International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(1): 117-124

Review Article

PHARMACOLOGICAL AND THERAPEUTIC POTENTIAL OF SOUTH INDIAN MUSHROOMS

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(Received: 05 January, 2013; Accepted: 20 February, 2013; Published: 25 February, 2013)
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Abstract: This review describes pharmacologically active compounds from mushrooms. Compounds and complex substances with antimicrobial, antiviral, antitumor, antiallergic, immunomodulating, anti-inflammatory, antiatherogenic, hypoglycaemic, hepatoprotective and central activities are covered, focusing on the review of recent literature. The production of mushrooms or mushroom compounds is discussed briefly.
Key**words:** antiatherogenic, antimicrobial, antitumor, basidiomycetes, bioactive compounds

INTRODUCTION

'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 hypogeous or epigeous, large enough to be seen with the naked eye and to be picked by hand'. 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. 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, Tolypocladiuminflatum* W. Gams, *Clavicepspurpurea* (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 *Cordycepssinensis* (Berk.) Sacc.or*Paecilomycestenuipes* (Peck) Samson are not closely allied to mushrooms[1]. 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.

Medicinal mushrooms are mushrooms that are used or studied as possible treatments for diseases. Research shows that various species of mushrooms produce antiviral, antimicrobial, compounds. Lentinan and PSK are mushroom extracts which are licensed pharmaceuticals in certain countries. Fungi that do not produce mushrooms, were the original source of penicillin, griseofulvin, mycophenolate, ciclosporin, mizorib ine, mycophenolic acid, the first statins, and cephalosporins, and are used to producepaclitaxel[2].

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 market value of medicinal mushrooms and their derivative dietary supplements worldwide was ~US $1.2 billion in 1991 and was estimated to be US $6 billion in 1999.Many clinically used drugs such as aspirin, digitoxin, progesterone, cortisone, morphine, vincristine, vinblastine, taxol and several others are derived directly or indirectly from higher plants. Clinically important and well recognized drugs of fungal origin are penicillin, griseofulvin, ergot alkaloids and cyclosporine. Among the large resources of fungi, higher Basidiomycetes especially mushrooms are unlimited sources of therapeutically useful biologically active agents. There are approximately 700 species of higher Basidiomycetes that have been found to possess significant pharmacological activities. Modern scientific studies on medicinal mushrooms have expanded exponentially during the last two decades not only in Japan, Korea and China but also in USA and scientific explanation to show mushrooms derived compounds function in human system are increasingly being established. Medicinal mushrooms have an established history of use in traditional oriental medicine. Many traditionally used mushrooms from genera, Auricularia, Flammulina, Ganoderma, Grifola, Lentinus,Trametes (Coriolus) and Tremella have been demonstrated to possess significant medicinal properties[3].Thus the pursuit for anti-tumor drugs takes a compelling urgency. Attempts have been made in many parts of the world to explore the use of mushrooms and their metabolites for the treatment of a variety of human ailments. The most significant medicinal effect of mushrooms and their metabolites that have attracted the attention of the public is their antitumor property. Lucas and his collaborators first demonstrated the antitumor activity of the higher Basidiomycetes in 1957.

The significant pharmacological effects and physiological properties of mushrooms are bioregulation (immune

enhancement), maintenance of homeostasis and regulation of biorhythm, cure of various diseases and prevention and improvement from life threatening diseases such as cancer, cerebral stroke and heart diseases. Mushrooms are also known to have effective substances for antifungal, anti-inflammatory, antitumor, antiviral, antibacterial, hepatoprotective, antidiabetic, hypolipedemic, antithrombotic and hypotensive activities.

The oxidative properties of oxygen play a vital role in diverse biological functions such as utilization of nutrients, electron transport to produce ATP and the removal of xenobiotic.swhile oxygen is essential for life, it also can provoke damaging oxidative events within cells. Oxygen, by its transformation to more reactive forms i.e., superoxide radical (O_{2-}), hydroxyl radical ($^{\cdot}OH$) and hydrogen peroxide (H_2O_2) can nick DNA, can damage essential enzymes and structural proteins and can also provoke uncontrolled chain reactions, such as lipid peroxidation or autooxidation reactions (e.g. polymerization of catecholamines)

Oxygen derived free radicals are generated during the oxidative metabolism and energy production in the body and are involved in the regulation of signal transduction and gene expression, activation of receptors and nuclear transcription factors[4].Overwhelming evidences indicate that oxidative stress can lead to cell and tissue injury. In most of the cases free radicals are secondary to the diseases but in some instances they are causal. In addition to reactive oxygen species (ROS), researches on reactive nitrogen species (RNS) are gathering momentum, an area of enormous importance in biology and medicine. Current hypothesis favors the idea that lowering oxidative stress can be a health benefit.

