Bioactive metabolites from the plant endophyte *Pestalotiopsis fici*

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The plant endophytes, *Pestalotiopsis* spp., are prolific producers of bioactive secondary metabolites. Chemical studies on the fungus, *Pestalotiopsis fici*, have provided over 70 new natural products from different biosynthetic routes. Some metabolites have shown biological activities, including cytotoxic, antimicrobial and anti-HIV effects. This review covers the structure, bioactivities and putative biosynthetic pathways of selected metabolites published by us over the past three years.

**Keywords:** endophytic fungi; *Pestalotiopsis* spp; new secondary metabolites; structure elucidation; cytotoxic; antimicrobial; anti-HIV

**Introduction**

Endophytic fungi, which inhabit normal tissues of hosts without causing apparent symptoms of pathogenesis (Aly et al. 2010), are rich sources of bioactive natural products (Tan and Zou 2001; Schulz et al. 2002; Strobel 2003; Strobel et al. 2004). The widely distributed endophytes, *Pestalotiopsis* spp., have attracted much attention in recent years for their ability to produce a variety of bioactive secondary metabolites (Lee et al. 1996; Li et al. 2001; Harper et al. 2003; Xu et al. 2009a,b, 2010), including the anticancer agent, taxol (Strobel et al. 1996, 1997). Our chemical investigations of some selected species of this genus have afforded structurally unique and biologically active secondary metabolites (Ding et al. 2008a,b, 2009a,b, 2011; Li et al. 2008a,b). In particular, *Pestalotiopsis fici* was found to be highly “creative” in producing novel natural products (Liu et al. 2008a,b, 2009a,b, 2010, 2011), from which over 70 new bioactive secondary metabolites have been isolated by in-depth chemical studies. This review focuses on the structures, biological activities and putative biosynthetic pathways of some representative metabolites identified from *P. fici* and subsequently published by us.

**The fungus Pestalotiopsis fici**

The culture of *P. fici* (Figure 1) was isolated from branches of *Camellia sinensis* (Theaceae) in the suburb of Hangzhou (China) in April, 2005. The isolate was identified as by Professor Liangdong Guo at the Institute of Microbiology, Chinese Academy of Sciences, on the basis of sequence (GenBank accession number DQ812914) analysis of the ITS region of ribosomal DNA and assigned the accession number AS 3.9138 in China General Microbial Culture Collection (CGMCC) at the Institute of Microbiology, Chinese Academy of Sciences, Beijing (Liu et al. 2009c).

Bioactive secondary metabolites from *Pestalotiopsis fici*

The crude extract prepared from solid-substrate fermentation of this fungus on rice showed cytotoxic effects against human tumor cell lines, HeLa (cervical epithelium) and HT29 (colon adenocarcinoma), and showed an inhibitory effect on HIV-1 replication in C8166 cells. Bioassay-directed separation of the extract led to the discovery of the first chlorinated pupukeanane metabolite, named chloropupukeananin (1, Figure 2), together with its putative biosynthetic precursors, pestheic acid (2) (Ogawa et al. 1995; Shimada et al. 2001) and iso-A82775C (3) (Liu et al. 2008a) (Figure 2). Iso-A82775C (3) is a stereoisomer of the known A82775C, which was initially isolated from an unidentified fungus (Sanson et al. 1991).

The gross structure of chloropupukeananin (1) was determined by nuclear magnetic resonance (NMR) experiments and was confirmed by single-crystal X-ray crystallography. Due to the presence of one chlorine atom, the X-ray data also allowed determination of the absolute configuration of all chiral centres in these metabolites. Structurally, chloropupukeananin possesses a unique and highly functionalized tricyclo-[4.3.1.03,7]-decane (pupukeanane) skeleton, with a sesquiterpenoid moiety attached to C-5 and a 2,6-dihydroxy-4-methylbenzoic acid unit further connected to the sesquiterpenoid via an ester linkage. Compound 1 is the first pupukeanane chloride discovered from any sources, and its tricyclo core structure was encountered for the first time in fungal secondary
metabolites. Compounds 2 and 3 appeared to be the biosynthetic precursors for 1, first via a Diels–Alder reaction (Stocking and Williams 2003), and followed by a cascade of reactions as illustrated in Figure 2 (Liu et al. 2008a). Chloropupukeananin (1) showed an inhibitory effect on HIV-1 replication in C8166 cells, with an IC$_{50}$ value of 14.6 µM, and also displayed cytotoxic effect against HeLa and HT29 cells, showing IC$_{50}$ values of 1.4 and 6.7 µM, respectively. In addition, modest antimicrobial activity was observed for this metabolite against the Gram-positive bacterium, Staphylococcus aureus (ATCC 6538) (Liu et al. 2008a).

