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Review Article

Biologically Active Substances and Extracts of Fungal Origin

Hristova Dilyana[1], Rusinova-Videva Snezhana[2,*], Konstantinov Spiro[1]

ABSTRACT
Studying the biological activity of fungi is crucial to discovering their potential for the treatment and prevention of various diseases. The diverse composition and various substances they produce are the basis of their application in medicine. Pullulan can be used as blood plasma substituent, carrier in drug delivery systems. Chitin possess antimicrobial, anticoagulant and antitumor activities. Inotodiol and the other substances from *Inonotus obliquus* possess strong cytotoxic activity against breast and gastric cancer. Camptothecin derivatives are used for treatment of ovarian and colorectal cancers. In our study we used a strain Antarctic yeasts *Cryptococcus laurentii* AL_{65}. We found out that these psychrophilic yeasts possess antineoplastic activity. Their action is observed in solid tumors-bladder cancer. Along with their cytotoxic effects yeasts possess a very good safety profile and can be part of future antitumor therapy.
Key words: Antarctic yeast, Antineoplastic action, Biological activity, Fungi, Polysaccharides.

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INTRODUCTION

A fungus is every member of the group of eukaryotic organisms that includes micro-organisms such as yeasts and molds, as well as the more familiar mushrooms. Fungi have a worldwide distribution, and grow in a wide range of habitats, including extreme environments such as deserts or areas with high salt concentrations or ionizing radiation, as well as in deep sea sediments and in the freezing water of the Arctic and Antarctic sea. Current classification recognizes 8 phyla, 12 sub-phyla, and 46 classes within the kingdom.[1] Fungi have been used as a direct source of human food, as a leavening agent for bread, and in the fermentation of various food products such as wine, beer, and soy sauce.

A characteristic that places fungi in a different kingdom from plants, bacteria, as well as from some protists is chitin in their cell walls (Figure 1).

The yeast cell wall is a thick envelope (100 to 200 nm) representing 15–25% of the dry mass of the cell. The major components of cell wall are polysaccharides (up to 90%), mainly β-D-glucans and α-D-mannans with a minor amount of chitin that constitutes only about 1–2% of the polysaccharides and is located predominantly in the bud scars. According to Kogan *et al.* (2008) the cell wall of the baker's yeast *Saccharomyces cerevisiae* could be represented schematically as shown in Figure 2.

Biological activity

Studying the biological activity of fungi is crucial to discover their therapeutic and preventive potential in various diseases. Most of the useful biologically active compounds from yeast biomass are part of the polysaccharide fraction.

Originally, the extracellular synthesized by *Aureobasidium pullulans* pullulan (Figure 3) has been used as a layer impermeable to oxygen and resistant to oils and aggressive changes in temperature and pH.[3]

It is important to mention, that pullulan can replace dextran as a substitution of blood plasma under certain requirements for molecular weight of the biopolymer.[4] There is also growing evidence of a hypocholesterolemic effect of this biopolymer, too.[5] Coral-associated mushrooms such as *Aspergillus versicolor* have antioxidant activity due to the mananoglucan containing exopolysaccharides synthesized by them.[6] Baets[7] summarizes data on extracellular *Tremella* polysaccharides, drawing attention because of several perspective pharmacological activities. Their ability to stimulate the immune system stimulation and their hypoglycemic activity were described.[8,9] Exopolysaccharides synthesized by *Tremella fuciformis* can accelerate gastric erosion healing. They also lead to reduction of total plasma cholesterol and triglycerides by decreasing cholesterol absorption.[10,11] In addition, in some experimental mouse models exopolysaccharides were reported to reduce plasma glucose by 52%.[12] Extracellular polysaccharides from *Tremella aurantia* showed similar activities and led to plasma glucose level reduction, as well as plasma cholesterol decrease.

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These beneficial effects were accompanied by certain immunostimulation due to activation of neutrophils.[13]

Many authors studied the properties of biopolymers of mushroom origin thus revealing their pharmacological and cosmetic application potential. Noteworthy, the strain *Sporobolomyces salmonicolor* AL_1 was selected as a strong producer of glucomannan (Figure 4), which has being proposed for industrial use as emulsifier and rheological modifier in cosmetic compositions.[14,15]

Glucomannan is being used as a pharmaceutical carrier in tablets, film-forms, micro-drops and hydrogels.[16-18] In the treatment of pulmonary diseases, the presence of glucomannan in the drug formulation may have crucial importance for the respective spray-on-inhaled formulations.[19] The use of glucomannan-based nanoparticles may contribute for stability in ionic environment and may enable sustained release of proteins.[20,21]

According to *in vitro* and *in vivo* studies on intestinal epithelium acquisition of mucoadhesive properties was found.[21] According to published data by Table 1 summarizes some of the basic properties of the fungal polysaccharides that determine their potential pharmaceutical use.[22]

The species *Cordyceps sinensis* has been described in ancient Chinese and Tibetan medicine scripts. This species is also known as a medical food and energy source. *Cordyceps sinensis* was described to improve appetite, endurance, sexual libido and sleep as well. It was used as medication for cancer, asthma, diabetes, cough, erectile dysfunction and hepatitis.

