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Review

The Pharmacological Potential of Mushrooms

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This review describes pharmacologically active compounds from mushrooms. Compounds and complex substances with antimicrobial, antiviral, antitumor, antiallergic, immunomodulating, anti-inflammatory, antiatherogenic, hypoglycemic, hepatoprotective and central activities are covered, focusing on the review of recent literature. The production of mushrooms or mushroom compounds is discussed briefly.

Keywords: antiatherogenic – antimicrobial – antitumor – basidiomycetes – bioactive compounds

Introduction

The medicinal use of mushrooms has a very long tradition in the Asian countries, whereas their use in the Western hemisphere has been slightly increasing only since the last decades. The edition of the new scientific journal *International Journal of Medicinal Mushrooms* (Begell house, Editor-in-Chief S. P. Wasser), several books and reviews about medicinal mushrooms (1–6) and biologically active compounds from mushrooms (7) as well as international conferences about this topic confirm this trend. The market value of medicinal mushrooms and their derivative dietary supplements worldwide was ∼US $1.2 billion in 1991 (8) and was estimated to be US $6 billion in 1999 (9).

What is a 'Mushroom'?

'Mushroom' is not a taxonomic category. The term 'mushroom' should be used here according to the definition of Chang and Miles as 'a macrofungus with a distinctive fruiting body, which can be either hypogeous or epigeous, large enough to be seen with the naked eye and to be picked by hand' (10). From a taxonomic point of view, mainly basidiomycetes but also some species of ascomycetes belong to mushrooms. Mushrooms constitute at least 14 000 and perhaps as many as 22 000 known species. The number of mushroom species on the earth is estimated to be 140 000, suggesting that only 10% are known. Assuming that the proportion of useful mushrooms among the undiscovered and unexamined mushrooms will be only 5%, which implies 7000 yet undiscovered species will be of possible benefit to mankind (11). Even among the known species the proportion of well investigated mushrooms is very low. This fact together with the knowledge about the great potential of microscopic fungi for production of bioactive metabolites [e.g. *Penicillium, Aspergillus, Tolypocladium inflatum* W. Gams, *Claviceps purpurea* (Fr.) Tul.], the experience in ethnomedicinal use of mushrooms, the ecologic need for fungi to produce bioactive secondary metabolites and the improved possibilities for genetic, pharmacological and chemical analysis let us assume that mushrooms have a great potential for successful bioprospecting. This minireview should give an overview about the present knowledge about the pharmacological potential of mushrooms and related problems. Caterpillar fungi like *Cordyceps sinensis* (Berk.) Sacc. or *Paecilomyces tenuipes* (Peck) Samson are not closely allied to mushrooms. Because they are used as valuable tonic foods and herbal medicines in China and interesting investigations have recently been published, they are discussed here, as well.

Antibacterial and Antifungal Mushrooms

Mushrooms need antibacterial and antifungal compounds to survive in their natural environment. It is therefore not surprising that antimicrobial compounds with more or less strong activities could be isolated from many mushrooms and that they could be of benefit for human (12). But only

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compounds from microscopic fungi are on the market as antibiotics till now.

Activities against Multiresistant Bacteria

Of special interest are compounds with activities against multiresistant bacterial strains. We could show that new sesquiterpenoid hydroquinones produced by the European *Ganoderma* species *Ganoderma pfeifferi* Bres. and named ganomycins (**1**) inhibit the growth of methicillin-resistant *Staphylococcus aureus* and other bacteria (13). Besides, we found that whole extracts of this mushroom inhibit the growth of microorganisms responsible for skin problems (*Pityrosporum ovale, Staphylococcus epidermidis, Propionibacterium acnes*, unpublished results).

Antimicrobial Activities of Known Compounds

Applanoxidic acid A (**2a**), isolated from *Ganoderma annulare* (Fr.) Gilbn., shows weak antifungal activity against *Trichophyton mentagrophytes* (14). Steroids like 5α-ergosta-7,22-dien-3β-ol (**3**) or 5,8-epidioxy-5α,8α-ergosta-6,22-dien-3β-ol (**4**), isolated from *Ganoderma applanatum* (Pers.) Pat., proved to be weakly active against a number of gram-positive and gram-negative microorganisms (15). Oxalic acid is one agent responsible for the antimicrobial effect of *Lentinula edodes* (Berk.) Pegler against *S. aureus* and other bacteria (16). Ethanolic mycelial extracts from *L. edodes* possess antiprotozoal activity against *Paramecium caudatum* (17) (Figure 1). The antimicrobial activity of *Podaxis pistillaris* (L.: Pers.) Morse, used in some parts of Yemen for the treatment of 'nappy rash' of babies and in South Africa against sun burn (18), is caused by epicorazins (**5**). These substances belong to the group of epipolythiopiperazine-2,5-diones, an important class of biologically active fungal metabolites (18). Other antimicrobial compounds from the Aphyllophorales were summarized by Zjawiony (7).

Figure 1. *Lentinula edodes*; Photo: Prof. Jan Lelley.

Antiviral Mushrooms

In contrast to bacterial infectious diseases, viral diseases cannot be treated by common antibiotics and specific drugs are urgently needed. Antiviral effects are described not only for whole extracts of mushrooms but also for isolated compounds. They could be caused directly by inhibition of viral enzymes, synthesis of viral nucleic acids or adsorption and uptake of viruses into mammalian cells. These direct antiviral effects are exhibited especially by smaller molecules. Indirect antiviral effects are the result of the immunostimulating activity of polysaccharides or other complex molecules (19).

Small Molecular Compounds with Antiviral Activities

Several triterpenes from *Ganoderma lucidum* (M. A. Curtis: Fr.) P. Karst. [i.e. ganoderiol F (**6a**), ganodermanontriol (**7a**), ganoderic acid B (**8a**)] are active as antiviral agents against human immunodeficiency virus type 1 (HIV-1) (Figure 2). The minimum concentration of ganoderiol F (**6a**) and ganodermanontriol (**7a**) for complete inhibition of HIV-1 induced cytopathic effect in MT-4 cells is 7.8 μg ml^{-1}. Ganoderic acid B (**8a**) inhibits HIV-1 protease with an IC 50 value of 0.17 mM (20). Ganodermadiol (**6b**), lucidadiol (**9a**) and applanoxidic acid G (**2c**), isolated from *G. pfeifferi*, but also known from other *Ganoderma* species, possess *in vitro* antiviral activity against influenza virus type A (IC 50 values in MDCK cells >0.22; 0.22 and 0.19 mmol l^{-1}, respectively). Further, ganodermadiol (**6b**) is active against herpes simplex virus type 1, causing lip exanthema and other symptoms [IC 50 in Vero cells 0.068 mmol l^{-1} (21)]. *In vitro* antiviral activity against influenza viruses type A and B was demonstrated for mycelial extracts of *Kuehneromyces mutabilis* (Schaeff.: Fr.) Singer & A. H. Sm. (22), extracts and two isolated phenolic compounds from *Inonotus hispidus* (Bull.: Fr.) P. Karst (23) and ergosterol peroxide (**4**), present in several mushrooms (24). The antiviral

Figure 2. *Ganoderma lucidum*; Photo: Prof. Jan Lelley.

