

Bioorganic Chemical Investigations of Bioactive Compounds from Mushrooms

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学位論文要旨

Abstract of Doctoral Thesis

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論文題目：キノコ由来の生物活性物質に関する生物化学的研究

Title of Thesis : Bioorganic Chemical Investigations of Bioactive Compounds from Mushrooms

論文要旨：

Abstract :

Fungi have been used as food and traditional medicines around the world for decades, primarily in Asian countries. Furthermore, higher fungi in particular Basidiomycetes have been identified as a promising source of bioactive metabolites with high structural diversity and a wide range of biological activity such as plant and fungal growth regulatory activity and cytotoxic secondary metabolites. Moreover, mushrooms contain secondary metabolites which exhibit a range of beneficial properties, such as antioxidant, antibacterial, antiviral, anticancer, and anti-inflammatory properties. Based on this circumstance, the present study investigated the bioactive metabolites of three mushrooms *Pleurocybella porrigens*, *Pholiota lubrica* and *Cortinarius caperatus*.

1) Isolation and structural elucidation of bioactive compounds from the toxic mushroom *Pleurocybella porrigens*

Pleurocybella porrigens is a species belongs to Marasmiaceae family. This mushroom is distributed in temperate forests of the northern hemisphere, including Japan. *P. porrigens* is known as the angel's wing mushroom or Sugihiratake in Japanese, a white-rot wood-decay fungus on conifer wood. In the rainy season, *P. porrigens* is abundant and was a popular edible mushroom in Japan. However, in 2004, there was a poisoning outbreak due to the intake of this mushroom. The outbreak caused 55 people poisoned and among them 17 people died because of acute encephalopathy. The case led to the investigations of toxic substances from this mushroom. Our group has reported a novel lectin, unusual amino acids, and a structurally unique and unstable compound, pleurocybellaaziridine, which might be a toxic principle.

1.1) Fruiting bodies

A novel butenolide (**1**) along with three known ones (**2–4**) were isolated from the fruiting bodies of *P. porrigens*. The chemical structure, including the absolute configuration of the novel compound (**1**) was determined based on the interpretation of 1D, 2D NMR, HRESIMS, specific rotation, and CD spectra.

Compounds **1–3** reduced the expression of Axl, programmed death-ligand 1 (PD-L1), and programmed death-ligand 2 (PD-L2). Compounds **1** and **2** showed inhibition activity against mycelial growth of *Flammulina velutipes*.

1.2) Culture broth

One novel compound (**5**) and four known compounds (**6–9**) were isolated from the culture broth of *P. porrigens*. The planar structure of compound **5** was determined by extensive NMR and HRESIMS spectroscopic analysis. Compounds **7** and **9** showed the most potent inhibition activity against mycelial growth of *F. velutipes*.

2) Isolation and structural elucidation of bioactive compounds from the edible mushroom *Pholiota lubrica*.

Pholiota lubrica (Japanese name: Chanametsumutake) is an edible mushroom belongs to the Strophariaceae family, which is distributed in the temperate zone of the northern regions. This mushroom typically grows in the forest and its fruiting bodies occur in autumn. This mushroom has been reported to produce an allelopathy substance that inhibited the growth of lettuce. In addition, other species of the genus *Pholiota* produced an antitumor substance, prebiotic, therapeutic agent, antihyperlipidemic and hepatoprotective substances.

A bioassay-guided fractionation resulted in the isolation of a new cinnamamide, *N*-(1-cinnamoylpyrrolidin-2-yl)cinnamamide (**10**), along with eight known compounds (**11–18**). Their structures were determined by the interpretation of spectroscopic data. Compounds **10**, **12** and **18** exhibited the inhibitory activity against lettuce, while compounds **11** and **16** promoted the growth of lettuce.

3) Isolation and structural elucidation of bioactive compounds from the edible mushroom *Cortinarius caperatus*

Cortinarius caperatus (Japanese name: Shogenji; English name: gypsy mushroom) is a mushroom that belongs to Cortinariaceae family, which grows widely in the temperate zone of the northern hemisphere. This mushroom has a mild taste and it has been eaten all over the world, particularly in Japan. This species has been reported to produce an antiviral substance against enveloped virus, the herpes simplex virus (HPV).

Nine compounds (**19–27**) were isolated from the fruiting bodies of *C. caperatus*. Their structures were identified by comparison of spectroscopic data to those of reported data. Compound **22** was first isolated from a natural source. Compounds **19**, **21**, **23**, and **24** inhibited growth of *F. velutipes*. Compounds **20–27** exhibited growth regulatory activities towards rice seedling, while compounds **22–25** and **27** regulated the growth of lettuce. In order to investigate their suppressing activity against Axl and immune checkpoint molecules, compounds **19–22** and **24** were examined toward lung cancer cells A549. As a result, compound **22** effectively inhibited the Axl, PD-L1 and PD-L2 gene expression, while compound **24** showed strong inhibition against PD-L2.