Mushrooms – From Traditional Remedies to the Modern Therapeutics

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Abstract Although the living standard and life expectancy have been increasing significantly, we face numerous arising challenges in modern medicine, such as the presence of increasing exogenous triggers of oxidative stress that lead to the emergence of multiple diseases and disorders, the appearance of an increasing number of resistant microorganisms, an immense number of patients suffering from cardiovascular diseases, cancers, diabetes, neurodegenerative disorders as well as autoimmune and rare diseases. Therefore, we need the help of natural sources of active compounds, among which mushrooms are important. They have been an integral part of traditional medicine for centuries, and modern research has confirmed their bioactivities and given them a scientific basis. Numerous species, primarily from the genera *Ganoderma*, *Lentinus*, *Pleurotus*, *Innonotus*, *Trametes*, *Cordyceps*, *Agaricus*, etc., have shown exceptional immunomodulatory, antioxidative, antihypercholesterolemic, antihypertensive, antitumor,

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antineurodegenerative, antidiabetic, antimicrobial as well as numerous other potentials. Studies have shown that the mushrooms' crude extracts, as well as various metabolites, especially polysaccharides, phenolic compounds, terpenoids, and proteins, possess mentioned activities and thereby could be the basis for the development of new, more efficient drugs. However, numerous problems and challenges need to be overcome before mushrooms from the domain of traditional medicine move into the modern one and become part of conventional therapy.

Keywords Bioactivities · Drug development · Functional food · Medicinal mushrooms · Traditional medicine

List of Abbreviations

ACE	angiotensin-converting enzyme
AChE	acetylcholinesterase
AP-1	transcription factor
Bax	a central cell death regulator
Bcl-2	a protein that regulates cell apoptosis
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
CAT	catalase
DPPH•	2-diphenyl-1-picryl-hydrazyl-hydrate free radical
EC_{50}	half maximal effective concentration
GLUT-2	glucose 2 transporter in the liver
GLUT-4	glucose 2 transporter in the muscles
GPx	glutathione peroxidase
HDL	high-density lipoproteins
HMG-CoA reductase	hemoglobin-coenzyme A reductase
IFN-γ	interferon gamma
IL	interleukin
IARC	International Agency for Research on Cancer
LDL	low-density lipoproteins
L-DOPA	amino acid known as l-3,4-dihydroxyphenylalanine
LEP	polysaccharide from *Lentinus edodes*
mRNA	messenger RNA
NF-κB	nuclear transcription factor
NO	nitric oxide
p53	a nuclear transcription factor
PG	propyl gallate
PPAR-γ	peroxisome proliferator-active receptor-γ
PSK	Krestin
PSP	polysaccharide-peptide complex
SOD	superoxide dismutase

TBHQ	tert-butylated hydroxyquinone
Th2	T helper 2 cell
TNF	tumor necrosis factor

1 Introduction

The finding of *Piptoporus betulinus* and *Fomes fomentarius* pieces in the bag of a Neolithic man whose corpse was found in the Alpine Glacier, at an altitude of 3200 m, in 1991 is an excellent indicator that mushrooms have been used as a medicine since prehistoric times. Throughout history, many mushrooms have been used to treat various diseases, but in different regions, preference was given to different species. *Psilocybe* spp. and *Amanita muscaria* were highly prized species by North American Indians who believed that each serious illness was a malfunction of the spirit. *Geastrum* spp. and *Sarcoscypha coccinea* were used by Maya and Cherokee Indians to stop the bleeding and *Fomes officinalis* for the treatment of fever, diarrhea, dysentery, and hepatitis. In sub-Saharan Africa, for about 9000 years, *Calvatia cyathiformis* was used for wound healing, *Phallus aurantiacus* for leprosy, and *Termitomyces microcarpus* for gonorrhea treatment, while ground *Podoxis pistillaris* fruiting bodies have been used for the treatment of patients suffering from cancer as early as the eighteenth century. In India, *Bovista pusilla*, *Geastrum fornicatum,* and *C. cyathiformis* were used to stop bleeding and wound healing, *Cyathus limbatus* and *C. stercoreus* for treating ear diseases, *Phallus rubicundus* for various stomach problems, *T. microcarpus* in paralysis, and *Xylaria polymorpha* for increasing lactation. However, the greatest admirers of mushrooms for thousands of years have been the people of Russia and Far East countries, who used more than 1100 species for the treatment of various diseases. Especially prized species in China, Japan, and Mongolia were *Ganoderma lucidum*, *Lentinus edodes*, *Auricularia auricula*, *Tricholoma matsutake, T. mongolicum*, *Tremella fuciformis*, *Grifola frondosa*, *Cordyceps sinensis,* and even some poisonous species because of the belief that similar treats “similar” and that “there is no such mushroom in nature that could not be used as a medicinal agent.” Diet therapy was widely accepted in the Chinese palace and among the population. Mushrooms were used as food by healthy persons, as food supplements for people with mild disorders, and as medicine for sick ones. In Russia, mushrooms have been used not only for treating humans but also for animals. The first clinical studies of the effect of *P. betulinus* against cancers of parotid glands and lips were done as early as the nineteenth century. Figure 1 shows the most commonly used mushrooms in traditional medicine in different parts of the world.

The second half of the twentieth century and the beginning of the 21st one represent the period of the reign of four global evils: (i) intensive industrial and economic development, (ii) poverty, (iii) illnesses, and (iv) wars. The “first evil” attacks nature and humans by increasing air, water, and soil pollution levels,