To identify other minor active components and/or Diels-Alder analogues of 1, the fungus was refermented on a larger scale on rice (1 kg) to afford a crude extract showing inhibitory effects on growth of the human cancer cell lines, HeLa, HT29, MCF-7 (human breast adenocarcinoma) and MDA-MB-231 (human breast adenocarcinoma), as well as replication of the HIV-1 virus in C8166 cells. Its HPLC fingerprint revealed the presence of metabolites which were different from those isolated previously. Bioassay-guided separation afforded a highly functionalized spiroketal chloride named chloropestolide A (4, Figure 3) (Liu et al. 2009a). The structure of 4 was determined by NMR spectroscopy and was further confirmed by X-ray crystallography. Chloropestolide A (4) possesses a previously undescribed chlorinated spiroketal skeleton derived from a chlorinated bicyclo-[2.2.2]-oct-2-en-5-one ring and a 2,6-dihydroxy-4-methylbenzoic acid moiety. Biogenetically, compound 4 could be derived from the same biosynthetic precursors as chloropupukeananin (1), first via a Diels–Alder reaction to form the key intermediates a and b (Figure 3), and followed by a series of reactions through different routes to form 1 and 4, as
illustrated. The isolation of 4 implies that the biosynthetic pathway initially proposed for 1 is more complex, possibly with more intermediates (such as g, Figure 3) involved prior to formation of the tricyclo-[4.3.1.0³⁷]-decane skeleton (Liu et al. 2008a). Chloropestolide A (4) showed significant cytotoxicity against HeLa and HT29 cells, with IC₅₀ values of 0.7 and 4.2 µM, respectively (Liu et al. 2009a).

To identify other “missing” building blocks for chloropupukeananin (1), different fractions of the scaled-up fermentation extract were also subjected to chemical studies. Chloropupukeanolides A (5) and B (6) (Figure 4), two spiroketal peroxides with an unprecedented skeleton and chloropupukeanone A (7), a new analogue of 1, were isolated with 5 as the anti-HIV-1 principle (Liu et al. 2010). The structures of compounds 5–7 were determined by NMR spectroscopy, and their absolute configurations were deduced by analogy to metabolites 1 and 4, which were secured by X-ray crystallography. Chloropupukeanolides A (5) and B (6) feature an unprecedented spiroketal peroxide skeleton, in which the tricyclo-[4.3.1.0³⁷]-decane core not only spirally joined the 2,6-dihydroxy-4-methylbenzoate-originated 1,3-dioxan-4-one moiety at C-10, but also formed a six-membered peroxide with the 2,3-epoxycyclohex-5-en-1,4-diol unit, completing a highly complex octacyclic structure.

Biogenetically, the metabolites 5–7 share the same Diels-Alder precursors as 1 and 4 (Liu et al. 2010). In a recent work, an alternative biosynthetic hypothesis involving maldoxin (Adeboya et al. 1996) was proposed (Suzuki and Kobayashi 2010), in which the core skeleton of chloropupukeananin (1) was considered to be constructed from a masked o-benzoquinone (MOB; a) and a vinylallene (b) precursors (Figure 5) via a reverse electron-demand Diels-Alder (REDDA) reaction and intramolecular carbonyl-ene reaction sequence. Therefore, it is proposed that pestheic acid is first oxidized to maldoxin, which possesses a reactive diene known as masked o-benzoquinone (Liao and Peddinti 2002; Liao 2005), and then via REDDA reaction of the diene in maldoxin with the terminal alkene in iso-A82775C to form the core structure of this class of metabolites (Figure 4). Compound 5 showed an inhibitory effect on HIV-1 replication in C8166 cells, with an EC₅₀ value of 6.9 µM, and significant cytotoxicity against the human tumor cell lines, MDA-MB-231, HeLa and MCF-7, with IC₅₀ values of 16.9, 15.5, and 15.9 µM, respectively. Compounds 6 and 7 also showed modest cytotoxicity against the three cell lines (Liu et al. 2010).

