Metabolites from *Clonostachys* Fungi and Their Biological Activities

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**Abstract:** *Clonostachys* (teleomorph: *Bionectria*) fungi are well known to produce a variety of secondary metabolites with various biological activities to show their pharmaceutical and agrochemical applications. Up to now, at least 229 secondary metabolites, mainly including 84 nitrogen-containing metabolites, 85 polyketides, 40 terpenoids, and 20 other metabolites, have been reported. Many of these compounds exhibit biological activities, such as cytotoxic, antimicrobial, antileishmanial, antimalarial activities. This mini-review aims to summarize the diversity of the secondary metabolites as well as their occurrences in *Clonostachys* fungi and biological activities.

**Keywords:** secondary metabolites; *Clonostachys* fungi; *Bionectria*; *Gliocladium*; *Nectria*; structural diversity; biological activities

1. Introduction

The fungal genus *Clonostachys* (formerly named *Gliocladium*), teleomorph *Bionectria* (formerly named *Nectria* or *Nectriopsis*), belongs to the family Bionectriaceae of Sordariomycetes in Ascomycota [1]. The *Clonostachys* fungi are widely distributed all over the world. They are saprotrophs, destructive mycoparasites, lichenicole, or inhabitants of recently dead trees and decaying leaves. At present, there are about 44 species in the genus *Clonostachys* [1], and among them, about 18 species have been studied for their secondary metabolites, including *B. byssicola*, *B. ochroleuca*, *B. pityrodes*, *C. canadibum*, *C. compactiuscula*, *C. rogerisoniana*, *C. rosea*, *G. roseum*, *N. cocinea*, *N. coryli*, *N. erubescent*, *N. fuckeliana*, *N. galligena*, *N. haematococca*, *N. inventa*, *N. lucida*, *N. pseudotrichia*, and *N. viridescens*.

*Clonostachys* fungi are abundant in many classes of secondary metabolites, mainly including nitrogen-containing compounds, polyketides, and terpenoids. Many metabolites exhibit biological activities, such as antimicrobial, insecticidal, nematocidal, antiparasitic, phytotoxic and cytotoxic activities. Until now, secondary metabolites of *Clonostachys* fungi and their biological activities have not been reviewed. This mini-review describes the classification, occurrences, and biological activities of the secondary metabolites from *Clonostachys* fungi.

2. Nitrogen-Containing Metabolites and Their Biological Activities

The nitrogen-containing metabolites from *Clonostachys* fungi mainly include linear oligopeptides, cyclopeptides, and piperazines. The nitrogen-containing metabolites, their isolated *Clonostachys* fungi and biological activities are shown in Table 1.
Table 1. Nitrogen-containing metabolites in *Clonostachys* fungi and their biological activities.

| Metabolite Class             | Metabolite Name                              | Fungal Species                          | Biological Activity                                      | Ref. |
|------------------------------|----------------------------------------------|-----------------------------------------|----------------------------------------------------------|------|
| Linear oligopeptides         | Clonostachin (1)                             | *Clonostachys* sp. F5898                | Inhibition on platelet aggregation                       | [2]  |
|                              |                                               | *Bionectria* sp. MSX 47401              |                                                          | [3]  |
|                              | Clonostachin B (2)                           | *Bionectria* sp. MSX 47401              |                                                          | [3]  |
|                              | Pullularin F (3)                             | *Bionectria ochroleuca*                |                                                          | [4]  |
| Cyclopeptides                | Argadin (4)                                  | *Clonostachys* sp. FO-7314             | Inhibitory activity on chitinase                        | [5]  |
|                              |                                               | *Gliocladium* sp. FTD-0668             | Inhibitory activity on chitinase                        | [6,7]|
|                              | Arthrichtin (6)                              | *Nectria* sp.                          |                                                          | [8]  |
|                              | Clonostachysin A (7)                         | *Clonostachys rogersoniana*            | Antifungal activity on the yeasts                       | [9]  |
|                              | Clonostachysin B (8)                         | *Clonostachys rogersoniana*            | Anti-dinoflagellate activity                            | [10] |
|                              | Cyclo-(Gly-o-Leu-o-allo-Ile -i-Val-o-Trp-β-Ala) (9) | *Clonostachys rosea*                   | Cytotoxic activity                                       | [11] |
|                              |                                               | *Clonostachys rosea*                   |                                                          | [11] |
|                              |                                               | *Clonostachys rosea*                   |                                                          | [11] |
|                              | Cyclo-(Gly-o-Leu-o-allo-Ile -o-allo-Ile-o-Val-o-Trp-β-Ala) (11) | *Clonostachys rosea*                   |                                                          |       |
|                              |                                               | *Nectria* sp. F-4908                    | Immunosuppressive and antifungal activities             | [12] |
|                              |                                               | *Nectria* sp. F-4908                    | Immunosuppressive and antifungal activities             | [12] |
|                              |                                               | *Clonostachys* sp. ESNA-A009           | Cytotoxic activity                                       | [14] |
|                              |                                               | *Gliocladium* sp. F5898                | Antileishmanial activity                                | [15] |
|                              | Pullularin A (15)                            | *Bionectria ochroleuca*                | Cytotoxic activity                                       | [4]  |
|                              | Pullularin C (16)                            | *Bionectria ochroleuca*                | Cytotoxic activity                                       | [4]  |
|                              | Pullularin E (17)                            | *Bionectria ochroleuca*                |                                                          | [4]  |
| Piperazines                   | Bionectin A (18)                             | *Bionectria byssicola F120             | Antibacterial activity                                  | [16] |
|                              |                                               | *Bionectria byssicola F120             |                                                          | [16] |
|                              | Bionectin B (19)                             | *Bionectria byssicola F120             | Antibacterial activity                                  | [16] |
|                              | Bionectin C (20)                             | *Bionectria byssicola F120             |                                                          | [16] |
|                              | Bionectin D (21)                             | *Bionectria* sp. Y1085                 | Antibacterial activity                                  | [17] |
|                              | Bionectin E (22)                             | *Bionectria* sp. Y1085                 | Antibacterial activity                                  | [17] |
|                              | 3,6-Bis(methylthio)-cyclo(a lanyltryptophyl) (23) | *Nectria inventa*                     | Trypanocidal activity                                   | [18] |
|                              |                                               | *Nectria inventa*                      |                                                          | [18] |
|                              | Chaetocin (24)                               | *Nectria inventa*                      |                                                          | [18] |
|                              |                                               | *Nectria inventa*                      |                                                          | [18] |
|                              | Chetosominudin B (25)                        | *Nectria inventa*                      |                                                          | [18] |
|                              |                                               | *Clonostachys compactiwsula FKR-0021   | Antimalarial activity                                   | [19] |
|                              | Clonocoprogen A (26)                         | *Clonostachys compactiwsula*           | Antimalarial activity                                   | [19] |
|                              | Clonocoprogen B (27)                         | *Clonostachys compactiwsula*           | Antimalarial activity                                   | [19] |
| Compound | Source | Activity |
|----------|--------|----------|
| FKR-0021 | Clonostachys compactiuscula | Antimalarial [19] |
| N^4-Plmitoylcorogen (29) | Clonostachys compactiuscula | Antimalarial [19] |
| Cyclo (−-Pro-−-Leu) (30) | Bionectria sp. Y1085 | - [17] |
| Dioxopiperazine (31) | Bionectria sp. Y1085 | - [17] |
| Glioclacidin A (32) | Bionectria sp. Y1085 | - [17] |
| Glioclacidin C (33) | Bionectria sp. Y1085 | Antibacterial activity [17] |
| Clonostachys rogersoniana | | Cytotoxic activity [20] |
| Gliocladin A (34) | Gliocladium roseum OUPS-N132 | - [21] |
| Gliocladin B (35) | Gliocladium roseum OUPS-N132 | - [21] |
| Gliocladin C (36) | Gliocladium roseum OUPS-N132 | Cytotoxic activity [21] |
| Gliocladin E (41) | Gliocladium roseum 1A | Antinematodal activity [23] |
| Gliocladine (42) | Gliocladium roseum YMFI.00133 | Antinematodal activity [24] |
| Glioerazine (43) | Gliocladium sp. OUPS-N132 | - [21] |
| Glioerazine B (44) | Bionectria byssicola F120 | - [25] |
| Glioerazine C (45) | Bionectria byssicola F120 | - [25] |
| Haematocin (46) | Nectria haematococca | Antifungal activity [26] |
| Lasiodipline D (47) | Bionectria sp. Y1085 | - [17] |
| Sch52900 (48) | Gliocladium roseum 1A | Antinematodal activity [23] |
| Sch52901 (49) | Gliocladium roseum 1A | Antinematodal activity [23] |
| Verticillin A (50) | Gliocladium roseum 1A | Antinematodal activity [23] |
| 11'-Deoxyverticillin A (51) | Gliocladium roseum 1A | Antinematodal activity [23] |
| 11,11'-Dideoxyverticillin A (52) | Bionectria sp. Y1085 | - [17] |
| Verticillin B (53) | Nectria inventa | Trypanocidal activity [18] |
| Verticillin D (54) | Bionectria byssicola F120 | - [16] |
| Bionectria ochroleuca | | Cytotoxic activity [4] |
| Clonostachys rosea | | Cytotoxic activity [11] |
2.1. Linear Oligopeptides