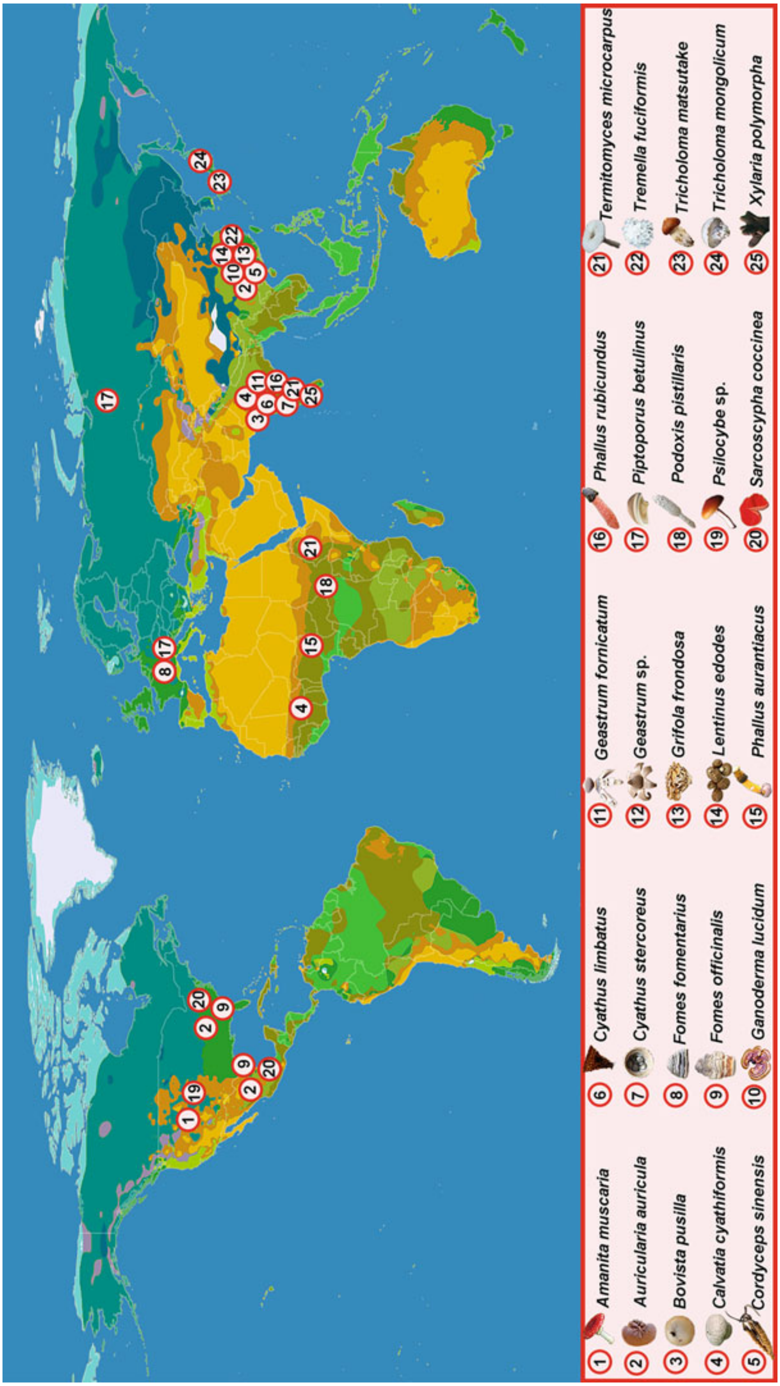

Fig. 1 The most commonly used mushrooms in traditional medicine in different parts of the world

biodiversity loss, natural resources reduction, the gap between the rich and the poor, and massive world migration. Data from United Nations annual reports can demonstrate the severity of the "second evil" effect. Namely, in 2019 one billion people lived in extreme poverty, and the number of hungry and death rates were extremely high. The greater problem is that the United Nations' idea to eradicate famine in 2015 was unrealizable, and globally the number of hungry people has increased since 2015. The realization of one of the Millennium Development Goals, zero hunger in 2030, presents a huge challenge.

The "third evil" also has a terrifying effect; today, humanity is facing many pandemics. One of the biggest is HIV/AIDS, especially in Africa, where only in Swaziland, 41% of pregnant women are HIV+, and their lifespan is less than 43 years. The latest one is COVID-19, a pandemic of a previously unknown virus, which rapidly raced and became one of the top global killers that took approximately 6,066,000 lives in only 2 years. Obesity is one more pandemic in modern society which becomes a serious problem. Data from 2011 have shown that more than two-thirds of adults and one-third of children in the United States are obese. However, according to a report by the World Health Organization from 2019, ischemic heart disease was the first cause of death; stroke and chronic obstructive pulmonary disease were second and third, while lower respiratory infections and neonatal conditions ranged in the fourth and fifth place, respectively. The sixth place was taken by lung cancer and the seventh by neurodegenerative disorders (Alzheimer's and Parkinson's diseases and various forms of dementia). In the last 20 years, kidney diseases and diabetes have become the top 10 causes of death. However, the leading causes of mortality vary from country to country and depend primarily on the living standard. To this list of diseases, we have to add the disease of crazy cows, foot-and-mouth disease, and other animal diseases, reducing the amount of available food and putting pressure on the world's population to change its diet drastically. Thus, although longevity is a trend in modern society, poverty and the number of diseases and disorders significantly reducing the quality of life are constantly increasing.

Today, on the world market, there are a considerable number of drugs against the mentioned and numerous other diseases, and a large number of new drugs are also tested every year. However, numerous commercial drugs have many side effects and disadvantages besides the potential to repress mentioned diseases and disorders. Thus, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), the most commonly used synthetic antioxidants, have carcinogenic and hepatotoxic effects. At the same time, conventional therapies against Alzheimer's and Parkinson's diseases are insufficiently efficient, i.e., they cause progression delay for a short time and gastrointestinal problems. Chemo- and radiotherapy give satisfactory results only in the treatment of early cancer development stages, are not effective for some cancer types, and can cause numerous side effects (Chen et al. 2006). Likewise, cytostatics currently available on the world market are not tumor-specific and cause numerous harmful effects in patients. Based on everything mentioned, the twenty-first century should be a century of world education on the importance of disease prevention and supplementing commercial medicines with natural ones. Diseases prevention has particular importance not only because of its positive financial and social impact but also because of maintaining and improving the life quality.

The edible and medicinal mushrooms present a promising and relatively unused source of substances with a high potential for the human diet and disease prevention and treatment. Nowadays, 14,000 mushroom species are described, of which 50% to 70% possess some edibility, and about 700 are medicinal (Wasser 2010; Ayeka 2018). Mushrooms' therapeutic potential is based on the synthesis of numerous biologically active compounds such as proteins, polysaccharides, glycoproteins, lipopolysaccharides, lectins, organic acids, sterols, alkaloids, etc. These metabolites positively affect the immune and cardiovascular systems and possess antioxidative, antitumor, antihypercholesterolemic, antihyperglycemic, antineurodegenerative, antimicrobial, antiparasitic, detoxification, and hepato-protective activities (Table 1). Because mushrooms have high nutritional value and produce numerous biologically active compounds, they are considered functional foods, i.e., food that, besides good nutritional effects, positively affects one or more functions in the body and thereby improves health or reduces the risk of illness. Therefore, dietary mushroom-based supplements help prevent and alleviate diseases. However, mushrooms and their derivates cannot replace commercial drugs but combined with conventional medical treatments, and they can allow patients to feel better. Despite very intensive studies and a considerable amount of results, the overall mushroom medical potential has not yet been fully realized because the biological potentials of many species have not yet been studied, and a large number of species have not yet been discovered and identified. It is estimated that the number of mushroom species on the planet is even ten times higher. Thus, it can be concluded that the mushrooms' medicinal potential is immense.