The isolation of metabolites 4–7 from the same source and their possible joint biogenesis led us to postulate the presence of further minor Diels–Alder reaction analogues in the fractions from which these compounds had been isolated. Due to sample limitations, the fungus was fermented again (3 kg) and those particular fractions were subjected to detailed chemical studies. Three additional pupukeane metabolites featuring a unique spiroketal skeleton derived from the chlorinated tricyclo-[4.3.1.0³⁷]-decane and 2,6-dihydroxy-4-methylbenzoic acid moieties, are presented.
Figure 4. Structures of compounds 5–10 and putative biosynthetic pathways.
Figure 5. Synthetic strategy toward the core skeleton of chloropupukeanin (1).

Figure 6. (a) Comparison of HPLC-UV chromatograms of compounds 1 and 9 (Waters Symmetry® C18 column, 2.1 × 150 mm; H2O/MeOH, 30:70 (v/v), flow rate: 0.8 ml min⁻¹, detection wavelength 220 nm). (b) Assignment of the absolute configuration of 9 by comparison of the experimental LC-CD spectrum of Peak A with calculated CD spectra.

and named chloropupukeanolides C–E (8–10, Figure 4) (Liu et al. 2011). The constitutions of compounds 8–10 were elucidated primarily by NMR experiments. Their relative configurations were deduced by analogy to metabolites 4–6, which were previously isolated from the same fungus. The absolute configuration of 8 was assigned by
X-ray crystallography and those of 9 and 10 by quantum-chemical circular dichroism (CD) calculations. Along with 1, chloropupukeanolide D (9) was obtained as a mixture of 9 and 1 in a 10:1 ratio, which slowly changed to a 5:1 ratio over a period of 24 h, as determined by integration of some well-resolved 1H NMR resonances (e.g. H-4 and H-9) for each one. Efforts to obtain pure 9 were unsuccessful due to repeated rearrangement from 9 to 1 (Liu et al. 2011). The absolute configuration of 9 was assigned by online high performance liquid chromatography (HPLC)-CD (Bringmann et al. 2008) measurements (Figure 6a) in combination with TDA B2PLYP/SV(P) (Schäfer et al. 1992; Grimme and Neese 2007) quantum-chemical calculations (Figure 6b). Similarly, the absolute configuration of 10 was again deduced by a comparison of the experimental CD spectrum with that of quantum chemically calculated spectrum (Figure 7) and, in this case, additionally by biosynthetic considerations (Liu et al. 2011).

Compounds 8 and 9 are analogues of 5 and 6, all with a 5-hydroxy-7-methyl-4H-benzo[d][1,3]dioxin-4-one unit spirally joined to the pupukeananin core via C-10, but differ by the absence of the six-membered peroxide moiety and the hybridization states of C-8 and C-9. Compound 9 is a diastereomer of 8, whereas 10 is a analogue of 9 with a significant difference in the isoprenylated 2,3-epoxycyclohex-5-en-1,4-diol and the tricyclo-[4.3.1.0^3,7]-decane moieties. Specifically, a series of reactions of the isoprenyl group in 8 and 9 with the epoxycyclohexen-diol moiety could afford the additional cyclopropane and tetrahydrofuran rings, leading to the formation of an unusual substructure with the 2,2-dimethyl-3-oxabicyclo[3.1.0]hexane unit cis-fused to the cyclohexen-diol moiety (Liu et al. 2011). The discovery of 9 as a putative biosynthetic intermediate permits establishment of an advanced proposal for the origin of 1 (Figure 4). This initial, oxidation-induced Diels–Alder reaction seems to lack a high degree of stereoselectivity, since compounds 4 and 8 show an oppositely configured southern tricyclic moiety compared to the compounds 1, 5, 6, 9 and 10, which originate from the same pathway. Thus, once a reactive putative diene intermediate (assumedly the known metabolite maldoxin) has been generated, the Diels–Alder reaction itself may occur (nearly) spontaneously, without major enzymatic assistance (Liu et al. 2011). Compounds 8–10 showed significant cytotoxicity against a small panel of human tumor cell lines and activities against the pathogens of tropical diseases (Liu et al. 2011).