The antioxidant status in human reflects the dynamic balance between the antioxidant defence and prooxidant conditions and this has been suggested as a useful tool in estimating the risk of oxidative damage. ROS have been implicated in the pathophysiology of various clinical disorders, including ischemia, reperfusion injury, myocardial infarction, rheumatoid arthritis, neurodegenerative, atherosclerosis, acute hypertension, hemorrhagic shock and diabetes mellitus.

Antibacterial and Antifungal Properties of 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. But only compounds from microscopic fungi are on the market as antibiotics till now[5].

Activities of mushrooms against Multiresistant Bacteria

Of special interest are compounds with activities against multiresistant bacterial strains. We could show that new sesquiterpenoidhydroquinones produced by the European *Ganoderma* species *Ganoderma pfeifferi* Bres. and named ganomycins inhibit the growth of methicillin-resistant *Staphylococcus aureus* and other bacteria. Besides, we found that whole extracts of this mushroom inhibit the growth of microorganisms responsible for skin problems[6] (*Pityrosporumovale, Staphylococcus epidermidis, Propionibacterium acnes*, unpublished results).

Antimicrobial Activities of Known Compounds

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

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[8]. 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.

Small Molecular Compounds with Antiviral Activities

Several triterpenes from *Ganoderma lucidum* (M. A. Curtis: Fr.) P. Karst. [i.e. ganoderiol F ganodermanontriol,ganoderic acid B] are active as antiviral agents against human immunodeficiency virus type 1 (HIV-1) (Figure 2). The minimum concentration of ganoderiol F and ganodermanontriol for complete inhibition of HIV-1 induced cytopathic effect in MT-4 cells is 7.8 μg ml^{-1}. Ganoderic acid B inhibits HIV-1 protease with an IC 50 value of 0.17 mM.Ganodermadiol,lucidadiol and applanoxidic acid G, 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 is active against herpes simplex virus type 1, causing lip exanthema and other symptoms [IC 50 in Vero cells 0.068 mmol l^{-1}] *In vitro* antiviral activity against influenza viruses type A and B was demonstrated for mycelial extracts of *Kuehneromycesmutabilis* (Schaeff.: Fr.) Singer & A. H. Sm. extracts and two isolated phenolic compounds from *Inonotushispidus* (Bull.: Fr.) P. Karst and ergosterol peroxide present in several mushrooms[9].The antiviral

activity of *Collybiamaculata*(Alb. &Schwein.: Fr.) P. Kumm. (Vesicular stomatitis viruses in BHK cells) is caused by purine derivatives.

Figure 2: *Ganoderma lucidum*

High Molecular Compounds with Antiviral Activities

Water-soluble lignins isolated from *Inonotusobliquus* (Pers.: Fr.) Pilát, commonly known as 'Chaga', inhibited HIV protease with an IC 50 value of 2.5 μg ml^{-1}. Anti-HIV activities were reported for mycelial culture medium of *L. edodes* (LEM) and water-soluble lignin in LEM .Sulfatedlentinan from *L. edodes* completely prevented HIV-induced cytopathic effect .The protein-bound polysaccharides PSK and PSP (to the differences between both substances see Table 1) from *Trametesversicolor* (L.: Fr.) Pilát [syn. *Coriolusversicolor* (L.: Fr.) Quelet] were also found to have an antiviral effect on HIV and cytomegalovirus *in vitro* .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 .Inhibition of HIV-1 reverse transcriptase was caused by velutin, a ribosome inactivating protein from *Flammulinavelutipes* (M. A. Curtis: Fr.) P. Karst., as well. The maitake D-fraction (MD-fraction) from *Grifolafrondosa* (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[10].

Figure 3: *Grifolafrondosa*

Table 1: Immunomodulating drugs from mushrooms

Mushroom Scientific name	Mushroom Common Name	Immunomodulator
A. brasiliensis	Royal sun Agaricus, Himematsutake	FIo-a-β
G. lucidum	Reishi, Ling Zhi	GLP(AI), Ganopoly, Ganoderans
G. frondosa	Maitake, Hen-of-the-Woods	MD-fraction

Antitumor Mushrooms

Experience from Ethnomedicine

Tumor diseases are one of the main causes of death worldwide. Experience from Asian and Eastern Europe countries shows that mushrooms could play an important role in prevention and treatment of cancer. *Piptoporusbetulinus* (Bull.: Fr.) P. Karst. was used traditionally in Bohemia for the treatment of rectal cancer and stomach diseases 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[11].