2 Immunomodulatory Activity

Nowadays, there is a particularly great interest in natural immunomodulators as alternatives to commercial medicines. Mushrooms represent rich natural sources of these compounds that show stimulatory activity on the innate and adaptive immune systems (El Enshasy and Hatti-Kaul 2013). They cause the proliferation and activation of natural killer cells, neutrophils, and macrophages and stimulate the expression and secretion of cytokines that activate adaptive immunity (Table 1). Immunomodulatory lectins, terpenes and terpenoids, proteins, and polysaccharides are the main four groups of mushroom compounds. Some of them are available on the market (lentinan, schizophyllan, grifolan, Krestin, and PSP). They are used simultaneously with radio- and chemotherapy and as auxiliaries to antibiotics and vaccines to minimize harmful effects (Stajić 2015). Besides the purified biologically active compounds, crude extracts of mushroom fruiting bodies and mycelium are also characterized by high immunomodulatory activity. Božić Nedeljković et al. (2022) reported that ethanol extract of *G. lucidum* fruiting bodies cultivated on wheat

Table 1 Bioactive compounds of some mushrooms and their activities

Mushroom	Active compound	Structure	Activity
Agaricus blazei	Agaritin	Hydrazine derivative	Arrest proliferation and induction of apoptosis of leukemia cells
	Blazein	Steroid	Initiation of morphological changes in stomach and lung cancer cells and their apoptosis
Agaricus bisporus	ABL	Lectin	Arrest proliferation and induction of apoptosis of colon cancer cells
Agaricus polytricha	APP	Protein	Immunostimulatory activity
Androdia camphorata	FIP-aca	Immunomodulatory protein	Induction of cytokine and chemokine synthesis
Calvatia utriformis	Calcetine	Ribosome inactivating protein	Reduction of breast cancer cell proliferation
Clitocybe maxima	Laccase	Enzyme	Antimitotic activity against liver and breast cancer cells
Clitocybe nebularis	CNL	Immunomodulatory protein	Antiproliferative activity on leukemia cells
Cordyceps sinensis	Cordycepin	Adenosine derivative	– Inhibition of NF-κB, antiproliferative and proapoptotic activity on leukemia and colon, bladder, and liver cancer cells; – Antidiabetic activity
	Cordlan	Polysaccharide	Induction of dendritic cell maturation
	Cs-HK1	Polysaccharide-protein complex (65%–70%:25%)	Radical neutralization, reduction of Fe^{3+} into Fe^{2+}, and its chelation
Cyathus striatus	Striatins and ciatins	Diterpenoids	Antibacterial, fungicidal, and cytotoxic activity
Flammulina velutipes	Proflamin	Glycoprotein	Cytotoxic activity on melanoma cells
	FIP-fve	Immunomodulatory protein	Stimulation of mitogenesis in human peripheral lymphocytes, stimulation of IL-3 and INF-γ transcription; inhibition of hepatoma growth; anti-HIV activity
	Flammulin	Ribosome inactivating protein	Inhibition of leukemia cell proliferation
Ganoderma spp.	Ganoderic acids F, B, D, H, and Y	Terpens and terpenopids	Antihypertensive activity
	Ganoderic acids T and Me		Inhibition of colon tumor invasion and metastasis

(continued)

Table 1 (continued)

Mushroom	Active compound	Structure	Activity
	Ganoderiol		Anti-HIV activity
	Ganomycin		Antibacterial activity
	Ganoderans A, B, and C		Antidiabetic activity
Ganoderma annulare	Applanoxidic acid A	Terpenoid	Antifungal activity
Ganoderma applanatum	Applanoxidic acid A-H	Terpenoids	Cytotoxic activity on skin tumor cells
Ganoderma australe	Australic acid	Terpenoid	Antibacterial and antifungal activity
Ganoderma atrum	PSG	Polysaccharide-protein complex	Neutralization of DPPH radicals and superoxide anions
Ganoderma lucidum	Ganoderan	B-glucan +4% protein	Stimulation of TNF-α, IL-1, and IFN-γ production
	GLP1	Polysaccharide	Neutralization of free radicals and Fe^{2+} chelation
	GLP2	Polysaccharide	
	LZ-8	Immunomodulatory protein	Stimulation of IL-2, IL-3, IL-4, IFN-γ and TNF-α transcription
	Ganodermin	Protein	Antifungal activity
Ganoderma microsporum	FIP-gmi	Immunomodulatory protein	TNF-α regulation
Ganoderma sinensis	FIP-gsi	Immunomodulatory protein	Stimulation of IL-2, IL-3, IL-4, INF-γ and TNF-α production
Ganoderma tsuge	FIP-gts	Immunomodulatory protein	Induction of cytokine and IFN-γ secretion; proliferation of human peripheral mononuclear cells; antitumor activity against lung adenocarcinoma cells
Grifola frondosa	Grifolan	Polysaccharide	Activation of macrophages and increase of IL-6, IL-1, and TNF-α levels
	GFPPS1b	Polysaccharide-peptide complex	Antiproliferative and pro-apoptotic activity on gastric cancer cells
Hypsizigus marmoreus	Marmorin	Ribosome inactivating protein	Inhibition of hepatoma and breast cancer cell proliferation and HIV-1 reverse transcriptase activity
Lentinus edodes	Lentinan	B-(1 → 3)-glucan with β-(1 → 6) branches	– Induction of non-specific cytotoxicity of macrophages and stimulation of cytokine production; – Increase in SOD and GPS activity;

(continued)

Table 1 (continued)

Mushroom	Active compound	Structure	Activity
			– Reduction of tumor size and inhibition of metastasis; – Vasodilatation
	Lentin	Protein	– Antifungal activity; – Inhibition of HIV-1 reversible transcriptase activity and leukemia cells proliferation
	Eritadenin	Uridine derivative	Antihypercholesterolemic activity
Phellinus linteus	Hispolon	Phenolic compound	Pro-apoptotic effect on breast, bladder, stomach, and lung cancer cells
Pleurotus spp.	Lovastatin	Naphthalene, Polycyclic aromatic hydrocarbon	Antihypercholesterolemic activity
Pleurotus eryngii	Eyingin	Peptide	Antifungal activity
	Ergothioneine	Steroid	Antioxidative activity
	Ribonuclease	Enzyme	Antiviral, immunomodulatory, and antineoplastic activity
Pleurotus nebrodensis	Nebrodeolysin	Triterpenoid	Anti-HIV activity
Pleurotus ostreatus	Pleuran	Polysaccharide	Stimulation of humoral and cellular immunity
	POPS-1	Polysaccharide	Antitumor activity against cervical cancer cells
	Pleurostrin	Peptide	Antifungal activity
Poria cocos	FIP-PCP	Immunomodulatory protein	Increase of IL-1β, IL-6, IL-18, TNF-α and NO production
Russula cyanoxantha	Ergon	Steroid	Antiproliferative and pro-apoptotic activity to liver cancer cells
Shizophyllum commune	Schizophyllan	B-(1 → 3)-glucan with β-(1 → 6) branches	Immunostimulatory and antitumor activity
Suillus placidus	Illudin	Sesquiterpene	Antitumor activity
Trametes versicolor	Krestin	B-(1 → 3)-glucan with β-(1 → 6) branches +25% - 38% protein	Activation of T cells. Induction of IFN-γ, IL-2, TNF-α, IL-1, IL-6, IL-8 production; neutralization of free radicals; arrest of cancer cells cycle and induction of their apoptosis; antiviral activity.
	PSP	B-(1 → 3)-glucan with β-(1 → 6) branches +25% - 38% peptid	
	FIP-tve	Immunomodulatory protein	Proliferation of human peripheral lymphocytes;

(continued)

Table 1 (continued)