The oligopeptides from fungi include linear and cyclic peptides. Two linear tetradecapeptides, named clonostachin (1) and clonostachin B (2) were isolated from Clonostachys fungi (Figure 1).
Clonostachin (1) was first isolated from Clonostachys sp. F5898, and both clonostachin (1) and clonostachin B (2) were then isolated from Bionectria sp. MSX 47401, and each oligopeptide contained an N-terminal acetyl group and a C-terminal mannitol unit [3]. Clonostachin (1) inhibited ADP-induced aggregation of human platelets by 80% at 150 μM [2]. Pullularin F (3) was isolated from the endophytic fungus Bionectria ochroleuca from the mangrove plant Sonneratia caseolaris [4].

![Figure 1](image-url)  
**Figure 1.** Linear oligopeptides isolated from Clonostachys fungi.

2.2. Cyclopeptides

Cyclopeptides are cyclic compounds formed mainly by the amide bonds between either proteinogenic or non-proteinogenic amino acids [13,39]. The structures of the cyclopeptides isolated from Clonostachys fungi are shown in Figure 2.

![Figure 2](image-url)  
**Figure 2.** Structures of the cyclopeptides isolated from Clonostachys fungi.
Argadin (4), a cyclic pentapeptide, was isolated from Clonostachys sp. FO-7314. It showed inhibitory activity against blowfly (Lucilia cuprina) chitinase with IC\textsubscript{50} values of 150 nM at 37 °C and 3.4 nM at 20 °C, respectively [5]. Another cyclic pentapeptide, namely argifin (5), from Gliocladium sp. also exhibited inhibitory activity against blowfly chitinase [6,7].

Arthrichitin (6) was a cyclic tetradepsipeptide isolated from Nectria sp. [8]. This lipodepsipeptide was also isolated from other fungi to show inhibitory activity on the yeasts Schizosaccharomyces pombe and Rhodotorula glutinis [9].

Clonostachysins A (7) and B (8) were two cyclic nonapeptides isolated from Clonostachys rogersoniana. They exhibited a selectively inhibitory effect on a dinoflagellate Prorocentrum micans at 30 μM but had no effect on other microalgae and bacteria, even at 100 μM [10].

Three cyclic heptapeptides, named cyclo-(Gly-d-Leu-d-allo-Ile-L-Val-L-Val-d-Trp-β-Ala) (9), cyclo-(Gly-d-Leu-L-Val-L-Val-L-Val-β-Ala) (10), and cyclo-(Gly-d-Leu-d-allo-Ile-d-allo-Ile-L-Val-d-Trp-β-Ala) (11), were isolated from the soil-derived fungus Clonostachys rosea. Among them, cyclo-(Gly-d-Leu-d-allo-Ile-L-Val-L-Val-d-Trp-β-Ala) (9) exhibited significant cytotoxic activity against the L5178Y mouse lymphoma cell line with an IC\textsubscript{50} value of 4.1 μM [11].

Two cyclic undecapeptides cyclosporin A (12) and C (13) were isolated from Nectria sp. F-4908 [12]. They showed immunosuppressive and antifungal activities [13].
IB-01212 (14), a cyclic hexadepsipeptide from the marine fungus *Clonostachys* sp. ESNA-A009, exhibited antitumor activity on the cell lines of LN-caP (prostate cancer), SK-BR3 (breast cancer), HT29 (colon cancer), and HeLa (cervix cancer) [14]. In addition, IB-01212 (14) showed antileishmanial activity [15].

Three cyclic hexadepsipeptides pullularins A (15), C (16) and E (17) were isolated from the endophytic fungus *Bionectria ochroleuca*. Both pullularins A (15) and C (16) showed moderate cytotoxic activity against mouse lymphoma cells [4]. Furthermore, pullularin A (15) from another fungus *Pullularia* sp. BCC 8613 exhibited antimalarial, antiviral and antitubercular activities [40].

