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# ANTIVIRAL PROPERTIES OF LIGNICOLOUS FUNGI OF SERBIA

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**Abstract:** *Fungi have multiple roles in nature. However, from his point of view, man most often views them as useful or harmful (depending on his primary activity). Thus, wood decaying fungi are most often seen as parasitic and saprophytic organisms, economically harmful, overlooking their useful functions. One of their useful functions is a possibility of their use in the treatment of various diseases. The results of the research of antiviral properties of lignicolous fungi are presented in this paper. Samples for isolation and identification of fungi are collected on several sites in Serbia. It has been determined that the fungi that cause wood decay have various antiviral properties, most often against viruses such as influenza, hepatitis, herpes, SARS-CoV-2 and HIV.*
**Keywords:** viruses, fungi, polysaccharides, fruiting bodies.

# ANTIVIRUSNA SVOJSTVA LIGNIKOLNIH GLJIVA SRBIJE

**Sažetak:** *Gljive imaju višestruku ulogu u prirodi. Međutim, čovek ih sa svog stanovišta najčešće posmatra kao korisne ili štetne (zavisno od svoje primarne aktivnosti). Tako i gljive truležnice drveta najčešće posmatra kao parazitske i saprofitske organizme, ekonomski štetne, previđajući njihove korisne funkcije. Jedna od korisnih funkcija je njihova mogućnost korišćenja u lečenju različitih bolesti. U radu su prikazani rezultati proučavanja antivirusnih svojstava lignikolnih gljiva. Uzorci za izolaciju i identifikaciju gljiva prikupljani su na više lokaliteta u Srbiji. Konstatovano je da gljive izazivači truleži drveta imaju različita antivirusna svojstva i to najčešće protiv virusa gripa, hepatitisa,* herpesa, SARS-CoV-2 i HIV-a.
**Ključne reči:** virusi, gljive, polisaharidi, plodonosna tela.

## 1. INTRODUCTION

The majority of lignicolous fungi cause wood decay and in this way they cause relatively large damages to the forest economy (due to the loss of wood mass). These fungi cause white or brown rot of the wood depending on whether they break down lignin (causing the white rot) or cellulose and hemicellulose (causing the

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brown rot). Although some fungi sometimes cause large damages, causing die-back of the trees, still the importance of fungi in the process of organic matter circulation is immeasurable.

In addition to causing the wood rot and reducing the value of wood mass, large number of lignicolous fungi have medicinal properties. Thanks to the content of immunomodulatory polysaccharides, proteins, polysaccharide-protein complexes, polyphenols, steroids, triterpenoids, fatty acids, nucleotides, pigments, and polyacetylene components, fungi started to be used for obtaining antibiotics and other medicines (Karadžić, D., *et. al.* 2022).

Nowadays, according to Lindequist, U. *et al.*, (2005) between 80 and 85% of medicinal preparations obtained on the basis of fungi are extracted from fruiting bodies, collected in nature or artificially cultivated. Only 15% of preparations are obtained from the extract of mycelia (PSK and PSP from *T. versicolor*), and very small percent is obtained by filtering a pure fungi culture (schizophyllan from *S. commune*).

Viruses cause great epidemics on all continents, which leads to severe symptoms and mortality in humans and huge treatment costs. In addition, the constant emergence of new strains represents the additional challenge in the fight against the viruses. The antiviral properties of fungi and the possibility of their application in the treatment of various human diseases caused by viruses have been discovered lately.

## 2. MATERIAL AND METHODS

Global research of lignicolous fungi has been carried out on the territory of the whole Serbia (except Kosovo), while somewhat more detailed researches have been carried out in the territories of Goč, National Park Tara, National Park Fruška Gora, National Park Đerdap, Natural Park Stara Planina, Majdanpečka Domena and Srem.

The determining of the species has been carried out based on the appearance of the fruiting bodies (carpophores), type of the rot, and the appearance of the obtained pure culture. From the rotten parts of the trunks the isolation of the fungi was carried out on appropriate nutrient substrates (PDA- Potato Dextrose Agar; MEA- Malt Extract Agar). Nutrient substrates have been prepared according to the recipe of Bootha, C. (1971). The objective of these isolations was to isolate pure cultures of fungi from a rot-affected wood and to carry out identification based on their appearance. For determination of the fungi publications of the following authors were used: Bondarcev, A.S. (1953), Breitenbach, J. et Kränzlin, F. (1986), Hagara, L. (2014), Karadžić, D. and Anđelić, M. (2002) and others.