Table 1. Immunomodulating drugs from mushrooms (selected)

Mushroom scientific name	Mushroom common names	Immunomodulator	Structure of immunomodulator(s)	Selected references
A. brasiliensis	Royal sun Agaricus, Himematsutake	FIo-a-β	(1→6)-β-D-glucan, heteropolysaccharides, polysaccharide–protein complex	(144,145)
		FA-2-b-Md	RNA–protein complex (MW 6200 daltons)	
C. volvatus		H-3-B	(1→3)-β-D-glucan	(146)
F. velutipes	Winter mushroom, Enokitake	Flammulin	Protein	(147)
G. lucidum	Reishi, Ling Zhi	GLP(AI), Ganopoly, Ganoderans	β-D-glucans, heteropolysaccharides, Glykoproteins	(148)
		Protein LZ 8		
G. frondosa	Maitake, Hen-of-the-Woods	MD-fraction	(1→6)-β-D-glucan with (1→3)-β-D side chains	(46,47)
		Grifolan	(1→3)-β-D-glucan with (1→6)-β-D side chains	(149)
H. caput-medusae Syn. *H. erinaceus*	Lion's Mane, Monkey's Head, Yamabushitake		Glucoxylan; Heteroxyloglucan, Glucoxylan–protein complex; Galactoxyloglucan–protein complex	(40)
L. edodes	Shiitake, Golden Oak mushroom	Lentinan, KS-2	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches	(39,150)
		LEM	Complex mixture of polysaccharides and lignin	
Lentinus strigellus			Polysaccharides	(151)
P. linteus			Polysaccharides	(87,152)
S. commune		Schizophyllan, Sonifilan, SPG	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches	(5,49)
S. crispa	Cauliflower mushroom	SCG	(1→3)-β-D-glucan with (1→6)-β-D-glucosyl branches	(153)
T. versicolor	Turkey Tail, Kawaratake, Yun Zhi	Krestin (PSK), PSP	PSK and PSP: heteroglucans with α(1→4)- and β- (1→3) glycosidic linkages with a protein component; the presence of fucose in PSK and rhamnose and arabinose in PSP distinguishes the compounds	(7,51,154)
T. fuciformis	White Jelly fungus, Yin-erh	Tremellastin	Glucuronoxylomannans	(125,155)
T. mesenterica				
T. lobayense			Polysaccharide–peptide complex	(156)
Tricholoma mongolicum	Mo-ku		Lectin	(157)

activity of *Collybia maculata* (Alb. & Schwein.: Fr.) P. Kumm. (vesicular stomatitis viruses in BHK cells) is caused by purine derivatives (25).

High Molecular Compounds with Antiviral Activities

Water-soluble lignins isolated from *Inonotus obliquus* (Pers.: Fr.) Pilát, commonly known as 'Chaga', inhibited HIV protease with an IC 50 value of 2.5 μg ml^{-1} (26). Anti-HIV activities were reported for mycelial culture medium of *L. edodes* (LEM) and water-soluble lignin in LEM (27,28). Sulfated lentinan from *L. edodes* completely prevented HIV-induced cytopathic effect (29). The protein-bound polysaccharides PSK and PSP (to the differences between both substances see Table 1) from *Trametes versicolor* (L.: Fr.) Pilát [syn. *Coriolus versicolor* (L.: Fr.) Quelet] were also found to have an antiviral effect on HIV and cytomegalovirus *in vitro* (30). Besides immunostimulation, other effects of the polysaccharide–protein complexes contribute to the antiviral activity, e.g. inhibition of binding of HIV-1 gp120 to immobilized CD4 receptor and of reverse transcriptase activity of viruses (31). Inhibition of HIV-1 reverse transcriptase was caused by velutin, a ribosome inactivating protein from *Flammulina velutipes* (M. A. Curtis: Fr.) P. Karst., as well (32). The maitake D-fraction (MD-fraction) from *Grifola frondosa* (Dicks: F) S.F. Gray was tested in a long-term trial with 35 HIV patients. A total of 85% of responders reported an increased sense of well-being with regard to various symptoms and secondary diseases caused by HIV (Figure 3). Twenty patients showed an increase in CD4+ cell counts to 1.4–1.8 times and eight patients a decrease to 0.8–0.5 times (33).

Antitumor Mushrooms

Experience from Ethnomedicine

Tumor diseases are one of the main causes of death worldwide. Experience from Asian and Eastern Europe countries shows

Figure 3. *Grifola frondosa*; Photo: Prof. Jan Lelley.

that mushrooms could play an important role in prevention and treatment of cancer. *Piptoporus betulinus* (Bull.: Fr.) P. Karst. was used traditionally in Bohemia for the treatment of rectal cancer and stomach diseases (34). It is also known as fungus of the 'iceman' from the Copper Age found in 1991, who carried *P. betulinus* fruiting bodies attached to his clothing on his journey in the Alps.

In Eastern Europe, the fruiting bodies of *I. obliquus* have been used as a folk medicine for cancer and stomach diseases since the 16th or 17th century (35). Antitumor effects of several extracts and isolated compounds could be demonstrated in tumor cell systems and in animal assays (36,37). Several triterpenes and ergosterol peroxide contribute to the activity. The melanin complex of *I. obliquus* has high antioxidant and genoprotective effects on peroxidase-catalyzed oxidation of aminodiphenyls (38).

So called 'immunomodulators' (biological response modifier, immunopotentiators and immunostimulants) are the most important medicinal mushroom drugs used especially in Japan, China, Korea and other East Asian countries today. They are summarized in the following sections.

