

Medicinal Properties of Coprinoid Mushrooms (Basidiomycetes, Agaricales)

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Myco-pharmacological investigations of bioactive metabolites and medicinal properties of mushrooms play an important role in the development of new biotech products and biopharmaceuticals. Concerning physiological activities and medicinal properties, Coprinoid mushrooms are poorly studied and not at all exploited. The majority of these organisms are fimicolous. However, many of them have also been found on trees and decaying wood (Navarro-González et al., in preparation). Based on molecular data, the traditional genus *Coprinus* Pers. has now been divided into four clades: *Coprinus*, *Coprinopsis*, *Coprinellus*, and *Parasola* (Redhead et al., 2001). For simplicity, we use the traditional nomenclature.

Important in view of biological safety, Coprini are generally nonpathogenic to humans or animals. Less than 10 cases of opportunistic mycoses by Coprini have been recorded worldwide. About 30 years ago, mycelia were isolated from two hearts of immunosuppressed patients who had undergone heart surgery and, in more recent times, from the lungs of three patients suffering from leukemia, known as non-Hodgkin's lymphoma, who received intensive cytotoxic treatment. Recently, a strain has also been isolated from human skin lesions (Kües et al., 2003). *Coprinus comatus* (O.F.Müll.) S.F.Gray may aggravate eczematous skin lesions and induce delayed-type allergic reactions by spores in individuals with atopic dermatitis. Intense efforts have been invested to identify clinically relevant allergens. *C. comatus* rCop c1, a protein of no known function,

was able to induce strong specific skin reactions in sensitized individuals (Helbling et al., 2002).

Mushrooms are very good dietary sources of food (referred to as nutraceuticals) contributing to the general well-being. They are rich in proteins, carbohydrates, fibers, unsaturated fatty acids, vitamins, and minerals, but low in calories (Kües et al., 2003). While most *Coprinus* species are inherently not eaten for practical reasons (fast autodigestion of the fruiting bodies), a few species are regularly consumed by humans, and a toxic-lethal species does not appear to exist. However, among the chosen edible species is *C. atramentarius* (Bull.) Fr., users of which, in combination with alcohol consumption, describe hot flushes of the face and neck, a metallic taste, tingling sensation in the limbs, nausea, and vomiting. Occasionally, these symptoms occur also upon ingesting *C. africanus* Pegler (in Nigeria called "Ajeimutin" for *aje*=eat + *imu*=without drinking + *otin*=alcohol), *C. insignis* Peck, *C. quadrifidus* Peck, and *C. variegatus* Peck together with alcohol. The unpleasant effects are mediated by the rather unique toxin Coprine, an atypical amino acid that inhibits acetaldehyde dehydrogenase and thus blocks the metabolism of ethanol. Remission takes place within a few hours. This *Coprinus* syndrome is analogous to the non-lethal symptoms of Antabuse (disulfiram) that is applied in the treatment of alcoholism without resulting in the negative mutagenic and gonadotoxic side effects of Coprine.

Many Coprini appear to be useful natural sources

of antibacterial, antifungal, and antiviral antibiotics. For example, Coprinol, a new antibacterial cupranane (sesquiterpenoid), was isolated from fermentations of an unnamed species and was shown to be active against multidrug-resistant Gram-positive bacteria *in vitro*. Antimicrobial activity against *Bacillus cereus* and *B. subtilis* has been detected in *Coprinus plicatilis* (W.Curt.) Fr. A wide spectrum of strain-specific antimicrobial activity against Gram-positive and Gram-negative bacteria (*B. subtilis*, *B. mycoides*, *B. pumilis*, *Leuconostoc mesenteroides*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Comamonas terrigena*, and *Pseudomonas aeruginosa*) and microfungi (*Saccharomyces cerevisiae*, *Candida albicans*, and *Aspergillus niger*) was revealed in mycelia of *Coprinus micaceus* (Bull.)Fr., *C. delicatulus* Apinis, *C. comatus*, *C. congregatus* (Bull.)Fr., *C. radiatus* (Bolton) S.F.Gray, *C. digitalis* (Batsch)Fr., and other unidentified strains. Aqueous extracts from *C. comatus* and *C. atramentarius* inhibited vegetative growth and sporulation of *Penicillium expansum* and phytopathogens, too. A strong antiviral activity was described in *C. micaceus*.