Antiviral properties of fungi have been researched by searching the references in PubMed search engine, by combining the terms “mushroom” and “antiviral”. Some properties are listed from the available literature in the Russian language. Only antiviral properties of fungi recorded in Serbia were taken into account.

## 3. RESULTS

The obtained results are presented in Table 1.

**Table 1.** *Antiviral properties of lignicolous fungi*

| Fungus | Biological activity | Bioactive component or the part of a fungus with medicinal properties | References |
|---|---|---|---|
| *Daedaleopsis confragosa* (Bolt.: Fr.) J. Schröt. | Antiviral effect | Aqueous extracts of mycelia | Teplyakov a, P. T., *et. al.* (2012) |
| *Fomes fomentarius* (L.) Fr. | Antiviral effect (virus of influenza H1N1 and herpes simplex virus type HSV-2, strain BH). | Mycelia of fungi | Krupodorova, T., *et. al.,* (2014) |
| *Ganoderma lucidum* (Fr.) Karst. | Antiviral effect (herpes, herpes zoster, viral hepatitis A, B and C and HIV) | Triterpenes (ganoderic acid beta, lucidumol B, ganodermanondiol, ganodermanontriol, and ganolucidic acid A) | Min, B.S., et. *al.* (1998). |
| *Grifola frondosa* (Dicks.) Gray | Hepatitis B | D – fraction of polysaccharides | Gu, C.Q., *et al.* (2006) |
| | HIV | β-glucans | Halpern, G. M. (2007) |
| *Inonotus obliquus* (Fr.) Pilát | Antiviral effect | Fruiting body | Мелькумов, Г. М., Золототрубов а, А. С. (2017) |
| *Laetiporus sulphureus* (Bull.) Murrill. | Antiviral effect against HSV-1 | Extracts of mycelia | (Квачева, З.Б., *et. al.* 2005). |
| *Lentinus edodes* (Berk.) Singer | COVID 19 | Lentinan | Murphy, E., *et. al.,* (2020) |
| | Hepatitis B, AIDS, | Polysaccharides (LEP-1 and LEP-2), lentinan, eritadenine | Zhaoa, Y.M., *et. al.,* (2018,); Bisen, P.S., *et. al.,* (2010) |
| *Lentinus tigrinus* (Bull.) Fr. | Antiviral effect (HIV-1) | Laccase from fungal mycelia | Xu, L., *et al.* (2012) |
| *Lenzites betulina* (L.) Fr | Antiviral effect on viruses H5N1 and H3N2 | Aqueous extracts of mycelia | Teplyakova, T. V. et. al., (2012) |
| *Phellinus igniarius* (L. ex Fr.) Quél | Antiviral effect (Influenza viruses A and B, H9N2, human H3N2, bird H9N2 and viruses H1N1 resistant to oseltamivir (Tamiflu). | Aqueous extract | Lee, S., et al. (2013); Власенко, В. А., et *al.* (2012) |
| *Phellinus pini* (Thore. Ex Fr.) Pilát. | Antiviral (SARS-CoV-2) | Aromatic sesquiterpenoides of fruiting body | Li, X., et *al.*, (2021) |
| | Antiviral effect against herpes simplex virus 1 (HSV-1). | Polysacccharides of aqueous extract of hot water (variants of β-1,3-glucan) | Lee, S.M., et *al.*, (2010) |
| *Schizophyllum commune* Fr. | Hepatitis B | Polysaccharide sizophyran (SPG) | Kakumu, S., *et al.* (1991) |
| *Sparassis crispa* (Wulfen) Fr. | Inhibits the synthesis of the HIV virus | Fungal extract | Wang, J. et al. (2007) |

## 4. DISCUSSION

Antiviral properties of basidiomycetes from the territory of the Altai Mountains have been researched by Teplyakova, P. T., *et. al.* (2012). Properties of several fungi were examined and among them also *Daedaleopsis confragose,* to viruses H5N1 (subtype of the virus influenza A, causative agent of bird flu) H3N2 (subtype of the virus influenza A). Aqueous extracts of mycelia of these fungi contain proteins, polysaccharides and terpenoids which prevent replication of viruses in cells.

