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Current state of scientific research and prospects for using basidiomycetes in veterinary medicine: A literature review

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Abstract. The relevance of the study is conditioned upon the need to summarise current data on the pharmacological properties of *Basidiomycota* and to provide scientific justification for their use in veterinary medicine. The purpose of the research was to analyse the results of recent experimental studies on the pharmacological and toxicological properties of basidiomycetes and the possibilities of their use in veterinary medicine. The research uses theoretical methods of analysis and comparison of literature data with the development of substantiated conclusions and recommendations for the future. Basidiomycetes belong to the higher fungi, their vegetative body is represented by a branched cellular mycelium. They are a healthy food and rich in biologically active substances. Analysis of the literature demonstrates a high degree of scientific interest in the research of their pharmacological properties. Consequently, scientific research is designed to establish new data on the pharmacodynamics and pharmacokinetics of biologically active substances of basidiomycetes. For example, the mushroom *Inonotus obliquus (I. obliquus)* has been commonly used to treat patients with various gastrointestinal diseases. In recent years, there has been a growing body of scientific evidence indicating the effectiveness of its extracts in treating

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infections and infestations, cancer, and diabetes. It was established that the biologically active substances of *I. obiquus* stimulate the immune system, show hypoglycaemic potential, are sensitive to insulin, and have an antioxidant effect. In the current scientific discourse, researchers are trying to identify the molecular mechanism of action of *I. obliquus* extracts. The presented review of the literature demonstrates that basidiomycetes exhibit pharmacological properties in cancer and neurodegenerative diseases, diseases of the digestive, respiratory and cardiovascular systems, metabolic disorders, antimicrobial, antiviral, immunomodulatory effects, etc. Currently, using basidiomycetes in the world, considering their scientifically proven and experimentally proven pharmacological properties, is extremely promising. The material of the research is of practical value for expanding the possibilities of using fungotherapy in veterinary medicine

Keywords: fungi; prevention; diseases; fungotherapy; biologically active substances; molecular mechanisms

Introduction

With the continuous development of veterinary medicine, new ways of preventing diseases and treating sick animals are emerging. Along with the expansion of the pharmaceutical market for synthetic medicines, the number of new veterinary medicines of natural origin is growing. Since the first use of penicillin in medical practice, which was obtained from the mouldy fungi of the genus *Penicillium*, fungus-based medicines have remained relevant. The results of modern scientific research indicate their new pharmacological properties (Alvandi *et al.,* 2020; Lu *et al.,* 2021). It is a prerequisite for expanding the possibilities of their use in modern veterinary medicine.

A distinct class of fungi that have not previously received sufficient attention from scientists, physicians and veterinarians is the *Basidiomycota*. They belong to the division of higher fungi and have a vegetative body represented by a branched cellular mycelium. The evolutionary development of basidiomycetes occurred in parallel with the evolution of ascomycetes, or marsupial fungi. Nowadays, this division of fungi is the second largest after the Ascomycota in terms of the number of species; it includes about thirty thousand species belonging to almost all ecological groups of fungi, including saprotrophs on various substrates, parasites of higher plants, mycorrhizal mycorrhizae, wood-destroying fungi, coprotrophs, mycotrophs, etc. It is well known that many species of basidiomycetes are poisonous or edible fungi, but some of them have pharmacological properties (Doğan *et al.,* 2020; Lu *et al.,* 2021).

Currently, chemotherapy, which has many disadvantages, is being replaced by new methods that have a direct effect on tumour cells (Xiong *et al.,* 2016; Bian *et al.,* 2022; Chis *et al.,* 2022). Therefore, therapies based on biopolymer systems are an alternative. In addition, current trends are focused on natural sources, which are considered biocompatible, biodegradable, valuable and renewable sources (Alvandi *et al.,* 2020; Zhao & Zheng, 2021). Chis *et al.* (2022) analyse recent studies focusing on polymer-drug conjugates containing natural polymers such as chitosan, hyaluronic acid, dextran, pullulan, silk fibroin, heparin and polysaccharides from *Auricularia auricula (A. auricula)*.

In recent years, a large number of studies have been conducted to establish their pharmacological effects as antibiotics, antiviral or antitumour agents, etc. (Fig. 1)

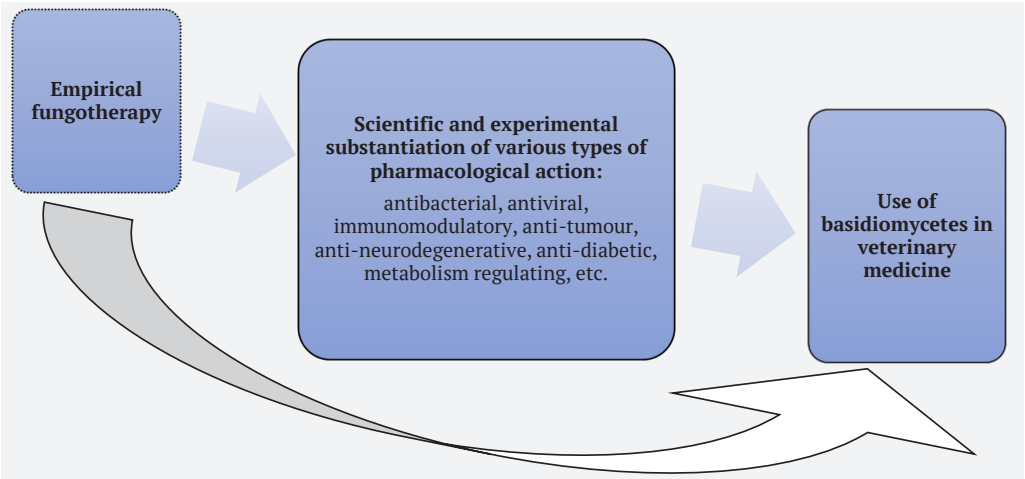

Figure 1. Prerequisites for using basidiomycetes in modern veterinary medicine
Source: *compiled by the authors based on the analysis of literature*

The purpose of the research was to analyse the literature data on the results of modern scientific studies of the pharmacological properties of basidiomycetes and promising areas of their use in veterinary medicine.

