Natural Products from the genus *Daldinia* and Their Bioactivities

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Abstract  Genus *Daldinia* is a unique source of natural products, which possess many pharmacological effects such as antibacterial activity, cytotoxicity, antioxidant activity, α-glucosidase inhibitory activity, and so on. Recently, most studies of genus *Daldinia* were focused on *D. eschscholzii*, *D. concentrica* and *D. sp*. This paper covers nearly a decade of research on *Daldinia*, focusing on the chemical structures and related biological activities of the secondary metabolites produced.

Keywords  *Daldinia*, chemical constituents, bioactivities, *D. eschscholzii*, *D. concentrica*

Introduction

Genus *Daldinia* belongs to Ascomycota phylum, Pyrenomycetes class, Xylariales order, Xylariaceae family, and it is an important class of wood-decaying fungi. The genus was established in 1863 by Cesati & De Notaris with the *D. concentrica* (Bolton: Fr) Ces & De Not as the type species. Up to now, more than 40 species of this genus have been found worldwide, and the diversity of secondary metabolites has been reported, which can produce active metabolites such as cytotoxic, antioxidant and anti-HIV. Even the genus *Daldinia*, which has been studied for a long time, has not been exhaustively explored for its bioactive secondary metabolites. Therefore, we reviewed the studies related to genus *Daldinia* in recent ten years and summarized the compound types and biological activities to further understand the potential of lead compounds of this genus.

Natural Products of Various Species of the genus *Daldinia*

From species *D. eschscholzii*

Endophytic fungi *D. eschscholzii* came from a wide range of sources, including mantises, marine algiculous, medicinal plants, mangroves, and broad-leaf forests, etc. The wide range of host types indicated that species *D. eschscholzii* had strong adaptability and survival ability in a variety of different environments, which may be related to the active substances produced by species *D. eschscholzii*.

From mantis-associated *D. eschscholzii*, Zhang et al. found seven new structurally unique polyketones (1–7) with substantial immunosuppressive effects (Figure 1). Wang et al. also found three new polyketides from mantis-associated fungus *D. eschscholzii*, named daldinone F (8), nodulisporin G (9), and dalmanol C (10). And then, Zhang et al. found a novel polyketide natural product named galewone (11–12). From the marine algiculous strain of *D. eschscholzii*, Tarman et al. obtained a new lactone helicascolide C (13, Figure 2). From medical plants, Shylaja et al. isolated *D. eschscholzii* from Mussaenda luteola and purified compound 5-methoxy-2-methyl-3-pentacosyl-1,4-benzoquinone (14). From the mangrove endophytic fungus *D. eschscholzii* HJ001, Yang et al. obtained a new cytochalasin (15). And then, the group isolated two new polyketides 8-O-methylnodulisporin F (16) and nodulisporin H (17), two new naphthoquinones, 5-hydroxy-2-methoxy-6,7dimethyl-1,4-naphthoquinone (18), and 5-hydroxy-2-methoxy-naphtho [9-c] furan-1,4-dione (19), and a new naphthofuran 1,3,8-trimethoxynaphtho [9-c] furan (20). After that, this group found five new tetralones, daldiniones...
A—E (21—25), three new chromones, 7-hydroxy-5-methoxy-2,3-dimethylchromone (26), 5-methoxy-2-propylchromone (27), and 7-ethyl-8-hydroxy-6-methoxy-2,3-dimethylchromone (28), and two new lactones, helicascolides D and E (29—30).

From the indole-3-carbinol exposed culture of *D.eschscholzii*, Lin *et al.* [13] obtained two new alkaloids named dalesindoloids A (31) and B (32), shown in Figure 3. And then, this group [14] found two skeletally undescribed polyketide-indole hybrids from the indole-3-carbinol-exposed culture of *D. eschscholzii* named indolchromins A and B (33—34). By replacement of the native promoter of the global regulator LaeA-like gene of *D.eschscholzii* by a strong *gpdA* promoter, Zhou *et al.* [15] obtained two novel anti-inflammatory cyclopentenone metabolites named dalesones A and B (35—36). From metabolites of *D.eschscholzii* JC-15 cultured in red ginseng medium, Wang *et al.* [16] obtained an unprecedented benzopyran-naphthalene hybrid daldinsin (37) and a new lactone, 8-hydroxyhelicascolide A (38).

**From species *D.concentrica***

*D.concentrica* is the type species of *Daldinia*, which is distributed all over the world. Lee *et al.* [17] obtained a novel isodolinone antioxidant from the fruiting body of *D.concentrica* named daldinan A (39, Figure 4). From the fruit bodies of *D.concentrica*, Quang *et al.* [18] isolated three cytotoxic constituents, 6,8-dihydroxy-3-methyl-3,4-dihydroisocoumarin (40), (22R)-hydroxylanosta-7,9(11),24-trien-3-one (41) and ergosterol (42). Kamauchi *et al.* [19] also found two new isodolinone compounds, daldinans B and C (43—44), two new phthalide compounds, daldinolides A and B (45—46), and a new naphthoquinone, daldiquinone (47). Later, Trung *et al.* [20] purified one new cytochalasin daldinin (48), two known cytochalasins (49—50), along 2 steroids (51—52).
From species D.sp

Du et al. purified a biosynthetically related epoxide-containing daldinone B (53) from D.sp and treated the fungus with the epigenetic modifier suberoylanilide hydroxamic acid (SAHA) to obtain a new chlorinated pentacyclic ring polyketide daldinone E (54), as shown in Figure 5. Gu et al. found two new cyclopentenone derivatives daldispones A and B (55—56) from the fungus D.sp. CPCC 400770.

Figure 5 Chemical structures of secondary metabolites from species D.sp.