In their research, Krupodorova, T., *et. al.,* (2014) have examined *in vitro* antiviral activity of mycelia of 10 fungi against the type A influenza virus. (serotype H1N1) and the herpes simplex virus type 2 (HSV-2), strain BH. All the examined species of fungi have inhibited reproduction of the influenza virus H1N1. Four species, *Pleurotus ostreatus, Fomes fomentarius, Auriporia aurea* and *Trametes versicolor* have shown efficiency against virus HSV-2, strain BH, with levels of inhibition similar as for influenza virus type A.

*G. lucidum* is efficient against viral diseases by strengthening immunity of an organism and preventing reproduction of viruses. Therefore, it is very effective in viral diseases, such as herpes, herpes zoster (viral diseases caused by chickenpox in childhood, that affect skin and nerve endings), viral hepatitis A, B and C and HIV. In case of HIV, it was shown that triterpenes isolated from fruiting bodies and spores (ganoderic acid beta, lucidumol B, ganodermanondiol, ganodermanontriol, and ganolucidic acid A) inhibit HIV-1 protease (M i n, B.S., *et. al.* 1998).

The results of the research of Gu, C.Q., Li, J., Chao, F.H. (2006), indicate that D-fraction of polysaccharides extracted from *G. frondosa,* in combination with human interferon alpha-2b (IFN), increases nine times the antiviral activity of interferon, so they can be used for efficient therapy against chronical infections of the hepatitis B virus.

According to Halpern, G. M. (2007) active ingredients of *G. frondosa* are β-glucans fractions D and MD and grifon-D. *G. frondosa* helps in control of diabetes, weight loss, control of high blood pressure, it is efficient against HIV virus, as well as in treatment of prostate and bladder cancer.

*I. obliquus* (chaga) has anti-inflammatory, anti-tumour, antiviral and immunomodulatory effects. On the basis of this fungus for anti-tumour and immunomodulatory effect commercial preparations have been produced (Melkumov, G. M., Zolotorubova, A. S. 2017).

Extracts of mycelia of the fungus *L. sulphureus* are efficient against variants of herpes simplex virus type 1 (HSV-1) which showed resistance to inhibitors acyclovir and phosphonoacetic acid (Kvacheva, Z.B., *et al.* 2005).

Murphy, E., *et. al.,* (2020), have researched immunomodulatory and cytoprotective properties of lentinan from the fruiting body of the fungus *L. edodes* and lentinan from commercial preparation (Carbosynth-Lentinan). The commercial preparation has contained larger quantities of α-glucan and smaller quantities of β-glucan. Both extracts have decreased the activation of NF-κB transcription factor caused by cytokine in alveolar epithelium of cell line of human lung adenocarcinoma A549. The extract from the fruiting body showed greater efficiency in smaller doses.

In contrast, in macrophages activated by THP-1 cells (cells of acute monocytic leukaemia), the extract of commercial preparation decreased more efficiently the production of proinflammatory cytokines (tumour necrosis factor alpha (TNF-α), interleukin-8, interleukin-2, interleukin-6, interleukin-22) as well as transforming growth factor beta (TGF-β) and interleukin-10.

The commercial extract has weakened early apoptosis (death) of cells caused by oxidative stress, while the "natural" extract weakened late apoptosis.

The obtained results show significant physical-chemical differences between these two lentinan extracts, which cause different *in vitro* immunomodulatory and lung cytoprotective effects which can have positive effect for COVID-19 patients with cytokine storm. COVID-19 causes inflammatory or cytokine storm in lungs with excessive and uncontrolled release of proinflammatory cytokines. Therefore, to reduce the mortality rate of the patients, it is very important to block the cytokine storm and start anti-inflammatory therapy quickly.

By studying optimal conditions for ultrasound-assisted extraction of polysaccharides of *L. edodes*, Zhaoa, Y.M., *et. al.*, (2018) have determined that the amount of extracted polysaccharides is the largest when the temperature of extraction is 45°C, the time of extraction 21 minute and ultrasound power is 290 W. Under these optimal conditions the experimental yield of polysaccharides of *L. edodes* has been 9.75%, which represents the increase of 1.62 times compared to the conventional method in the hot water. In the further procedure, crude polysaccharides have been purified to obtain two polysaccharide fractions (LEP-1 and LEP-2). The chemical analysis showed that these two fractions are rich in glucose, arabinose and mannose. The continuation of the research showed that both polysaccharide fractions *in vitro* have strong antiviral activity against the hepatitis B virus. LEP-2 showed a stronger inhibitory activity than LEP-1. The results suggested that the polysaccharides with relatively high molecular mass have stronger inhibitory activity than the ones with lower molecular mass.