Efficiency of basidiomycetes in cancer treatment

Historical chronicles describe the treatment of Prince Volodymyr Monomakh of Kyiv with the mushroom *Inonotus obliquus* (*I. obliquus*) for a tumour on his lip. It has now been established that chemically diverse bioactive metabolites provide *I. obliquus* with great potential for inhibiting tumour growth and metastasis. Thus, Zhao & Zheng (2021) proved that *I. obliquus* has the potential to reduce the incidence of tumour development in healthy people. For people whose complete remission has been achieved by chemotherapy, the administration of the fungus inhibits the activation of advanced oncogenic signals, preventing metastases. After chemotherapy, fungus supplementation sensitises tumour cells, enhancing chemotherapeutic effects and helping to restore weakened immunity and protect against gastrointestinal ulcers and other side effects caused by chemotherapy.

A. auricula – a fungus of the Auriculariaceae family, which is common in Eurasia. It contains biologically active substances such as polysaccharides, melanin, flavonoids, adenosine, sterols, alkaloids, and terpenes. Liu *et al*. (2021) explored the properties of lectins (AAL) isolated by affinity chromatography from *A. auricula*. Their protein identification results, according to the UniProt database, demonstrated that the lectin contains four peptide chains, and the analysis of its physical and chemical properties showed that AAL is sensitive to changes in temperature and pH. The antitumour activity assay demonstrated that AAL inhibited the proliferation of A549, with an IC50 value of 28.19±1.92 μg/mL. Due to RNA sequencing and analysis of the TCGA dataset, it was identified that AALs can regulate the expression of JUN, TLR4 and MYD88 to suppress tumour proliferation. Thus, the lectin protein isolated from the basidiomycete *A. auricula-judae* regulates the expression of some cancer-related genes and has anti-tumour properties. Therewith, researchers predict its successful use to influence the lung microflora.

A conjugated complex of folic acid (FA) with the Auricularia auricular polysaccharide (AAP) – cis-diamidine dichloroplatin (CDDP) (FA-AAP-CDDP) was used for the treatment of cervical carcinoma (Qiu *et al.*, 2018). With this combination, the researchers could increase the anti-tumour effect of CDDP and reduce the toxic side effects of CDDP. The kidneys of mice treated with the FA-AAP-CDDP complex had increased superoxide dismutase, catalase and glutathione peroxidase activity and lower levels of malondialdehyde. The FA-AAP-CDDP complex has the ability to induce more interleukin-2, interleukin-4 and interferon-γ in mice. In addition, the FA-AAP-CDDP complex significantly promoted the expression of Bax and caspase-3 proteins but inhibited the expression of Bcl-2 protein, which activated the mitochondrial apoptotic pathway of tumour cells in laboratory mice. These results provide a new area for the research of polymers targeting folic acid receptors to increase the antitumour activity but reduce the side effects of CDDP.

Qiu *et al.* (2018) explored the anti-tumour activity of *Calvatia gigantea (C. gigantea)* extract, which belongs to the Lycoperdaceae family. Changes in CCND1, CCND2, CDK4, p21, Akt, Bax, Bcl-2, p53, caspase-3 and caspase-9 were assessed in A549 lung cancer cells using CTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide). The results obtained on A549 cells treated with *C. gigantea* extract at a dose of 500 μg/mL for 72 h presented that the expression of CCND1, CCND2, CDK4, Akt and Bcl-2 decreased, while the expression of Bax, p53, caspase-3 and caspase-9 increased. However, no changes in p21 expression were observed. The examined *C. gigantea* extract induced cell cycle arrest and apoptosis by decreasing the expression of CCND1, CCND2, CDK4, Akt and Bcl-2 and increasing the expression of Bax, p53, caspase-3 and caspase-9 in A549 cells. Eroğlu *et al.* (2016) believe that *C. gigantea* extract can be an effective treatment for lung cancer patients and can be used both alone and in combination with other drugs.

It is well known that the edible tinder fungus *Fomes fomentarius* (*F. fomentarius*) has anti-cancer, anti-inflammatory and anti-diabetic effects. Lee *et al.* (2019) explored its effectiveness in cancer treatment. To determine the molecular mechanism of the anticancer effects of *F. fomentarius*, the researchers used various methods, including activated fluorescence cell sorting, Western blot, migration and crystal violet analysis. Ethanolic extract of *F. fomentarius* ethanolic extract (FFE) decreased cell viability in six cancer cell lines (MDA-MB-231, MCF-7, A549, H460, DU145 and PC-3). FFE reduced the migration of MDA-MB-231 cells without causing cellular toxicity. In addition, FFE attenuated the expression of matrix metalloproteinase-9 and Akt phosphorylation and enhanced E-cadherin in MDA-MB-231 cells. FFE arrested S and G2/M populations by inhibiting the expression of cell cycle regulatory proteins such as cyclin-dependent kinase 2, cyclin A/E and S-phase kinase-associated protein 2. FFE increased the sub-G1 population and the expression of cleaved caspase-9, -3 and cleaved polyadenosine diphosphate (ADP-ribose) polymerase after 72 h and suppressed B-cell lymphoma 2. FFE and AKT inhibitors caused similar effects in MDA-MB-231 cells. In addition, FFE contained betulin, which inhibited p-AKT in MDA-MB-231 cells. The results obtained by the authors showed that FFE inhibits cell motility and growth and induces apoptosis by inhibiting the phosphoinositide 3-kinase/AKT pathway and activating caspase.

Alvandi *et al.* (2020) established that the antiproliferative effect of fungal polysaccharides on cancer cells depends on the type of cancer and increases with increasing concentration. The results of initial experiments on biomass and polysaccharide production by *F. fomentarius* demonstrated that after 4 days

of cultivation in the desired culture medium, biomass production reached 15 g/L, and polysaccharide production reached 4.06 g/L. Thus, a culture medium including glucose, peptone, malt extract, yeast extract, MgSO4-7H2O and KH2PO4 is a suitable culture medium for the growth and production of polysaccharides by this fungus. Supplements made from tinder fungus polysaccharides with selenium can be used to inhibit the proliferation of cancer cells.