Mushroom	Active compound	Structure	Activity
			increasing the production of TNF-α and NO
Tremella fuciformis	Glucuronoxylomannan	1,3 D mannose with xylose and glucuronic acid in the side chains	Improving the immune system and stopping the development of cancer; lowering blood glucose levels
Tremella mesenterica			
Tricholoma giganteum	Trichogin	Peptide	Antifungal activity; inhibition of HIV-1 reverse transcriptase activity
Tricholoma mongolicum	TML-1 and TML-2	Lectins	Immunostimulatory and antitumor activity
Volvariella volvacea	FIP-vvo	Immunomodulatory protein	Stimulation of IL-2, IL-2, IFN-γ and TNF-α production

straw, an alternative substrate, stimulated metabolic and phagocytic activity, adhesion capability, and NO produce ability of peritoneal macrophages initiated the production of certain cytokines and activated monocyte-derived dendritic cells. These authors emphasized that these activities of the extract could be the basis of dendritic cell-based anti-tumor vaccines. However, despite numerous in vitro and in vivo studies of the immunomodulatory potential of mushrooms' extracts, clinical trials have been done only for lentinan, schizophyllan, grifolan, and polysaccharides from *L. edodes*, *Schizophillum commune,* and *G. frondosa*, respectively. Clinical trials showed that immunochemotherapy (cytostatics + lentinan in a daily dose of 0.5–1.0 mg) extended the lifespan of patients with stomach cancer by about 70%. In contrast, in patients with colon cancer, the value was 112% compared to those who received only chemotherapy (Hazama et al. 1995). The addition of schizophyllan to conventional postoperative therapy for patients suffering from cancer also resulted in a longer and more quality of life (Fujimoto et al. 1991). These authors showed that 72.2% of selected patients who began to receive intramuscularly schizophyllan in a dose of 40 mg per week with the cytostatics survived 5 years compared with 61.9% in the control group treated only with cytostatics. Similar results were reported by Mitomi et al. (1992) and Yang (1993), who studied the effect of commercial cytostatic therapy enrichment with Krestin (PSK) or polysaccharide-peptide complex (PSP) on patients who suffered from rectal and esophagus cancer, respectively. *Trametes versicolor*, the producer of these active compounds, was also very efficient in treating breast cancer patients since it caused the production of B cells and reduced the number of IL-2 receptors located on the surface of the malignant cells. Kodama et al. (2002) showed very high efficiency of the mixture of MD-fraction. They milled fruiting bodies of *G. frondosa* in the treatment of patients in later stages (II-IV stage) of liver, lung, and breast cancers (58.3%, 62.5%, and 68.8%, respectively) based on the stimulation of natural killer cell activity.

The antimicrobial efficiency of mushrooms' metabolites and extracts is also based on immune system stimulation. Thus, lentinan is an effective immunostimulator in HIV+ patients. Gordon et al. (1995) observed that combined therapy of these patients with didanosine and lentinan significantly increased the number of auxiliary T cells (CD4+ cells), macrophages, and dendritic cells with specific CD4+ glycoprotein on the surface. Stimulation of humoral and cellular immunity was also reported in patients suffering from respiratory infections after treatment with Immunoglucan P4H, the product based on *Pleurotus ostreatus* polysaccharide pleuran (Jesenak et al. 2013).

A significant decrease in cholesterol level (even 69%) in patients with mild hypercholesterolemia treated with α-glucan originated from *Agaricus bisporus* was based on induction of TNF-α production. At the same time, stimulation of all cytokines' synthesis was the mechanism of action of *A. blazei* fruiting bodies extract (Roupas et al. 2012).

Nowadays, numerous immunomodulators from mushrooms are used in the cosmetics industry as the main ingredients of wound healing and anti-aging creams (Taofiq et al. 2016). Likewise, they are increasingly used as alternatives to antibiotics, which were common additives in feed and whose use has been prohibited in Europe since 2006. Lee et al. (2010) reported that extract of *L. edodes* fruiting bodies improved the immune system of chickens by activation of lymphocytes and macrophages and by increasing the levels of mRNA that encode IL-1β, -6, -12, and -18, while Harikrishnan et al. (2011) and Chang et al. (2013) noted the increase of resistance of cultivated scarps and shrimps fed with feed enriched with *Phellinus linteus* extract, which stimulated the activity of lysozymes and phagocytes, and *Hericium erinaceum* one that increased activity of phenoloxidases, superoxide dismutases, and glutathione peroxidases.

3 Antioxidative Activity

Oxidative stress is one of modern society's most common causal agents of diseases and disorders. It occurs when the level of free radicals overcomes the capacity of the body to neutralize them, i.e., when the capacity of the cellular antioxidative defense system is insufficient (Limón-Pacheco and Gonsebatt 2009). Numerous exogenous and some endogenous factors can be responsible for the formation of increased amounts of free radicals, which in high concentrations can attack nucleic and amino acids, proteins, carbohydrates, lipids, and phospholipids changing their function, and consequently leading to the production of organic radicals, peroxidation of cell membrane lipids, onset and development of various disorders, and cellular death (Burton and Jauniaux 2010; Leopoldini et al. 2011). Different antioxidants can be found on the world market, and mostly used are BHA, BHT, tert-butylated hydroxyquinone (TBHQ), and propyl gallate (PG). Although their main role is organism protection, they can have toxic and mutagenic effects, which unfortunately does not prevent their usage as food stabilizers (Ito et al. 1985; Ćilerdžić et al. 2013). The current trend is a replacement of synthetic antioxidants with natural ones. Mushrooms rich in vitamin C, polyphenols, flavonoids, carotenoids, and low molecular weight peptides present highly effective antioxidants (Table 1). Their regular consumption reduces the risk of cardiovascular diseases, cancers, and stroke (Sarmadi and Ismail 2010; Ćilerdžić et al. 2013). Their antioxidative mechanisms are based on: (i) catalytic removal of free radicals by glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT), and thiol-specific antioxidants; (ii) increase of the activity of these antioxidative enzymes by trace elements such as selenium, copper, zinc, and magnesium, presented in the mycelium and fruiting bodies, which act as the enzymes cofactors; (iii) binding proteins to pro-oxidant metal ions (iron and copper); (iv) protection against macromolecular damage by stress or heat shock proteins; (v) reduction of free radicals by electron donors (glutathione, vitamins E and C, β-carotene and bilirubin) (Stajić et al. 2013).

