

GENERAL

BIOLOGICALLY ACTIVE COMPOUNDS OF FUNGAL ORIGIN
DISPLAYING ANTITUMOR ACTIVITY*

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Abstract: This review describes biologically active natural products displaying antitumor activities derived from fruit bodies and cultured mycelium of macromycetes. Among these compounds the most important are: polisaccharides, phenols, terpenes and others. Polisaccharides produce their antitumor effects by activating different immune responses in the host. Other compounds are examples of cytotoxic and immunomodulating activities.

Keywords: mushrooms; mycelial cultures; biologically active metabolites; antitumor activity; polisaccharides

Until discovery of antibiotics, studies on chemical composition of fungi had not been very popular. People preferred to look for medicinal compounds in plants, while fungi remained distrusted and wrapped in superstitious fear. In ancient times, indigenous people of North and South America made use of hallucinogenic properties of fungi of the *Psiilocybe*, *Stropharia* genera. Cultures of Asian countries, particularly of China and Japan, preserved belief that fungi had rejuvenating, regenerating and tonic effects in humans. They even cultivated such fungal species as *Cordyceps sinensis* and *Hericium erinaceum*. Folk medicine of European countries also utilized fungi as a source of medicinal substances used in such diseases as tumors, hepatitis, asthma, hemorrhoids. Of our indigenous species, *Fomitopsis officinalis* (= *Laricifomes off.*), *Inonotus bliquus* and *Piptoporus betulinus* deserve to be mentioned.

Discovery of penicillin confirmed in the scientific way the fact that fungi can be a very rich source of natural medicinal substances, including life-saving drugs. This greatly widened research horizons, raised their many-sided significance and joined efforts of researchers working in different and apparently unconnected fields like mycology, chemistry, pharmacy and medicine.

The increased interest in chemical composition of fungi in the search for biologically active metabolites led to discovery of substances endowed with multifarious actions. However, as plant research still

prevails, higher fungi are less valued and considered to be of minor significance. Lesser interest in fungi results mostly from difficulties in collection of material growing in a natural environment i.e., exclusively fruit bodies, and from troubles with proper systematic identification of fungi. These problems facilitated efforts aimed to obtain mycelial cultures of fungi. Success in those fields has made the last three decades, the period of the most intensive studies of substances isolated from fungi.

Among an array of substances of fungal origin, polisaccharides have been a focus of the greatest interest of biochemistry and medicine, due to their antitumor and immunomodulating properties. The earliest report of antitumor activity of polisaccharides was published in 1943, when a compound isolated from bacteria *Serratia marcescens* was shown to possess such activity (1). This polisaccharide induced cytostatic effect on Sarcoma-37 cells in mice after its intraperitoneal administration. However, clinical tests were not continued because of severe side effects and toxicity of this compound. The interest in cytotoxic substances included in fungi began in the early 40s of the 20th century when a strongly immunostimulating polisaccharide complex was isolated from *Saccharomyces cerevisiae* cell wall. It was demonstrated to induce macrophage activation and to stimulate reticuloendothelial system (2).

Long-term research carried out by the Chair and Department of Pharmaceutical Botany Collegium Medicum, Jagiellonian University, made a fundamental contribution to searching for biologi-

* Dedicated to Prof. S. Kohlünzer.

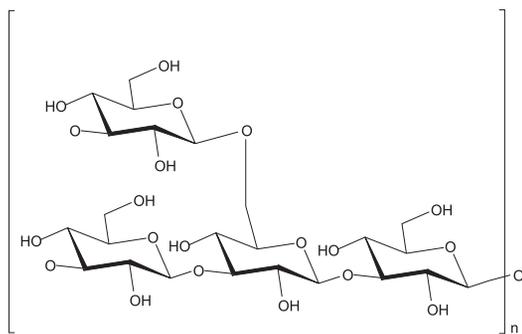


Figure 1. Structure of tylopolian

cally active substances that could be isolated from mushrooms and their mycelial cultures (3-6).

In 1992, there were isolated mitotatically active polysaccharides from T-411 strain of *Saccharomyces cerevisiae* Meyen (7). Other biologically active polysaccharides obtained from *Saccharomyces cerevisiae* were studied in vasoprotective aspects showing an inhibition of filtration of microvessels in the course of inflammatory pleural effusion in rats (8).

Japanese researchers are given the greatest credit for isolating and evaluating antitumor activity of fungal polysaccharides. It is reflected in a number of papers in this field as well as in the introduction of preparations of fungal origin in the health care (9,10).