Immunomodulators from Mushrooms and Adjuvant Tumor Therapy

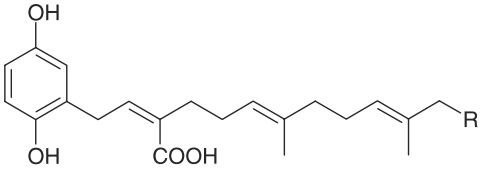
Polysaccharides from *L. edodes*, *G. frondosa*, *Schizophyllum commune* and *T. versicolor*

Mode of Action

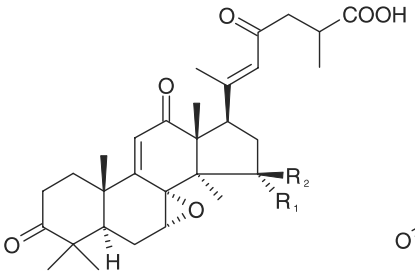
Some polysaccharides or polysaccharide–protein complexes from mushrooms are able to stimulate the non-specific immune system and to exert antitumor activity through the stimulation of the host's defence mechanism (39–42). The drugs activate effector cells like macrophages, T lymphocytes and NK cells to secrete cytokines like TNF-α, IFN-γ, IL-1β, etc., which are antiproliferative and induce apoptosis and differentiation in tumor cells. Table 1 summarizes the most important immunomodulators from mushrooms [for a more extensive survey see (41,42)]. There is evidence that β-D-glucans induce a biological response by binding to membrane complement receptor type 3 (CR3, alphaMβ2 integrin or CD11b/CD18) on immune effector cells. The ligand–receptor complex can be internalized. The intercellular events that occur after glucan-receptor binding have not been fully determined till now (43). In a recent experimental approach it could be shown that schizophyllan produced by *S. commune* Fr.: Fr. is able to bind the mRNA poly(A) tail (44). Molecular weight, degree of branching, number of substituents, as well as ultrastructure, including the presence of single and triple helices, significantly affect the biological activities of β-glucans (45). Higher antitumor activity seems to be correlated with higher molecular weight, lower level of branching and greater water solubility of β-glucans (7). However, the high branched MD-fraction from *G. frondosa* (MW 1 000 000–1 200 000 dalton) exerts a high antitumor activity (46,47).

Clinical Trials

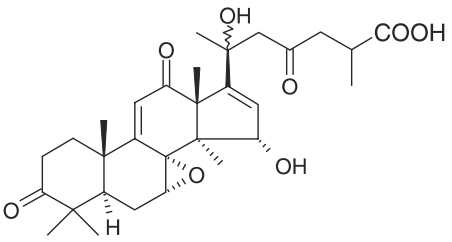
Lentinan from *L. edodes*, schizophyllan from *S. commune*, MD-fraction from *G. frondosa* and compounds from *T. versicolor* (PSK and PSP) are in clinical use (i.e. 0.5–1.0 mg lentinan per day, intravenous), especially in Japan and China, for the adjuvant tumor therapy (immunotherapy) in addition to the major cancer therapies like surgical operation, radiotherapy and chemotherapy. Clinical studies have been done especially in Asian countries [(reviewed in (1,3,4)]. Application of lentinan (parenteral) in addition to chemotherapy led to prolongation of survival time, restoration of immunological parameters and improvement of life quality in patients with stomach cancer, colon cancer and other carcinomas in comparison to patients who had chemotherapy alone (48). In a randomized multicentric study with 89 stomach cancer patients, the median survival time in the immunochemotherapy group (chemotherapy and lentinan 2 mg per week, intravenous) was 189 days and in the control group (only chemotherapy) 109 days (49). In another study of patients with advanced colorectal cancer, the median survival time was 200 days in the lentinan-treated group (2 mg per week, 23 patients) and 94 days in the control group (50). In a controlled randomized study, 130 patients were treated with schizophyllan (intramuscular 40 mg per week, totally ~1134 mg) after surgical removal of the whole tumor tissue additionally to application of mitomycin and futraful. The schizophyllan treatment started at day 14 after operation. The median survival time after 5 years was 72.2% in the schizophyllan group and 61.9% in the control group (134 patients, chemotherapy only). Schizophyllan had no effect on the survival time when the tumor tissue could not be removed totally (51). In a randomized controlled study with 462 curatively resected colorectal cancer patients, PSK was given orally for >3 years following mitomycin C (intravenous on the day of surgery and 1 day following) and 5-fluorouracil (orally for 5 months). The average study



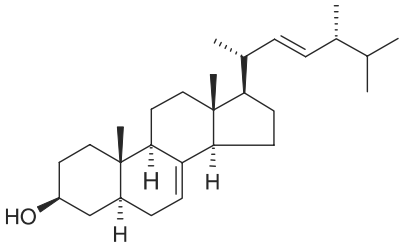
ganomycin A (**1a**) R=OH
ganomycin B (**1b**) R=H



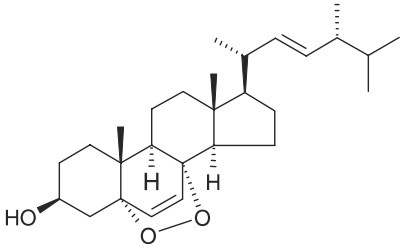
applanoxidic acid A (**2a**) R_1=OH, R_2=H
applanoxidic acid B (**2b**) R_1=R_2=O



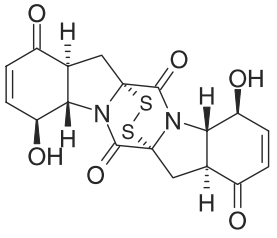
applanoxidic acid G (**2c**)



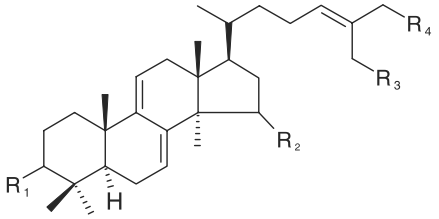
5α-ergosta-7,22-dien-3β-ol (**3**)



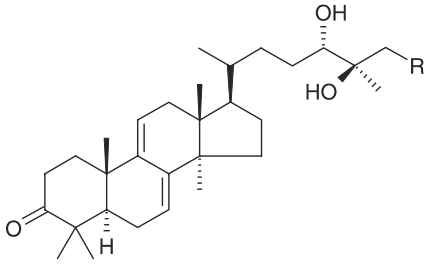
5,8-epidioxy-5α,8α-ergosta-6,22-dien-3β-ol (**4**)