Rehman *et al.* (2020) proposed an alternative method for the synthesis of nanoparticles (NPs). In particular, titanium oxide nanoparticles and silver nanoparticles (TiO_2 and Ag nanoparticles, respectively) were obtained by mixing the intracellular extract of a wild fungus, *F. fomentarius* – with aqueous solutions of titanium isopropoxide and silver nitrate, respectively. Success was achieved in obtaining NFs of various shapes and forms and their antibacterial and antitumour activity was established. The researchers argued that NFs synthesised using wild fungi have great potential in biomedicine due to the effective combination of enzymes that allows them to modify various chemical compounds into less toxic forms, which is essential for environmentally friendly and safe biomaterials for drug synthesis. To evaluate the antitumour activity and study drug resistance, Doğan *et al.* (2020) prepared aqueous, methanolic and ethanolic extracts of *F. fomentarius* and *Tricholoma anatolicum (T. anatolicum)*. It was established that the methanolic extract of *F. fomentarius* and ethanolic extract of *T. anatolicum* have potential value in the development of drugs for the treatment of breast cancer patients and can be used as a natural multidrug resistance modulator (MDR modulator).

The Chaga mushroom – *Inonotus obliquus* (*I. obliquus)* – is known as a foodstuff and is used for medicinal purposes, especially in China, Korea and some Western countries. Among the *I. obliquus* extracts, *Inonotus obliquus* polysaccharide (IOPS) is considered to be one of the main bioactive components of *I. obliquus*, which has antitumour, antioxidant, antiviral, hypoglycaemic and hypolipidaemic effects. The review by Lu *et al*. (2021) summarised the current advances in the extraction, purification, structural characteristics and biological activity of IOPS, which provides significant insight into the biological activity of IOPS as it summarised *in vitro* and *in vivo* data and listed some possible mechanisms. In addition, the potential applications of IOPS were analysed and it was found that IOPS could be a potential drug for the treatment of cancer and type 2 diabetes.

Inonotus obliquus is a parasitic fungus that grows on birch trees and is used in traditional medicine (especially by the Khanty) for therapeutic purposes for various pathologies. The purpose of the research conducted by Géry *et al.* (2018) was to quantify 3 metabolites often described in the literature, namely betulin, betulinic acid and inotodiol in chaga found in the forests of Normandy (France) and compare their concentrations with Ukrainian and Canadian Chaga. The cytotoxicity of French chaga against cancer cells and transformed cells was explored. It was established that French chaga contains more betulin and betulinic acid than chaga from other localities, while the concentration of inotodiol was higher in Canadian Chaga. In addition, the results highlighted the cytotoxic activity of the aqueous Chaga extract after 48 and 72 h of exposure, with a higher effect on A549 cancer cells than on normal transformed BEAS-2B cells (P=0.025 after 48 h of exposure and P=0.004 after 72 h of exposure).

Efficiency of basidiomycetes for metabolic disorders

Obesity

Obese animals develop metabolic changes that can cause significant adverse effects at various levels in their bodies.

Researchers Liu *et al.* (2022) explored the effect of polysaccharides derived from the mushroom Auricularia auricula-judae on dietary obesity in C57BL/6J mice induced by high-fat, high-fructose diets (HFFD). The results demonstrated that dietary supplementation with Auricularia auricula-judae polysaccharides (AAP) significantly improved the insulin resistance of mice, altered serum lipid metabolites and delayed the weight gain induced by HFFD. In addition, AAP supplementation reduced inflammatory factor levels and alleviated changes in liver histomorphology. Therewith, AAP suppressed the expression of genes related to liver adipogen, inhibited the levels of genes responsible for cholesterol synthesis, enhanced the expression of genes related to fatty acid β-oxidation, and promoted the expression of genes affecting cholesterol efflux, which improved the homeostasis of lipid metabolism in the liver of mice. Liu *et al.* (2022) emphasise the importance of mitochondrial functions in this process, and the results obtained by the researchers provide a scientific basis for the further development and utilisation of *Auricularia auricula-judae* resources.

Yu *et al.* (2022) explored the effects of two extracts of *Inonotus obliquus* (*I. obliquus,* chaga, birch black mushroom) on mice induced by a high-fat diet. They were administered an ethanolic extract (IOE) and a polysaccharide (IOP) of *I. obliquus*. The authors established that IOE and IOP effectively corrected the increase in body weight and energy use in the body, affected the metabolism of glucose in the liver and triglyceride metabolism, the tricarboxylic acid cycle, and the metabolism of carbohydrates, lipids and proteins in general. Two extracts containing different bioactive substances of *I. obliquus* reduced obesity in mice due to different effects on the synthesis of microbial metabolites in the intestine.

Diabetes

Type 2 diabetes mellitus is an urgent problem, therefore, scientists are actively developing non-toxic ways to treat animals and humans with this disease. Thus, it has been established that *Auricularia auricula* polysaccharides (AAP) promote recovery from this pathology (Liu *et al.*, 2022).

Liu *et al*. (2022) demonstrated that AAP achieves remission by altering the gut microbiota in mice with type 2 diabetes. As a result, a model of type 2 diabetes mellitus (T2DM) induced by a high-fat diet (HFD) combined with streptozotocin (STZ) was established, and a decrease in fasting blood glucose (FPG) and oral glucose tolerance test (OGTT) was observed after 5 weeks of AAP administration. In addition, AAP enhanced the activity of total superoxide dismutase (T-SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) and reduced malondialdehyde (MDA), which alleviated oxidative stress. The best effect was observed with AAP-M (200 mg/kg/day). Therewith, 16S rRNA results demonstrated that AAP decreased the number of *Firmicutes* and increased the number of *Bacteroidetes*. AAP can reduce the number of *Desulfovibrio*, *Enterorhabdus* and *Helicobacter*. Overall, these results suggest that AAP may improve glucose and lipid metabolic disorders by regulating the gut microbiota structure.

The research by Gery *et al.* (2018) confirms a decrease in fasting glucose and insulin levels and an improvement in insulin resistance in mice.