2.3. Piperazines

The piperazines (also called 2,5-diketopiperazines) are formed by the condensation of two amino acids [41]. Piperazines are the common nitrogen-containing metabolites as monomers or dimers in *Clonostachys* fungi, and most of them contain disulfide bonds. The structures of piperazines isolated from *Clonostachys* fungi are shown in Figure 3.
Bionectins A (18), B (19) and C (20), and verticillin D (54) were isolated from the liquid fermentation cultures of Bionectria byssicola F120. Both bionectins A (18) and B (19) exhibited antibacterial activity against Staphylococcus aureus including methicillin-resistant Staphylococcus aureus (MRSA) and quinolone-resistant Staphylococcus aureus (QRSA), with MIC values of 10-30 μg/mL [16]. Bionectins D (21) and E (22), cyclo (L-Pro-L-Leu) (30), dioxopiperazine (31), and gliocladicillins A (32) and C (33) were isolated from Bionectria sp. Y1085. Among them, bionectins D (21) and E (22), as well as gliocladicillin C (33) showed antibacterial activity on Escherichia coli, Staphylococcus aureus and Salmonella typhimurium [17].

Four diketopiperazines: 3,6-bis(methylthio)-cyclo(alanyltryptophyl) (23), chaetocin (24), chetoseminudin B (25) and verticillin B (53) from deep water marine-derived fungus Nectria inventa showed trypanocidal activity on Trypanosoma brucei [18].

Four siderophore analogs, clonocoprogens A (26), B (27) and C (28) and N14-plmitoylcoprogen (29), were isolated from Clonostachys compactiucula FKR-0021. They exhibited antimalarial activity
against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* strains, with IC₅₀ values ranging from 1.7 μM to 9.9 μM [19].

Glioclads A (34), B (35) and C (36) and glioeperezine (43) were isolated from *Gliocladium* sp. originally separated from the sea hare (*Aplysia kurodai*). Gliocladin C (36), which was a structurally unique trioxopiperazine, showed significant cytotoxicity against the murine P388 lymphocytic leukemia cells with IC₅₀ value of 2.4 μg/mL [21]. Gliocladin C (36) from *Gliocladium roseum* YMF1.00133 was further screened to show antinematodal activity against nematodes *Panagrellus redivivus, Caenorhabditis elegans* and *Bursaphelenchus xylophilus* [22].

Nine epipolysulfanyldioxopiperazines isolated from *Gliocladium roseum* 1A displayed antinematodal activity against *Caenorhabditis elegans* and *Panagrellus redivivus*. The dimers, including gliocladine A (37), gliocladine B (38), sch52900 (48), sch52901 (49), verticillin A (50), and 11'-deoxyverticillin A (51) are more active than the monomers with the indole moiety, namely, glioclades C (39), D (40) and E (41). Among them, 11'-Deoxyverticillin A (51) was the most potent antinematodal compound [23].

Three dioxopiperazines: glioperazine (43), glioperazine B (44) and glioperazine C (45) were isolated from *Bionectria byssicola* F120. Among them, glioperazine B (44) showed weak antibacterial activity against *Staphylococcus aureus* [25].

Haematocin (46) was isolated from the culture broth of *Nectria haematococa*, the blight disease pathogen of ornamental plants. Haematocin (46) inhibited the germ-tube elongation and spore germination of rice blast pathogen *Pyricularia oryzae* at the IC₅₀ values of 30 and 160 μg/mL, respectively [26].

Verticillins were the dimeric epipolythiodioxopiperazines widely distributed in Bionectriaeous fungi. Most of verticillins exhibited cytotoxic activities [11,27]. Among them, verticillin A (50) showed obviously cytotoxic activity by causing apoptosis and reducing tumor burden in high-grade ovarian cancer by inducing DNA damage [42]. Verticillins D (54) and G (55) were isolated from *Bionectria byssicola*, and verticillin G (55) was screened to have antibacterial activity on *Staphylococcus aureus* with MIC values of 3–10 μg/mL [25]. Verticillin D (54) from the endophytic fungus *Bionectria ochroleuca* showed pronounced cytotoxic activity against mouse lymphoma cells [4].

### 2.4. Other Nitrogen-Containing Metabolites

The structures of the other nitrogen-containing metabolites, including amides and amines isolated from *Clonostachys* fungi are shown in Figure 4.
Figure 4. Other nitrogen-containing metabolites isolated from Clonostachys fungi.
Both N-benzyl-3-phenyllactamide (57) and N-benzyl-3-phenylpropanamide (58) were isolated from Clonostachys compactiiscula FKR-0021 [19].

Fusarin C (64), (5Z)-fusarin C (65) and (7Z)-fusarin C (66) were isolated from Nectria coccinea A56-9. They showed antifungal activity against Pyricularia oryzae by inhibiting dihydroxynaphthalene-melanin biosynthesis [31].

Gliocladiosins A (67) and B (68), the dipeptides conjugated with macrolides, were isolated from an O-methyltransferase gene, verM disruption mutant of the Cordyce- colonizing fungus Clonostachys rogersoniana. These two compounds showed moderate antibacterial activity on Klebsiella pneumonia and Bacillus subtilis [32]. Similarly, rogersonins A (69) and B (70) were two indole-polyketide hydrids isolated from verG disruption mutant of Clonostachys rogersoniana [33]. Blocking the biosynthesis of secondary metabolites through the disruption of the biosynthesis-related genes provide a method to activate cryptic or silent secondary metabolites in fungi.

Three tetramic acid derivatives namely 1,2-dehydrovirginene (75), virgineone (76) and virgineone aglycone (77) were isolated from Bionectria sp. MSX 47401. They showed obviously antibacterial activity against Staphylococcus aureus and several MRSA isolates. In addition, virgineone (76) showed moderate antifungal activity against Candida albicans, Cryptococcus neoformans, and Aspergillus niger with an MIC value of 14.4 μg/mL [3].

FR-900483 (80), which was called nectrisone or 3-(R)-4-(R)-dihydroxy-5-(R)-hydroxymethyl-1-pyrrorne, was an immunoactive substance produced by Nectria lucida F-4490. FR-900483 (80) could restore the capacity of immunosuppressed mice to produce antibody against sheep red blood cells [35].

Penicolinate A (83) was induced from the endophytic fungus Bionectria sp. through bacterial co-culture. Penicolinate A (83) exhibited potent cytotoxic activity against the human ovarian cancer cell line A2780 with an IC50 value of 4.1 μM [28].