Other species

From D.loculata, Nadeau et al. purified three polyketides (57—59) and one aromatic alcohol tyrosol (60) shown in Figure 6. Pažoutová et al. isolated a novel pyrone from D.hawksworthii named dalsymbiopyrone (61). From the fruiting bodies of D.chilidae, Zhao et al. obtained seven previously undescribed polyketides, namely childinins A—G (62—68), and one previously undescribed 8,14-seco-ergosterol namely childinasterone A (69).

Figure 6 Chemical structures of secondary metabolites from other species.

Bioactivities of Natural Products from genus Daldinia

Antibacterial activity

Many compounds have either strong or weak antibacterial activity. In an MIC range of MICs, 1.3—8.6 μmol/L, (2S,4R)- and (2R,4S)-indolchromins A and (2R,4S)-indolchromin B (33—34) were shown to be inhibitory on the growth of four anaerobic (Clostridium perfringens, Clostridium difficile, Veillonella sp, and Bacteroides fragilis) and a Gram-positive bacteria (Streptococcus pyogenes). The observed potency was comparable to those of co-assayed streptomycin (MICs, 0.5—7.5 μmol/L) and tinidazole (MICs, 1.0—4.0 μmol/L).

Figure 7 Antibacterial activity of secondary metabolites against Staphylococcus aureus.

Eighty-one compounds (2S,4R)- and (2R,4S)-indolchromin B (33) exhibited remarkable activity against S. aureus subsp. aureus with an MIC value of 54.9 μmol/L (167.4 μM).

Cytotoxicity

(2S,4R)-Indolchromins A and (2S,4S)-indolchromins B (33—34) were inhibitory against the human breast cancer cell line MDA-MB-231 with IC50 values of 27.9 and 131.2 mmol/L, respectively. Moreover, (2S,4R)-indolchromins A (33) is also active against another human breast cancer cell line MCF-7 (IC50, 94.4 mmol/L). However, positive control drug doxorubicin with the IC50 values being 8.0 and 8.7 μmol/L against the MDA-MB-231 and MCF-7 cell lines, respectively. Dalesindoloid A (31) displayed selective cytotoxicity against the HL-60 cell line with an IC50 value of 1.01 μmol/L, and dalesindoloid B (32) showed discernible cytotoxicity against six of the seven cancer cell lines with an IC50 range of 7.44—14.64 μM.

Figure 8 Cytotoxicity of secondary metabolites.

Antioxidant activity

Daldinone A (39) exhibited potent 2,2’-azinobis(3-ethylbenzothiazoline-6-sulfonate) radical-scavenging activity with an IC50 value of ~10.4 μM, comparable to those of butylated hydroxyanisole (BHA, 10.8 μM) and trolox (IC50 = 11.5 μM). When reducing power was expressed as activity relative to trolox, daldinone A (39) was about three times less active than trolox.

Figure 9 Antioxidant activity of secondary metabolites.

α-Glucosidase inhibitory activity

5-Hydroxy-2-methoxy-naphtho[9-c]furan-1,4-dione (19) displayed potent inhibitory activity against α-glucosidase with the IC50 values of 5.7 μg/mL. Daldinone E (B) (53 and 54) displayed DPPH radical scavenging activities with IC50 values of 3.6 and 3.1 μM, respectively.

Other bioactivities

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Compounds (1–7) displayed substantially immunosuppressive activity with corresponding IC_{50} values 5.96, 0.025, 1.72, 5.56, 5.00, 0.87, and 2.14 μg/mL, respectively, and the IC_{50} data of closporin A was 0.06 μg/mL. Childeadosterone A (68) showed significant anti-NO activity (IC_{50} = 21.2 μM). Daldiquinone (47) actively inhibits HUVEC growth (IC_{50} = 7.5 μM), and cytochalasin B was used as positive control (IC_{50} = 0.2 μM). (−)/(+)–Galewones (11–12) showed an anti-fibrotic effect on activated hepatic stellate cell line CFSC-BB with the IC_{50} values being 3.73 ± 0.21 and 10.10 ± 0.41 μM, respectively. (7) Dalestones A and B (35–36) have anti-inflammation activity and inhibit the gene expression of TNF-α and IL-6 in LPS-induced RAW264.7 macrophages. Daldispones A and B (55–56) displayed significant anti-IAV (H1N1) activities with the IC_{50} values of 16.0 and 7.4 μM, respectively. Daldinsin (37) showed anti-acetylcholinesterase activity with an inhibition ratio of 38.8% at 50 μM. (16)

Conclusions

Endophyte is known as a rich source of structurally diverse and biologically active secondary metabolites. Many chemical constituents have been isolated and identified by spectroscopic analysis and chemical methods. In this paper, we reviewed natural products from the genus Daldinia, which are mainly derived from D. eschscholzii, D. concentrica and D. sp, while others D. loculata, D. hawksworthii and D. childiae are less studied. Some of them possess pharmacological effects such as antibacterial activity, cytotoxicity, antioxidant activity and α-glucosidase inhibitory activity. At present, researchers have isolated many compounds from the genus Daldinia. New chemical constituents and bioactivities are being found, which will offer better medicinal values for clinical application in the future. However, in-depth investigations on the bioactive mechanism are rarely reported in modern researches, and they should be strengthened on this aspect. To obtain more drug resources, the research on the natural products of genus Daldinia should be continued.

Acknowledgement

This work was supported by funding plan for the Key Scientific Research Projects of Henan Universities in 2021 (No. 21A350008) and the Special Project of Henan Science and Technology Department in 2021 (No. HNGD2021047).

Conflict of Interest

The authors declare no conflict of interest.

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Received March 31, 2021

Accepted May 30, 2021