However, despite intensive mycological studies, only approximately 5% of the species are well-studied. Among the genus *Agaricus*, *A. silvaticus* was the strongest antioxidant, with EC_{50} values ranging between 2.08 mg/mL and 5.37 mg/mL (Barros et al. 2008). Methanol extracts of *Macrolepiota procera* var. *procera*, *Amanita rubescens* var. *rubescens*, *Boletus edulis*, *B. pseudosulphureus*, *B. erythropus* var. *erythropus,* and *Suillus luteus* had the significantly lower potential of DPPH• scavenging than commercial antioxidants α-tocopherol, BHA and BHT (77%, 85%, and 97%, respectively). In contrast, the same extracts of *Russula delica*, *Boletus badius*, *Polyporus squamosus*, *P. ostreatus*, *Lepista nuda,* and *Verpa conica* and acetone extract of *B. edulis* neutralized from 97.7% to 99.7% of radicals (Elmastas et al. 2007; Keles et al. 2011). Jayakumar et al. (2007, 2011) and Reis et al. (2012a) showed that *P. ostreatus* ethanol extract was also a highly effective inhibitor of lipid peroxidation level, reducer of Fe^{3+} into Fe^{2+}, as well as a good inducer of vitamins C and E, and SOD, CAT, and GPx activities in aged rats. Similar results were obtained for methanol extracts of *P. ostreatus* and *P. eryngii* mycelia and basidiocarps, as well as for *P. cystidiosus* methanol extract, which chelated 52% of Fe^{2+} (1.0 mg/mL), neutralized 42% of DPPH• (5.0 mg/mL), and inhibited lipid peroxidation by 44% (10.0 mg/mL) (Yang et al. 2002a; Oke and Aslim 2011; Reis et al. 2012a). According to several studies, extracts of *L. edodes*, *Laetiporus sulphureus*, *Hericium erinaceus*, *Agrocybe aegerita*, *G. lucidum,* and *G. applanatum* are effective free radical neutralizers and inhibitors of lipid peroxidation (Yang et al. 2002a; Cheung and Cheung 2005; Mau et al. 2005; Turkoglu et al. 2007; Karaman et al. 2010; Mujić et al. 2010; Carneiro et al. 2013; Ćilerdžić et al. 2014; Milovanović et al. 2015a). Water extract of *G. Tsugae* mycelium is an excellent DPPH• scavenger, even better than basidiocarp one and almost twice as effective as fermentation broth (91.2% vs. 79.3% vs. 58.8%), while *G. lucidum* extracts besides this activity were also good inhibitors of lipid peroxidation (Mau et al. 2002; Ćilerdžić et al. 2014). However, numerous studies showed that the ability of radical neutralization in *L. edodes*, *Flammulina velutipes*, *Lenzites betulinus,* and *G. applanatum* was improved by mycelium enrichment with selenium (Turło et al. 2010; Milovanović et al. 2015a, 2015b, 2015c).

Phenols, including flavonoids, vitamins, polysaccharides, peptides, proteins, organic acids, carotenoids, alkaloids, and nucleotides, are the main carriers of mushroom antioxidative activity (Stajić et al. 2013). Oke and Aslim (2011) and

Vaz et al. (2011) noted significant concentrations of protocatechuic and *p*-hydroxybenzoic acids in *Fistulina hepatica*, while *p*-hydroxybenzoic, gallic and caffeic acids were the major phenolic components in *P. eryngii* and *Auricularia auricula-judae* extracts. Carriers of antioxidative activity in *G. lucidum, G. Applanatum, Meripilus giganteus, L. sulphureus, F. velutipes, Coriolus versicolor, P. Ostreatus,* and *Panus tigrinus* were gallic and protocatechuic acids, which also were dominant in *A. Bisporus* together with *p*-hydroxybenzoic and cinnamic acids (Karaman et al. 2010; Reis et al. 2012a). However, Barros et al. (2008) reported that species of the genus *Agaricus* also synthesize flavonoids, ascorbic acid, β-carotene, and lycopene, but in lower concentrations. Eight ganoderic acids, which belong to phenols, have a key role in the antioxidative activity of *Ganoderma atrum*, while in hot water extracts from *G. tsugae* fruiting body and mycelium, besides phenols, ascorbic acid, α- and δ-tocopherols possessed that function (Mau et al. 2005; Li et al. 2012). Lee et al. (2007) reported that in *P. citrinopileatus*, phenols were the main carriers of antioxidative activity since ascorbic acid, tocopherols, β-carotene, and cysteine were insignificantly present. However, ascorbic acid and β-carotene were important radicals' neutralizers in *P. eryngii* and *P. ostreatus* (Jayakumar et al. 2009; Oke and Aslim 2011; Mishra et al. 2013). In several studies, positive correlations between the high antioxidative capacity of *P. cystidiosus*, *P. eryngii*, *P. ostreatus,* and *P. ferulae* and significant amounts of tocopherols, gallic, protocatechuic, *p*-hydroxybenzoic, *p*-coumaric, and cinnamic acids have been observed (Yang et al. 2002a; Tsai et al. 2009; Oke and Aslim 2011; Reis et al. 2012a). Phenols were the major antioxidant components in *Agrocybe cylindracea* and *A. aegerita* var. *alba*, and *L. sulphureus*, where flavonoids also had an important role (Lo et al. 2005; Huang et al. 2006; Tsai et al. 2006; Turkoglu et al. 2007). However, in the case of the main carriers of *L. edodes* antioxidative activity, opinions differed. According to Yang et al. (2002a) and Cheung et al. (2003); Cheung and Cheung (2005), various phenols were the main DPPH• neutralizers, while according to Carneiro et al. (2013), tocopherols had this function. The high content of tocopherols was also responsible for DPPH• neutralizing activity in *Clitocybe alexandri*, *Laccaria laccata*, *Mycena rosea*, *A. blazei,* and *A. brasiliensis* (Camelini et al. 2005; Tsai et al. 2007; Soares et al. 2009; Heleno et al. 2010). However, in *A. brasiliensis*, β-glucans, phenols, citric, malic, tartaric, oxalic, succinic, lipoic, and phytic acids were also synthesized (Keles et al. 2011; Vaz et al. 2011). Flavonoids were the main antioxidative compounds in numerous species (Stajić et al. 2013), while in *Inonotus* spp. and *Phellinus* spp. highly oxygenated and unsaturated polyphenols-hispidin derivatives (interfungins A, B, and C) had this role (Lee and Yun 2007).

Among polysaccharides, extracellular ones are the leader antioxidants in most mushrooms, and only some, such as *P. eryngii*, *P. cornucopiae,* and *P. nebrodensis* intracellular polysaccharides have this role (Liu et al. 2010a; Stajić et al. 2013). In *G. lucidum,* low molecular weight polysaccharides, as well as free amino acids, peptides, and proteins, were highly effective DPPH• neutralizers, an inhibitor of linoleic acid peroxidation, and stimulators of SOD and CAT activities, even more effective than ascorbic acid (Jia et al. 2009; Saltarelli et al. 2009; Liu et al. 2010b;

Kozarski et al. 2012). On the other hand, polysaccharide-protein complexes from *G. atrum*, *P. ostreatus*, *Phellinus rimosus*, *C. sinensis,* and *Antrodia camphorata*, polysaccharide-peptide complexes from *G. lucidum* and *Grifola umbellata*, as well as krestin from *T. versicolor* were responsible for strong free radical scavenging activities (Song and Yen 2002; Behera et al. 2005; Chen et al. 2008; Tseng et al. 2008; Janardhanan et al. 2009; Leung et al. 2009; Xia et al. 2011). Similar to *G. lucidum*, lentinan and LEP from *L. edodes* had high antioxidative potential based on the increase of SOD and GPx activity, while its high efficiency in lipid peroxidation inhibition was in positive correlation with high content of free amino acids and proteins (Cheung and Cheung 2005; Yu et al. 2009; Feng et al. 2010). However, in this species and *Cantharellus cibarius*, *Calocybe gambosa,* and *Clitocybe odora,* unsaturated fatty acids nucleotides and nucleic acids also significantly contributed to antioxidative activity (Ames et al. 1981; Vaz et al. 2011; Cheng et al. 2012; Carneiro et al. 2013). Likewise, nucleotides and nucleic acids were responsible for the activity of *Agrocybe chaxingu*, *Coprinus comatus*, *A. bisporus*, *Armillariella mellea,* and *F. velutipes* to inhibit lipid peroxidation and convert free radicals to stable forms (Stajić et al. 2013).

