inhibition of tumor cell growth in vitro | [172,175] |
| Arborcandin A (232) | Unidentified fungus SANK 17997 | Inhibitory activity on 1,3-β-glucan synthase                                        | [173,174] |
| Arborcandin B (233) | Unidentified fungus SANK 17997 | Inhibitory activity on 1,3-β-glucan synthase                                        | [173,174] |
| Arborcandin C (234) | Unidentified fungus SANK 17997 | Inhibitory activity on 1,3-β-glucan synthase                                        | [173,174] |
| Arborcandin D (235) | Unidentified fungus SANK 17997 | Inhibitory activity on 1,3-β-glucan synthase                                        | [173,174] |
| Arborcandin E (236) | Unidentified fungus SANK 17997 | Inhibitory activity on 1,3-β-glucan synthase                                        | [173,174] |
| Arborcandin F (237) | Unidentified fungus SANK 17997 | Inhibitory activity on 1,3-β-glucan synthase                                        | [173,174] |

### 10. Cyclic Undecapeptides

Twenty-six cyclosporin analogs were identified in fungi. They belong to the cyclic undecapeptide group, and their distributions, biological activities and structures are shown in Table 9 and Figure 9, respectively.

Among them, cyclosporin A (238) has received the most meticulous attention owing to its immunosuppressive and antifungal activity [176]. Cyclosporin A (238) can be produced by a series of fungi such as Aspergillus fumigatus [177], Aspergillus terreus [178], Beauveria nivea [179], Fusarium oxysporum [180], Trichoderma polysporum [181], Tolypocladium inflatum [182], and Tolypocladium sp. [183]. It was mainly produced by various types of fermentation techniques using Tolypocladium inflatum. It has a variety of biological activities including immunosuppressive, anti-inflammatory, antifungal and antiparasitic properties. The mechanism of action has been considered as the phosphatase activity inhibition of calcineurin, and production of IL-2 and other cytokines [176].

FR901459 (263), a derivative of cyclosporin A (238), was discovered in the fermentation broth of Stachybotrys chartarum No. 19392 (isolated from soil collected in Tokyo Prefecture, Japan). This compound showed antifungal activity, and was capable of prolonging the survival time of skin allografts in rats with one-third the potency of cyclosporin A [184]. It also prevented mitochondrial swelling and protected against delayed neuronal cell death [185].
Figure 9. Structures of the cyclic undecapeptides isolated from fungi.
Table 9. Fungal cyclic undecapeptides and their biological activities.

| Name | Fungus and Its Origin | Biological Activity | Ref. |
|------|-----------------------|---------------------|------|
| Cyclosporin A (238) | Aspergillus fumigatus<br>Aspergillus terreus NRC FA 200<br>Beauveria nivea<br>Fusarium oxysporum<br>Tolypocladium inflatum<br>Tolypocladium sp.<br>Trichoderma polysporum | Immunosuppressive, antifungal, anti-inflammatory, anti-parasitic and anticancer activities<br>-<br>-<br>Antifungal activity | [177,178,179,180,182,183,181] |
| Cyclosporin B (239) | Tolypocladium inflatum<br>Trichoderma polysporum | Immunosuppressive and antifungal activities<br>Antifungal activity | [182,186,181] |
| Cyclosporin C (240) | Acremonium luchae<br>Tolypocladium inflatum | Antifungal activity | [187] |
| Cyclosporin D (241) | Tolypocladium inflatum<br>Trichoderma polysporum | Immunosuppressive and antifungal activities<br>Antifungal activity | [182,186,181] |
| Cyclosporin E (242) | Trichoderma polysporum<br>Tolypocladium inflatum | Immunosuppressive and antifungal activities<br>- | [181,186,188] |
| Cyclosporin F (243) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186,188] |
| Cyclosporin G (244) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [182,186,188] |
| Cyclosporin H (245) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [188] |
| Cyclosporin J (247) | Tolypocladium terricola | Increased cell proliferation | [189] |
| Cyclosporin K (248) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin L (249) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin M (250) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin N (251) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin O (252) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin P (253) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin Q (254) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin S (255) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin T (256) | Epichloe bromicola<br>Tolypocladium inflatum | Antifungal activity<br>Immunosuppressive and antifungal activities | [180,186] |
| Cyclosporin U (257) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin V (258) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin W (259) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin X (260) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin Y (261) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| Cyclosporin Z (262) | Tolypocladium inflatum | Immunosuppressive and antifungal activities | [186] |
| FR901459 (263) | Stachybotrys chartarum No. 19392 from a soil collected in Tokyo, Japan | Immunosuppressive activity | [184] |