Chemical structure of fungal polysaccharides

Fungal polysaccharides include mostly glucans, mannans and galactans. Their molecular weights are high ranging from 100 000 to 1 000 000 Da (10). Biological activity is characteristic of β -glucans in contrast to α -glucans which are rarely active. Activity is determined by their chemical structure, particularly by the type of glycoside bond (α or β) and spatial structure of a polysaccharide molecule. Polysaccharides with linear structure and without long side chains show the highest activity, which is connected with their better solubility and thereby easier assimilability by the human body. Most often $\beta(1\rightarrow3)$ bonds occur in the main chain while branches are formed by $\beta(1\rightarrow6)$ bonds.

Mechanism of action of polysaccharides from fungi

Mechanism of antitumor action of polysaccharides consists in the stimulation of certain components of the immune system, mainly T and B-lymphocytes, macrophages, and induction of interleukin release by NK cells (10,11).

Since β -glucans did not show any cytotoxic or cytostatic effects on tumor cells in *in vivo* tests, it

has been assumed that these compounds can act indirectly by activation of the immune system, but are unable to destroy directly tumor cells. Immunostimulating action involves activation of natural non-specific immunity (12). At present, such drugs are most frequently used in combination with other methods of therapy like radiotherapy or chemotherapy after surgical removal of primary tumor. These drugs were shown to prolong patients' survival, inhibiting cancer development and improving general condition of a patient. Polysaccharides are most often administered parenterally, sometimes orally, when the presence of peptide fragment allows for such route. Method of administration of these compounds, resulting mostly from their chemical structure is not burdensome to patients, which is the undoubted advantage of these compounds. Importantly, these compounds are usually non-toxic and side effects during treatment are rarely observed, most often only local slight irritation can be noted on the injection site. Small increase in body temperature and vomiting occur sporadically, but the most frequently used intramuscular injections up to seven times a week at a daily dose between 5-50 mg are well-tolerated by patients. Proven positive therapeutic effect without burdensome side effects is an undeniable advantage of these compounds (11-13). Detailed mechanism of antitumor activity of individual polysaccharides is described below.

The most important fungal polysaccharides used in antitumor therapy

Therapeutically important polysaccharides have been found as well in microscopic as in higher fungi. These secondary metabolites have been isolated both from fruiting bodies and from mycelial cultures. Apart from their antitumor properties, these compounds can also show other biological actions e.g. anti-inflammatory, antibacterial, antiviral, antiparasitic, hypotensive, hypoglycemic and vasoprotective (10-12). Of many known pharmacologically active fungal polysaccharides, lentinan and krestin (so-called PSK) are used in clinical practice.

Lentinan was isolated from arboreal fungus *Lentinus edodes* (shi-take). In terms of chemical structure, it is $\beta(1\rightarrow3)$ glucan with branches at $\beta(1\rightarrow6)$ bond, having molecular weight of 500 kDa and structure of dextrorotatory helix (14). This substance is considered to be the most active among known polysaccharides endowed with antitumor potential. It prevents neoplastic transformation caused by chemical carcinogens and viruses, and inhibits development of allogenic and some syngenic tumors (15). This polysaccharide is most often used in the

treatment of solid tumors of the stomach, large intestine, breast, lungs and malignant leukemia. Probable mechanism of its action consists in stimulation of T lymphocytes, induction of interleukin 1 and 3 and nitric oxide production by the immune cells, elevation of CSF (colony stimulating factor) and acute phase proteins levels, and direct and indirect (through T lymphocytes) effect on macrophages (15). It is used in combination with chemo- and radiotherapy. It is important that lentinan has slight side effects: local irritation after injection and sporadic fever and vomiting, but usually is well tolerated by patients (16). Shi-take mushroom is native to Japan, China and other Asian countries and it usually grows on fallen broadleaf trees.

The second most frequently used antitumor polysaccharide, krestin (PSK), is obtained from mycelium of an arboreal fungus *Trametes versicolor* (17). This compound is a branched heteroglucan composed of glucose (74.6 %), mannose (15.5 %), xylose (4.8 %), galactose (2.5 %) and fructose (2.2 %) with branches at β (1 \rightarrow 3) and at β (1 \rightarrow 6) connected with a peptide fragment containing 18 amino acids (13). Its molecular weight was estimated at 9-100 kDa. Like the above-mentioned lentinan, krestin shows a considerable antitumor activity against allogenic and syngenic animal tumors (13). Its mechanism of action consists in modification of host immune response to tumor PSK increases lymphocyte activation and stimulates cytokine production by the cells. Activation of NK and LAK (lymphocyte activated killer) cells was confirmed *in vivo* and *in vitro*. This substance was also proven to inhibit activity of metalloproteinases and other enzymes participating in metastasizing of tumor cells (13), and to possess antioxidant properties, so it can protect healthy tissues during the combined therapy. Protein-bound polysaccharide PSK exhibits marked antitumor effects against allogenic tumors such as Sarcoma 180 and Erlich carcinoma of experimental animals by both intraperitoneal and oral administration (18). As it has a protein fragment, it can be used orally. PSK is also able to inhibit development of tumors induced by various chemical and biological factors (viruses) (18). This attractive bracket fungus is also known as *Coriolus versicolor*. This species is very common and widespread. It usually grows on hardwood logs and stumps.