4 Effects on Cardiovascular System

Numerous mushroom species have antioxidative, hypocholesterolic, hypotensive, and anti-inflammatory effects. Therefore, they are recommended for the prevention or treatment of cardiovascular diseases, which are the main causal agents of death in most developed countries and countries in transition. The main biomarkers of coronary heart disease have increased low-density lipoproteins (LDL) and triglycerides, reduced high-density lipoproteins (HDL), and high blood pressure.

4.1 Antihypercholesterolemic Activity

Due to the insignificant amount of fats, the dominant presence of polyunsaturated fatty acids, and the absence of trans fatty acids, as well as the high content of soluble fibers, mushrooms are ideal food for reducing the ratio of total and LDL cholesterol in serum (Kalač 2009; Reis et al. 2012b; Wang et al. 2014). Besides that, mushrooms have no side effects contrary to statins, conventional therapy for patients with increased LDL cholesterol levels. Mushrooms' hypocholesterolemic action is based on two mechanisms: (i) increase in the excretion of short-chain bile and fatty acids and inhibition of the cholesterol and triglycerides absorption and (ii) production of inhibitors of hemoglobin-coenzyme A reductase (HMG-CoA reductase), a key enzyme in the hemoglobin synthesis (Schneider et al. 2011; Meneses et al. 2016). Thus, fruiting bodies of *A. auricula* and *Tremella fuciformis*, owing to the presence of soluble dietary fibers, reduce the level of blood cholesterol by the first mechanism, while erythadenin from the *L. edodes* fruiting bodies and mevinolin (lovastatin) from *P. ostreatus*, *P. eryngii* var. *ferulae* and *P. cornucopiae* basidiocarps and *P. sapidus*, *P. saca* and *P. ostreatus* mycelia by the second mechanism (Gunde-Cimerman et al. 1993; Guillamón et al. 2010; Zhang et al. 2020). Chitin and chitosan from the mushrooms' cell walls have functions similar to dietary fibers. Chitosan is now commercialized as a dietary supplement for obese people and people with problems with high cholesterol levels in the blood (Neyrinck et al. 2009).

Hu et al. (2006a) and Alam et al. (2011) showed that the *P. ostreatus* and *P. citrinopileatus* fruiting bodies have a positive effect on rats with hypercholesterolemia induced by the consumption of fatty foods or alcohol, by diabetes, or by a congenital disorder of cholesterol metabolism. The decrease of total lipids, cholesterol, and triglycerides levels in plasma and liver of rabbits with hypercholesterolemia and an increase in HDL/total cholesterol and HDL/LDL cholesterol ratio was caused by a diet enriched with dry *P. florida* fruiting bodies, which increased bile acid excretion (Guillamón et al. 2010). *P. ostreatus* caused a similar effect in humans. Schneider et al. (2011) observed that regular intake of dry fruiting bodies at the daily dose of 30 g for 21 days reduced triglyceride concentrations by about 0.44 mmol/L, oxidized LDL by about 7.2 U/mL, and total cholesterol by about 0.47 mmol/L. Contrary to that, in the control group, which consumed potato soup, the concentration of triglycerides increased significantly. These authors showed that the carriers of the hypocholesterolemic effect of *P. ostreatus* were linoleic acid, mevinolin, ergosterol, and its derivatives, as well as dietary fibers whose content was about sixfold higher than in the potato.

Erythadenin or lentinacin is a carrier of the hypocholesterolemic effect of *L. edodes* and *A. bisporus* basidiocarps (Guillamón et al. 2010). These authors reported that this compound reduced cholesterol levels in rats by 25% after 7 days of consumption at a dose of only 0.005% of the food. The mechanism of its action is based on the modification of phospholipid metabolism in the liver and the change in the fatty acid profile in the liver and plasma. It is well known that body weight reduction leads to a decrease in triglyceride and cholesterol levels in the blood. Enrichment of feed of obesity mice (fat-induced obesity) with 5% chitosan from *A. bisporus* led to a decrease in the level of lipid and adipocytokine absorption in the serum, resulting in a reduction of fat accumulation and triglyceride content in the liver and muscles by 39% and 66%, respectively. Likewise, adding *P. ostreatus* fruiting bodies to the diet of experimental animals, at a dose of about 5% of daily calories, for 6 weeks significantly increased the HDL concentration (Alam et al. 2011). Studies by a group of Baltimore scientists have shown that the replacement of minced beef with *A. bisporus* in only one meal for 4 days significantly reduced fat usage without influencing appetite and satiety (Stajić 2015). If replacement is constantly done once per week, 20,000 kcal can be reduced in a year, and thus obesity can be significantly decreased. The author also reported a reduction in body weight and blood cholesterol level in 90 volunteers who used polysaccharide-protein complexes from *A. blazei* and *L. edodes*.

4.2 Antihypertensive Activity

Hypertension, also known as a "silent killer," presents one more risk of cardiovascular diseases. Because of the high frequency, even at the epidemic level, hypertension is a global threat to modern humans. According to World Health Organization, more than a billion people worldwide suffer from hypertension, and it is assumed that in 2025 this number may increase to 1.6 billion.