11. Cyclic Dodecapeptides

Omphalotin analogs are the only cyclic dodecapeptides isolated from fungi so far. Omphalotins (264–272) were isolated from the basidiomycetes mushroom Omphalotus olearius. These compounds are toxic to humans and animals. Their distributions, biological activities and structures are shown in Table 10 and Figure 10, respectively. Nine cyclic dodecapeptides omphalotins A–I (264–272) with nematicidal activity were identified in the mushroom O. olearius [191,192]. They have been considered as the potent nematicidal agents that seemed to be highly selective for Meloidogyne incognita [193]. Omphalotins were recently identified as the ribosomally synthesized and posttranslationally modified peptides (RiPPs). A self-sacrificing N-methyltransferase was shown to be the precursor of omphalotin A (264) [194–196].
Table 10. Fungal cyclic dodecapeptides and their biological activities.

| Name            | Fungus and Its Origin    | Biological Activity                                    | Ref.              |
|-----------------|--------------------------|--------------------------------------------------------|-------------------|
| Omphalotin A    | Mushroom *Omphalotus olearius* | Nematicidal activity                                   | [191,197–199]    |
| Omphalotin B    | Mushroom *Omphalotus olearius* | Nematicidal activity                                   | [191]             |
| Omphalotin C    | Mushroom *Omphalotus olearius* | Nematicidal activity                                   | [191]             |
| Omphalotin D    | Mushroom *Omphalotus olearius* | Nematicidal activity                                   | [191]             |
| Omphalotin E    | Mushroom *Omphalotus olearius* | Nematicidal activity on *Meloidogyne incognita*         | [192]             |
| Omphalotin F    | Mushroom *Omphalotus olearius* | Nematicidal activity on *Meloidogyne incognita*         | [192]             |
| Omphalotin G    | Mushroom *Omphalotus olearius* | Nematicidal activity on *Meloidogyne incognita*         | [192]             |
| Omphalotin H    | Mushroom *Omphalotus olearius* | Nematicidal activity on *Meloidogyne incognita*         | [192]             |
| Omphalotin I    | Mushroom *Omphalotus olearius* | Nematicidal activity on *Meloidogyne incognita*         | [192]             |

Figure 10. Structures of the cyclic dodecapeptides isolated from fungi.

264. *Oompha-metalin*-I
265. *Oompha-metalin*-II, $R_1=\text{3-hydroxy-3-methylbutanoyl}$, $R_2=\text{H}$
266. *Oompha-metalin*-III, $R_1=\text{3-hydroxy-3-methylbutanoyl}$, $R_2=\text{acetyl}$
267. *Oompha-metalin*-IV, $R_1=\text{R}_2=\text{acetyl}$
268. *Oompha-metalin*-V, $R_1=R_2=R_3=\text{H}$
269. *Oompha-metalin*-VI, $R_1=R_2=\text{H}$, $R_3=\text{OH}$
270. *Oompha-metalin*-VII, $R_1=R_2=\text{H}$, $R_3=\text{OH}$
271. *Oompha-metalin*-VIII, $R_1=R_2=\text{OAc}$, $R_3=\text{OH}$
272. *Oompha-metalin*-IX, $R_1=\text{OCOC}_{\text{H}}\text{C}(\text{CH})_{\text{A}}\text{OH}$, $R_2=\text{OAc}$, $R_3=\text{OH}$
12. Cyclic Tetradecapeptides

Only four cyclic tetradecapeptides, verrucamides A–D (273–276), were identified from the plant pathogenic fungus *Myrothecium verrucaria* that attacked important crop plants and weeds. Their distributions, biological activities and structures are shown in Table 11 and Figure 11, respectively. They were screened to show antibacterial activity against *Staphylococcus aureus* [200].

Table 11. Fungal cyclic tetradecapeptides and their biological activities.

| Name              | Fungus and Its Origin                  | Biological Activity                          | Ref.    |
|-------------------|---------------------------------------|----------------------------------------------|---------|
| Verrucamide A (273) | Plant pathogenic fungus *Myrothecium verrucaria* on crops and weeds | Antibacterial activity on *Staphylococcus aureus* | [200]   |
| Verrucamide B (274) | Plant pathogenic fungus *Myrothecium verrucaria* on crops and weeds | Antibacterial activity on *Staphylococcus aureus* | [200]   |
| Verrucamide C (275) | Plant pathogenic fungus *Myrothecium verrucaria* on crops and weeds | Antibacterial activity on *Staphylococcus aureus* | [200]   |
| Verrucamide D (276) | Plant pathogenic fungus *Myrothecium verrucaria* on crops and weeds | Antibacterial activity on *Staphylococcus aureus* | [200]   |

Figure 11. Structures of the cyclic tetradecapeptides isolated from fungi.