Another polysaccharide with wider application spectrum is schizophyllan, obtained from mycelial cultures of the species *Schizophyllum commune*. It is a branched β -glucan with β (1 \rightarrow 3) bonds in skeletal chain and β (1 \rightarrow 6) in side chains. Experimental studies with this compound showed that it inhibited

Sarcoma-180 in mice (11). Further studies also indicated that it was active against tumors of the lung, digestive tract, breast and uterus. After removal of primary tumor, it inhibited lung metastases in mice with Lewis carcinoma. It was efficient in urinary bladder cancer (in rats). Considering its relatively wide spectrum of activities, it can be assumed that its effects rely mostly upon activation of natural defense of the body against pathological changes. It was also noticed that the best results with these compounds could be achieved when used in combination with cytostatic drugs i.e., so-called immuno-chemotherapy (11). *Schizophyllum commune* is common, grow whole year, gregarious on dead and living wood of deciduous trees, rarely on conifers.

Studies of polysaccharides isolated from fruiting bodies of higher fungi and from mycelial cultures have demonstrated differences between secondary metabolites. Polysaccharide KS-2, isolated from *Lentinus edodes* mycelial cultures is a mannan containing a peptide fragment. Laboratory tests demonstrated its ability to inhibit development of Ehrlich carcinoma and Sarcoma-180 in mice after intraperitoneal and oral administration. It also induced interferon biosynthesis in experimental animals (14, 18).

Mycelial cultures of *Agaricus blazei* are the source of a number of polysaccharides possessing immunomodulatory properties, which include β -D (1 \rightarrow 6)-(1 \rightarrow 3) glucan, β -D(1 \rightarrow 6)-(1 \rightarrow 4) glucan, glucomannan complex ATOM and protein-mannan complex (AB-FP). These fractions showed antitumor activity against breast cancer and ovarian, and hepatic carcinoma cells (19-21). The mushroom was first identified to modern science in 1917 from a specimen found in Louisiana by the mycologist R. Murrill. It has been found on the grasslands of Florida and South Carolina, but it is generally thought to be extremely rare in nature. The only place that it has been found readily growing in nature is a small area of Brazil.

The experiments have been carried out on such species as *Tylopilus felleus*, *Trametes gibbosa*, *Trametes hirsuta*, *Inonotus bliquis* (22-26). A polysaccharide isolated from *Tylopilus felleus* named tylophilan has a structure of homoglycan of β (1 \rightarrow 3) type with branches at β (1 \rightarrow 6). In laboratory tests, it exhibited antitumor activity against transplantable Sarcoma-180 in mice (more than 98 % inhibition), and destroyed glioma cells (23). It showed immunomodulatory properties, influencing non-specific cellular immunity and some stages of specific humoral response. It also showed mitostatic effect at a cellular level. At the same time it was found that tylophi-

lan also evoked cytostatic effects in tests on animal neoplastic cells HeLa and KB (24). These species are very common and grow under pine or spruce on acid soils.

Literature data provide information about polysaccharides exhibiting antitumor properties and only fragmentary characterized in terms of their chemical structure. The most interesting of them with respect to antitumor potential are polysaccharide fractions containing glucuronoglucans, xyloglucans, mannoglucans and xylomannoglucans, isolated from *Ganoderma lucidum*. They suppress development of Sarcoma-180 in mice (27). Glucans with a similar structure and activity were isolated from mycelial cultures of this species.

Polysaccharides described above and other representatives of macromycetes are listed in Table 1.

Other metabolites of fungal origin possessing cytotoxic, antitumor and immunomodulating activities

Cytotoxic, antitumor and immunomodulating activities of fungal extracts can usually be attributed to the presence of polysaccharide compounds. However, recently a great deal of substances have been

obtained which are not polysaccharides, but which have cytotoxic effect on tumor cell lines. Montadial A (**1**) is one of such compounds. It is an example of cytotoxic monoterpene isolated from *Bondarzewia montana* (45). It is cytotoxic for lymphocytic leukemia cells in mice. It showed similar activity against human promyelocytic leukemia HL 60, which indicated that in the future it might be used in the treatment of this type of tumor.