According to Bisen, P.S., *et. al.*, (2010) *L. edodes is* used in medicine for treatment of diseases which include weakened immunological function (including AIDS), cancer, fungal infections, bronchitis, heart diseases, hyperlipidaemia (including high blood cholesterol), hypertension, infectious diseases, diabetes, hepatitis and the regulation of urinary incontinence (involuntary flow of urine). The most significant substances that have pharmacological properties are lentinan, eritadenine, mycelium of shiitake and extracts from fungi culture.

Reverse transcriptase is DNA polymerase enzyme which transcribes single-stranded RNA into single-stranded DNA. Transcription is the conversion of genetic information from DNA form into RNA. In their research, Xu, L., *et al.* (2012) from mycelium of culture of the fungus *L. tigrinus* have isolated the enzyme laccase which in concentration $IC_{50}$ = 2.4 μM has an inhibitory effect on the reverse transcriptase of the virus HIV-1 (human immunodeficiency virus), preventing the normal replication of this virus. Laccase has inhibited reverse transcriptase of the virus HIV-1 in the range from 27.7% to 86.3%, depending on the concentrations of laccase (1.5 μM to 15 μM). The maximum laccase activity has been observed at a pH of 4, at a temperature of 60°C. The mechanism of the inhibitory reaction is most probably the protein-protein interaction.

In their research, Teplyakova, T. V. et. al., (2012) state that aqueous solution of mycelia of 11 species of fungi shows antiviral activity on influenza viruses (bird flu H5N1) and H3N2. Against the H5N1 virus, *Datronia mollis, Laricifomes officinalis, Trametes gibbosa* and *L. betulina* have shown the greatest effect. Against the H3N2 virus all the researched species have shown antiviral activity and *Daedaleopsis confragosa* and *Ischnoderma benzoinum* have had the greatest effect.

Lee, S., et al. (2013) researched the effect of aqueous extract of *P. igniarius* on viruses. They have determined that the aqueous extract is efficient against influenza viruses A and B, including the pandemic virus H9N2 from 2009, human virus H3N2, bird virus H9N2 and viruses H1N1 resistant to oseltamivir (Tamiflu). Virologic tests have discovered that the extract can interfere with one or more stages in the influenza virus replication cycle, including binding of the virus to the target cell.

In their research, Vlasenko, V. A., et *al*. (2012) have determined antiviral properties of aqueous extract of the fungi *Phellinus igniarius* and *Phellinus conchatus*. *P. igniarius* can be used for treatment of humans infected by viruses H5N1 and H3N2. These authors state also *P. hartigii, P. laevigatus, P. laricis, P. lundellii, P. punctatus* and *P. tremulae* as the species that have various biological activities.

The COVID-19 epidemic caused by the SARS-CoV-2 virus has led to a large amount of research to develop effective inhibitors to block the interaction of SARS-CoV-2 virus spikes and angiotensin-converting enzyme (ACE2) on the human cell membrane. In this way, the entry of the virus into a cell is obstructed or blocked. Five aromatic cadinane sesquiterpenoids have been isolated by chemical analysis of fruiting bodies of *P. pini*, four of which are new, named piniterpenoids (A, B, C and D), as well as three known lignans. All the aromatic cadinane sesquiterpenoids inhibited the interaction of SARS-CoV-2 spikes and ACE2, with the values of $IC_{50}$ in the range from 64.5 to 99.1 μM. These results have shown that aromatic sesquiterpenoids of *P. pini* can be useful in the development of agents for supressing the virus SARS-CoV-2 (L i, X., et *al*., 2021).

Out of the aqueous extract (hot water) of *P. pini* Lee, S.M., et *al*. (2010) have isolated the compounds EP-AV1 and EP-AV2. They have determined that those are polysaccharides which consist of glucose as the main sugar residue, as well as other secondary sugars such as galactose, xylose, and mannose. They represent the variants of β-1,3-glucan, with high molecular masses. In addition, these polymers contain up to 10% of phenolic compounds. In further research, these polysaccharides have shown antiviral activity against herpes simplex virus 1 (HSV-1).

According to Kakumu *et al.* (1991), patients suffering from hepatitis B virus can use polysaccharide sizophyran (SPG), since it enhances immune response of the organism to the virus, increasing especially the production of interferon gamma (IFN-γ).