13. Cyclic Octadecapeptides

Only two highly N-methylated cyclic octadecapeptides namely gymnopeptides A (277) and B (278) were isolated from the mushroom *Gymnopus fusipes* (Table 12 and Figure 12). They exhibited striking antiproliferative activity on several human cancer cell lines [201]. So far, gymnopeptides A (277) and B (278), constituted by 18 monomers, are the largest cyclic peptides to be isolated from fungi. Fortunately, the total synthesis of gymnopeptides A (277) and B (278) has been achieved [202]. Further biological studies are needed to clarify the aspects of absorption and metabolism of gymnopeptides A (277) and B (278) after consumption of the fruiting bodies by humans, as well as to explore the potential role of these metabolites in the parasitic lifestyle of the mushroom *G. fusipes*.

Table 12. Fungal cyclic octadecapeptides and their biological activities.

| Name              | Fungus and its Origin                  | Biological Activity                          | Ref.    |
|-------------------|---------------------------------------|----------------------------------------------|---------|
| Gymnopeptide A (277) | Mushroom *Gymnopus fusipes*           | Antiproliferative activity on several human cancer cell lines | [201]   |
| Gymnopeptide B (278) | Mushroom *Gymnopus fusipes*           | Antiproliferative activity on several human cancer cell lines | [201]   |
Cochliobus victoriae (previously as Tyr-Ala-Ile-Gly, that was converted into the cyclic moiety of ustiloxin B (peptide is not clear yet though [214]).

The oxidative cyclization of the core inactivation, heterologous expression, and in vitro functional analyses the entire biosynthetic pathway synthesized and post-translationally modified peptides (RiPPs). The cluster possessed a gene, termed a non-proteinogenic amino acid. They are biosynthesized by the ribosome, and are ribosomally synthesized and post-translationally modified peptides (RiPPs). The cluster possessed a gene, termed

Isolated from the water extract of the false smut balls caused by Ustilaginoidea virens and cytotoxic activities [206,207]. They have a structure similar to HV-toxin M (207). They have a structure similar to HV-toxin M (207). Phomopsins are mycotoxins known to be responsible for fatal liver disease of lupin-fed sheep, and displayed phytotoxic and cytotoxic activities [206,207].

HV-toxin M (282), with phytotoxic activity, was isolated from the plant pathogenic fungus Cochliobus victoriae (previously as Helminthosporium victoria) from oat (Avena sativa). This compound had three amino acids in the core rings, and two amino acids linked and attached as the side chains [204].

Phomopsins A (283), B (284) and F (285) were isolated from Phomopsis leptostromiformis [205,206] and Diaporthe toxica [207]. They have a structure similar to HV-toxin M (282). Phomopsins are mycotoxins known to be responsible for fatal liver disease of lupin-fed sheep, and displayed phytotoxic and cytotoxic activities [206,207].

Ustiloxins (286–291) have a 13-membered ring including a phenol ether linkage. They were isolated from the water extract of the false smut balls caused by Ustilaginoidea virens on the panicles of rice plants [208–212]. There are three amino acids in the core ring for each ustiloxin. For ustiloxins C (288), D (289), F (290) and G (291), there is a glycine in the side chain. For ustiloxins A (286) and B (287), there are two amino acids in the side chains, whose tyrosine was modified with norvaline, a non-proteinogenic amino acid. They are biosynthesized by the ribosome, and are ribosomally synthesized and post-translationally modified peptides (RiPPs). The cluster possessed a gene, termed ustA, whose translated product, UstA, contained a 16-fold repeated peptide embedding a tetrapeptide, Tyr-Ala-Ile-Gly, that was converted into the cyclic moiety of ustiloxin B (287) [213]. Through gene inactivation, heterologous expression, and in vitro functional analyses the entire biosynthetic pathway of the ustiloxins was unveiled to involve at least nine enzymes. The oxidative cyclization of the core peptide is not clear yet though [214].