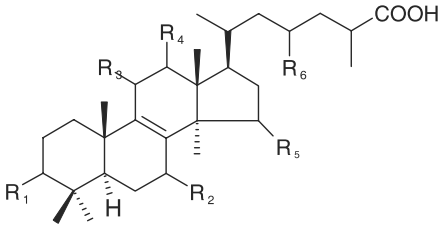
epicorazine A (**5**)



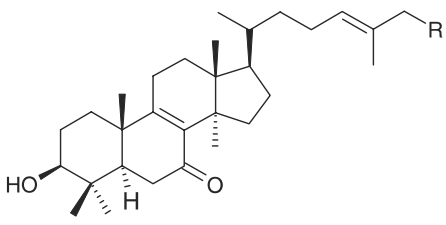
ganoderiol F (**6a**) R_1=O, R_2=H, R_3=R_4=OH
ganodermadiol (**6b**) R_1=β-OH, R_2=R_3=H, R_4=OH
5a-lanosta-7,9(11),24-triene-15a-26-dihydroxy-3-one (**6c**) R_1=O, R_2=α-OH, R_3=H, R_4=OH



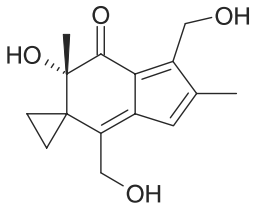
ganodermanontriol (**7a**) R=OH
ganodermanondiol (**7b**) R=H



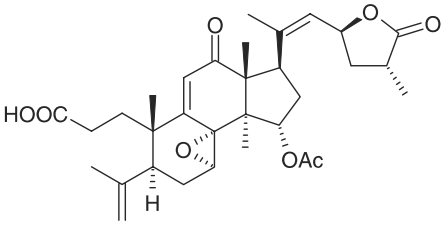
ganoderic acid B (**8a**) R_1=R_3=R_5=R_6=O, R_2=β-OH, R_4=H
ganoderic acid Z (**8b**) R_1=β-OH, R_2=R3=R_4=R_5=R_6=H
ganoderic acid A (**8c**) R_1=R_3=R_6=O, R_2=R_5=β-OH, R_4=H
ganoderic acid C (**8d**) R_1=R_3=R_5=R_6=O, R_2=β-OH, R_4=H
ganoderic acid D (**8e**) R_1=R_3=R_5=R_6=O, R_2=R_4=β-OH,
ganoderic acid F (**8f**) R_1=R_2=R_3=R_5=R_6=O, R_4=β-OH
ganoderic acid G (**8g**) R_1=R_2=R_4=β-OH, R_3=R_5=R_6=O
ganoderic acid H (**8h**) R_1=β-OH, R_2=R_3=R_5=R_6=O, R_4=β-OAc
ganosporeric acid A (**8i**) R_1=R_2=R_3=R_4=R_5=R_6=O



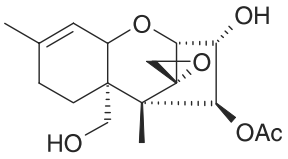
lucidadiol (**9a**) R=OH
lucialdehyde C (**9b**) R=O



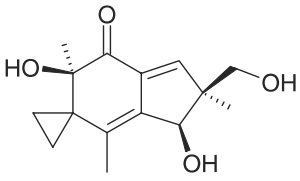
leaianafulvene (**10**)



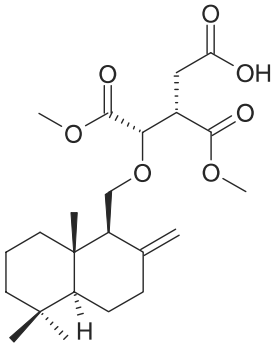
australic acid (**11**)



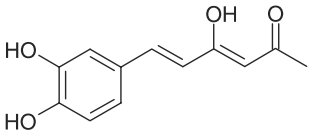
acetoxyscirpenediol (**12**)



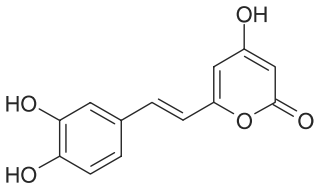
illudin S (**13**)



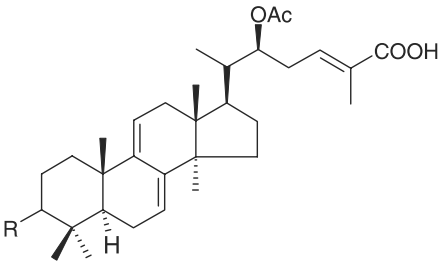
cryptoporic acid A (**14**)



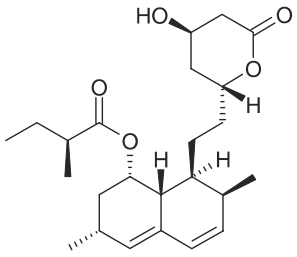
hispolon (**15**)



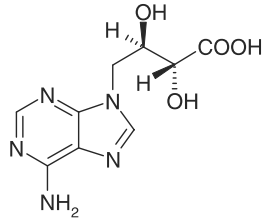
hispidin (**16**)



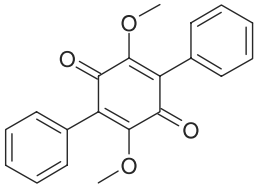
ganoderic acid R (**17a**) R=α-OAc
ganoderic acid S (**17b**) R=O



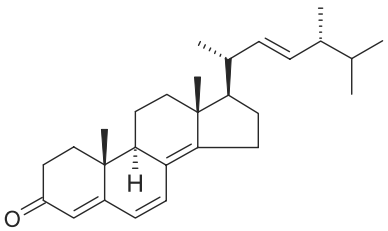
lovastatin (**18**)



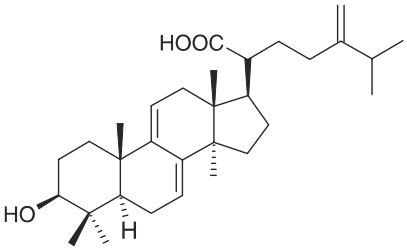
eritadenine (**19**)



betulinan A (**20**)



ergosta-4,6,8(14),22-tetraen-3-one (**21**)



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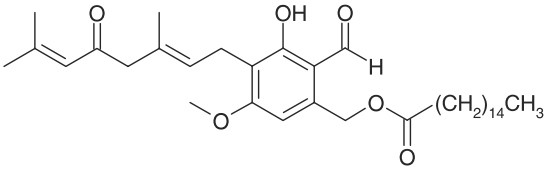