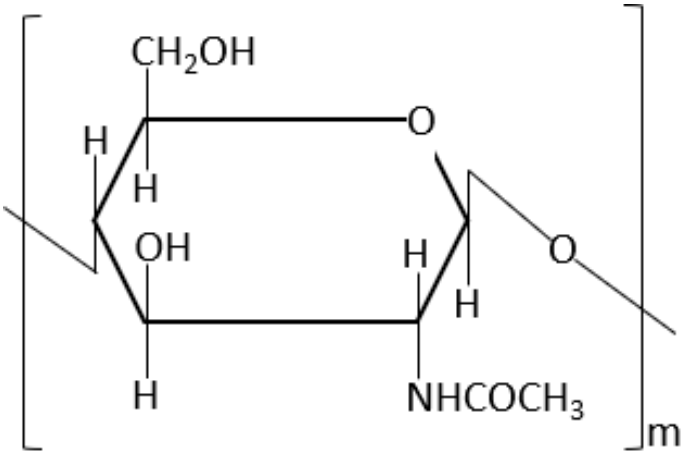

Figure 1: General structure of Chitin.

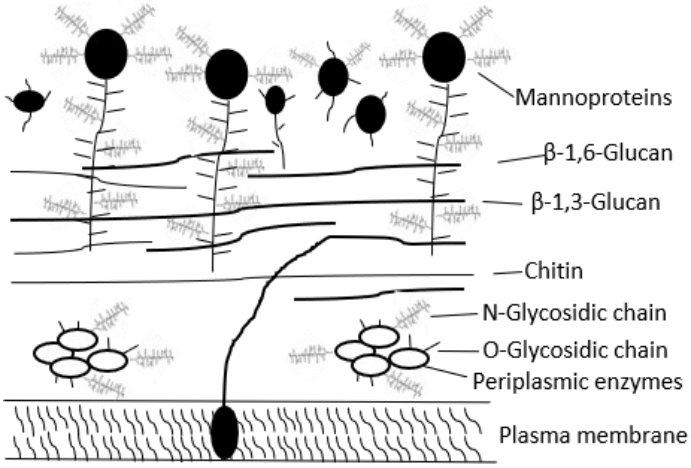

Figure 2: Composition and structure of the yeast cell wall.

Chemical analysis of the fungus showed the content of many amino acids, polyamines, cyclic dipeptides, saccharides and their derivatives, sterols, nucleotides and nucleosides, twenty eight saturated and unsaturated fatty acids, their derivatives and many organic acids, vitamins and some inorganic microelements. Main pharmacological activities include: stimulation of bio-energetic metabolism; reduction of aminoglycoside-induced nephrotoxicity; hematuria and proteinuria amelioration in IgA nephropathy; stimulation of corticosteroid production in animals; inhibition of platelet aggregation; proliferation of fibroblasts *in vivo* and *in vitro*; and platelet production increase.[23]

Polyporus biformis (Trichaptum biforme) is a producer of two antibiotic substances referred to as biformin and biforminic acid (Figure 5). These substances inhibit many Gram negative and Gram positive bacteria.[24]

Derivatives of the aminoacids synthesized by the fungus *Tricholomopsis rutilans* showed antiviral and antihyperlipidemic activity.[24]

The two biologically active substances of *Mycena viridimarginata* exerted high activity against Gram negative and Gram positive bacteria, as well as pathogenic filamentous fungi.[24]

The aromatic acetylene derivatives of *Stereum frustulosum* isolated are fructolosin and fructulosinol. They have activity against *S. aureus, Bacillus mycoides, B. subtilis, Vibrio cholera* and phage of *Vibrio cholera*.[24]

Aureobasidium pullulans extracts are rich in β-glucans and showed efficient protection of mice infected with lethal dose (PR8; H1N1) influenza strain virus. Replication of the PR8 virus has been found to be significantly suppressed through β-glucan pretreatment.[25]

The n-butanol exogenous extract of the strain *Aspergillus protuberus* SP1 exhibited *in vitro* antibacterial as well as hepatoprotective activity.[26] (Figure 6)

Secondary metabolites were identified in the species *Aspergillus aculeatus* strain KKU-CT2, which also showed substantial antimicrobial

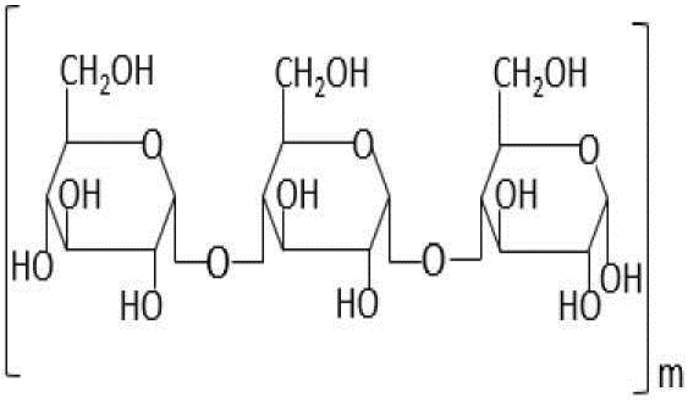

Figure 3: General structure of pullulan.