3. Polyketides and Their Biological Activities

A variety of polyketides occur widely in the Clonostachys fungi. According to the structure characteristics, these metabolites were classified into aromatic, aliphahtic and mixed biogenic polyketides [43]. The aromatic polyketides mainly include pyranones, quinones, sorbicillinoids, and others. The polyketides, their isolated Clonostachys fungi and biological activities are shown in Table 2.

| Metabolite Class | Metabolite Name          | Fungal Species       | Biological Activity                      | Ref. |
|------------------|--------------------------|----------------------|------------------------------------------|------|
| Pyranones        | AGI-7 (85)               | Bionectria sp. MSX 47401 | -                                        | [3]  |
|                  | Alternariol (86)         | Clonostachys rosea YRS-06 | -                                        | [44] |
|                  | Alternariol 3-O-methyl ether (87) | Clonostachys rosea YRS-06 | -                                        | [44] |
|                  | Cephalochromin (88)      | Nectria viridescens   | -                                        | [45] |
|                  |                         |                      | Cytotoxic activity                       | [46] |
|                  | Coniochaetone G (89)     | Clonostachys compactiiscula FKR-0021 | -                                        | [19] |
|                  | Citreoisocoumarinol (90) | Nectria sp. HN001    | Inhibitory activity on α-glucosidase     | [47] |
|                  | 12-Epicitreoisocoumarinol (91) | Nectria sp. HN001    | -                                        | [47] |
|                  | Citreoisocoumarin (92)   | Nectria sp. HN001    | Inhibitory activity on α-glucosidase     | [47] |
|                  | 6,8-Dihydroxyisocoumarin -3-carboxylic acid (93) | Co-cultivation of Bionectria sp. with Bacillus subtilis or Streptomyces lividans | -   | [28] |
|                  | Macarpon C (94)          | Nectria sp. HN001    | Inhibitory activity on α-glucosidase     | [47] |
|                  | 3-(3-Chloro-2-hydroxypropyl)-8-hydroxysorbinol (95) | Clonostachys sp. AP4.1 | -                                        | [48] |
| Compound                                      | Source                        | Activity            | Ref. |
|-----------------------------------------------|-------------------------------|---------------------|------|
| Dichlorodiaportin (96)                        | Clonostachys sp. AP4.1        |                     | [48] |
| Mellein (97)                                  | Nectria fukeliana             |                     | [49] |
| 3,4-Dimethyl-6,8-dihydroxyisocoumarin (98)    | Nectria pseudotrichia         | 120-1NP             | [50] |
| Nectriapyrone A (99)                          | Nectria pseudotrichia         | 120-1NP             | [50] |
| Nectriapyrone B (100)                         | Nectria pseudotrichia         | 120-1NP             | [50] |
| (5)-4-Methoxy-6-pentanoyl-5,6-dihydroxy-2H-pyran-2-one (101) | Nectria sp.                  | 120-1NP             | [51] |
| Nectryone A (102)                             | Nectria sp.                   |                     | [51] |
| Nectryone B (103)                             | Nectria sp.                   |                     | [51] |
| Nectryone C (104)                             | Nectria sp.                   |                     | [51] |
| Nectryone D (105)                             | Nectria sp.                   |                     | [51] |
| Nectryone E (106)                             | Nectria sp.                   |                     | [51] |
| LL-P880a (107)                                | Nectria sp.                   |                     | [51] |
| LL-P880b (108)                                | Nectria sp.                   |                     | [51] |
| Quinones                                      |                               |                     |      |
| Anhydrofusarubin lactone (112)                | Nectria haematococca          |                     | [52] |
| Aurantiogliocladin (113)                      | Clonostachys candelabrum      |                     | [53] |
| 2,5-Dimethoxy-3,6-dimethyl-1,4-benzquinone (114) | Nectria coryli              | Antibacterial activity | [54] |
| Fusarubin (115)                               | Nectria haematococca          |                     | [36] |
| 4-Deoxyfusarubin (116)                        | Nectria haematococca          |                     | [55] |
| 4-Deoxyanhydrofusarubin (117)                 | Nectria haematococca          |                     | [55] |
| 5-Deoxyfusarubin (118)                        | Nectria haematococca          |                     | [55] |
| 5-Deoxyanhydrofusarubin (119)                 | Nectria haematococca          |                     | [55] |
| Fusarubinoic acid (120)                       | Nectria haematococca          |                     | [56] |
| 13-Hydroxynorjavanicin (121)                  | Nectria haematococca          |                     | [56] |
| Herbarin (122)                                | Nectria pseudotrichia         | Antibacterial and phytotoxic activities | [50] |
| O-Methylherbarin (123)                        | Nectria pseudotrichia         | Cytotoxic activity   | [38] |
| Dehydroherbarin (124)                         | Nectria pseudotrichia         | Cytotoxic activity   | [38] |
| 2-Acetoxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (125) | Nectria pseudotrichia     | Cytotoxic activity   | [38] |
| Pseudonectrin A (126)                         | Nectria pseudotrichia         | Cytotoxic activity   | [38] |
| Pseudonectrin B (127)                         | Nectria pseudotrichia         | Cytotoxic activity   | [38] |
| Pseudonectrin C (128)                         | Nectria pseudotrichia         | Cytotoxic activity   | [38] |
| Pseudonectrin D (129)                         | Nectria pseudotrichia         |                     | [38] |
| Nectriafurone (130)                           | Nectria haematococca          |                     | [52] |
| Nectriaquinone A (131)                        | Nectria pseudotrichia         | Antibacterial activity | [50] |
| Nectriaquinone B (132)                        | Nectria pseudotrichia         | Antibacterial and cytotoxic activities | [50] |
| P-Toluquinone (133)                           | Nectria erubescens            |                     | [57] |
| Fungi | Sorbicillinoids | Rhodotricin (128) | Clonostachys rosea YRS-06 | - | [44] |
|-------|-----------------|-------------------|---------------------------|----|-----|
| Other polyketides | 3,5-Dihydroxyfuran-2(5H)-one (141) | Gliocladium roseum 1A | - | [23] |
| | Sapinofuranone B (142) | Gliocladium roseum 1A | - | [11] |
| | (-)-Vertinolide (143) | Clonostachys rosea B5-2 | - | [58] |
| | (-)-Dihydrovertinolide (144) | Clonostachys rosea B5-2 | Phytotoxic activity | [58] |
| | Clonostachydiol (145) | Clonostachys cylindrospora FH-A 6607 | Anthelmintic activity | [59] |
| | Bionectriol A (146) | Bionectria sp. | - | [60] |
| | Bionectriol B (147) | Bionectria ochroleuca | - | [61] |
| | Bionectriol C (148) | Bionectria ochroleuca | Antifungal activity | [61] |
| | Bionectriol D (149) | Bionectria ochroleuca | - | [61] |
| | Rogerson A (150) | Clonostachys rogersoniana | - | [62] |
| | Rogerson B (151) | Clonostachys rogersoniana | - | [62] |
| | Neexisting A (152) | Nectria sp. HN001 | - | [47] |
| | Neexisting B (153) | Nectria sp. HN001 | Inhibitory activity on α-glucosidase | [47] |
| | Neexisting C (154) | Nectria sp. HN001 | Inhibitory activity on α-glucosidase | [47] |
| | Curvularin (155) | Clonostachys compactiuscula FKR-0021 | - | [19] |
| | α,β-Dehydrocurvularin (156) | Nectria glligena | Cytotoxic and phytotoxic activities | [63] |
| | Neexisting B (157) | Nectria sp. B-13 | - | [64] |
| | Neexisting C (158) | Nectria sp. B-13 | - | [64] |
| | TMC-151A (159) | Clonostachys rosea | - | [65] |
| | Gliocladium catenulatum | Moderate cytotoxicity to tumor cells | - | [66] |
| | Bionectria ochroleuca | - | [67] |
| | TMC-151B (160) | Clonostachys rosea | - | [67] |
| | Gliocladium catenulatum | Moderate cytotoxicity to tumor cells | - | [66] |
| | TMC-151C (161) | Clonostachys rosea | - | [67] |
| | Gliocladium catenulatum | Moderate cytotoxicity to tumor cells | - | [66] |
| | TMC-151D (162) | Clonostachys rosea | - | [67] |
| | Gliocladium catenulatum | Moderate cytotoxicity to tumor cells | - | [66] |
| | TMC-151E (163) | Clonostachys rosea | - | [67] |
| | Gliocladium catenulatum | Moderate cytotoxicity to tumor cells | - | [66] |
| | Bionectria ochroleuca | Antifungal activity | - | [61] |
| | TMC-151F (164) | Clonostachys rosea | - | [67] |
| | Gliocladium catenulatum | Moderate cytotoxicity to tumor cells | - | [66] |
| | Bionectria ochroleuca | Antifungal activity | - | [61] |
| | TMC-154 (165) | Gliocladium roseum | - | [67] |
| | TMC-171A (166) | Gliocladium roseum | - | [67] |
| | TMC-171B (167) | Gliocladium roseum | - | [67] |
| | TMC-171C (168) | Gliocladium roseum | - | [67] |
| | Usnic acid (169) | Bionectria ochroleuca Bo-1 | Antibacterial activity | [68] |
3.1. Pyranones