14. Cyclic Peptides Containing Ether Bonds in the Core Ring

This group of cyclic peptides contained at least one ether linkage except the normal amide and carbon-carbon bonds in the core ring of each molecule. Their distributions, biological activities and structures are shown in Table 13 and Figure 13, respectively.

Asperipin-2a (279) containing five amino acids was isolated from Aspergillus flavus. It was a bicycle peptide containing two ether linkages that was converted from the repeated sequence containing aromatic residues [203].

HV-toxin M (282), with phytotoxic activity, was isolated from the plant pathogenic fungus Cochliobus victoriae (previously as Helminthosporium victoria) from oat (Avena sativa). This compound had three amino acids in the core rings, and two amino acids linked and attached as the side chains [204].

Phomopsins A (283), B (284) and F (285) were isolated from Phomopsis leptostromiformis [205,206] and Diaporthe toxica [207]. They have a structure similar to HV-toxin M (282). Phomopsins are mycotoxins known to be responsible for fatal liver disease of lupin-fed sheep, and displayed phytotoxic and cytotoxic activities [206,207].

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**Table 13.** Fungal cyclic peptides containing ether bonds in the core ring and their biological activities.

| Name | Fungus and Its Origin | Biological Activity | Ref. |
|------|----------------------|---------------------|------|
| Asperipin-2a (279) | Aspergillus flavus | - | [203] |
| S-Deoxyustiloxin H (280) | Aspergillus flavus | - | [214] |
| N-Desmethylustiloxin F (281) | Aspergillus flavus | - | [214] |
| HV-toxin M (282) | Plant pathogenic fungus Cochliobus victoriae (Helminthosporium victoria) from oat | Phytotoxic activity | [205] |
| Phomopsin A (283) | Plant pathogenic fungus Phomopsis leptostromiformis from lupinis (Lupinus spp.) | Phytotoxic activity, toxic to animals | [206] |
Table 13. Cont.

| Name               | Fungus and Its Origin                         | Biological Activity                        | Ref.     |
|--------------------|-----------------------------------------------|--------------------------------------------|----------|
| Phomopsin B (284)  | Plant pathogenic fungus *Phomopsis leptostromiformis* from lupinis (*Lupinus* spp.) | Toxic to animals                           | [207]    |
| Phomopsin F (285)  | Plant pathogenic fungus *Diaporthe toxica*    | Cytotoxic activity against Hepg2 cells      | [208]    |
| Ustiloxin A (286)  | Plant pathogenic fungus *Ustilaginoidea virens* from rice false smut balls | Cytotoxic, phytotoxic activities [209,211] |          |
| Ustiloxin B (287)  | Plant pathogenic fungus *Ustilaginoidea virens* from rice false smut balls | Cytotoxic, phytotoxic activities [209,211] |          |
|                    |                                               |                                             | [213]    |
| Ustiloxin C (288)  | Plant pathogenic fungus *Ustilaginoidea virens* from rice false smut balls | Cytotoxic, phytotoxic activities [208]    |          |
| Ustiloxin D (289)  | Plant pathogenic fungus *Ustilaginoidea virens* from rice false smut balls | Cytotoxic, phytotoxic activities [208]    |          |
| Ustiloxin F (290)  | Plant pathogenic fungus *Ustilaginoidea virens* from rice false smut balls | Cytotoxic, phytotoxic activities [209]    |          |
| Ustiloxin G (291)  | Plant pathogenic fungus *Ustilaginoidea virens* from rice false smut balls | Cytotoxic, phytotoxic activities [212]    |          |
| Ustiloxin H (292)  | Plant pathogenic fungus *Aspergillus flavus*  | Cytotoxic, phytotoxic activities           | [214]    |
| Victorin C (293)   | Plant pathogenic fungus *Cochliobus victoriae* = *Helminthosporium victoria* | Phytotoxic activity                        | [215]    |

Figure 13. Cont.
Villosiclva virens

[Images of structures of fungal cyclic peptides]

15. Conclusions and Future Perspectives

In this review, we describe the progress on the chemistry and biological activities of the cyclic peptides (excluding cyclic dipeptides and peptides containing ester bonds in the core ring) discovered from fungi during the past 50 years, especially the recent 20 years.

It seems that the fungi in genus Aspergillus can produce various types of cyclic peptides, especially cyclic tripeptides to pentapeptides, while the mushrooms, which we call macroscopic fungi, produce relatively big cyclic peptides such as amanin (an octapeptide), amanexitide (a nonapeptide), antamanide (decapptide), omphalotins (dodecapeptide), and gymnopeptides (octadecapeptides). Most of cyclosporins, which belong to the cyclic undecapeptides, show immunosuppressive and antifungal activities. The isolated cyclic dodecapeptides have nematicidal activity, tetracapeptides possess antibacterial activity, and octadecapeptides show antiproliferative activity on several human cancer cell lines. The cyclic peptides with a big ring seem to display more biological activities than the small-ring peptides.