Reverse transcriptase is one of the main enzymes in replication of human immunodeficiency virus (HIV virus). The compound obtained by extraction of fruiting bodies of 16 species of fungi in hot water inhibits reverse transcriptases and in this way stops replication of the HIV virus. Extracts of *Lactarius camphoratus, Trametes suaveolens, Sparassis crispa, Pleurotus sajor-caju, Pleurotus pulmonarius* and *Russula paludosa* show inhibition over 50% in the concentration of 1mg/mL.

The greatest inhibitory activity (97.6%) has been shown by extract of *R. paludosa*. Extract of *S. crispa* has shown inhibition of 70.3% in the concentration of 1 mg/mL, but it has not been determined which component of the extract causes it. (Wang, J., *et al.*, 2007).

## 5. CONCLUSION

Based on the obtained results we concluded the following:

- Numerous lignicolous fungi have some antiviral properties;
- Compounds with antiviral properties are most frequently isolated from aqueous extract of mycelia or fruiting body;
- Polysaccharides of fungi (D-fraction of polysaccharides, lentinan, eritadenine, various variants of β-1,3-glucan and sizophyran), aromatic sesquiterpenoides (piniterpenoides A, B, C and D) and triterpenes (ganoderic acid beta, lucidumol B, ganodermanondiol, ganodermanontriol, and ganolucidic acid A) have antiviral properties;
- The researched fungi have shown effect against the following viruses: influenza virus A, (subtypes H5N1, H3N2, H9N2 and H1N1), influenza virus B, herpes simplex virus (HSV-1 and HSV-2), herpes zoster virus, virus causing hepatitis A, B and C and HIV virus;
- Fungi *L. edodes* and *P. pini* can be used in fight against the epidemic of COVID-19 acting in different ways. Lentinan blocks cytokine storm in patients, while aromatic sesquiterpenoids *P. pini* obstruct or block entry of virus into a cell;
- For a more significant application of fungi in treatment of viral diseases a better knowledge of the mechanism of action of antiviral compounds as well as significantly larger number of laboratory and clinical tests are necessary. For now, fungi can be used as auxiliary remedy for treatment of viral diseases.

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## REFERENCES

Bisen, P.S., Baghel, R.K., Sanodiya, G.S., Thakur, B.S., Prasad, G.B.K.S. (2010): *Lentinus edodes*: A Macrofungus with Pharmacological Activities. Current Medicinal Chemistry, Vol. 17, No 22, (2430-2419).

Бондарцев, А.С. (1953*):* Трутовые грибы евроиейской части СССР и Кавказа. Издательство АН СССР, (str. 1-1106).

Booth, C. (1971): Methods in Microbiology, Volume 4. Academic Press- London and New York, ( 1-795).

Breitenbach, J., Kränzlin, F. (1986): Champignons de Suisse. Tome 2. Champignons sans lames. Edition Mycologia, CH-6000 Lucern 9, (p. 1-310).

Gu, C.Q., Li, J., Chao, F.H. (2006): Inhibition of hepatitis B virus by D-fraction from *Grifola frondosa*: synergistic effect of combination with interferon-alpha in HepG2 2.2.15. Antiviral Research. Vol.72, No. 2, p. 162-165.

Hagara, L. (2014): Ottova Encyklopedie HUB. Vydalo Ottovo Nakladatelstvi, Praha, (p. 1-1152).

Halpern, G. M. (2007): Healing Mushrooms. Square One Publishers, United States of America, 1-182.

Kakumu, S., Ishikawa, T., Wakita, T., Yoshioka, K., Ito, Y., Shinagawa, T. (1991): Effect of sizofiran, a polysaccharide, on interferon gamma, antibody production and lymphocyte proliferation specific for hepatitis B virus antigen in patients with chronic hepatitis B. International Journal of Immunopharmacology, Vol.13, Issue 7, p. 969–975

Karadžić, D., Radulović, Z., Milenković, I. (2022): Neke česte lignikolne gljive u šumama Srbije i njihova lekovita svojstva. Izdavač Univerzitet u Beogradu Šumarski fakultet, (1-282). [Karadžić, D., Radulović, Z., Milenković, I. (2022): Some common lignicolous mushrooms in the forests of Serbia and their medicinal properties. Publisher University of Belgrade Faculty of Forestry (1-282).]