Pyranones (also named pyrones) from fungi include α-, β- and γ-pyranones [69]. Most pyranones produced by *Clonostachys* fungi belong to α-pyranones. Their structures are shown in Figure 5.

Cephalochromin (88), a bisnaphtho-γ-pyrene, was isolated from *Nectria viridescens* [45]. This compound was screened to exhibit cytotoxic activity by inducing G0/G1 cell cycle arrest and apoptosis in A549 human non-small-cell lung cancer cells by inflicting mitochondrial disruption [46].

Citreoisoumarinol (90), citreoisoumarin (92) and macrocarpon C (94) showed moderate inhibitory activity on α-glucosidase with IC₅₀ values ranging from 300 to 600 μM [47].

Two isocoumarin derivatives, 3-(3-chloro-2-hydroxypropyl)-8-hydroxy-6-methoxyisochromen-1-one (95) and 3-[(R)-3,3-dichloro-2-hydroxypropyl]-8-hydroxy-6-methoxy-1H-isochromen-1-one (dichlorodiaportin, 96), were identified from *Clonostachys* sp. AP4.1 [48].
3.2. Quinones

The quinones isolated from Clonostachys fungi were mainly naphthoquinones except for three p-benzoquinones. Their structures are shown in Figure 6.
2,5-Dimethoxy-3,6-dimethyl-1,4-benzoquinone (114) from Nectria coryli inhibited the growth of Staphylococcus aureus at a concentration of 1 μg/mL [54].

Herbarin (122) and nectriaquinone B (132) isolated from the brown rice culture of Nectria pseudotrichia 120-1NP exhibited antibacterial activities against Staphylococcus aureus and Pseudomonas aeruginosa [50]. Herbarin (122), O-methylherbarin (123), nectriaquinone A (131), and nectriaquinone B (132) displayed cytotoxic activity against human promyelocytic leukemia HL60 cells with IC₅₀ values of 11.9, 1.33, 1.93, and 11.6 μM, respectively. The structure-function relationship elucidated that the higher cytotoxicity of herbarin (122) and nectriaquinone B (132), compared to that of the related compounds O-methylherbarin (123) and nectriaquinone A (131) was attributed to their increased cell membrane permeability due to the presence of the hydroxyl group [38,50]. In addition, herbarin (122) showed a significant inhibition on lettuce seedling growth [50].

Seven naphthoquinones, named pseudonectrins A (126), B (127), C (128), D (129), herbarin (122), dehydroherbarin (124) and 2-acetoxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (125) were isolated from Nectria pseudotrichia. They all showed cytotoxic activity except for pseudonectrin D (129). In addition, pseudonectrins A (126), B (127) and C (128) had a skeleton of pyranonaphthoquinone [38].

3.3. Sorbicillinoids

Sorbicillinoids are important hexaketide metabolites produced by fungi [70]. Six dimeric and one monomeric sorbicillinoids were extracted from culture broth of Clonostachys rosea YRS-06 [44]. Their structures are shown in Figure 7. Dihydrotrochidimer ether A (135), dihydrotrochidimer ether B (136) and tetrahydrotrochidimer ether (137) are rare bisorbicillinoids with a γ-pyrene moiety. Dihydrotrochidimer ether A (135), dihydrotrochidimer ether B (136), dihydrotrochidimerol (138) and tetrahydrotrochidimerol (139) showed antibacterial activity against Bacillus subtilis, Clostridium perfringens, and Escherichia coli [44].
3.4. Other Polyketides

The structures of the other polyketides isolated from *Clonostachys* fungi are shown in Figure 8. These metabolites mainly belong to aliphatic polyketides. Some of them contain a glycosyl group and exist as glycosides.
Four α-furanones were obtained. Both 3,5-dihydroxyfuran-2(5H)-one (141) and sapinofuranone B (142) were isolated from Gliocladium roseum 1A [23]. Both (-)-vertinolide (143) and (+)-dihydrovertinolide (144) were isolated from Clonostachys rosea B5-2. (+)-Dihydrovertinolide (144) displayed phytotoxic activity against lettuce seedlings at a concentration of 50 μg/mL [58].

Clonostachydiol (145) was a 14-membered macrodiolide isolated from the fungus Clonostachys cylindrosperma (strain FH-A 6607). It exhibited anthelminthic activity against abomasum nematode Haemonchus contortus in artificially infected lambs [59]. Four stereocenters in clonostachydiol were revised later [71].