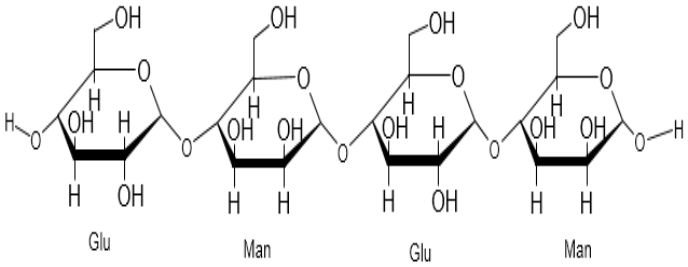

Figure 4: General structure of glucomannan, a main chain of β-1,4 linked mannose and glucose residues.

Table 1: Basic properties and pharmaceutical use of fungal polysaccharides.

Polysaccharide	Monosaccharide content	Microbial producer	Probable pharmacological application
Pullulan	D- glucose	*Aureobasidium pullulans, Cryphonectria parasitica*	Blood plasma substituent, carrier in drug delivery systems
Scleroglucan	D- glucose	*Sclerothinia*	Anticancer activity
Chitin	N- acetyl-D- glucosamine	*Aspergillus, Penicillium, Allomyces, Fusarium*	Antimicrobial activity, anticoagulant activity, antitumor activity, wound healing
Chitosan	D- glucosamine, N- acetyl-D- glucosamine	*Mucor, Absidia, Rhizopus*	Anticancer activity, antimicrobial activity, anticoagulant activity, immunostimulatory activity, wound healing agent, carrier in drug systems

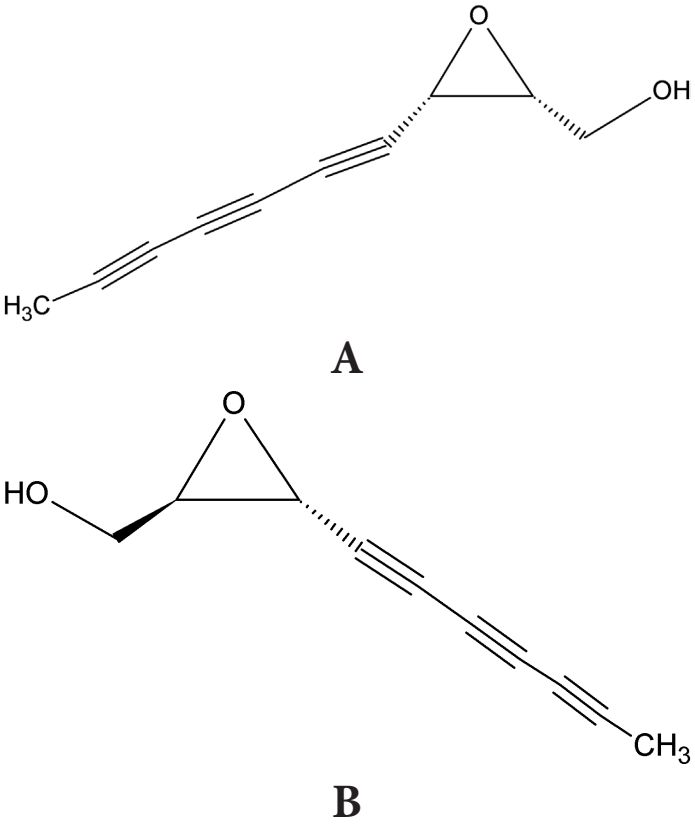

Figure 5: Structutures of A) biformin and B) biforminic acid by *Polyporus biformis*.