The identification and authentication of the giant porchavaca fungus using molecular tools was performed and its antidiabetic properties were explored. In an acute *in vivo* test, a dose of 400 mg/kg body weight presented the best activity with a 29.3% reduction in blood glucose levels, while glibenclamide at a dose of 5 mg/kg body weight reduced glucose levels by 15%. The in vitro assay demonstrated that the extract was highly active with an IC50 of 0.46 µg/mL

compared to its DCM, butanol and acarbose fractions (IC50 5.3 μg/mL, 5.6 μg/mL, 45 μg/mL), respectively. Therewith, BLAST analysis demonstrated that the fungus was 98% identical to *Calvatia gigantea*. Thus, Ogbole *et al.* (2019) confirmed its pronounced anti-diabetic effect.

According to Lu *et al.* (2021), a polysaccharide from *Inonotus obliquus* reduces the risk of developing type 2 diabetes by affecting intestinal barrier dysfunction.

Szychowski *et al.* (2021) established two mechanisms of action of *I. obliquus* extracts, which are explained by the effect on antioxidant enzymes and reactive oxygen species levels and by the effects of the peroxisome proliferator-activated receptor gamma (PPARγ). This receptor may be a key factor in the anti-inflammatory, antioxidant and anti-cancer activity of *I. obliquus* extracts. Researchers claim that *I. obliquus* has potentially positive health effects, but there is a need for studies that meet the criteria of evidence-based medicine.

The protective effect of chaga on the kidneys has been confirmed by biochemical data, colour Doppler ultrasound, light and electron microscopy, and histopathological studies (Su *et al.,* 2022). In addition, this effect of Chaga is associated with its effect on slowing the progression of kidney damage. An 8-week administration of chaga demonstrated excellent hypoglycaemic and hypolipidaemic effects in rats with type 2 diabetes mellitus induced by a high-fat diet (Su *et al.*, 2022; Zhang *et al.*, 2022).

The study conducted by Su *et al.* (2022) isolated a single homogeneous polysaccharide from Inonotus obliquus (IN) and explored the protective effect and mechanism of IN on type 2 diabetes mellitus from the intestinal barrier. IN, which was mainly composed of 9 monosaccharides with an Mw of 373 kDa, reduced body weight loss, alleviated pathological damage and suppressed the production of pro-inflammatory cytokines. In addition, IN contributed to the restoration of the intestinal barrier by increasing the expression of Ki-67, ZO-1 and MUC2. The number of *Firmicutes* increased significantly during treatment with IN, while the levels of *Bacteroidetes* were significantly suppressed. The scientists concluded that IN protects against type 2 diabetes by reducing the degree of intestinal barrier dysfunction and can be recommended as a new drug for the treatment of animals and humans with type 2 diabetes.

Diabetic kidney disease (DKD) is currently the leading cause of end-stage renal disease. To explore the therapeutic potential of *Inonotus obliquus* (Chaga) in the treatment of diabetic patients, Zhang *et al.* (2022) used Chaga extract to determine the renal protective effects in a rat model of DKD induced by a high-fat diet and streptozotocin injection. For the 17-week experiment, biological parameters of blood serum and urine were examined, renal arteries were colour Doppler, periodic acid-Schiff staining, and electron microscopy of kidney tissue were performed. The results of biochemical studies demonstrated that, compared to the control group, the DKD model developed insulin resistance, increased levels of glucose and total cholesterol in the blood, and increased urinary protein excretion and serum creatinine levels. Ultrasound examination confirmed the deterioration of blood flow parameters of the left intercalated artery in rat models. It has been established that ultrasound Doppler examination using biochemical parameters has an important role in the assessment of renal damage in rats. Based on the biochemical, ultrasound and histopathological data, the therapeutic effect of Chaga on diabetes-induced renal damage was confirmed, and the above effects may be associated with delaying the progression of DKD.

Antioxidant features

Su & Li (2020) explored the structural characterisation and antioxidant activity of four

Auricularia polysaccharides (*A. cornea*, ACP; *A. auricula*, AAP; *A. polytricha*, APP; M. *fungus*, MFP). The results obtained by the researchers demonstrated that *Auricularia* polysaccharides consisted mainly of mannose and galactose, containing uronic acid and a pyran ring structure. A significant difference was observed in the total antioxidant capacity, in particular, in ARP it was significantly higher than in other polysaccharides. It was found that the ability of ARR to scavenge DPPH and hydroxyl radicals was higher than that of other polysaccharides, respectively. Molecular weight was significantly positively correlated with DPPH radicals, superoxide anion radicals and hydroxyl radicals. Total antioxidant capacity was significantly negatively correlated with fucose and galactose. The results demonstrated that fucose and galactose jointly determine the total antioxidant capacity. The polysaccharide from four auriculars presented resistance to oxidation and is recommended by the authors as a natural antioxidant.

Extracellular polysaccharides of *Fomes fomentarius* have a rather pronounced antioxidant activity (Alvandi *et al.,* 2021). Zhang *et al.* (2020) explored the isolation, cultivation, and purification of extracellular polysaccharides from *Fomes fomentarius*. They optimised the extraction of polysaccharides from the culture based on extracellular polysaccharides of *F. fomentarius*, comparative experiments on the fermentation of extracellular polysaccharides were conducted and the optimal fermentation method was obtained; extracellular polysaccharides were sulfated, experiments with phosphorylation, selenium acidification were conducted, the preparation of polysaccharide derivatives was examined, etc. The results obtained by the authors presented that the extracellular polysaccharide and derivatised polysaccharide of *F. fomentarius* have certain antioxidant activity.

Efficiency in diseases of the stomach and intestines

Using the polysaccharide of *A. auricula-judae* to maintain and regulate the composition of the intestinal microbiota is promising. In particular, Liu *et al.* (2022a) found the ability to regulate the structure and composition of the gut microbiota in diabetic mice and increase the number of beneficial bacteria that produce short-chain fatty acids, including Lachnospiraceae, Faecalibaculum, Dubosiella and Alloprevotella, which play a crucial role in maintaining the composition of the gut microbiota.