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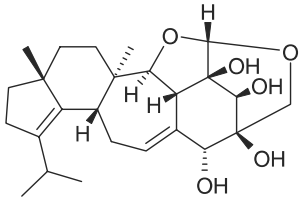

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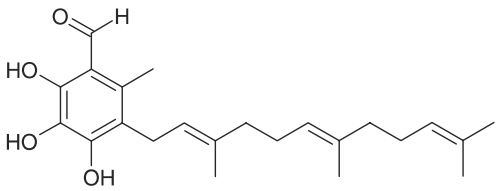
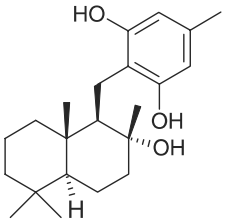


scutigeral (**25**)



albaconol (**26**)

follow-up was 4 years. The increased disease-free survival curve of the PSK group over the control group was statistically significant (1,52). A controlled clinical trial of PSP was conducted in 485 cancer patients (211 control patients, cancers of the esophagus, stomach and lung). As a result of PSP admission [3 g per day, peroral (p.o.) 30 days], side effects from the conventional therapy (esophagus cancer: Co^{60}-gamma ray radiotherapy, DT 65–70 Gy per 6–7 months) significantly lessened. PSP raised the 1 year survival rate of patients with esophagus cancer by 11% (1,53).

The immunostimulating effect of lentinan was also investigated in patients with AIDS. In a phase II study, 107 HIV positive patients were treated with didanosin (400 mg per day, p.o. 6 weeks). After that time, 88 patients got additionally 2 mg lentinan per week intravenous for 24–80 weeks, the patients of the control group got only didanosin. The combined treatment resulted in a significant increase of the number of CD4+ cells after 38 weeks in comparison to control group (54).

In a non-random case series, a combination of MD-fraction and whole powder of *G. frondosa* was investigated to determine its effectiveness for 22- to 57-year-old cancer patients in stages II–IV. Cancer regression or significant symptom improvement was observed in 58.3% of liver cancer patients, 68.8% of breast cancer patients and 62.5% of lung cancer patients. The trial found a <10–20% improvement for leukemia, stomach cancer and brain cancer patients (55). MD-fraction appears to repress cancer progression and primarily exerts its effect through stimulation of NK cells activity (47). The MD-fraction has been approved by the Food and Drug Administration (FDA) for an Investigational New Drug application to conduct a phase II pilot study on patients with advanced breast and prostate cancer (56).

Mode of Application

Effects could be shown after p.o. application, as well. The p.o. application of lentinan to mice resulted in raised levels of several cytokines. Lentinan, once ingested, may encounter the gut-associated lymphoid tissue or may be absorbed into the systemic circulation (57). Related effects of polysaccharides from plants were explained by targeting immunocompetent cells in the intestinal tract and recirculation of these cells in the organism (58). An interesting option is the transfer of lentinan-activated immune cells into immunodeficient mice. Resulting tumor inhibition could be shown (57).

Polysaccharides from *G. lucidum*

Polysaccharides from *G. lucidum* (Ganopoly) are marketed as over-the-counter-product in several Asian countries. Ganopoly is composed of the polysaccharide fraction from the fruiting bodies of wood-cultured *G. lucidum* (59). In a clinical study with 100 patients with advanced solid cancer palliative effects of Ganopoly (1800 mg, three times per day, p.o.) on cancer-related symptoms, such as sweating and insomnia, have been observed in many patients. Objective responses (complete or partial disappearance of all tumor masses) could not be found in this study (60). A randomized double-blind, placebo-controlled, multicenter clinical trial with Ganopoly (600 mg, three times per day p.o.) was done for 12 weeks in 68 patients with histologically confirmed advanced lung cancer. Patients were evaluated with respect to their extent of disease and quality of life (Karnofsky score), and hematological, immunological and biochemical parameters. In 32 assessable patients, treatment with Ganopoly resulted in a significant increase in the KPS scores in 16 patients; 4 patients obtained significant increase in the control group with 29 assessable patients. Three episodes of mild toxicity (nausea, 2 and insomnia, 1) were recorded in the verum group. Further studies are needed to explore the optimum dosing, efficacy and safety alone or in combination with chemotherapy or radiotherapy (59).

Polysaccharides from *Sparassis crispa* and Some Further Mushrooms

Further mushrooms with immunomodulating polysaccharides are used as delicious food or as health-promoting food supplement (nutraceutical) or as drug in limited geographic regions. Scientific or clinical studies are not sufficient for use as 'official' drug worldwide till now. However, some examples should be reported.

In a small clinical trial, powder of *S. crispa* (Wulfen): Fr. (300 mg per day) was given orally to several cancer patients after one course of lymphocyte transfer immunotherapy. Performance status of 14 cases were monitored after several months, and 9 cases were improved (61,62). In China, several preparations from *Hericium caput-medusae* (Bull.: Fr.) Pers. [syn. *Hericium erinaceus* (Bull.: Fr.) Pers.] are on the market for treating chronic stomach diseases and other purposes (63). *Agaricus brasiliensis* Wasser *et al*. is a new cultivated medicinal and gourmet mushroom with benzaldehyde and

its precursor benzoic acid as major components of the volatile fraction (64). Because the North American endemic species *Agaricus blazei* Murrill and the widely cultivated medicinal *A. blazei* ss. Heinem. proved to be different species, *A. blazei* ss. Heinem. was described as a new species, *A. brasiliensis* (65). The biggest group of active substances is composed of polysaccharides, obtained from fruit bodies, mycelium and culture filtrate (66,67). Acetone extract of fruit bodies contained six antitumor-active steroids (66). Antimutagenic effects were also found (68).