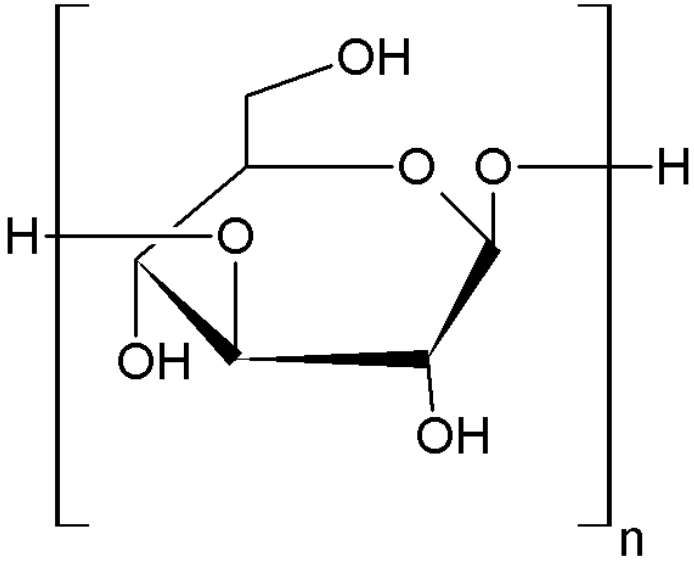

Figure 6: Structure of β-1,3 glucan.

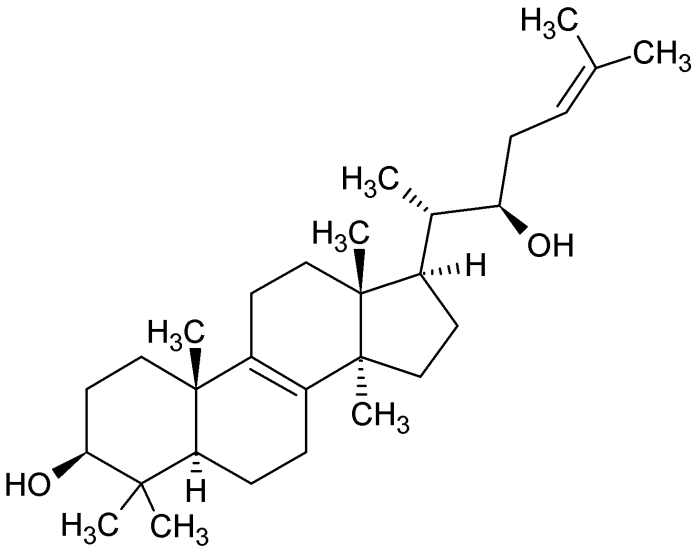

Figure 7: Structure of endopolysaccharide inotodiol by *Inonotus obliquus*.

activity against gram positive and gram negative bacteria, as well as against fungal pathogens as *Cryptococcus neoformans*. Some of the secondary metabolites from *Aspergillus aculeatus* were found to possess antimalarial activity against *Plasmodium falciparum*.[27]

The preventive effect of probiotic yeast is thought to be related to their biologically active substituents such as folic acid and β-glucan, which have direct effect on pathogenic gut bacteria and indirectly influence the inactivation of carcinogenic compounds. Probiotic yeast was suggested to induce positive modulation of the immune response, as well as to exert selective antiproliferative effects.[28]

Exo- and endopolysaccharides from *Pleurotus ostreatus* showed high antioxidant activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) tests as well as ion-chelating activity.[29] The β-D-glucan isolated from *Saccharamyces cerevisiae* has pronounced antioxidant activity against free radicals, as well as ability to neutralize peroxides produced by ultraviolet A radiation (UVA). This effect of the glucan is stronger than that of hyaluronic acid frequently used to protect skin against UVA.[2]

Behind or based on the antioxidant activity of fungal polysaccharides antimutagenic and anticancer activities can be expected.

Fungal components with antineoplastic activity

Some fungi have also been studied for cytotoxicity to malignant cell lines. *In vitro* antitumor activity was found for some edible fungi, such as *Aspergillus protuberus* SP1 and *Tricholomopsis rutilans*.[26,24] Antitumor activity due to polysaccharides, sterols and adenosine in *Cordyceps sinensis* was reported.[30] Synthesized by *Streptomyces* sp. streptochlorin is known to possess anti-angiogenic and antiproliferative properties against malignant cells from histiocytic lymphoma.[31] *Mycena viridimarginata* showed pronounced activity against murine Ehrlich carcinoma.[24]

Inonotus obliquus, commonly known as chaga (a Latinisation of the Russian word "чага") is used as a functional food (so called nutraceutical) in China. Extracts of this fungus exerted antitumor effects on models of prostate, breast and other cancers. As pharmacologically active compounds lanosterol, 3β-hydroxy-8,24-diene-21-al, ergosterol, inotodiol (Figure 7), ergosterol peroxide and tramethenolic acid B (TAB) (Figure 8) were suspected.[32] TAB possesses strong cytotoxic activity against breast cancer and gastric cancer. This effect could be explained by following mechanisms: inhibition of the P- glycoprotein (P-gp) transporter and down-regulation of its expression level; TAB-induced suppression of the H+/K+-ATPase activity both *in vitro* and *in vivo*. TAB showed significant antineoplastic activity in gastric cancer cells.[33] Synergism with other anticancer substances, e.g. Taxol was reported as well.[34]