Liu *et al.* (2022b) explored the effects of polysaccharides extracted from *A. auricula* on the overall metabolism and gut microbiota in healthy C57BL/6J mice. Based on the metabolic results of LC-MS/MS, 51 AAP-regulated metabolites were identified, mainly enriched in the arginine biosynthesis pathway, which had the highest correlation, and the following metabolites: arginine and proline; glycine, serine and threonine; glycerophospholipid, etc. Furthermore, the addition of AAP significantly changed the composition of the gut microbiota in mice. The relative numbers of *Lactobacillus johnsonii, Weissella cibaria, Kosakonia cowanii, Enterococcus faecalis, Bifidobacterium animalis* and *Bacteroides uniformis* increased markedly, while the relative number of Firmicutes M10-2 bacteria decreased. The biological activity of AAP may be related to the regulatory effects of endogenous metabolism and gut microbiota composition.

Oral administration of a polysaccharide from *Hericium erinaceus* can affect the diversity and abundance of the gut microbiota. Changes in the flora lead to changes in the proportion of probiotics and modulation of immune responses Yang *et al*. (2021).

Hericium erinaceus polysaccharides (HEPs) were identified by Yang *et al*. (2021) from the fruiting bodies of *H. erinaceus* (hedgehog

geranium, lion's mane). To explore the effect of HEP on the diversity and abundance of the intestinal microbiota, adult, middle-aged, and elderly mice were fed HEP for 28 days. Based on the results of 16S sequencing of the intestinal microbiota, it was determined that the relative abundance of *Lachnospiraceae* and *Akkermansiaceae* increased significantly, while the relative abundance of *Rikenellaceae* and *Bacteroidaceae* decreased. Bacterial flushes from different segments of the mouse intestine and faeces were collected for *in vitro* fermentation of HEP. It was determined that HEP significantly promoted the production of NO, IL-6, IL-10, INF-γ and TNF-α. Moreover, HEP significantly enhanced the phosphorylation of signalling molecules, indicating that the immunomodulatory activity was completed through the NF-kB, MAPK and PI3K/Akt pathways. The researchers note that HEPs can be used as active ingredients in medicines.

Efficiency in diseases of the cardiovascular system

With the increasing number of cardiovascular diseases, the demand for safe and effective drugs for the treatment and prevention of thrombosis has grown. In a study conducted by Bian *et al.* (2022), the structural characteristics and thrombolytic (fibrinolytic) activity of a new polysaccharide isolated from the fruiting bodies of *A. auricula* were determined. The purified polysaccharide AAP-b2 (12.02 kDa) consisted of mannose, glucuronic acid, glucose and xylose with a molar ratio of 89.25::30.50:4.25:1.00. The thrombolytic (fibrinolytic) activity of AAP-b2 has been proven to be associated with inhibition of platelet activation by regulating endothelial nitric oxide synthases (eNO), endothelin-1 (ET-1), prostacyclin (PGI2) and thromboxane B2 (TXB2), along with enhanced anticoagulant activity by affecting antithrombin III (AT-III) and protein C (PC).

Wang *et al.* (2019) explored the effect of *Coriolus versicolor* (CV) on cardiac function in rats with diabetes mellitus (DM). It was established that the heart function in rats with diabetes mellitus was significantly improved by treatment with CV extract. The administration of CV extract significantly attenuated cardiac fibrosis in diabetic rats, which was accompanied by inhibition of transforming growth factor-beta 1 (TGF-β1)/Smad. It was evidenced by a decrease in the levels of TGF-β1, p-Smad2 and p-Smad3 and an increase in Smad7. In addition, an anti-inflammatory effect was observed after treatment with CV extract. In addition, it is known that cardiac fibrosis develops with high glucose content, but the development of this pathology was inhibited by using CV extract. Thus, the pharmacological effect of CV is associated with the inhibition of TGF-β1/Smad signalling and attenuation of NLRP3 inflammatory activation, which suggests that CV extract may be a potential therapeutic agent for cardiovascular diseases.

Efficiency in neurodegenerative diseases

Abitbol *et al.* (2022) used mushrooms in neurodegenerative diseases. In their studies, mushrooms were identified as a rich and largely untapped source of bioactive compounds in both *in vitro* and *in vivo* models of neurodegenerative diseases, which was partially confirmed by successful clinical trial evaluations. Researchers indicate that mushrooms are effective in the treatment of patients with neurodegenerative diseases.

The results obtained by Bai *et al.* (2019) demonstrated that protea-β-glucan, a polysaccharide derived from *Grifola frondosa* (PGM), can improve learning and reduce memory decline, and in laboratory animals, attenuate neuronal loss and histopathological abnormalities in APP/PS1 mice. In addition, PGM treatment can activate microglia and astrocytes and

promote the interaction of microglia and Aβ plaques. It was established that PGM can enhance Aβ phagocytosis and thus reduce Aβ burden and pathological changes in the cerebral cortex and hippocampus in APP/PS1 mice. PGM had no significant effect on the body weight of mice. In summary, these results demonstrated that PGM administration can reduce memory impairment through its immunomodulatory effect, and dietary supplementation with PGM will have a positive therapeutic effect on memory dysfunction associated with brain ageing.

Earlier, Wei *et al.* (2018) reported ten new polyoxygenated cyanoditerpenoids, neocytins A-J, and their anti-inflammatory effects from the liquid culture of the basidiomycete *Cyathus africanus*. Subsequently, the scientists examined 8 new highly polyoxygenated cyanotannoditerpenoids, named neocyanins K-R, which were isolated from a solid culture of *C. africanus* grown on cooked rice, along with three known congeners. All compounds were evaluated for their neurotrophic and anti-inflammatory activities. The isolates obtained at 1-25 μM caused differential nerve growth factor-induced activity. The researchers claim that these substances can be used to treat patients with neurodegenerative diseases.

Li *et al.* (2020) determined the efficacy and safety of a capsule formulation containing *H. erinaceus mycelia* (EAHE) (350 mg/capsule; 5 mg/g active ingredient erynacin A) in the treatment of patients with mild Alzheimer's disease (AD). Trinacin A enriched with *H. erinaceus* is a safe and well-tolerated supplement that may contribute to neurocognitive benefits. Studies have demonstrated higher scores on cognitive screening, mini-mental state examination and activities of daily living, and higher contrast sensitivity in patients with mild Alzheimer's disease compared to patients in the placebo group.