Secondary metabolites isolated from *Laetiporus sulphureus* var. *miniatus* are other examples of antitumor compounds. Of them, egonol (**2**), demethoxyegonol (**3**) and egonol glucoside (**4**) showed weak cytotoxicity against Kato III cells (46). The species *Pyroformes demidoffi* was a source of two polyphenols, fomecin A and B. However, it was experimentally demonstrated that only fomecin B (**5**) was cytotoxic for HeLa, EMDCK and FL cells (47). Semisynthetic sesquiterpenoid coriolin B analog, diketocoriolin B (**6**), isolated from *Coriolus consors* was demonstrated to block growth and development of Yoshida sarcoma (48).

Sesquiterpene derivatives of hirsutane like hypnophilin (**7**), pleurotellol (**8**) and pleurotellic acid (**9**) isolated from *Pleurotus hypnophilus* are al-

Table 1. Antitumor polysaccharides from mushrooms

Species	Active component	References
<i>Agaricus blazei</i>	hetero-glucan	19, 20, 21
<i>Agrocybe cylindracea</i>	α -glucan	28
<i>Amanita muscaria</i>	α -glucan	28, 29
<i>Auricularia auricula</i>	β -glucan, glucuronoxylomannan	30
<i>Cryptoporus volvatus</i>	β -glucan	31
<i>Dictyophora indusiata</i>	β -glucan	32
<i>Flamulina velutipes</i>	β -glucan	33
<i>Ganoderma lucidum</i>	β -glucan, ganoderan	27
<i>Grifola frondosa</i>	β -glucan	34
<i>Hypsizigus marmoreus</i>	β -glucan	35
<i>Lampteromyces japonicus</i>	mannan	36
<i>Lentinus edodes</i>	β -glucan, lentinan	14, 15
<i>Omphalia lapidescens</i>	β -glucan	38, 39
<i>Pleurotus ostreatus</i>	β -glucan	40
<i>Polyporus mylittae</i>	β -glucan	41
<i>Schizophyllum commune</i>	β -glucan, krestin	11
<i>Trametes gibbosa</i>	glucan	25
<i>Trametes versicolor</i>	heteroglucan	17
<i>Tricholoma giganteum</i>	heteroglucan	42
<i>Tylopilus felleus</i>	β -glucan, tylopilan	22, 23, 24
<i>Volvaria volvacea</i>	β -glucan	43