Cytostatic Activities

High Molecular Compounds with Cytostatic Activities

Cytostatic activities against tumor cells were shown *in vitro* for several mushrooms or mushroom components, e.g. ubiquitin-like proteases [peptide with a MW of 8 kDa, (69)] from the fruiting bodies of *Handkea utriformis* (Bull.: Pers.) Kreisel [syn. *Calvatia caelata* (Bull.) Morgan], ribosome inactivating proteins, e.g. from *Hypsizygus marmoreus* (Peck) H. E. Bigelow [hypsin, (70)], *F. velutipes* [flammulin and velutin (32)] and other mushrooms and lectins from *Agaricus bisporus* (J. E. Lange) Imbach (71) or *Pleurotus ostreatus* (Jacq.: Fr.) P. Kumm. [also *in vivo* effects (72)]. The contribution of these high molecular weight molecules to an *in vivo* effect of mushrooms after p.o. application remains unclear. Cancer protective effects of *P. ostreatus* fruit bodies were demonstrated in rats (73). Besides, *P. ostreatus* diminishes the toxicity of cyclophosphamide in mice (74). The ethylacetate extract (50 mg kg^{-1} p.o. per day) of the sporocarps of *Phellinus rimosus* (Berk.) Pilát. possess significant antitumor activity comparable to the activity of cisplatin (4 mg kg^{-1} per day, intraperitoneal) in ascites and solid tumor models in mice (75).

Small Molecular Compounds with Cytostatic Activities

Many small molecular weight compounds exhibit cytotoxic activities against tumor cells. To them belong the illudins, tricyclic sesquiterpenes from *Omphalotus olearius* (DC.: Fr.) Singer and *Lampteromyces japonicus* (Kawam.), Singer and their derivatives (76), the terpenoid leaianafulvene (**10**) from *Mycena leaiana* (Berk.) Sacc. (77), triterpenes [ganoderic acids Z (**8b**), Y, X, W, V, T; lucialdehydes A, B, C (**9b**) and australic acid (**11**)] from *G. lucidum* (78–80) or *Ganoderma australe* (Fr.) Pat. (81), acetoxyscirpenediol (**12**), ergosterol peroxide (**4**) from *P. tenuipes* (82) and sterols from the mycelia of *C. sinensis* (Berk.) Sacc. (83). Acetoxyscirpenediol (**12**) exerts its activity by inducing apoptosis in leukemia cell lines *in vitro* (84). Apoptosis in HL-60 cells could be induced by triterpenes from *Ganoderma concinnum* Ryvarden [i.e. 5α-lanosta-7,9(11),24-triene-15α-26-dihydroxy-3-one (**6c**)], as well (85). The triterpenes applanoxidic acid A-H (**2**), isolated first from *G. applanatum*, were effective against mouse skin tumor promoters, applanoxidic acid B (**2b**) being the most potent of the acids. The activities were shown in the short-term *in vitro* assay of Epstein–Barr virus early antigen activation in Raji cells induced by 12-O-tetradecanoylphorbol-13-acetate (86,87). A derivative of illudin S (**13**) has progressed to phase II human clinical trials (88). The specificity of the cytotoxic action against tumor cells remains to determine.

Cytostatic Compounds with Specific Targets

Recently, more attention is given to the identification of molecular pathogenesis mechanisms of cancer. In this connection more specialized targets for potential antitumor drugs were identified. It could be shown that some compounds from mushrooms act on such targets. Some examples are provided below.

Ganoderic acids A (**8c**) and C (**8d**) from *G. lucidum* are inhibitors of farnesyl protein transferase. Because this enzyme participates in Ras-dependent cell transformation, inhibitors represent a potential therapeutic strategy for the treatment of cancer (89). *Phellinus linteus* (Berk. & M. A. Curtis) Teng was found to contain antiangiogenic activity in the chick embryo chorioallantoic membrane assay (90) and to inactivate cancer-related kinases (91). Antiangiogenic activity was also reported for polysaccharides from *A. brasiliensis* (92). The sesquiterpenoid cryptoporic acids A-G (**14**) from *Cryptoporus volvatus* (Peck) Murrill inhibit the tumor promotion activity of okadaic acid in two-stage carcinogenesis experiments. The effect is possibly related to their strong radical scavenging activity (93). Antimutagenic effects were found for methanolic extracts of *P. ostreatus* (94), methanolic extracts of *Lactarius vellereus* (Fr.) Fr. (95) and for water extracts of *A. bisporus* and *G. lucidum*. The genoprotective effect of *A. bisporus* has been related to the enzyme tyrosinase (96).

A dried oyster mushroom (*P. ostreatus*) diet (5%) reduced pathological changes in dimethylhydrazine-induced colon cancer in rats but did not influence significantly the incidence of tumors. This effect is explained by the antioxidant properties of this mushroom and by its fiber content (97).

Immunosuppressive and Antiallergic Mushrooms

Although extracts of many mushrooms can stimulate the immune system, some suppress immune responses. This could be of interest, e.g. for the treatment of allergic diseases that are increasing worldwide.

Inhibition of Allergic Reactions

Ethanolic extracts of the edible Japanese basidiomycetes *H. marmoreus, F. velutipes, Pholiota nameko* (T. Ito) S. Ito and *Pleurotus eryngii* (DC.: Fr.) Quél. show significant antiallergic effects in mice (oxazolone-induced type IV allergy) also after p.o. application (98). Some compounds from *G. lucidum* [ganoderic acids C (**8d**) and D (**8e**);

cyclooctasulfur] inhibit the histamine release from rat mast cells (99,100). Eating of *Tricholoma populinum* J. E. Lange led to the regression of severe allergic symptoms in a patient with thromboangitis obliterans and in another patient with urticaria. The effects could be confirmed in animal models, as one responsible compound ergosterol peroxide (**4**) was identified (101,102). Hispolon (**15**) and hispidin (**16**), isolated from fruit bodies of *I. hispidus,* inhibit the chemiluminescence response of human mononuclear blood cells and the mitogen-induced proliferation of spleen lymphocytes of mice (103).

Influence on Lipopolysaccharide Binding

Septic shock is a complex syndrome mediated by binding of lipopolysaccharide (LPS) from gram-negative bacteria to CD14 receptor on immune cells and the following release of a cascade of inflammatory mediators and reactive oxygen species. Because of the large number of patients with septic shock a great deal of effort is necessary to develop new therapeutic possibilities. Extracts of the fruiting bodies of *Polyporus badius* (Gray) Schwein., *L. vellereus* (Fr.) Fr., *Heterobasidion annosum* (Fr.) Bres., *T. versicolor* and *P. betulinus* inhibit *in vitro* binding of LPS to the receptor (104) and could therefore contain lead structures for drugs against LPS-mediated septic shock.

Anticomplement Activities

Activation of the complement system, inducing the release of mediators from mast cells, can cause a variety of diseases and can be fatal if occurring after an organ transplantation. Several triterpenes from *G. lucidum* [ganoderiol F (**6a**), ganodermanontriol (**7a**) and ganodermanondiol (**7b**)] show strong anticomplement activity against the classical pathway of the complement system with IC 50 values of 5–40 μM (105).