The main factors that lead to hypertension are the hyperactivity of the sympathetic nervous system induced by stress, the large production of vasoconstrictors and mineralocorticoids, reduced vasodilators' production, obesity, and diabetes (Mills et al. 2021). Therefore, hypertension should be treated with diuretics, beta-blockers, inhibitors of angiotensin-converting enzyme (ACE), and blockers of angiotensin receptors and calcium channels. However, antihypertensive drugs have various side effects, and therefore great attention is given to finding the natural sources of safe and effective antihypertensive agents. Numerous mushrooms present one of these sources (Table 1). Due to the low sodium and high potassium concentrations in the fruiting bodies, they are used in an antihypertensive diet. Their peptides act as ACE inhibitors and decrease blood pressure without side effects (Wang et al. 2014). Compared with other mushrooms, the water *G. lucidum* extract was the best inhibitor of ACE and the sympathetic nervous system, whose secondary effect was hypotension (Yahaya et al. 2014). Although ganodal A, ganoderols A and B, and ganoderic acids K and S, triterpenoids present in this extract in significant amounts, were slightly weaker ACE inhibitors, regular usage of the extract for 4 weeks led to a significant decrease in blood pressure. Inhibition of this enzyme was also the mechanism of action of *P. ostreatus*, *P. cornucopiae,* and *P. nebrodensis* (Jang et al. 2011; Yahaya et al. 2014). Jang et al. (2011) showed that D-mannitol and two easily absorbed peptides isolated from *P. cornucopiae* were highly effective in the treatment of spontaneous hypertension. Biologically active compounds with a similar structure and mode of action are isolated from the fruiting bodies of *P. eryngii*, *P. flabellatus*, *P. sajor-caju*, *P. cystidiosus,* and *P. florida* (Abdullah et al. 2012). Good ACE inhibitors and, consequently, reducers of systolic blood pressure are also chitin-deacetylated derivatives. Therefore, *L. edodes* fruiting bodies rich in chitin (8.07% of dry weight) present an excellent hypotensive agent (Vetter 2007). However, its activity is also based on high potassium content because it is known that the best way of hypertension prevention is maintaining potassium ions amount at a higher level and the concentration of sodium ions and aldosterone at a lower level (Manzi et al. 1999). Lau et al. (2012) reported that *L. edodes* water extract inhibited the activity of ACE by 90%, while lentinan caused vasodilation and, consequently, blood pressure reduction. *F. velutipes*, *H. erinaceus,* and three peptides isolated from *A. bisporus* basidiocarps were also highly effective ACE inhibitors, i.e., they inhibit the activity by 96%, 90%, and 87%, respectively (Lau et al. 2012). Likewise, *Tricholoma giganteum* and *G. frondosa* showed significant antihypertensive capacity (Lee et al. 2004; Yahaya et al. 2014). Lee et al. (2004) noted that *T. giganteum* extract inhibited the activity of this enzyme by 61%, while low molecular weight peptide isolated from its basidiocarps has shown very high potential in blood pressure reduction, even like some commercial drugs. A significant decrease in systolic blood pressure in rats on a diet enriched with the *G. frondosa* fruiting bodies or extracts (5% of the total food amount) for only 35 days was noted by Yahaya et al. (2014). These authors also observed that peptides isolated from *G. frondosa* water extract significantly inhibited ACE.

5 Antitumor Activity

Nowadays, half of the men and more than a third of women worldwide have cancer, and even a quarter of adult deaths are caused by cancer (Parker 2014). The global situation, as predicted by International Agency for Research on Cancer (IARC), is more pessimistic. Namely, each year until 2030, over 21 million persons worldwide will be new cancer-diagnosed. Besides the high annual rate of new-cancer patients, low curability rate, and high treatment cost represent serious problems, which require good knowledge of cancer causal agents and mechanism of cancer development, creating an effective strategy for cancer prevention, as well as the development of more efficient drugs.

Nowadays, potential carcinogens are numerous, and they can be divided into three groups, chemical, physical and biological. They can cause oxidative stress and/or inflammation that can cause direct and irreversible changes in the genome, cell morphology, polarity, adhesion, communication, mobility, and the synthesis of metalloproteinases and angiogenic factors. All these processes consequently lead to increased cell proliferation, resistance to apoptosis, i.e., the transformation of normal cells into neoplastic ones, and other aggressive tumors neovascularization and metastases (Reuter et al. 2010; Stajić et al. 2019).

The common treatment for cancer patients is surgery combined with chemo- and/or radiotherapy. However, chemo- and radiotherapy have several disadvantages, such as ineffectiveness in the treatment of some cancer types as well as in the treatment of later cancer development stages, absence of tumor-specificity, and causing numerous harmful effects in patients (Chen et al. 2006). Nowadays, preference is given to integrative medicine, presenting a combination of conventional, complementary, and alternative medicines. Preparations based on mushroom extracts or metabolites are important in complementary medicine (Table 1). However, it should be emphasized that mushrooms are not drugs but dietary supplements whose consumption eliminates the accompanying harmful effects of chemo- and radiotherapy (Chang and Wasser 2012).

The anticancer activity of the mushroom extracts and/or metabolites is based on several mechanisms, one of which is the stimulation of the immune system. Numerous studies have shown that species of the genus *Agaricus*, *G. lucidum*, *Cordyceps militaris*, *Phellinus linteus*, *H. erinaceus, L. edodes*, *G. frondosa*, *T. versicolor*, *Clitocybe nebulares,* and many others possess the cytotoxic activity and strengthen the immune system (Chihara 1992; Fortes et al. 2009; Patel and Goyal 2012; Ren et al. 2012; Roupas et al. 2012; El Enshasy and Hatti-Kaul 2013). For example, *G. lucidum* extract stimulates TNF-γ synthesis, *C. militaris* one production of IFN-γ and IL-18, *Ph. linteus* extract induces the production of IL-12, IFN-γ, and TNF-α synthesis, as well as macrophage and dendritic cells proliferation, and *H. erinaceus* extract activates natural killer cells and macrophages. In such a way, these species act against stomach cancer, leukemia, hepatoma, and colon cancer, respectively (Patel and Goyal 2012). Lentinan, grifolan, *G. lucidum* polysaccharide, and *C. nebulares* lectin stimulate the production of certain cytokines. At the same time, krestin and *A. bisporus* proteoglycans initiate ILs and INF-γ production and activate natural killer cells, while cordlane from *C. militaris* and *C. nebulares* lectin induce the maturation of dendritic cells (Chihara 1992; Patel and Goyal 2012; Ren et al. 2012; Roupas et al. 2012; El Enshasy and Hatti-Kaul 2013).

Some mushrooms, such as *P. ostreatus* and *Phellinus rimosus*, base their strong cytostatic effect on neutralizing free radicals, i.e., on high antioxidative potential (Stajić et al. 2013). On the other hand, ethanol extracts of *T. versicolor*, *T. hirsuta, T. gibbosa,* and Se-enriched *G. lucidum* basidiocarps, methanol extract of *Lactarius vellereus*, as well as water extracts of *A. bisporus*, *G. lucidum* and *Agrocybe cylindracea* possess strong antimutagenic activity, i.e., effectively protect cells against H_2O_2-induced DNA damage and in such a way prevent the transformation of a normal cell to malignant one (Mlinrič et al. 2004; Zhao et al. 2008; Roupas et al. 2012; Ćilerdžić et al. 2016a; Knežević et al. 2018). The same effect was noted for *A. brasiliensis* and *A. blazei* β-glucans, and *A. bisporus* thermolabile protein (Angeli et al. 2006, 2009). Strong anti-inflammatory activity is the basis of the cytotoxic activity of *Ph. rimosus* and *P. ostreatus* (Joseph et al. 2012; El Enshasy and Hatti-Kaul 2013). Namely, these authors observed that *Ph. rimosus* polysaccharide-protein complex increased SOD and GPx activity and decreased the level of reduced glutathione, while *P. ostreatus* β-(1,3/1,6)-D-glucan changed cytokines level in plasma.