Based on the biosynthetic machineries of fungal cyclic peptides, most of them belong to nonribosomal peptides (NRPs) which are synthesized by multimodular nonribosomal peptide synthetases (NRPSs). Just a few of them belong to the ribosomally synthesized and post-translationally modified peptides (RiPPs) such as α-amanitin (218) from Amanita excilis [150], asperipin-2a (279) from Aspergillus flavus [203], phallacidin (191) from Amanita bisporigera [216], phomopsin A (283) from Phomopsis leptostromiformis [206], and ustiloxins (286-291) from Ustilaginoidea virens (teleomorph: Glarea lozoyensis) [208,209,212] and Aspergillus flavus [214], omphalotins (260–268) from Omphalotus olearius [194–196].

Some fungal cyclic peptides have potential to be developed into pharmaceuticals and agrochemicals. Some cyclic tetrapeptides such as 1-alaninechlamydocin (24) [30], apicidin (25) [35], AS1387392 (36) [37] and trapoxin A (83) [31] show inhibitory activity on histone deacetylase (HDAC) and have potential applications as therapeutics for spinal muscular atrophy [36], anti-cancer agents [30], antiprotozoal agents [35], and immunosuppressants [37]. Some cyclic peptides with phytotoxic activity show potential applications such as herbicides against weeds [217]. Biological analysis revealed a pro-apoptotic effect for most of the cyclic peptides that indicated that the cyclic peptides could be developed as the pro-apoptotic agents [218].

Some cyclic peptides have been developed as drugs, which are listed in Table 13. One noteworthy example is caspofungin which has strong antifungal activity. Caspofungin is a semisynthetic derivative of pneumocandin B₈ (170), a lipophilic cyclic hexapeptide from the fungus Glaerea lozoyensis. It was commercialized as the antifungal drug caspofungin acetate (CANCIDAS®) which has subsequently saved thousands of lives [14]. Micafungin was the second approved antifungal agent in the echinocandin series, and has been used worldwide in chemotherapy for life-threatening fungal infections. Micafungin is an inhibitor of 1,3-β-glucan synthase, an enzyme necessary for cell-wall synthesis of several fungal pathogens [121]. Other application examples included cyclosporin A (238), an immunosuppressant isolated from Tolypocladium inflatum [176]; omphalotin A (264), a potent
nematicidal agent from Omphalotus olearius [197]; and the echinocandins, antifungal lipopeptides isolated from Glarea lozoyensis, Coleophoma empetri, and Aspergillus nidulans var. echinulatus [219]. Commercial cyclic peptide-derived drugs are listed in Table 14.

| Product Name   | Original Cyclic Peptide | Development Way | Application                                                      | Ref.     |
|----------------|-------------------------|-----------------|------------------------------------------------------------------|---------|
| Anidulafungin  | Echinocandin B (144)    | Semisynthesis   | Antifungal agent                                                 | [220]   |
| CANCIDAS®      | Pneumocandin B0 (170)   | Semisynthesis   | Antifungal agent                                                 | [14]    |
| Caspofungin    | Echinocandins            | Direct application | Antifungal agent for many Candida infections                     | [120]   |
| Cyclosporin A  | Cyclosporin A (238)     | Direct application | Immunosuppressive and antifungal drug                             | [176]   |
| Micafungin     | Echinocandins            | Semisynthesis   | Antifungal agent                                                 | [221]   |

It is worth mentioning that many fungal cyclic peptides have been isolated from plant endophytic and marine-derived fungi, which indicates that plant endophytic and marine-driven fungi are mines of biologically active natural products [222–226]. Although the number of fungal cyclic peptides is gradually increasing, it remains a group of natural products with relatively little skeletal diversity. On many occasions, the relative or absolute configurations of the chiral centers have not been determined yet. This remains a challenge for future chemical and spectroscopic work. Many isolated cyclic peptides have not been screened for their biological activities as the quantities obtained were very limited. Even fewer compounds have been the subject of systematic investigations to establish structure-activity relationships. Further high throughput screening of biological activities as well as detailed studies on the action mechanisms of fungal cyclic peptides are needed.

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