Early reports of Kalhos *et al*. indicate that inotodiol can completely inhibit the proliferation of cancer lines.[35] In other similar studies, the endopolysaccharide from *Inonotus obliquus* demonstrated selective antitumor activity *in vivo*. The isolated fucoglucomannan contains α-bonds and was show to be useful for the prevention and treatment of tumors.[36]

An ethanol extract from the *Fomitopsis pinicola* fungus was found to induce apoptosis in malignant cells and showed pronounced antineoplastic effects *in vitro* and *in vivo*.[37]

Fumigaclavin C was found in *Aspergillus fumigatus* and showed pronounced inhibition of MCF-7 breast cancer cells.[38] The bioactive components of the *A. aculeatus* strain KKU-CT2 extract are ergosterol peroxide, secalic acid D, secalic acid F, varicolin, varicolactone and ergosterol. They were evaluated as highly effective against human epidermoid carcinoma of the mouth.[27]

Species *Fomitopsis* sp., *Alternaria alternate* and *Phomposis* sp. are producers of a camptothecin-quinoline alkaloid. Similar semisynthetic derivatives are used clinically for the treatment of ovarian and colorectal cancers (Figure 9). Moreover, ethanolic and ethyl acetate extracts exerted cytotoxic effects against breast and colon cancer cell lines.[39]

The extracellular polysaccharide from *Tremella* has also anti-tumor activity.[40]

Glucomannan producers are many plants and fungi such as *Lentinus*, *Cordyceps*, *Ganoderma lucidum*, *Hericium* and *Candida utilis*. The