The research by Cordaro *et al.* (2021) showed the effect of the antioxidant mushroom *Hericium erinaceus* on a laboratory rat model of Alzheimer's disease (AD). The animals were administered 70 mg/kg of $AlCl_3$ daily for 6 weeks, and *Hericium erinaceus* was administered daily through a gavage. A behavioural test was performed before the end of the experiment, behavioural changes were assessed at the end of the experiment and the animals were euthanised. Brain tissue was collected for further analysis. $AlCl_3$ mainly accumulates in the hippocampus, the main brain region involved in memory and learning functions. Using *Hericium erinaceus* reduced behavioural changes and neuronal degeneration in the hippocampus. In addition, it reduced the level of phosphorylated tau protein, aberrant overexpression of ARP and β-amyloid accumulation. *Hericium erinaceus* reduced AD-induced pro-oxidative and pro-inflammatory changes in the hippocampus and decreased the activation of NLRP3 inflammatory components, which are usually activated by increased oxidative stress in AD. Overall, the results obtained by the researchers demonstrated that *Hericium erinaceus* has a protective effect on behavioural changes and histological modifications associated with AD through modulation of oxidative and inflammatory pathways, and regulates brain cellular stress.

The mushrooms *H. erinaceus* and *C. versicolor* and their combination can influence specific molecular mechanisms that link chronic traumatic brain injury and Parkinson's disease. In particular, they act on microglia, reducing inflammation that spreads from the cortex to other parts of the brain. In addition, these compounds act on oxidative stress spreading to the midbrain, thus limiting the development of Parkinson's disease. Research conducted by D'Amico *et al.* (2021) suggests that *Hericium erinaceus* and *Coriolus versicolor* may be important in the mechanisms of redox stress response and neuroprotection, preventing the progression of neurodegenerative diseases.

Li *et al.* (2020) explored the effect of Coriolus versicolor plant polysaccharides (CVP) on neuronal apoptosis in a rat model of cerebral ischaemia-reperfusion injury (CIRI) and examined the mechanisms and efficacy of CVP in the treatment of rats with neuronal apoptosis in CIRI, including infarction, inflammation, etc. It was established that CVP is effective already at 6, 12, 24 and 48 hours, which is manifested by an improvement in the behavioural test, a decrease in the volume of cerebral infarction and inhibition of nerve cell apoptosis in CIRI rats. The expression levels of p-p38MAPK protein and cleaved caspase-3 demonstrated a downward trend after CVP administration. CVP significantly reduced the pathological characteristics of CIRI in rats and inhibited apoptosis of nerve cells around the lesions. The mechanism of its effectiveness is associated with the inhibition of activation of the p38MAPK signalling pathway.

Antimicrobial and antiviral efficiency

There are many reports in the literature on the antimicrobial and antiviral efficiency of basidiomycetes. This issue has been particularly explored by researchers.

Thus, the intracellular extract of the wild mushroom *Fomes fomentarius* mixed with aqueous solutions of titanium isopropoxide and silver nitrate has antibacterial effects (Rehman *et al*., 2020). Tinder fungus polysaccharide inhibits the growth of *S. aureus* and *E. coli* by 50% and 25%, respectively (Alvandi *et al*., 2020).

Alresly (2019) conducted a study of the biological and chemical potential of two European fungal species: Fomitopsis betulina and Calvatia gigantea. For this purpose, different extracts of both mushrooms were tested for antimicrobial, antifungal, cytotoxic, wound healing and anti-adhesive properties in vitro. Fractionation under bioanalysis control led to the isolation of bioactive compounds, and a total of 20 compounds were isolated and identified. The compounds were obtained from ethyl acetate extracts and included triterpenes, sterols and aromatic compounds. The biological activity of the isolated substances from both fungi was proven, and some of them showed antimicrobial and cytotoxic activity.

The extract from *Inonotus obliquus* has been established to have high antiviral activity, including against COVID-19 (Shahzad *et al*., 2020; Su *et al*., 2022).

There is currently no specific treatment for SARS-CoV-2 infection; however, some drugs have demonstrated clear efficacy in suppressing the viral disease. Natural sources of BARs, such as herbs and fungi, have previously demonstrated pronounced antiviral and anti-inflammatory effects. Shahzad *et al*. (2020) assessed the potential for using natural substances as effective treatments for COVID-19. They suggested that one potential source for SARS-CoV-2 drugs could be Inonotus obliquus (IO), a well-known chaga mushroom commonly found in Asia, Europe and North America and widely used as a raw material for the preparation of dosage forms for various diseases worldwide. Considering this, researchers have been evaluating the most effective herbs and mushrooms with antiviral and anti-inflammatory effects in the laboratory.

Impact on the immune system

Traditional medicine has long been interested in the effect of *Auricularia auricula-judae* on the body's immune system. However, in scientific circles, this issue is understudied.

Ibe *et al.* (2020) evaluated the immunomodulatory effects of the hot water extract (AAAJ) and the β-D-glucan-rich polysaccharide fraction of *A. auricula-judae* (BGPA) on specific and nonspecific humoral and cell-mediated immune responses in immunocompetent and immunosuppressed mice. Oral administration of AAAJ or BGPA (100, 200 or 400 mg/kg) induced

significantly higher titres of total OVA-specific or TT-specific IgG1 and IgG2a compared to their levels in untreated controls. Oral administration of AAAJ or BGPA (100, 200 or 400 mg/kg) caused a significant increase in carbon clearance at all doses, indicating stimulation of the reticuloendothelial system, and enhanced the delayed-type hypersensitivity reaction induced by sheep red blood cells (SRBC) compared to untreated mice. Total lymphocyte and neutrophil counts significantly increased ($P<0.05$) at all doses after administration of AAAJ or BGPA (100, 200 or 400 mg/kg), demonstrating increased protection against cyclophosphamide-induced myelosuppression compared to control (untreated). In the haemolytic complement assay, AAAJ and BGPA at all doses significantly ($P<0.05$) inhibited the haemolytic activity of complement proteins on sensitised SRBC. The results obtained by the researchers demonstrated that the extract is a promising immunomodulatory agent for use in veterinary medicine.

Thus, supplements with *Fomes fomentarius* polysaccharides with added selenium have been established to enhance immune system function due to their antioxidant properties (Alvandi *et al.*, 2021).