Karadžić, D., Anđelić, M. (2002): Najčešće gljive prouzrokovači truleži drveta u šumamma i šumskim stovarištima. Centar za zaštitu i unapređenje šuma Crne Gore-Podgorica, (str.1-154).[ Karadžić, D., Anđelić, M. (2002): The most common fungi causing wood rot in forests and timber yards. Centre for protection and improvement of forests of Montenegro – Podgorica, pp. 1-154.]

Krupodorova, T., Rybalko, S., Barshteyn, V. (2014): Antiviral activity of basidiomycete mycelia against influenza type A (serotype H1N1) and herpes simplex virus type 2 in cell culture. Virologica Sinica, Vol. 29, No 5, (p. 284-290).

Квачева, З.Б., Капич, А.Н., Вотяков, В.И., Николаева, С.Н. (2005): Противовирусная активность экстрактов мицелия базидиального гриба *Laetiporus sulphureus*. Успехи медицинской микологии, Том 5, (271-273).

Lee, S.M., Kim, S.M., Lee, Y.H., Kim, W.J., Park, J.K., Park, Y.I., Jang, W. J., Shin, J.D., Synytsya, A. (2010):. Macromolecules isolated from *Phellinus pini* fruiting body: Chemical characterization and antiviral activity. *Macromolecular Research.* Vol. 18, Iss. 6, p. 602–609.

Lee, S., Kim, J.I., Heo, J., Lee, I., Park , S., Hwang, M.W., Bae, J.Y., Park, M.S., Park, H.J., Park, M.S. (2013): The anti-influenza virus effect of *Phellinus igniarius* extract. Journal of Microbiology. Vol.51, No 5, p.676-681

Li, X., Gao, J., Li, M., Cui, H., Jiang, W., Tu, Z. C., Yuan, T. (2021): Aromatic Cadinane Sesquiterpenoids from the Fruiting Bodies of *Phellinus pini* Block SARS-CoV-2 Spike-ACE2 Interaction. Journal of natural products, Vol.84, No 8, p.2385–2389.

Lindequist, U., Niedermeyer, T.H.J., Jülich, W.-D. (2005): The pharmacological potential of mushrooms. Evidence-Based Complementary and Alternative Medicine, *Volume 2,* Issue *3*, p. *285-299.*

Мелькумов, Г. М., Золототрубова, А. С. (2016): Видовой состав и фармацевтические особенности базидиальных базидиальных макромицетов (Basidiomycota) Рамонского района Воронежской области. Вестник ВГУ, Серия Химия, Биология, Фармация, No 2, стр. 68-72.

Min, B. S., Nakamura, N., Miyashiro, H., Bae, K. H., Hattori, M. (1998): Triterpenes from the spores of *Ganoderma lucidum* and their inhibitory activity against HIV-1 protease. Chemical and Pharmaceutical Bulletin, Vol. 46, p. 1607-1612.

Murphy, E., Masterson , C., Rezoagli, E., O'Toole, D., Major, I., Stack, G., Lynch, M., Laffey, J., Rowan, N. (2020): β-Glucan extracts from the same edible shiitake mushroom *Lentinus edodes* produce differential in-vitro immunomodulatory and pulmonary cytoprotective effects— Implications for coronavirus disease (COVID-19) immunotherapies. Science of the Total Environment, Vol. 732, p.1-10.

Teplyakova, T. V., Psurtseva, N. V., Kosogova, T. A., Mazurkova, N. A., Khanin, V. A., Vlasenko, V. A. (2012): Antiviral activity of polyporoid mushrooms (higher Basidiomycetes) from Altai Mountains (Russia). International Journal of Medicinal Mushrooms, Vol.14, No 1, p. 37-45.

Власенко, В.А., Теплякова, Т.В., Мазуркова, Н.А., Косогова, Т.А., Бердашева, А.В., Псурцева, Н.В. (2012): Изучение противовирусной активно- сти лекарственных грибов рода *Phellinus* s.l. в Западной Сибири. Вестник Алтайского государственного аграрного университета № 4 (90), 29-31.

Xu, L., Wang, H., Ng,T. (2012): A laccase with HIV-1 reverse transcriptase inhibitory activity from the broth of mycelial culture of the mushroom *Lentinus tigrinus*. Journal of biomedicine & biotechnology, Vol.1, Article ID 536725, 7 p.