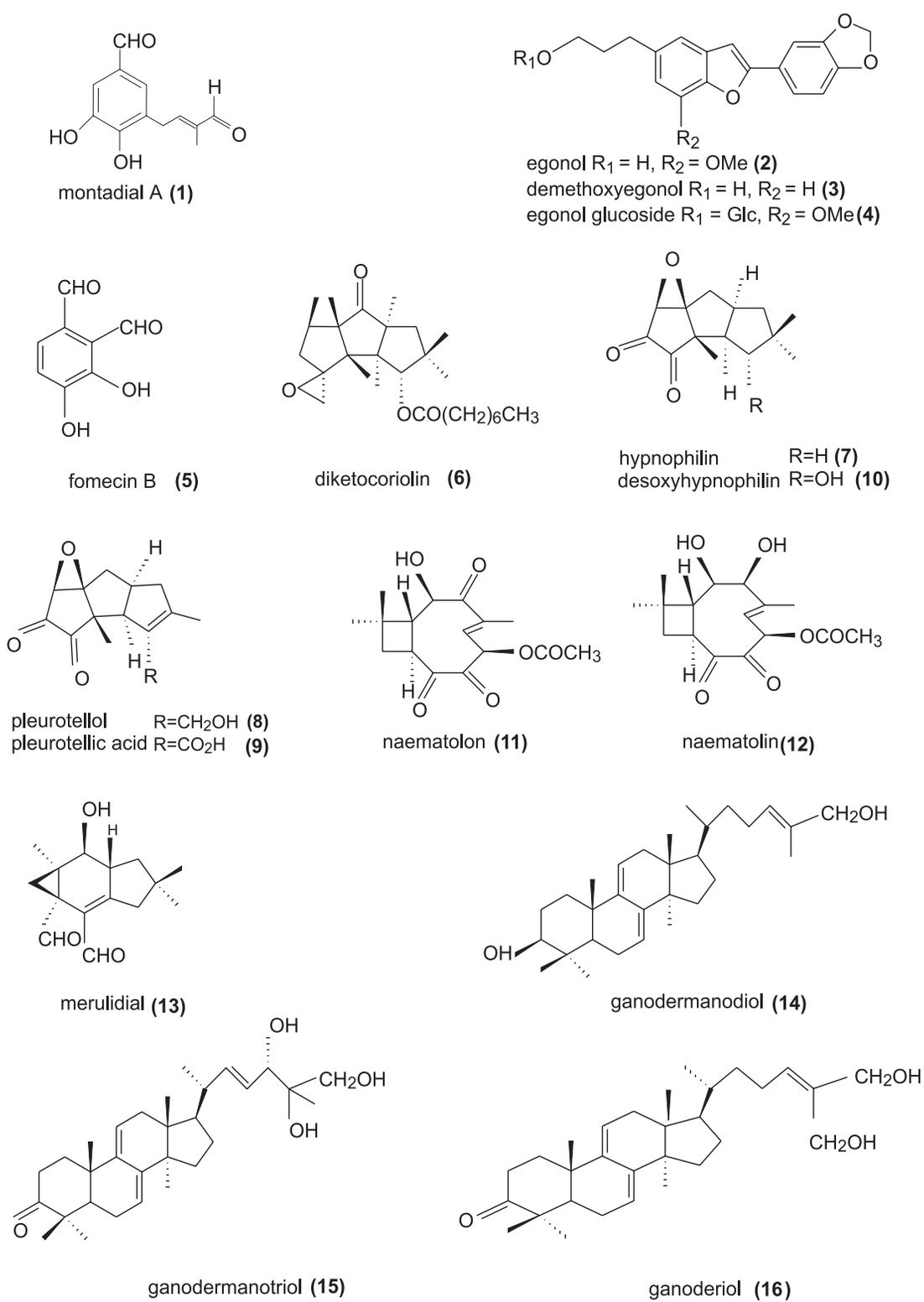


Figure 2. Structure of antitumor substances – derivatives from macromycetes.

so interesting since they are characterized by a strong cytotoxic activity (49). Moreover, two next hirsutane derivatives i.e., desoxyhynophilin (**10**) and 1-desoxyhynophanol, obtained by *Lentinus crinitus* fermentation, had cytotoxic effect on mouse fibroblastoma L929 (44). In addition, the genus *Panus* contains sesquiterpenes like naematolon (**11**) and naematolina (**12**), whose cytotoxicity is connected with the presence of α and β unsaturated ketone groups (49).

Apart from antitumor activity of the compounds originating in fungi, they can also influence other aspects of immunity. Efficient antifungal metabolites (merulidial, tremediol, tremetriol and α -bisabolol) were obtained from the species *Merulius tremellosus*, but only sesquiterpene – merulidial (**13**) showed cytotoxic activity, suppressing DNA biosynthesis in ECA cells, and had also character of a mutagen. The remaining above mentioned compounds caused apoptosis of promyelocytes of human leukemia HL 60 (50).

In the Far East, medicinal properties of fungal extracts have been known for ages. *Ganoderma lucidum* belongs to the fungi that have long been widely used in traditional medicine in such diseases as tumors, hepatitis, asthma, hemorrhoids. Fruiting bodies of this fungus and related *Ganoderma applanatum* were used to isolate numerous triterpenoids of lanostan type, such as lucidenic acid (**51**), ganodermanodiol (**14**), ganodermanotriol (**15**) and ganoderiol (**16**), which are strong activators of the complement system that plays a significant role in inducing humoral response in human body (52). Furthermore, ganoderic B, ganolucidic A acids and lucidumol B, isolated also from *Ganoderma pfeifferi*, were demonstrated to inhibit HIV protease (53).

A great attention has been focused on secondary metabolites isolated from mycelial cultures. For instance, calvatic acid (antibiotic) was isolated from *Calvatia craniformis*. It inhibits growth and development of Yoshida sarcoma and mouse leukemia L-1210 (54). Aranoflavins A and B, which affected growth of Yoshida sarcoma, were isolated from *Arachnotus flavoluteus* (55). Antitumor antibiotic SL-1846 was isolated from *in vitro* *Pseudeurotium ovalis* cultures. It was shown to suppress proliferation of P-815 mastocytoma in mice (56). Bredenin from *Eupenicillium brefeldianum* (micromycetes) is an example of imidazole nucleoside, which blocks development of leukemia (57).

Intensive search for new substances possessing antitumor activity and examination of their biologi-

cal properties may pave the way for introduction of new drugs into therapy. The described above examples authenticate the need of mycochemical research, which can lead to isolation, identification and defining biological activity of compounds that are contained in different species of fungi.

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