Antiatherogenic Mushrooms

Influence on Blood Lipids

Reactive oxygen species and increased levels of blood lipids are key elements in the pathogenesis of atherosclerosis, one of the main causes of death in industrial countries. The control of blood lipids, especially cholesterol, is important for reducing the risk of the development or progression of atherosclerosis. A pronounced hypocholesteremic effect of oyster mushroom (*P. ostreatus*), combined with inhibition of lipid peroxidation, was shown in rats and rabbits. Oyster mushroom diet (10% dried fruiting bodies) significantly reduced the incidence and size of atherosclerotic plaques in rabbits (106). Lovastatin (**18**), the lead compound for the statines (HMG-CoA reductase inhibitors), could be detected in this species (107) and is jointly responsible for the observed effects. Hypocholesteremic effects of *Auricularia auricularia-judae* (Bull.: Fr.) Wettst. and *Tremella fuciformis* Berk. are explained by similar mechanisms (1,108,109).

Antioxidative and Other Biological Activities

Some triterpenes from *G. lucidum* [ganoderic acid C (**8d**) and derivatives] are able to inhibit the biosynthesis of cholesterol, as well (110). Other triterpenes of this fungus contribute to atherosclerosis protection by inhibition of angiotensin converting enzyme [ganoderic acid F (**8f**) (111)] or of platelet aggregation [ganoderic acid S (**17b**) (112)]. The antioxidative and free radical scavenging effects of polysaccharides and triterpenoids from *G. lucidum* were shown in different oxidative injury models including tert-butylhydroperoxide damaged mice peritoneal macrophages, alloxan-induced diabetes and experimental liver injury models. The inhibition of low density lypoproteins (LDL) oxidation by endothelial cells and of monocyte adhesion to endothelial cells has been demonstrated (113). The antilipidemic effect of *L. edodes* is caused by eritadenin (**19**), a nucleotide derivative (114).

p-Terphenyl compounds from *Thelephora ganbajun* M. Zang, *Thelephora aurantiotincta* Corner, *Boletopsis grisea* (Peck) Bondartsev & Singer (115) as well as from *Paxillus curtissii* Berk. (116) showed strong antioxidative properties. Betulinan A (**20**) from *Lenzites betulinus* (L.: Fr.) Pilát is about four times more active as a radical scavenger than vitamin E in inhibition of lipid peroxidation (117). Lipid peroxidation is also inhibited by the sterins A and B from *Stereum hirsutum* (Willd.: Fr.) Pers. (118).

Ergosta-4-6-8(14),22-tetraen-3-one (**21**), isolable from many mushrooms, has been shown to possess antialdosteronic diuretic properties (119).

Potentiators of ADP-induced platelet aggregation have been found in *Polyporus umbellatus* (Pers.): Fr. (Cho-Rei) [5α,8α-epidioxy-ergosta-6,22-dien-3-ol (**4**)] and others (120).

Hypoglycemic Mushrooms

Diabetes mellitus is a metabolic disorder affecting ~250 million people worldwide. More effective and safer treatment modalities for type 2 diabetes patients need to be investigated, focusing on overcoming peripheral insulin resistance. A polysaccharide fraction of *G. frondosa* (SX fraction, p.o.) showed hypoglycemic action in five patients with type 2 diabetes (56).

Ganoderan A and B, glucans from *G. lucidum* fruiting bodies (121), coriolan, a β-glucan–protein complex obtained from submerged grown *T. versicolor* biomass (122) and an acidic glucuronoxylomannan from the fruiting bodies of *Tremella aurantia* Schwein. (123) exhibited hypoglycemic effects in several test systems and ameliorated the symptoms of diabetes.

Seventy-one patients with confirmed type 2 diabetes were treated with polysaccharide fractions from *G. lucidum* (Ganopoly, 1800 mg three times daily for 12 weeks). At week 12, mean post-prandial glucose values had decreased to 11.8 mmol l^{-1} in the Ganopoly group [significant difference to placebo group, (124)].

Tremellastin, containing 40–45% acidic polysaccharide glucuronoxylomannan and obtained by alcohol precipitation

of culture broth, decreased intrinsic blood glucose levels as well as triglyceride levels in rats after 15 treatment days (p.o. 100 mg kh^{-1}; 500 mg kg^{-1}). Hypoglycemic effects in glucose-loading and streptozotocin-induced hyperglycemic rats could not be found (125).

Preparations from the traditional Chinese drug Cordyceps (consisting of fungi parasitic in insects) and from fermented mycelia meliorate diabetes in a diabetic animal model using streptozotocin-induced rats after p.o. application (126). Crude polysaccharides from cultured mycelium of *Cordyceps* have shown significant activity after intraperitoneal injection (127). Besides, *Cordyceps* is highly appreciated by Chinese medical practitioners as a treatment for many ailments (128).

Dehydrotrametenolic acid **(22)**, found in several polypores including *Wolfiporia cocos* (Schwein.) Ryvarden & Gilbn., *Laricifomes officinalis* (Vill.: Fr.) Kotl. & Pouzar (syn. *Fomitopsis officinalis* (Vill.: Fr.) Bondartsev & Singer and *Laetiporus sulphureus* (Bull.: Fr.) Murrill, acts as an insulin sensitizer in glucose tolerance tests and reduces hyperglycemia in mice with noninsulin-dependent diabetes (129).

Anti-inflammatory Mushrooms

Ethanolic extracts and a proteoglycan from *P. linteus* show anti-inflammatory effect in the collagen-induced arthritis and in the croton oil-induced ear edema test in mice and antinociceptive effect in the writhing test (90,130). Other compounds effective in the writhing test are the ganoderic acids A (**8c**), B (**8a**), G (**8g**) and H (**8h**), isolated from *G. lucidum*. These substances showed a stronger effect in this animal model than acetylsalicylic acid (131).

Methanolic extract of *Pleurotus pulmonarius* (Fr.) Quél. fruiting bodies (500 and 1000 mg kg^{-1}) reduced carrageenan-induced and formalin-induced paw edema in mice. The activity was comparable to the reference diclofenac (10 mg kg^{-1}). The effect seemed to be related to the significant antioxidant activity of the extract. The IC 50 value for hydroxyl-radical scavenging was 476 μg ml^{-1} and for lipid peroxidation inhibition 960 μg ml^{-1}. Besides, the extract showed significant solid tumor-reducing activity in mice (132).

