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SPECIAL FEATURE: EDITORIAL

# Secondary metabolites from mushrooms

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Fungi with an estimated number of >1 million species inhabit a vast variety of terrestrial and aquatic habitats. In the interaction with a complex environment, secondary metabolites play a crucial role. Their classification as "secondary" has been deduced from the fact that contrary to primary metabolites in most cases their loss does not impede growth and survival in artificial culture. This, in fact, can pose problems for the maintenance of producing strains. Another characteristic feature is that secondary metabolites are often produced as families of compounds sharing the same biosynthetic pathway, e.g., non-ribosomal peptides or terpenoids. An interesting theory for the existence of secondary metabolism has been proposed [1]. Accordingly, during evolution, secondary metabolism serves as "playground" for the development of new chemical tools for the interaction in a changing environment. Examples for this gain of a function can be gleamed from the article of Wu and Kawagishi in this issue and some papers [2, 3]. Within the fungal kingdom, the most prolific producers of secondary metabolites are ascomycetes and basidiomycetes with both their sexual (fruiting bodies) and asexual (conidial, imperfect) stages. Conspicuous large fruiting bodies (mushrooms) are typically formed by basidiomycetes that make them amenable to chemical analysis, offering the chance to investigate the metabolites produced by both the sexual stage and vegetative mycelia. Few ascomycetes form larger mushroom-like fruiting bodies. Some (morels and truffles) are highly esteemed delicacies while others like *Ophiocordyceps sinensis* and *Cordyceps sinclairii* growing on insect larvae have been used in traditional Tibetan and Chinese medicine. As described in the article of Chiba, myriocin, a metabolite of *Isaria sinclairii* (the anamorph of *C. sinclairii*), served as template for a most important drug to treat multiple sclerosis. The often brightly colored fruiting bodies of basidiomycetes (for a review, see [4]) have attracted the interest of man worldwide and from early on in history. They have been used as food or for pharmacological uses. South American Indians have used the fruiting bodies of *Psilocybe* species for spiritual ceremonies. As reviewed by Nichols, psilocybin, the active pharmacological principle, is now under intensive investigation for uses in psychiatric medicine. The fruiting bodies of *Lentinula edodes* and *Flammulina velutipes* are highly esteemed as tasty food. The contribution of Sakuno reviews the biologically active metabolites of fruiting bodies and mycelia cultures and their pharmacological effects. The paper of Oba et al. deals with the elucidation of the stereochemistry of lascivol, the bitter principle that renders the fruiting bodies of three *Tricholoma* species inedible. The wood-inhabiting *Ganoderma* species form conspicuous fruiting bodies, which are commonly used in traditional Asian medicine. Their characteristic metabolites are highly oxygenated triterpenoids. Isaka et al. describe the isolation and characterization of ten new lanostanes from artificially cultivated fruiting bodies of a *Ganoderma* species. Four of these exhibited moderate antimalarial activity. The phallac acids A and B, two interesting new inhibitors of alpha-glucosidase from the edible and medicinal mushroom *Phallus luteus*, are described by Lee et al. Sometimes highly toxic fungi are gifted producers of not only toxic but also potentially useful metabolites. Investigating fruiting bodies of *Pleurocybella porrigens*, a highly poisonous mushroom, Ridwan et al. isolated four compounds that apparently are not the toxic principles but have an interesting pharmacological mode of action. The inter-relationship between plants and mushrooms is complex. Fungal metabolites that could play an important role are reviewed in the paper of Wu and Kawagishi where plant growth regulators from pathogenic, mycorrhizal, and saprophytic mushrooms, all basidiomycetes, are addressed. The large-scale cultivation of basidiomycete mycelia under sterile conditions is often

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time-consuming and can pose problems on the engineering side. This is reflected by the fact that of all the published antibiotics from these fungi only a pleuromutilin is produced by fermentation in an industrial scale. The tricyclic mutilin core is then used after chemical modification [5, 6] as antibacterial in veterinary (e.g., Thiamulin) or most recently in human (Lefamulin) medicine [7]. The antifungal strobilurins [8], the only other basidiomycete antibiotics that have gained access to the market are not produced by fermentation but their synthetic analogs are used as agricultural fungicides [9, 10]. There are now ten major strobilurins on the market that account for 23–25% of the global fungicide sales. In many cases, the industrial production of a mushroom metabolite by fermentation is not feasible because of very low yields or the unavailability of mycelial cultures and the alternative, chemical synthesis is economically not feasible. In these cases, genetic engineering can offer promising solutions. The article of Hoffmeister et al. describes the isolation of a polyketide synthase from *Laetiporus sulfureus* and its heterologous expression in *Aspergillus nidulans* and *Aspergillus niger* yielding a mixture of laetiporic acids. Watanabe describes an innovative approach to improve the production of metabolites by insertion of the gene of a key enzyme in the expression boost area of a chromosome of the producing basidiomycete. Thus, in *Coprinus cinerea*, the overexpression of the terpene cyclase cop6 increased the yield of the sesquiterpenoid lagopodin nearly 50-fold. Therefore, the breakthroughs in the genetic engineering of basidiomycetes make a fresh look at the metabolites hitherto only found in mushroom fruiting bodies seem very worthwhile.

## Compliance with ethical standards

**Conflict of interest** The author declares that he has no conflict of interest.

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