Polyketide glycosides bionectriols A (146), B (147) and C (148) were isolated from Bionectria ochroleuca [61]. TMC-151E (163), TMC-151F (164) and bionectriol C (148) moderately inhibited Candida albicans biofilm formation with IC₅₀ values of 36.3, 41.0 and 24.1 μM, respectively [61].

Nectriacids B (153) and C (154) showed stronger α-glucosidase inhibitory activity than positive control (acarbose, IC₅₀, 815.3 μM) with IC₅₀ values of 23.5 and 42.3 μM, respectively.

α,β-Dehydrocurvularin (156) from Nectria gliigena was proved to be cytotoxic to human lung fibroblasts with IC₅₀ value less than 12 μg/mL. In addition, α,β-dehydrocurvularin (156) significantly reduced radicle length and epicotyl growth in Lactuca sativa at 100 and 200 μg/disk [63].

Both nectriatones B (157) and C (158) were cyclohexanone derivatives from Nectria sp. B-13 [64].

A series of polyketides TMC-151 (159-164), TMC-154 (165) and TMC-171 (166-168) were found exclusively in Gliocladium and Clonostachys species [67]. They contained α-mannopyranoside and α-mannitol or α-arabinol and showed moderate cytotoxicity on several tumor cells [66].

Usnic acid (169) is a unique polyketide from Bionectria ochroleuca Bo-1 which was isolated as an endophytic fungus from rice. It showed antibacterial activity against Xanthomonas oryzae with MIC value of 200 μg/mL [68].

**Figure 8.** Other polyketides isolated from Clonostachys fungi.
4. Terpenoids and Their Biological Activities

The terpenoids from Clonostachys fungi include monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, polyterpenoids, and meroterpenoids. The terpenoids, along with their isolated Clonostachys fungi and biological activities are shown in Table 3.

Table 3. Terpenoids in Clonostachys fungi and their biological activities.

| Metabolite Class | Metabolite Name | Fungal Species | Biological Activity | Ref. |
|------------------|----------------|----------------|---------------------|------|
| Monoterpenoids   | Nectriapyrone  | Nectria sp. HLS206 | -                   | [72] |
|                  | Nectriapyrone C | Nectria sp. HLS206 | -                   | [72] |
|                  | Nectriapyrone D | Nectria sp. HLS206 | -                   | [72] |
| Sesquiterpenoids | 5,6-Dihydroxybisabolol | Bionectria sp. MSX 47401 | -                   | [3]  |
|                  | Nectrianolin C | Nectria pseudotrichia | Cytotoxic activity | [73] |
|                  | 10-Acetyl trichoderonic acid A | Nectria pseudotrichia | Leishmanicidal activity | [30] |
|                  | Hydrohepetelidic acid | Nectria pseudotrichia | Leishmanicidal activity | [30] |
|                  | Ophioceric acid | Clonostachys compactiuscula | -                   | [19] |
|                  | Xylaric acid D | Nectria pseudotrichia | -                   | [30] |
| Diterpenoids     | Agathic acid   | Bionectria sp. | -                   | [28] |
|                  | Nectriatone A  | Nectria sp. B-13 | Cytotoxic activity  | [64] |
|                  | Zythisotronic acid C | Nectria pseudotrichia 120-1NP | -                   | [50] |
| Triterpenoids    | Eburicol       | Clonostachys rosea MMS1090 | Cytotoxic activity | [74] |
|                  | Helvolic acid  | Nectria sp. | -                   | [51] |
|                  |                |                | Antimicrobial activity | [75,76] |
| Polyterpenoids   | Glisoprenin A  | Gliocladium sp. FO-1513 | Inhibition on acyl-CoA:cholesterol acyltransferase activity | [77] |
|                  | Glisoprenin B  | Gliocladium sp. FO-1513 | Inhibition on acyl-CoA:cholesterol acyltransferase activity | [77] |
|                  | Glisoprenin C  | Gliocladium roseum HA190-95 | Formation of Magnaporthe grisea | [78] |
|                  | Glisoprenin D  | Gliocladium roseum HA190-95 | Formation of Magnaporthe grisea | [78] |
|                  | Glisoprenin E  | Gliocladium roseum HA190-95 | Formation of Magnaporthe grisea | [78] |
| Meroterpenoids   | Ascochlorin - Illicicolin D - LL-Z 1272γ | Nectria lucida | -                   | [79] |
|                  | Dechloro-12,13-dihydroascoclorin - LL-Z 1272γ | Nectria lucida | -                   | [79] |
|                  | 3-Bromoaascholrin | Nectria coccinea | -                   | [80] |
|                  | Chloronectrin  | Nectria coccinea | -                   | [80] |
|                  | Deacetylchloronectrin | Nectria sp. B-13 | -                   | [34] |
|                  | Dechlorodihydroascoclorin | Nectria sp. B-13 | -                   | [34] |
Ilicicolin C = LL-Z 1272β (196)  

Nectria sp. B-13  
Nectria sp. B-13  
Nectria galligena  
Inhibitory activity on AChE and α-glucuronidase [34]

Ilicicolin E = 8',9'-Dehydroascorochlorin – Cylindrochlorin (197)  

Nectria sp. B-13  
Nectria sp.  
Nectria sp. B-13  
Antibacterial activity [34]

Ilicicolin F = LL-Z 1272γ (198)  

Nectria sp. B-13  
Nectria galligena  
Nectria sp.  
Antifungal activity  
Cytotoxic and antibacterial activities [8]

Nectrianol A (199)  

Nectria pseudotrichia 120-1NP  
Cytotoxic activity against HL60 and HeLa cells [73]

Nectrianol B (200)  

Nectria pseudotrichia 120-1NP  
Cytotoxic activity against HL60 and HeLa cells [73]

Ascofuranone (201)  

Nectria sp.  
Antifungal activity [8]

Chalmicrin (202)  

Nectria sp. HLS206  
- [81]

Colletochlorin B (203)  

Nectria sp. B-13  
Nectria galligena  
Inhibitory activity on AChE and α-glucuronidase [63]

Colletochlorin A (204)  

Nectria galligena  
Nectria sp. B-13  
Nectria coccinea  
- [80]

Colletochlorin B = LL-Z 1272β (206)  

Nectria lucida  
- [79]

MBJ-0009 (207)  

Nectria sp. E26111  
Cytotoxic activity [82]

MBJ-0010 (208)  

Nectria sp. E26111  
Cytotoxic activity [82]

Taxol = Paclitaxel (209)  

Gliocladium sp.  
Cytotoxicity on cancer cells [83]

4.1. Monoterpenoids

Three monoterpenoids named nectriapyrone (170), nectriapyrones C (171) and D (172) with α–pyrone skeletons were isolated from the fungus Nectria sp. HLS206 associated with the marine sponge Gelliodes carnosa [72]. Their structures are shown in Figure 9.