The remaining fractions of this fermentation extract showed potent antifungal activity against Aspergillus fumigatus (ATCC 10894) and anti-HIV-1 effect. Bioassay-guided fractionation led the isolation of five cyclohexanone derivatives including four heterodimers named pestalofoines A–E (11–15, Figure 8), along with the known

Figure 7. Assignment of the absolute configuration of compound 10 by comparison of the experimental CD spectrum with that calculated for 1S,3R,6S,7S,10R-10 and 1R, 3S,6R,7R,10S-diastereomer (both with the 15S,16R,17S,18R,20S(R) configuration).
compound isosulochrin (16) and its dehydrate (Shimada et al. 2001; Liu et al. 2009b). In addition, seven isoprenylated chromone derivatives (17–22, Figure 9), including a heterodimer (23, Figure 9), were also isolated (Liu et al. 2009c).

From biogenetic point of view, pestalofones B (12) and C (13) could be derived from two units of iso-A82775C (3), first via a Diels–Alder reaction to form the intermediate with a cyclohexene spirally joined to the epoxycyclohexane unit, and followed by selective oxidation of the hydroxy groups (Figure 8). Compounds 14 and 15 possess a new skeleton with two polyoxygenated cyclohexanes, one is spirally joined to the cyclohexene moiety, whereas the other is linked by an exo-cyclic olefin. Compound 14 could be derived from 3 and 16, whereas 15 was presumed to be derived from 14 through further reactions (Figure 8) (Liu et al. 2009b). Compounds 20–22 could be derived from 17–19 via oxidation, reduction and cyclization, whereas 23 could be derived from 22 and 16 (Liu et al. 2009c). Compounds 12 and 15 showed significant antifungal activity against Aspergillus fumigatus, with IC50 values of 1.10 and 0.90 μM, respectively (Liu et al. 2009b). Compound 21 showed an inhibitory effect on HIV-1 replication in C8166 cells, with an EC50 value of 8.0 μM, whereas 23 was cytotoxic to HeLa and MCF-7 cells, with IC50 values of 8.7 and 17.4 μM, respectively (Liu et al. 2009c).

Metabolites of Pestalotiopsis fici under a different fermentation culture

It is generally accepted that different fermentation conditions for microorganisms are likely to produce different types of secondary metabolites (Bode et al. 2002). On the basis of this consideration, a subculture of P. fici was grown in a different solid-substrate fermentation culture to examine its metabolite profile. Although its ethyl acetate (EtOAc) extract showed similar magnitude of anti-HIV-1 effect to that of chloropupukeananin (1), HPLC analysis revealed the presence of totally different secondary metabolites in the crude extract. Fractionation of this extract afforded five cyclopropane derivatives that have
been named pestaloficiols A–E (24–28, Figure 10) (Liu et al. 2008b). This group of compounds belong to the chromenone type of metabolites with a cyclopropane moiety spirally joined to a cyclohexene unit, with a putative mixed biogenesis of prenoid and polyketide. Compounds 24, 25 and 27 showed inhibitory effects on HIV-1 replication in C8166 cells, with EC\textsubscript{50} values of 26.0, 98.1, and 64.1 \(\mu\)M, respectively (Liu et al. 2008b).

**Discussion**

Chemical investigations of the fungus *P. fici* grown in different solid-substrate fermentation cultures have led to the isolation of over 70 new bioactive secondary metabolites originating from different biosynthetic routes, indicating that *P. fici* is a fungus with huge metabolic potential for the production of novel bioactive natural products. Some metabolites described in this review possess unique structural features and showed significant biological effects.

The discovery of the chlorinated pupukeananin type of metabolites 1 and 4–10, as well as their putative biosynthetic precursors 2 and 3 from the *P. fici* provide evidence for the existence of the Diels–Alder reaction pathway. However, the cycloaddition is stereochemically unselective, indicating that the reaction might not be enzyme-mediated, and other Diels–Alder intermediates and/or products are likely to be present in this reaction cascade, but in lower concentrations. By taking advantage of the remarkable metabolic potential of the fungus in future studies, the identification of further structurally related minor metabolites with interesting activities is possible.

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