It has been reported that proteo-β-glucan, a polysaccharide derived from *Grifola frondosa* (curly grifola, leafy grifola, ram's head mushroom, ram's head, maitake), has a pronounced immunomodulatory effect (Bai *et al.*, 2022).

Impact on the pharmacokinetics of medicinal substances

Food-derived nanoparticles (FNs) may have the potential to deliver micronutrients due to their biocompatibility and health benefits. In the work of Xiaoting *et al.* (2022), hydrophilic FNs with ultra-small sizes of 1.7 nm were prepared from an aqueous extract solution of *A. auricula* by a hydrothermal method. Structural characterisation showed that Zn(II)-FNs were formed after the interaction of many functional groups, such as amino, hydroxyl and carboxyl functional groups on the surface of FNs with Zn^2. Zn(II)-FNs demonstrated better cellular compatibility than $ZnSO_4$ and zinc gluconate, with no apparent cytotoxicity at concentrations up to 75 μg/mL for normal rat kidney cells. A haemolysis rate of less than 5% was detected when the concentration of Zn(II)-FN was 5 mg/mL after incubation for 3 hours. Biodistribution experiments demonstrated that Zn(II)-FN had no obvious toxic effect after oral administration at a dose of 500 mg/kg body weight to mice. In this case, Zn(II)-FNs were present in the stomach, intestines, lungs, liver and kidneys. The results obtained by the researchers indicate that FNs obtained from a solution of the aqueous extract of *A. auricula* can act as a safe and effective Zn(II) nanocarrier.

In the research by Xiong *et al.* (2016), a natural water-soluble polysaccharide, *A. auricular* polysaccharide (AAP), was extracted and purified as a carrier for the hydrophilic drug doxorubicin hydrochloride (Dox-HCl). It involved the preparation of polyelectrolyte complex nanoparticles (PEC NPs) using electrostatic interaction between cationic chitosan (CS) and anionic AAP. The establishment of AAP-CS-NPs was confirmed by FTIR and TEM. The Dox-loaded AAP-CS-NPs were found to have a spherical morphology with an average diameter of 237.6 nm and a Dox-HCl encapsulation efficiency of 74.1%. The stability of Dox AAP-CS-NPs was tested by suspending the nanoparticles in PBS (pH 7.4) at room temperature. The particle size of the nanoparticle samples remained stable and presented no obvious changes in drug content after half a month. In addition, *in vitro* cytotoxicity studies demonstrated that the empty AAP-CS-NPs did not exhibit any cytotoxic effects, while the Dox AAP-CS-NPs enhanced the cytotoxicity of Dox-HCl against MCF-7 cells as a result of a significant increase

in cellular uptake compared to free Dox-HCl. Thus, the overall results obtained indicate that AAP-CS-NPs are very effective in capturing Dox-HCl and penetrating tumour cells, making them promising carriers for hydrophilic anticancer drugs.

A drug delivery system based on a polysaccharide biopolymer is promising (Chis *et al.*, 2022). The FA-AAP-CDDP complex can be used for the selective transport of chemotherapeutic drugs to cancer cells (Eroğlu *et al.*, 2016).

The analysis of the literature demonstrates the wide possibilities of using basidiomycetes in veterinary medicine. It can be stated that scientific interest in their research has been growing significantly in recent decades (Eroğlu *et al.*, 2016; Géry *et al.*, 2018; Zhao & Zheng, 2021), and their use in medicine is changing from empirical ideas to scientifically based knowledge (Qiu *et al.*, 2018; Alvandi *et al.*, 2020). Basidium mushrooms have been established to be effective in treating cancer (Rehman *et al*., 2020; Lu *et al*., 2021), metabolic disorders such as obesity (Liu *et al.*, 2022; Yu *et al,* 2022), diabetes (Su *et al*., 2022; Zhang *et al*., 2022), their antioxidant properties (Su & Li, 2020; Zhang *et al*., 2020; Alvandi *et al.*, 2021), efficacy in gastrointestinal diseases (Liu *et al*, 2022; Yang *et al*., 2021), diseases of the circulatory system (Wang *et al*., 2019; Bian *et al*., 2022), neurodegenerative diseases (Cordaro *et al.*, 2021; D'Amico *et al.,* 2021; Abitbol *et al.*, 2022), positive effect on the immune system (Ibe *et al*., 2020; 2021; Bai *et al*., 2022), efficacy in the treatment of burns (Buyantogtokh *et al*., 2020), antimicrobial and antiviral efficacy (Shahzad *et al*., 2020; Su *et al*., 2022), etc. Thus, Shahzad *et al*. (2020) suggested that one of the potential sources of drugs against the SARS-CoV-2 virus could be Inonotus obliquus (IO), a well-known chaga mushroom that typically grows in Asia, Europe and North America and is widely used as a raw material for various diseases around the world. Considering this, researchers have been evaluating the most effective herbs and mushrooms with antiviral and anti-inflammatory effects in the laboratory. Wei *et al*. (2018) reported on the anti-inflammatory effect of new polyoxygenated thiatanditerpenoids, neocyanins, obtained from the liquid culture of the medicinal basidiomycete *Cyathus africanus*. Subsequently, the scientists investigated 8 new highly polyoxygenated cyanotannaditerpenoids, called K-R neocytins, which were isolated from the solid culture of *C. africanus*.