Wang, J., Wang, H.X., Ng, T. B. (2007): A peptide with HIV-1 reverse transcriptase inhibitory activity from the medicinal mushroom Russula paludosa. Peptides, Vol. 28, No. 3, p. 560–565

Zhaoa, Y.M., Yanga, J.-M., Liu, Y.-H., Zhao, M., Wang, J. (2018):Ultrasound assisted extraction of polysaccharides from *Lentinus edodes* and its anti-hepatitis B activity in vitro. International Journal of Biological Macromolecules, Vol. 107, Part. B, 2217-2223.

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### Summary

Viruses cause great epidemics on all continents, which leads to severe symptoms and mortality in humans and enormous treatment costs. In addition, the constant emergence of new strains represents an additional challenge in the fight against viruses. Thanks to the content of immunomodulatory polysaccharides, proteins, polysaccharide-protein complexes, polyphenols, steroids, triterpenoids, fatty acids, nucleotides, pigments, and polyacetylene components, fungi started to be used for obtaining antibiotics and other medicines. The antiviral properties of fungi and the possibility of their application in the treatment of various human diseases caused by viruses have been discovered lately. The studies showed that polysaccharides of fungi (D-fraction of polysaccharides lentinan, eritadenine, various variants of β-1,3-glucan and sizophyran), aromatic sesquiterpenoides (piniterpenoides A, B, C and D) and triterpenes (ganoderic acid beta, lucidumol B, ganodermanondiol, ganodermanontriol, and ganolucidic acid A) have antiviral properties. The researched fungi showed effect against the following viruses: influenza virus A (subtypes H5N1, H3N2, H9N2 and H1N1), influenza virus B, herpes simplex virus (HSV-1 and HSV-2 ), herpes zoster virus, virus causing hepatitis A, B and C and HIV virus. Fungi *L. edodes* and *P. pini* can be used in the fight against COVID-19 epidemic having effect in different ways. Lentinan blocks cytokine storm in patients while aromatic sesquiterpenoids of *P. pini* obstruct or block entry of viruses into a cell. For more significant application of fungi in treatment of viral diseases better knowledge of the mechanism of action of antiviral compounds is necessary as well as significantly larger number of laboratory and clinical tests. For now, fungi can be used as auxiliary remedy for treatment of viral diseases.

## ANTIVIRUSNA SVOJSTVA LIGNIKOLNIH GLJIVA

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### Rezime

Virusi izazivaju velike epidemije na svim kontinentima, što dovodi do teških simptoma i smrtnosti kod ljudi, i ogromnih troškova lečenja. Pored toga, stalna pojava novih sojeva predstavlja dodatni izazov u borbi protiv virusa. Zahvaljujući sadržaju imunomodulirajućih polisaharida, proteina, polisaharidno-proteinskih kompleksa, polifenola, steroida, triterpenoida, masnih kiselina, nukleotida, pigmenta i poliacetilenskih komponenti, gljive su počele da se koriste za dobijanje antibiotika i drugih lekova. U poslednje vreme su otkrivena antivirusna svojstva gljiva i mogućnost njihove primene u lečenju raznih bolesti čoveka izazvanih virusima. Istraživanja su pokazala da antivirusna svojstva imaju polisaharidi gljiva (D -frakcija polisaharida, lentinan, eritadenin, različite varijante β-1,3-glukana i sizofiran), aromatični seskviterpenoidi (piniterpenoidi A, B, C i D), i triterpeni (beta ganoderinska kiselina, lucidumol B, ganodermanondiol, ganodermanontriol i ganolucidna kiselina A). Proučavane gljive su pokazale dejstvo protiv sledećih virusa: virus gripa A (podtipovi H5N1, H3N2, H9N2 i H1N1), virus gripa B, herpes simpleks virusa (HSV-1 i HSV-2), herpes zoster virusa, virusa izazivača hepatitisa A, B i C i HIV virusa. Gljive *L. edodes* i *P. pini* mogu se koristiti u borbi protiv epidemije COVID-19 delujući na

različite načine. Lentinan kod pacijenata blokira citokinsku oliju dok aromatični seskviterpenoidi *P. pini* ometaju ili blokiraju ulazak virusa u ćeliju. Za značajniju primenu gljiva u lečenju virusnih bolesti neophodno je bolje poznavanje mehanizma delovanja antivirusnih jedinjenja kao i znatno veći broj laboratorijskih i kliničkih testiranja. Za sada se gljive mogu koristiti kao pomoćno sredstvo za lečenje virusnih bolesti.