![Monoterpenoids isolated from Clonostachys fungi.](image)

**Figure 9.** Monoterpenoids isolated from *Clonostachys* fungi.
4.2. Sesquiterpenoids

The structures of the sesquiterpenoids isolated from Clonostachys fungi are shown in Figure 10. Nectrianolin C (174) from Nectria pseudotrichia 120-1NP exhibited cytotoxic activity against HL60 and HeLa cells [73].

Three sesquiterpene acids: 10-acetyl trichoderonic acid A (175), hydroheptelidic acid (176), and xylaric acid D (178) were isolated from the endophytic fungus Nectria pseudotrichia of the tree Caesalpinia echinata. The 10-Acetyl trichoderonic acid A (175) and hydroheptelidic acid (176) showed strong antileishmanial activity [30].

![Figure 10. Sesquiterpenoids isolated from Clonostachys fungi.](image)

173. 5,6-Dihydroxybisabolol  174. Nectrianolin C  175. 10-Acetyl trichoderonic acid A

176. Hydroheptelidic acid, R=OH  177. Ophioceric acid  178. Xylaric acid D, R=H

4.3. Diterpenoids

Three diterpenoids (179–181) have been isolated from Clonostachys fungi so far (Figure 11). Nectriatone A (180) from Nectria sp. B-13 exhibited cytotoxic activity against the human cancer cell lines, including SW1990, HCT-116, MCF-7 and K562 [64].

![Figure 11. Diterpenoids isolated from Clonostachys fungi.](image)

179. Agathic acid  180. Nectriatone A  181. Zythiostromic acid C

4.4. Triterpenoids

Only two triterpenoids (182, 183) were described with their structures shown in Figure 12. Eburicol (182) exhibited cytotoxic activities on the four human cancer cell lines, which included MCF-7, MDA-MB-231, NSCLC-N6-L16 and A549 cells with IC50 values lower than 40 μM [74]. Helvolic acid (183) was a nortriterpenoid isolated from many other fungi, such as Pichia guilliermondii [75], and Aspergillus fumiatus [76]. This compound exhibited obvious antimicrobial activity [75,76].
4.5. Polyterpenoids

The polyterpenes in *Clonostachys* fungi were tetraterpenes or pentaterpenes whose structures are shown in Figure 13. Five polypropenol polyterpenoids, glioprenins A-E (184-188) were isolated from *Gliocladium* species [77, 78]. Glisoprenins A (184) and B (185) from *Gliocladium* sp. FO-1513 showed inhibitory activity on acyl-CoA:cholesterol acyltransferase [77], and glioprenins C (186), D (187) and E (188) from the submerged cultures of *Gliocladium roeum* HA190-95 showed inhibition on appressorium formation of *Magnaporthe grisea* [78].

Bionectin F (189), another polypropenol polyterpenoid, was isolated from the endophytic fungus *Bionectria* sp. Y1085 [17].

4.6. Meroterpenoids

Meroterpenoids are metabolites that are partially derived from terpenoid biosynthetic pathways. The structures of meroterpenoids isolated from *Clonostachys* fungi are shown in Figure 14.
Ascochlorin (also named illicolin D or LL-Z 1272γ, 190), dechlorodihydroaschochlorin (195) and illicolin B (or called LL-Z 1272β, 206) were isolated from Nectria sp. [79].

Illicolin D (190), E (197) and F (198), dechloroillicolin D (191) and ascofurane none (201) showed antifungal activity against plant pathogens Neurospora crassa, Botrytis cinerea, Fusarium culmorum, Pyricularia oryzae, and Penicillium digitatum [8].

Illicolin C (196) and E (197), and colletocillin B (203) from the phytopathogenic fungus Nectria galligena displayed inhibitory activity toward acetylcholinesterase (AChE) and α-glucuronidase with IC₅₀ values of 30-36 μg/mL in the AChE assay and 32-43 μg/mL in the α-glucuronidase test [63].

Illicolin E (197) obtained from soil-derived fungus Nectria sp. B-13 showed antibacterial activities against Escherichia coli, Bacillus subtilis and Staphylococcus aureus with MIC values of 4.0, 2.0 and 4.0 μg/mL, respectively [64]. Illicolin C (196) and illicolin F (198) obtained from phytopathogenic fungus Nectria galligena were active against Pseudomonas syringae with IC₅₀ values of 28.5 and 28.5 μg/mL, respectively [63].

Both nectrianolins A (199) and B (200) were sesquiterpene-epoxyclohexenone conjugates isolated from Nectria pseudotrichia 120-1NP [73].

Chalmicrin (202), a mannitol ether of methylated monocyclofarnesol, was isolated from Nectria sp. HLS206 that was associated with the marine sponge Gliolodes carnosa [81]. This compound was previously isolated from the fungus Chalara microspora [84].

Both MBJ-0009 (207) and MBJ-0010 (208), which were related to the eremophilane class and isolated from the saprobie fungus Nectria sp. f26111, showed moderate cytotoxic activity against human ovarian adenocarcinoma SKOV-3 with the IC₅₀ values of 24.7 and 11.2 mM, respectively [82].

Taxol (generic name paclitaxel, 209), the well-known anticancer agent, was isolated from the endophytic fungus Gliocladium sp. from Taxus baccata [83]. The backbone of taxol (209) is a diterpenoid, and the side chain is phenylalanine-derived. Both diterpenoid and phenylpropanoid pathways are required for taxol biosynthesis. Taxol (209) was found in both plants [85] and fungi [86]. It is a result of the co-evolution of plants and fungi in secondary metabolism [75].
5. Miscellaneous Metabolites and Their Biological Activities

The miscellaneous metabolites mainly including phenolics and fatty acids isolated from *Clonostachys* fungi are listed in Table 4, and their structures are shown in Figure 15.

Four phenolic metabolites were isolated and identified as 4-hydroxybenzoic aldehyde (210), 4-hydroxybenzoic acid (211), 3,4-dihydroxybenzoid acid (212), and 3,5-dihydroxybenzoic acid (213) from *Gliocladium roseum* CGMCC 3.3657 [87].

5-n-Heneicosylresorcinol (217) was isolated from *Gliocladium roseum* YMF1.00133. After 24 h incubation, 5-n-heneicosylresorcinol (217) showed antinematodal activity against *Caenorhabditis elegans* at 15 and 30 μg/mL, against *Panagrellus redivivus* at 50 and 80 μg/mL, and against *Bursaphelenchus xylophilus* at 200 and 180 μg/mL, respectively [22].

Five fatty acids named clonostach acids A (219), B (220), and C (221) were isolated from the endophytic fungus *Clonostachys rosea* B5-2 [58].