A prerequisite for the development of effective medicines in veterinary medicine is their preclinical (determination of acute and chronic toxicity parameters, cumulative properties, study of irritant action, allergenic properties) and clinical studies, study of their pharmacodynamics and pharmacokinetics parameters. In this context, an analysis of the results of studies on the effect of active substances of basidiomycetes on the transport of medicinal substances presented in the literature was conducted. Such experiments were performed by Eroğlu *et al*. (2016), Xiong *et al*. (2016), Xiaoting *et al*. (2022) using nanoparticles or a polysaccharide biopolymer. Li *et al*. (2020) explored the effects of Coriolus versicolor plant polysaccharides (CVPs) on neuronal apoptosis in a rat cerebral ischaemia-reperfusion model (CIRI) and explored the mechanisms and efficacy of CVPs in the treatment of neuronal apoptosis in CIRI rats, including neurological function, brain infarct volume, inflammatory factors, etc. Bai *et al*. (2019) proved that protea-β-glucan derived from *Grifola frondosa* (PGM) can improve learning and reduce memory decline in laboratory animals by attenuating neuronal loss and histopathological abnormalities in APP/PS1 mice. Wang *et al*. (2019) explored the effect of *Coriolus versicolor* (CV) on cardiac function in diabetic rats. The protective effect of CV was determined to be associated with the inhibition

of TGF-β1/Smad signalling and attenuation of NLRP3 inflammatory activation, suggesting that CV extract may be a potential therapeutic agent. In the studies of Yang *et al*. (2021), *Hericium erinaceus* polysaccharides (HEP), which were isolated from the fruiting bodies of *H. erinaceus* (hedgehog geranium, lion's mane), it was established that, based on the results of 16S sequencing of the intestinal microbiota in adult mice, and in middle-aged and old animals, the relative abundance of *Lachnospiraceae* and *Akkermansiaceae* significantly increased, while the relative abundance of *Rikenellaceae* and *Bacteroidaceae* decreased. Bacterial solutions from different segments of the mouse intestine and faeces were collected for HEP fermentation *in vitro*. HEPs significantly promoted the production of NO, IL-6, IL-10, INF-γ and TNF-α and enhanced the phosphorylation of signalling molecules, indicating the presence of immunomodulatory activity and the possibility that HEPs could be used as active ingredients in medicinal products. Gery *et al*. (2018) confirm the reduction of glucose and insulin levels and improvement of the overall state of insulin resistance in experiments on laboratory mice. Ogbole *et al*. (2019) confirmed a pronounced anti-diabetic effect in an acute *in vivo* test.

Thus, a large number of the analysed publications indicate a high degree of scientific interest in the study of the pharmacological properties of basidiomycetes in medicine, which provides ample opportunities for their use in veterinary medicine.

Conclusions

The presented review of literary sources demonstrates the relevance of scientific research on the pharmacological properties of *Basidiomycota*, which belong to the higher fungi and have a vegetative body with branched cellular mycelium. In addition to nutrients, they contain several biologically active substances, which is a prerequisite for their use in medicine. For many years, their use has been based on observations of the effects on changes in living things that they caused. Currently, the presence of biologically active substances that can become promising active ingredients of medicines explains the motivation of scientists from different countries to explore the pharmacological properties of basidiomycetes. Previously, fungotherapy (treatment with mushrooms) was used more as an empirical treatment based on practical experience, but now the results of studies of pharmacokinetics and pharmacodynamics of active ingredients of basidiomycetes using innovative methods provide ample opportunities for the scientifically based use of this species of mushrooms in veterinary medicine. The results of scientific research by many scientists from different countries demonstrate that basidium mushrooms have a wide range of pharmacological effects. They are effective in treating oncological and neurodegenerative diseases, diseases of the digestive, respiratory and cardiovascular systems, metabolic disorders, antibacterial, antiviral (including covid infection), immunomodulatory effects, and can be used for burn treatment, etc. Their involvement in the transport of drugs at the molecular level is being actively explored using modern molecular methods. Currently, using basidiomycetes for preventive purposes and the treatment of animals with various diseases is a scientifically sound and promising area of veterinary medicine. The results of modern research identify new properties of basidiomycetes, which indicates the prospects of their multidirectional use, in particular as a source of biologically active substances with valuable pharmacological properties in oncology, non-infectious and infectious pathology and as a transport form of drugs at the molecular level, which will significantly improve the effectiveness of prevention and treatment of animals with various diseases.

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None.

Conflict of Interest

None.

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Сучасний стан наукових досліджень та перспективи використання базидіоміцетів у ветеринарній медицині: літературний огляд

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Анотація. Актуальність дослідження зумовлена необхідністю узагальнення сучасних даних про фармакологічні властивості базидієвих грибів (*Basidiomycota*) та в науковому обґрунтуванні їх застосування у ветеринарній медицині. Метою роботи було провести аналіз результатів останніх експериментальних досліджень щодо фармако-токсикологічних властивостей базидієвих грибів та можливостей їх використання у ветеринарній медицині. Для цього використовували теоретичні методи аналізу та порівняння даних літературних джерел з формулюванням обґрунтованих висновків та рекомендацій на перспективу. Базидіоміцети належать до відділу вищих грибів, їх вегетативне тіло представлене розгалуженим клітинним міцелієм. Вони є корисним продуктом харчування та багаті на біологічно активні речовини. Аналіз даних літератури засвідчує високий ступінь наукового

інтересу до вивчення їх фармакологічних властивостей. У зв'язку з цим, науковий пошук спрямовано на встановлення нових даних про фармакодинаміку і фармакокінетику біологічно активних речовин базидієвих грибів. Наприклад, гриб *Inonotus obliquus (I. obliquus)* раніше традиційно використовувався для лікування хворих за різних шлунково-кишкових хвороб. Упродовж останніх років все більше з'являється науково обґрунтованих доказів, які вказують на ефективність його екстрактів за інфекцій та інвазій, онкологічних хвороб, цукрового діабету. Встановлено, що біологічно активні речовини *I. obiquus* стимулюють імунну систему, проявляють гіпоглікемічний потенціал, чутливі до інсуліну, мають антиоксидантний вплив. У сучасному науковому дискурсі дослідники намагаються з'ясувати молекулярний механізм дії екстрактів *I. obliquus*. Представлений огляд літературних джерел засвідчує, що базидіоміцети проявляють фармакологічні властивості за онкологічних та нейродегенеративних хвороб, за хвороб органів травлення, дихання та серцево-судинної систем, за розладів метаболічних процесів, володіють протимікробною, противірусною, імуномодулюючою дією тощо. Нині у світі застосування базидіоміцетів із врахуванням їх науково обґрунтованих та експериментально доведених фармакологічних властивостей є надзвичайно перспективним. Матеріал статті становить практичну цінність для розширення можливостей застосування фунготерапії у ветеринарній медицині

Ключові слова: гриби; профілактика; хвороби; фунготерапія; біологічно активні речовини; молекулярні механізми