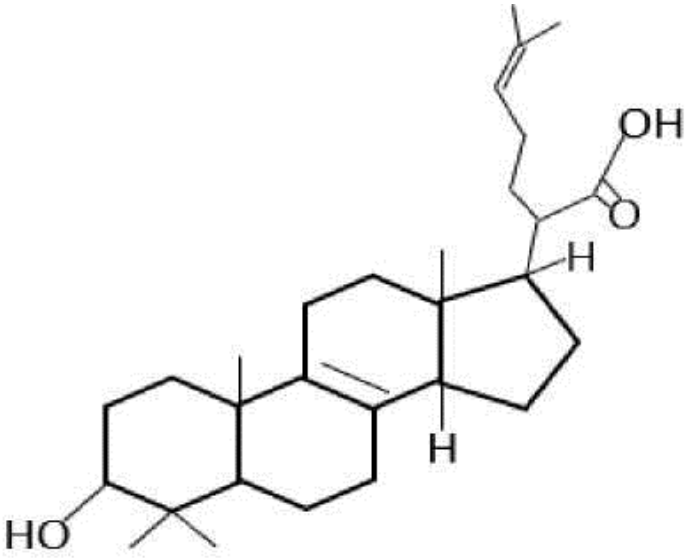

Figure 8: Structure of Trametenolic acid B by *Inonotus obliquus.*

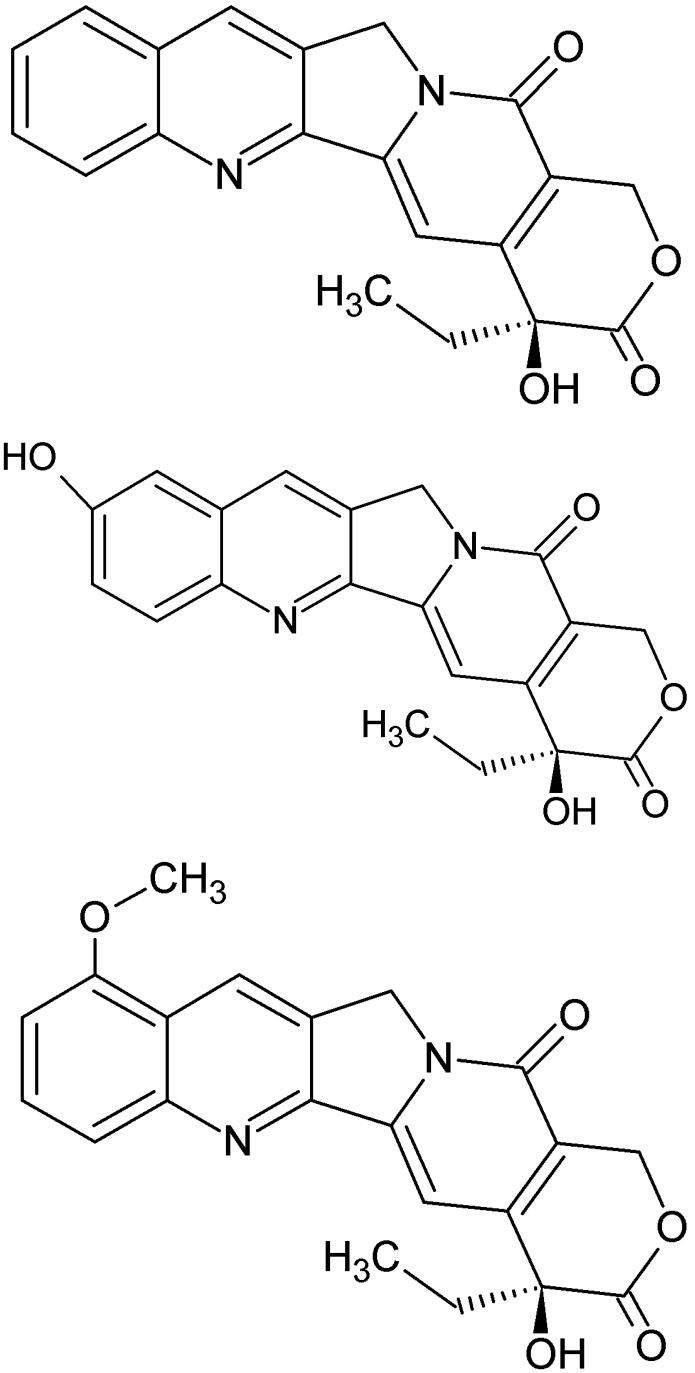

Figure 9: Structure of: A) Camptothecine; B) Hydroxycamptothecine; C) Methoxycamtothecine.

antitumor effect of this polysaccharide was shown to have an impact on tumor survival and metastasis. The overall antineoplastic efficacy is related to increased apoptosis and decreased migration of cancer cells. In addition, glucomannan was recognized as targeted drug carrier for the specific delivery of various bioactive compounds.[41]

In the marine species *Penicillium* sp. penicillatides A and B were identified and their selective cytotoxicity against human colorectal carcinoma HCT-116, breast cancer (MCF-7) and hepatocellular carcinoma (HEP-G2) was demonstrated as well.[42]

Information about the antineoplastic activity of unicellular fungi such as yeast is still very scarce. The *Pichia kudriavzevii*AS-12 secretes some metabolites of interest. They possess significant cytotoxic effects against HT-29 and Caco-2 colorectal cancer cells *in vitro* compared with control groups of human embryonic kidney normal cell line (KDR/293). The survival rates after treatment of H-29 and Caco-2 cells were 42.5% and 67.5% in comparison with KDR/293 cells (75% cell viability) respectively.[43] *Klyuiveromyces marxianus* AS41 was described to contain antineoplastic components with selective anticancer and proapoptotic effects in epithelial malignant cells.[44]

Apple callus yeast culture biomaterial showed selective antitumor effects in cervical cancer cells HeLa, as well as in breast cancer cells MCF-7.[45]

In our recent unpublished studies, we tested for the first time the antitumor effect of extracts of Antarctic yeasts. The psycchrophilic yeast *Cryptococcus laurentii* AL_{65} was part of Antarctic collection of Institute of Microbiology-BAS (Figure 10). The cultivation processes were carried out in flasks and in a 5L bioreactor (Figure 11). By using method of growing yeast cells in a bioreactor it was possible to easily control conditions, being independent from geographic location and climatic features of the area. Other advantages include short time to carry out the fermentation processes, low value of the substrates used and natural protection against contamination.

Our study aimed to determine and compare the antineoplastic activity of methanol yeast extract against a panel of different tumor cell lines: T-24 and CAL-29 (urinary bladder cancer). The cytotoxic efficacy was measured using the MTT-assay (Table 2). The results showed that yeasts extracts have anticancer activity against urinary bladder T-24 and CAL-29 cancer cells. In T-24 cells the extract of *C. laurentii* AL_{65} cultivated in flasks caused stronger antineoplastic effect, while in CAL-29 cells the extract of yeast cultivated in bioreactor was more effective (Table 2).

Flow cytometric data for T-24 cancer cells indicated increase of the subG1-fraction, which is typical for apoptosis induction (Figure 12A, B).

It can be speculated that the antineoplastic activity of our Antarctic yeast extracts could be related to the content of beta-carotene. The yellow-orange beta- carotene (BC) pigment is widely used in the pharmaceutical industry, in the cosmetic industry, in the food industry, and also has anti-tumor activity. BC has the ability to slow the growth of various tumor cells such as melanoma, prostate cancer, colon, lung and breast. Some yeasts such as *Rhudotorula glutinis* are used to produce large amounts of BC.[46]

Mode of action

Much of the research on the mechanisms of action of fungi was focused on the effects of their polysaccharide-rich extracts. In edible fungi *Ganoderma formosanum* a heteropolysaccharide was demonstrated to

Table 2: IC_{50} (μg/ml) in tumor cell lines- T-24 and Cal-29, after 72h treatment with extract of *C. laurentii* AL_{65}, cultivated in flasks and bioreactor

Cell lines	Parameters measured					
	C. laurentii (Flasks)			*C. laurentii* (Bioreactor)		
	IC_{50} (μg/mL)	95% CI	R	IC_{50} (μg/mL)	95% CI	R
T-24	109.2	89.75-128.7	0.96	97.22	87.74-107.7	0.97
Cal-29	118.9	105-134.7	0.96	97.2	89.36-105.7	0.98

Legend: IC_{50} – inhibitory concentration 50% (median); 95% CI – confidence interval 95%; R – correlation coefficient.