Three furan derivatives, named 2-furoic acid (222), 5-hydroxymethyl furoic acid (223) and 2-hydroxy-5-hydroxymethyl furan (224), were isolated from *Bionectria* sp. Y1085 [17].

Three piliformic acid derivatives were isolated from *Nectria pseudotrichia*. Both 3-(S)-piliformic acid (226) and 6’-acetoxy-piliformic acid (227) were screened to show leishmanicidal activity [30].

Table 4. Miscellaneous metabolites in *Clonostachys* fungi and their biological activities.

| Metabolite Name | Fungal Species | Biological Activity | Ref. |
|-----------------|----------------|---------------------|------|
| 4-Hydroxybenzoic aldehyde (210) | *Gliocladium roseum* CGMCC 3.3657 | - | [87] |
| 4-Hydroxybenzoic acid (211) | *Gliocladium roseum* CGMCC 3.3657 | - | [87] |
| 3,4-Dihydroxybenzoid acid (212) | *Gliocladium roseum* CGMCC 3.3657 | - | [87] |
| 3,5-Dihydroxybenzoic acid (213) | *Gliocladium roseum* CGMCC 3.3657 | - | [87] |
| 2,5-Dimethoxy-3,6-dimethylbenzene-1,4-diol (214) | *Nectria coryli* | - | [54] |
| 3,5-Dihydroxybenzyl alcohol (215) | *Nectria* sp. B-13 | - | [34] |
| 3,5-Dihydroxytoluene (216) | *Nectria* sp. B-13 | - | [34] |
| 5-n-Heneicosylresorcinol (217) | *Gliocladium roseum* YMF1.00133 | Antinematodal activity | [22] |
| Toluquinol (218) | *Nectria erubescens* | - | [57] |
| Clonostach acid A (219) | *Clonostachys rosea* B5-2 | - | [58] |
| Clonostach acid B (220) | *Clonostachys rosea* B5-2 | - | [58] |
| Clonostach acid C (221) | *Clonostachys rosea* B5-2 | - | [58] |
| 2-Furoic acid (222) | *Bionectria* sp. Y1085 | - | [17] |
| 5-Hydroxymethyl furoic acid (223) | *Bionectria* sp. Y1085 | - | [17] |
| 2-Hydroxy-5-hydroxymethyl furan (224) | *Bionectria* sp. Y1085 | - | [17] |
| 3-(R)-Piliformic acid (225) | *Bionectria* sp. | - | [28] |
| 3-(S)-Piliformic acid (226) | *Nectria pseudotrichia* | Leishmanicidal activity | [30] |
6′-Acetoxy-piliformic acid (227) Nectria pseudotrichia Leishmanicidal activity [30]
5′,6′-Dehydroxypiliformic acid (228) Nectria pseudotrichia - [30]
Hypocrealesate (229) Nectria sp. HLS206 - [81]

Figure 15. Miscellaneous metabolites isolated from Clonostachys fungi.

6. Conclusions and Future Perspectives

In this mini-review, we summarized chemical structures, occurrences and biological activities of the secondary metabolites from Clonostachys fungi. The main metabolites belong to nitrogen-containing compounds, polyketides, and terpenoids. Some piperazines (i.e., bionetins, gliocladsins and gliocladiins and verticillins), polyketides (i.e., nectriaquinones, pseudonectrins, bionectriols, and nectriacids) and terpenoids (i.e., glisoprenins and ilicicolins), which were only isolated from Clonostachys fungi, exhibited obvious biological activities, such as antimicrobial, cytotoxic, antinematodal, and AChE inhibitory activities (Tables 1–3). Some metabolites, such as alternariol (86) sorbicillinoids, were also distributed in other groups of fungi. Some metabolites, such
as cyclosporin A (12), cinnacidin (61), and taxol (209), have shown their medicinal and agricultural applications.

In order to search for new bioactive metabolites from Clonostachy fungi, some strategies, such as gene disruption, modification of the fermentation medium, co-cultivation and synthetic modification, have been proven to be effective. Gliocladiums A (67) and B (68), as well as rogersins A (69) and B (70) were alkaloid–polyketide hydriods isolated from gene disruption mutants of Clonostachys rogersoniana [32,33]. Fermentation of the Clonostachys rosea on white beans instead of rice afforded one γ-lactam clonalactalactam (62) and two γ-lactones 3,5-dihydroxyfuran-2(5H)-one (141) and sapinofuranone B (142) that were not detected in the former extracts [11]. The apple juice supplemented solid rice media led to significant changes in the secondary metabolism of the fungus, Clonostachys rosea B5-2, and induced the production of four new compounds, (-)-dihydrovertinolide (144), clonostach acids A (219), B (220) and C (221) together with the known compound, (−)-vertinolide (143) [58]. Co-cultivation of the Bionectria sp. with either Bacillus subtilis or Streptomyces lividans resulted in the production of bionectriamines A (59) and B (60), and 6,8-dihydroxyisocoumarin-3-carboxylic acid (93) [28]. In addition, based on the isolated compounds, more bioactive compounds can be synthesized. A typical example was the synthesis of cinnacidin (61) analogs. Two new structural analogs of cinnacidin (61), namely (2S,3S)-2-[(3RS,3aSR,6aRS)-3-methoxy-4-oxo-3,3a,4,5,6,6a-hexahydropentalen-1-ylcarbamoyl]-3-methylvaleric acid and benzyl (2S,3S)-2-[(3S,3aSR,6aRS)-3-methoxy-4-oxo-3,3a,4,5,6,6a-hexahydro pentalen-1-ylcarbamoyl]-3-methylvalerate, have been synthesized. The synthetic compounds were highly phytotoxic on a range of weeds to show their potential application as a herbicide [29]. Furthermore, the phenolic sesquiterpenoids which are also called ascolchlorin derivatives or illicolins were widely distributed in the fungi of genus Nectria (synonym: Clonostachy). The occurrence of these compounds further confirms the close chemotaxonomic relationships among the related Nectria species. Illicolin H (71) was considered to be of potential chemotaxonomic significance and could be used as the main chemotaxonomic marker of the Nectriaceae family [34]. Some piperazines, such as bionetins [16], glioclades [21], gliocolades [23], glioperazines, and verticillins were also only isolated from the fungal species of Clonostachy. Their chemotaxonomic significance should be further verified.

Though major fungal species of Clonostachy fungi have been studied for their metabolites [1], the remaining fungi need to be revealed in detail. Moreover, the biological activities, structure–activity relationships, mechanisms of action, as well as biosynthesis of the metabolites from Clonostachy fungi need to be further investigated. Clarification of the metabolites of Clonostachy fungi could not only be in favor of discovering more compounds with novel structures and excellent biological activities, but also better understand the chemotaxonomy of the genus Clonostachy.

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