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. Antitumor effects of several extracts and isolated compounds could be demonstrated in tumor cell systems and in animal assays. 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.

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[12]. They are summarized in the following sections.

Immunomodulator 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. 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[13].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 .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) tai. 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. Higher antitumor activity seems to be correlated with higher molecular weight, lower level of branching and greater water solubility of β-glucans However, the high branched MD-fraction from *G. frondosa* (MW 1 000 000–1 200 000 dalton) exerts a high antitumor activity.

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 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. 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[14]. 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.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. 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 follow-up was 4 years. The increased disease-free survival curve of the PSK group over the control group was statistically significant .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%.

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[15].

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. MD-fraction appears to repress cancer progression and primarily exerts its effect through stimulation of NK cells activity. 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.

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 .Related effects of polysaccharides from plants were explained by targeting immunocompetent cells in the intestinal tract and recirculation of these cells in the organism[16]. An interesting option is the transfer of lentinan-activated immune cells into immunodeficient mice. Resulting tumor inhibition could be shown.

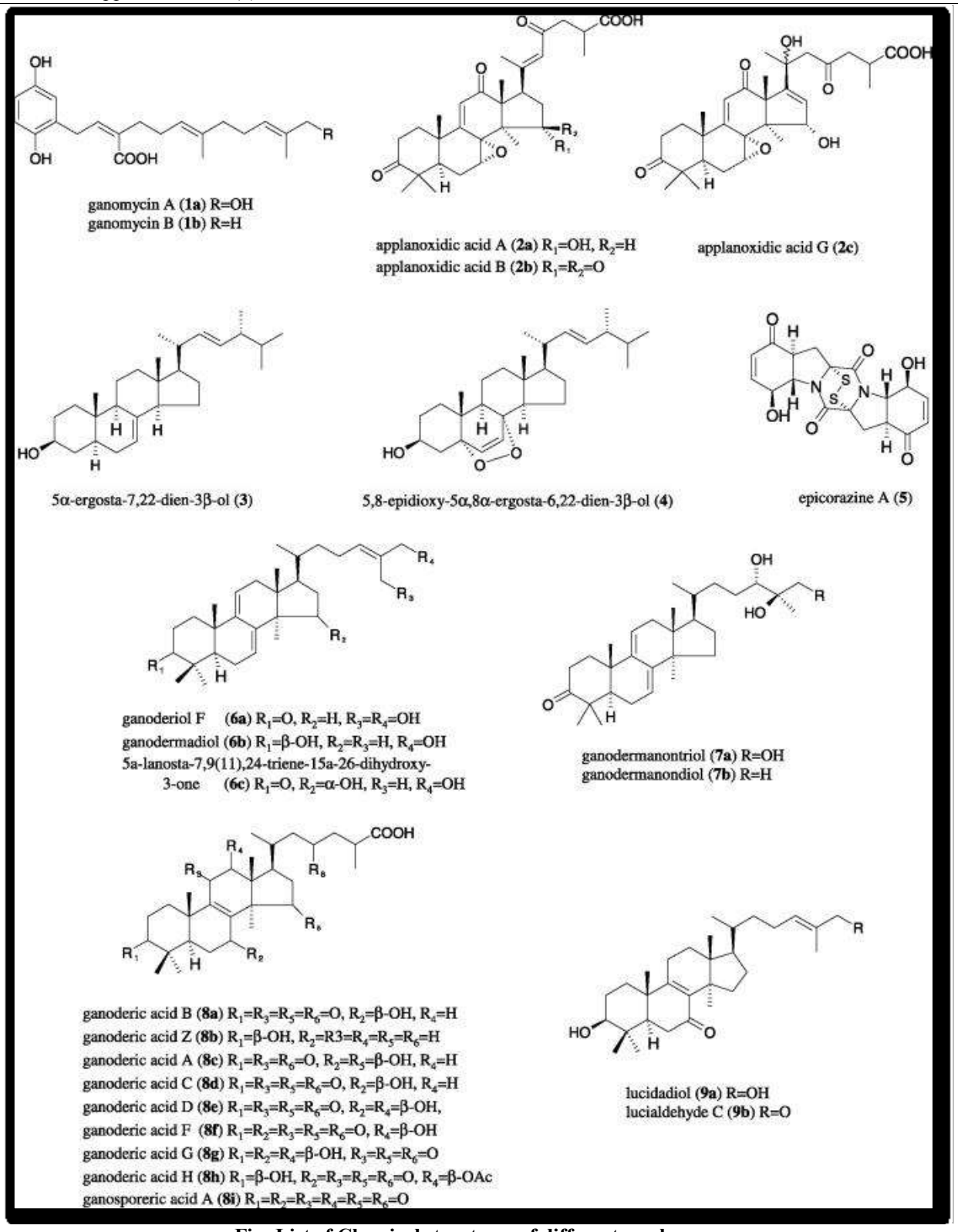

Fig: List of Chemical structures of different mushrooms

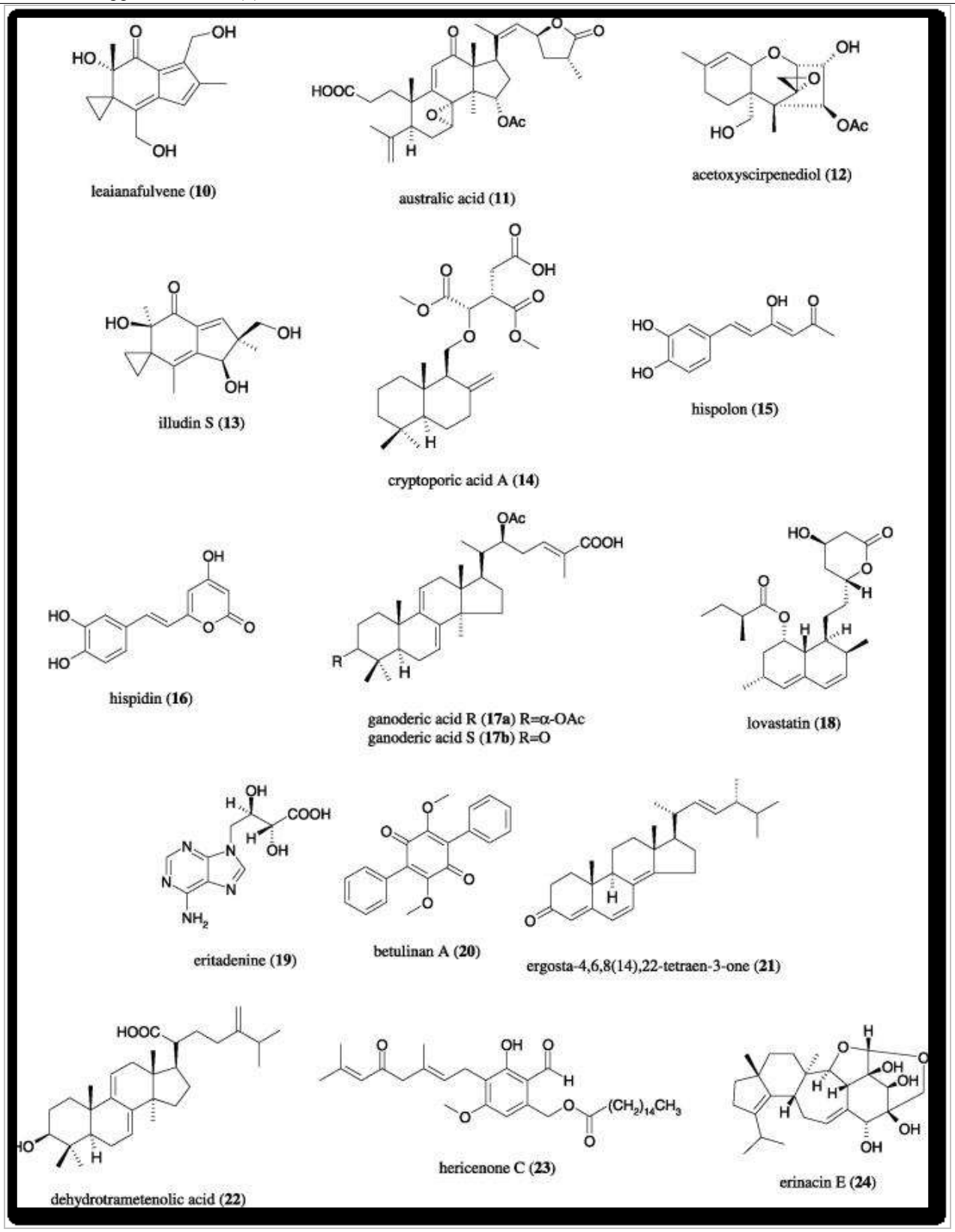

Fig: List of Chemical structures of different mushrooms

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* .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. 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[17, 18]. 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.

Production of Pharmacologically active Mushrooms

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[19].

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 *Tremellamesenterica*. (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 *Macrocybelobayensis* (R. Heim) Pegler & Lodge [syn. *Tricholomalobayense* R. Heim] After production, suitable galenic formulations like capsules, tablets or teas have to be developed, dependent on the material[20]. Mixtures of several mushrooms or of mushroom and substrate become more and more common.

CONCLUSION

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. 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.

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