Figure 10: Lyophilized biomass of *C. laurentii* AL_{65}.

Figure 11: Cultivation process by *C. laurentii* AL_{65} in a Bioreactor Sartorius Biostat Aplus.

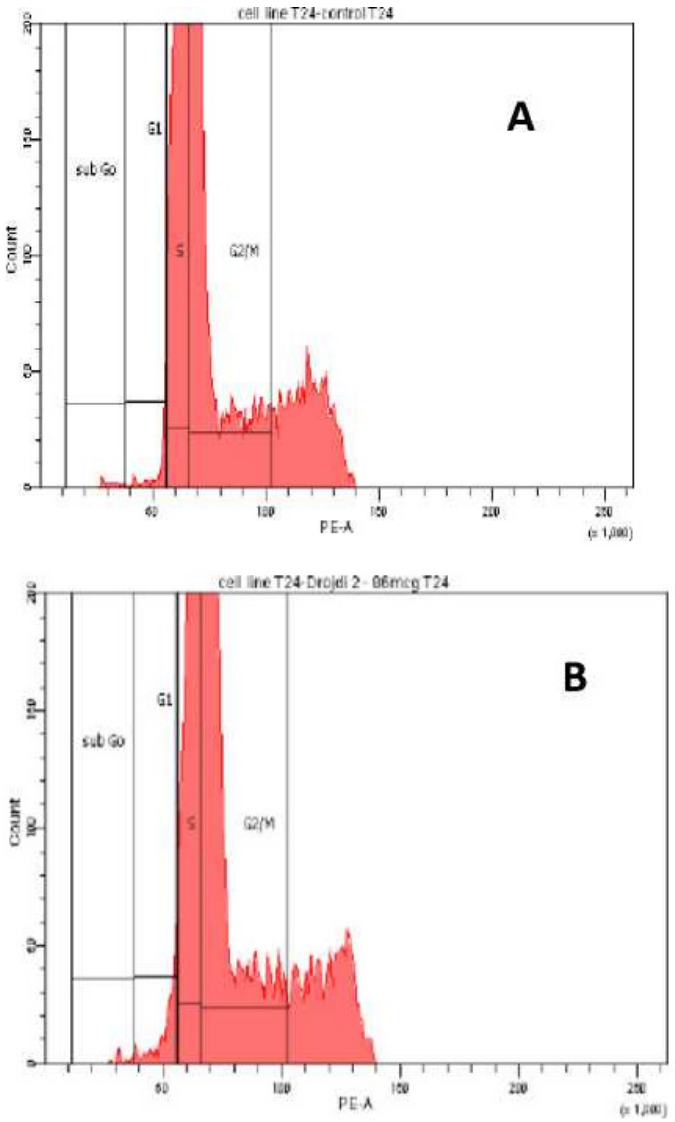

Figure 12: Flow cytometric assay in T-24, untreated control (A) and 24h treatment with extract of *C. laurentii* AL_{65}, cultivated in flasks (B).

cause macrophage activation. As a consequence, changes in cell signaling cascade of macrophages with TNF-α production occurred. Extracellular polysaccharides from *G. formosanum* are thought to possess potential for use as immunomodulatory agents for the prevention and treatment of infections and malignancies.[17]

Water-soluble polysaccharide from *I. obliquus* caused increased lymphocytic proliferation, activated phagocytosis and increased the TNF-α production.[47]

The effect of *Tremella fuciformis* exopolysaccharides on the induction of human monocytes, the production of IL-1, IL-2 and TNF *in vitro* was demonstrated, too.[48-51]

Comparison of the biological activity of several polysaccharide fractions of *Saccharomyces boulardii* and *Kluyveromyces marxianus* identified the insoluble glucan of *S. boulardii* as the most active ingredient for quinone reductase induction and as the most potent inhibitor of colorectal cancer cell growth.[43]

Mannans induced secretion of IL-1, IFN, and TNF, thus causing inhibition of tumor cell growth. The lack of common toxicity makes mannans perspective candidates for antitumor studies. Early reports referred to *Saccharomyces* mannan (150 mg / kg / d) as an agent for increased number of antibody producing cells in the spleen of mice.[52] *In vitro* studies with peritoneal cells (a mixture of macrophages and lymphocytes) from mice showed that some mannan and mannan-protein complexes stimulate the secretion of interferon *in vivo* and *in vitro* as well.[53] Mannans stimulated also the release of interferon by a mechanism similar to that of bacterial endotoxins, but in contrast, their toxicity is minimal. Mannan fractions of five yeast species *C. albicans* B-792, *C. albicans* A-207, *C. stellatoidea*, *C. utilis* and *S. cerevisiae* were tested for activity against the Sa-180 tumor model in mice.[54] The inhibitory activity reached 99%, 65%, 82%, 10% and 91%, respectively. The *C. utilis* mannan containing α-linked glucose showed lower activity. The extract from *C. albicans* B-792 mannan contains β-glucan component and possess highly activity. Antitumor activity is thought to be dependent on the presence of β-bonds. In addition, the degree of polymerization of mannans is assumed to be of paramount importance for the antitumor activity, as hydrolysis (up to one sixth of the original size of the molecule) leads to significant loss of activity.[55]