Antibacterial and antifungal activity in mutants of *C. cinereus* (Schaeff.) S.F.Gray was due to sesquiterpenoid quinones (lagopodins, hydroxylagopodins) found in mycelial extracts and supernatants of fungal cultures. Illudins are the best studied sesquiterpenes having antibacterial and, most importantly, also cytotoxic effects against tumor cells. *C. atramentarius* was shown to produce illudin C derivatives, C-2 and C-3, and *C. episcopalis* P.D. Orton to produce the three novel illudins I, I-2, and J2. *C. gonophyllus* Quél. produced only illudinic acid. Antitumor activity was detected in *C. atramentarius* and *C. comatus*. Polysaccharides isolated from *C. comatus* inhibited tumor growth. 1-aminocyclopropane-1-carboxylic acid is a component of the species affecting reproductivity of male mice of the SHN line (characterized by a high risk of spontaneous mammary tumorigenesis). Furthermore, culture broth extracts of *C. disseminatus* (Pers.) S.F.Gray inhibited proliferation and induced apoptosis in certain human cervical carcinoma cell lines. An antibiotic from a culture broth of *C. radiatus* showed *in vivo* an anti-leukemia effect.

Many Coprini are characterized by strong proteolytic activity (fibrinolytic, thrombolytic, casei-

nolytic) that can be of medicinal interest. Galectins, a specific class of lectins detected in fruiting bodies of *C. cinereus* (Schaeff.) S.F.Gray, might be tested for therapies of muscular dystrophy or T-cell-mediated liver disorders where positive effects by mammalian galectin-1 were reported. A mild hypoglycemic effect (reducing plasma glucose concentration) by *C. comatus* described in mice might be exploited through a dietary adjunct (nutriceutical) in treatment of diabetes. Finally, hydrophobins, small nontoxic hydrophobic surface-active fungal proteins found also in *C. cinereus*, are most interesting candidates for various medical and pharmacological applications such as increasing biocompatibility of medical implants, immobilization of antibodies in a biosensor, stabilizing oil vesicles for drug delivery, and patterning molecules at the cell surface. In conclusion, Coprini are producers of various types of biologically active molecules and proteins whose further investigation will assist in obtaining new preventive and curative mushroom-based biopharmaceuticals and food additives. A more detailed review with appropriate references will be given elsewhere.

In our own screening program of Coprini, antifungal activity of *C. cinereus*, *C. comatus*, and *C. atramentarius* was observed in *Aspergillus niger*, *A. versicolor*, *A. flavus*, *Penicillium simplicissimum*, *P. jensenii*, *P. chrysogenum*, *Fusarium sambucinum*, *Cladosporium atroseptum*, *Stemphylium botryosum*, and *Hormiscium* sp. *C. comatus* had the highest activity, followed by *C. cinereus* and then *C. atramentarius*, while from the tested fungi, *Aspergillus* species acted in the most antagonistic way against mushroom cultures. *C. disseminatus* (Pers.) S.F.Gray and *C. micaceus* prevented or markedly suppressed the growth of numerous fungi potentially pathogenic for humans and animals (*Aspergillus candidus*, *A. flavus*, *A. wentii*, *Fusarium tricinctum*, *Stachybotris chartarum*, *Acremonium alternatum*, *Chrysosporium keratophilum*, *Penicillium aurantiogriseum*, *P. griseofulvum*, *Alternaria alternata*, *Cladosporium cladosporoides*, and *Verticillium lecanii*). Only *A. flavus* exhibited a relatively high resistance against *C. micaceus*. Strong antiprotozoal activity against *Paramecium caudatum* was present in culture liquids of *C. comatus*, whereas different concentrations of mycelial extracts showed up to a 2.8-fold mitogenic stimulation towards the

protozoa. Culture medium of *C. disseminatus*, *C. micaceus*, *C. radiatus*, *C. domesticus*, *C. cinereus*, *C. comatus*, *C. curtus* Kalchbr., *C. strossmayeri* Schulzer, *C. xanthothrix* Romagn., and non-identified species cultures had caseinolytic (proteolytic) activity with a strong dose/effect correlation. The highest activity was observed after four weeks of cultivation, particularly in cultures of *C. xanthothrix*, *C. strossmayeri*, and *C. radiatus*. Cultural liquids and mycelial extracts of *C. comatus*, *C. disseminatus*, *C. domesticus* (Bolton) S.F.Gray, and *C. radiatus*, but those of *C. domesticus*, *C. lagopus*, and *C. micaceus* did not have a significant antioxidant activity.

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