The edible mushroom *G. frondosa* contains ergosterol, ergosta-4-6-8(14),22-tetraen-3-one (**21**) and 1-oleoyl-2-linoleoyl-3-palmitoylglycerol, which inhibit cyclooxygenases 1 and 2 activity (133).

Hepatoprotective Mushrooms

Ganoderic acids R (**17a**) and S (**17b**) and ganosporeric acid A (**8i**) from *G. lucidum* show *in vitro* antihepatotoxic activity in the galactosamine-induced cytotoxic test with primary cultured rat hepatocytes (134,135). *In vivo* two fractions of a total triterpenoids extract of *G. lucidum* (75% ethanol) can protect mice against hepatic necrosis induced by chloroform and D-galactosamine. The hepatoprotective effects were perhaps related to the ability to promote the activity of scavenging enzymes for hepatic free radicals in mice, and thus to raise the ability of antioxidation in mice (136).

Ganopoly, the polysaccharide-containing preparation of *G. lucidum*, was proven in a double-blind, randomized and multicentered study in patients with chronic hepatitis B (HBV DNA positive; application of Ganopoly for 12 weeks, then 13 weeks followed up, 600 mg three times per day equal to 27 g fruiting body, p.o.). Within the 6 months study period, 33% (17/52) of treated patients had normal aminotransferase values and 13% (7/52) had cleared hepatitis B surface antigen from serum, whereas none of the controls had normal enzyme values or had lost HBsAg. The drug was well tolerated (137).

Mushrooms with Central Activities

Apart from well investigated psychoactive mushrooms like *Amanita muscaria* (L.: Fr.) Pers. or *Psilocybe* species some further mushroom extracts and compounds have been found with special central effects that could be of pharmacological interest.

Phenol-analogous compounds [hericenons C (**23**), D, E, F, G, H] from *H. erinaceus* induce the synthesis of nerve growth factor and might have an ameliorative effect in Alzheimer's dementia (63). Erinacin E (**24**) from *Hericium coralloides* (Scop.: Fr.) Gray [syn. *Hericium ramosum* (Mérat) Letell.] fermentation broth is a highly selective agonist at the kappa opiod receptor (IC 50 of 0.8 μM, binding at the μ opiod receptor with an IC 50 of >200 mM). Such compounds may exhibit antinociceptive activity without side effects observed with μ receptor agonists like morphine (138).

Screening investigations of selected basidiomycetes indicate inhibitory effects of *P. betulinus, G. applanatum, H. annosum, Fomitopsis pinicola* (Sowerby: Fr.) P. Karst and *Daedaleopsis confragosa* (Bolton: Fr.) J. Schröt. on neutral endopeptidase (enkephalinase, EC 3.4.24.11) (IC 50 values between 40 and 55 μg ml^{-1}). Selective inhibitors of this metalloendopeptidase could be useful in the treatment of pain with a spectrum of activity similar to that of opioids (139).

Scutigeral (**25**), isolated from fruiting bodies of *Scutiger ovinus* (Schaeff.: Fr.) Murrill [syn. *Albatrellus ovinus* (Schaeff.: Fr.) Kotl. & Pouzar], has affinity to the brain dopamine D1 receptors and may act as an orally active pain killer targeting vanilloid receptors [VR1, (140)]. Albaconol (**26**) from the fruiting bodies of *Scutiger confluens* (Alb. & Schwein.: Fr.) Bondartsev & Singer [syn. *Albatrellus confluens* (Alb. & Schwein.: Fr.) Kotl. & Pouzar is an antagonist at the VR1 receptor with an IC 50 value of 5 μM (141).

Production of Pharmacologically Interesting Mushrooms or Compounds

In principle, whole mushrooms (mainly fruiting bodies), extracts (from fruiting bodies or mycelium) and isolated compounds are suitable for use. The material could be

obtained by collection from the wild, cultivation of mushrooms in farms and harvesting of the fruiting bodies or by cultivation of mycelium in fermenters with liquid or solid substrates. Extracts could be prepared by extraction of mushrooms (dried or fresh) with suitable solvents. Pure compounds could be obtained by isolation from the natural or cultivated material or by chemical synthesis. Very often, the natural compound serves as lead compound for the preparation of a high variety of derivatives. Because most mushrooms can be cultivated in an economic matter, the production of mushroom compounds, especially proteins, by genetically modified organisms seems not to be necessary.

At present, between 80 and 85% of all medicinal mushroom products are derived from the fruiting bodies, which have been either commercially farmed or collected from the wild, for example, lentinan and various products from *G. lucidum*. Only ~15% of all products are based on extracts from mycelia. Examples are PSK and PSP from *T. versicolor* and tremellastin from *Tremella mesenterica*. (Retzius): Fr. A small percentage of mushroom products are obtained from culture filtrates, e.g. schizophyllan from *S. commune* and protein-bound polysaccharide complex from *Macrocybe lobayensis* (R. Heim) Pegler & Lodge [syn. *Tricholoma lobayense* R. Heim (142)].

After production, suitable galenic formulations like capsules, tablets or teas have to be developed, dependent on the material. Mixtures of several mushrooms or of mushroom and substrate become more and more common (9).

Summary and Outlook

The review demonstrates that mushrooms, similar to plants, have a great potential for the production of useful bioactive metabolites and that they are a prolific resource for drugs.

The responsible bioactive compounds belong to several chemical groups, very often they are polysaccharides or triterpenes. One species can possess a high variety of bioactive compounds, and therefore of pharmacological effects. The best example is *G. lucidum*, which not only contains >120 different triterpenes but also polysaccharides, proteins and other bioactive compounds (43,143).

The spectrum of detected pharmacological activities of mushrooms is very broad. Dependent on increasing knowledge about chemistry, biotechnology and molecular biology of mushrooms as well as an improvement of screening methods (high throughput screening, genomics and proteomics), a rapid increase in the application of mushrooms for medicinal purposes can be expected.

Prerequisition for a use as drug, nutraceutical or other purpose is the continuous production of mushrooms (fruiting bodies or mycelium) in high amounts and in a standardized quality. In the opinion of Chang (142), mycelial products are the 'wave of the future' because they ensure standardized quality and year around production. A further necessity is the establishment of suitable quality parameters and of analytical methods to control these parameters. Nevertheless, the legal regulations for authorization as drug or as dietary supplements or as food should get more attention (9). Control of possible side effects (i.e. allergies) during broad use is necessary. Finally, also the nutritional value of mushrooms should be taken into account.

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