The most pronounced biological activity of mannans in mammals is the activation of macrophages and the stimulation of T-cells. Therefore, mannans act as potent immuno-stimulators with distinct activity against infectious diseases and tumors. The immunostimulatory and protective effects of yeastwere found to be related to β-D-glucans. Their effects include: stimulation of bone marrow activity associated with the increased release of monocytes and granulocytes, elevated antibody production, increased cytokine secretion (including interleukins IL-1, IL-2, IL-6 and tumor necrosis factor TNF-α), prostaglandin E2 and others.[2]

One of the repeatedly reported mechanisms for realizing the antitumor activity of yeast is by inducing apoptosis in tumor cells. Metabolites secreted by *P. kudriavzevii* AS-12 can induce apoptosis in human colon cancer cell lines (HT-29 and Caco-2). Bioactive yeast ingredients were found to increase levels of pro-apoptotic genes and decrease levels of anti-apoptotic genes, and to induce apoptosis in malignant cells selectively. The yeast extract from *S. cerevisiae* caused changes in the ratio Bax/Bcl-2, thus leading to apoptosis of metastatic breast cancer cells. Moreover, the proapoptotic BAD protein was described to bind to anti-apoptotic proteins such as Bcl-2 and Bcl-XL, thus neutralizing their anti-apoptotic functions after treatment with the extract.[28] Our newly presented and non-published data about extracts from Antarctic yeast culture biomass are indicative for apoptosis induction of urinary bladder cancer cells with formation of an apoptotic sub-G1 fraction as shown by flow cytometry (Figure 11).

Ganoderma lucidum components were described to suppress Wnt/beta-catehin signaling accompanied by reduction of the proliferation and migration of breast cancer cells.[56] It is suggested, that the glucomannan may alter the cytokine profile near the tumor (modulation of the tumor microenvironment). This polysaccharide caused cytotoxic effect by decreasing IL-10 level and by promoting the production of IFN-γ in tumor sites.[57,58] In addition, it is possible that glucomannan could increase macrophage phagocytic activity and cytokine secretion (TNFα and IL-6) and receptor activation (TLR4).[59]

CONCLUSION

In modern medicine the use of different agent combinations to treat tumors is very common. Some of these medications are herbal, but nevertheless they, as well as others, have very serious side effects. Yeast are micro-organisms that have a proven antineoplastic effect but at the same time have a very good safety profile. Future cancer treatment methods will focus on finding high-security agents with a well-defined

anti-tumor effect. For this reason, it is of great importance to study the activity of yeast against various types of malignancies.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

PR8: Strain of the influenza A virus; **H1N1:** Influenza A virus strain (swine flu); **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **ABTS:** 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); **UVA:** ultraviolet A radiation; **TAB:** tramethenolic acid B; **P-gp:** P- glycoprotein (gp179, MDR1); **ATPase:** Adenosinetriphosphatase; **HEP-G2**: cell line of hepatocellular carcinoma; **HCT-116:** cell line of human colorectal carcinoma; **MCF-7:** cell line of breast cancer; **T-24:** cell line of urinary bladder cancer; **CAL-29**: cell line of urinary bladder cancer; **Sa-180**: cell line of Sarcoma-180; **MTT-assay**: colorimetric assay for assessing cell metabolic activity and viability; **BC:** beta- carotene; **TNF-α**: Tumor necrosis factor- α; **IL-1:** Interleukin 1; **IL-2:** Interleukin 2; **IL-6:** Interleukin 6; **IL-10**: Interleukin 10; **IC_{50}:** inhibitory concentration 50%; **CI**: confidence interval; **R:** correlation coefficient; **Bax:** Bcl-2-like protein 4 (apoptosis regulator); **Bcl-2:** B-cell lymphoma 2 (anti-apoptotic member of the Bcl-2 family); **BAD:** Bcl-2 associated agonist of cell death (pro-apoptotic member of the Bcl-2 family); **Bcl-XL:** Bcl-2 associated agonist of cell death (anti-apoptotic member of the Bcl-2 family); **G1:** g1 phase, gap 1 phase, or growth 1 phase, is the first of four phases of the cell cycle that takes place in eukaryotic cell division; **IFN-γ**: interferon γ; **TLR4:** toll like receptor 4.

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