Some mushrooms can regulate some cell processes. Roupas et al. (2012) reported the high efficiency of *A. blazei* extracts and its metabolite agaritine in stopping proliferation and inducing apoptosis of some leukemia cell lines, based on induction of cytochrome c release, caspases activation, and Bcl-2 synthesis regulation. High inhibition of breast cancer by *A. bisporus* water extract and colon cancer by its lectin are based on the inhibition of aromatase activity and stimulation of caspase-3 activity, respectively (Grube et al. 2001; Hong et al. 2004). Also, strong antiproliferative activity against breast cancer cells was caused by theanine from *Boletus badius,* which stimulated cytochrome c release and activated caspase (Patel and Goyal 2012). Several studies have demonstrated that *G. lucidum* extract-based cytotoxic activity against stomach cancer cells is caused by caspases activation and inhibition of metalloproteinase expression, while antiproliferative activity against prostate cancer cells is based on inhibition of transcription factor AP-1 (Chen et al. 2010; Patel and Goyal 2012; Roupas et al. 2012). Triterpenoid ganoderic acid Me inhibits colon cancer development by stimulating the expression of p53, Bax, and caspase 3 and the release of cytochrome c (Patel and Goyal 2012). *G. frondosa* β-glucan inhibits bladder cancer cells by activating DNA-dependent protein kinase and arresting the cell cycle. At the same time, its polysaccharide-peptide complex stimulates the synthesis of Bax, inhibits the synthesis of Bcl-2, and activates caspase 3, leading to the apoptosis of stomach cancer cells (Louie et al. 2010; Patel and Goyal 2012). The development of various cancer types can be inhibited by suppression of nuclear transcription factor (NF-κB) activity which could be caused by extracts of *A. brasiliensis, C. sinensis, C. comatus, Sparassis crispa,* and *Phallus impudicus* (Grube et al. 2001; Hong et al. 2004; Petrova et al. 2008).

Numerous studies have demonstrated that arresting cell cycle in a specific phase and induction of rapid cell apoptosis was caused by *L. edodes* extract against leukemia and skin cancer cells, *C. comatus* and *F. velutipes* extracts against prostate and breast cancer, respectively, and *Ph. linteus* extract against liver, bladder, stomach, and lung cancer cells (Gu and Belury 2005; Guo et al. 2007; Zaidman et al. 2008; Patel and Goyal 2012). Arresting cell cycle in G_0/G_1 phase was at the base of melanoma reduction by *T. versicolor* and *Inonotus obliquus* extracts and breast cancer inhibition by *Pleurotus tuber-regium* carboxymethylated polysaccharide (Zhang et al. 2007; Youn et al. 2009; Roupas et al. 2012). On the other hand, arresting cell cycle in the G_2/M phase by *G. tsugae* extract, *G. frondosa* polysaccharide-peptide complex, cordlane from *C. militaris,* and ergon from *Russula cyanoxantha* led to inhibition of colon, stomach, bladder, and liver cancer (Hsu et al. 2008; Patel and Goyal 2012). Vaz et al. (2010) observed that *Clitocybe alexandri* extract had the same effect on colon adenocarcinoma and lung, breast, and stomach cancers but by cell cycle arrest in the S phase and apoptosis induction. Strong cytotoxic activity against breast and pancreas cancer was caused by theanine from *B. badius* and anthraquinones from *A. camphorata*, respectively, which stopped the cell cycle in the G_1 phase (Yu et al. 2012; Patel and Goyal 2012).

B. badius fermentation broth, *G. frondosa* polysaccharide-peptide complex, and ergon from *R. cyanoxantha* inhibited breast, stomach, and liver cancer, respectively, by induction of apoptotic bodies' appearance on cell, cell volume reduction, chromatin condensation, and DNA fragmentation, i.e., by disturbance of DNA synthesis and structure (Cui et al. 2007; Patel and Goyal 2012). On the other hand, some mushrooms cause changes in the morphology and mobility of malignant cells, inhibiting cancer development. Several researchers have demonstrated that the cytotoxic activity of *P. betulinus* fruiting bodies against colon and lung carcinoma and glioma cells and blazein from *A. blazei* against lung and stomach cancers are based on cells morphology and mobility changes, while anthraquinone from *A. camphorata* stimulated degradation of dysfunctional cellular components resulting in the inhibition of proliferation of pancreas cancer cells (Yu et al. 2012; Patel and Goyal 2012; Roupas et al. 2012). Cytotoxic activity of *H. erinaceus* water extract and *G. lucidum* polysaccharide-peptide complex against colon and lung cancer, respectively, were based on angiogenesis inhibition (Kim et al. 2011; Ren et al. 2012).

6 Antineurodegenerative Activity

The seventh leading cause of death is dementia affecting more than 55 million people. World Health Organization estimates that this number will be 78 million in 2030 and even 139 million in 2050. The most common form of dementia is Alzheimer's disease. It is estimated that every ninth man and every fifth woman will suffer from it in 2050. Parkinson's disease is the second most common age-related neurodegenerative disorder, and according to World Health Organization, 7–10 million people worldwide suffer from it, especially men. The probability of Parkinson's disease occurrence and development is 1.5 times higher in men than in women. These two neurodegenerative disorders have physical, psychological, social, and economic impacts. People with these diseases suffer, including their careers, families, and society.

Nearly 10 million new cases of Alzheimer's disease worldwide and about 60,000 with Parkinson's only in the USA are diagnosed yearly. The average cost of Alzheimer's treatment is US$ 20,461 per patient per year, while in the case of Parkinson's disease, the cost is US$2500. However, although numerous commercial antineurodegenerative drugs exist on the world market, their many side effects and disadvantages are known (Phan et al. 2014). Therefore, the current trend in the world is the creation of highly effective natural preparations. Owing to some mushrooms' medicinal properties, they could be efficient antineurodegenerative agents (Table 1). Mushrooms, as excellent antioxidants, can prevent disturbances in the structure of numerous metabolites as well as in the function of organelles and cells; thus, they can prevent the occurrence and development of Alzheimer's and Parkinson's diseases (Asanuma et al. 2003; Zhu et al. 2004; Halliwell 2006; Tessari et al. 2008; Tsang and Chung 2009; Tel et al. 2011; Janjušević et al. 2017). These authors have demonstrated high mushrooms' efficiency in the prevention of (i) abnormal mitochondrial function, (ii) lipid peroxidation and consequently change in cell membrane permeability, (iii) inflammatory responses, (iv) cell apoptosis, (v) neurons' senescence, (vi) inadequate synthesis of acetylcholine, a neurotransmitter that is directly related to increased activity of acetylcholinesterase (AChE) which is a trigger of Alzheimer's disease, (vii) production of highly active tyrosinase that catalyzes the conversion of L-DOPA into a reactive quinone form toxic to dopaminergic neurons, which progressive loss leads to the appearance of Parkinson's disease.

Due to their ability to inhibit neuroinflammation, mushrooms are known as "brain food" (Essa et al. 2012; Phan et al. 2014). However, mushrooms differ in their mechanism of action and efficiency. Numerous studies showed that mushroom can act by one of five the most common mode of action: (i) inhibition of amyloid peptide production or aggregation into amyloid plaques (*G. lucidum* extracts); (ii) inhibition of *p*-tau protein secretion and consequently neurone damage (*A. comphorata*); (iii) free radical neutralization (*Ganoderma* spp. Extracts, hispidin from *Ph. Linteus*, *I. obliquus* protein-bound polysaccharide, etc.); (iv) inhibition of AchE and tyrosinase (*Cortinarius infractus* alkaloids, extracts of *Tricholoma* spp., *Trametes* spp., *G. lucidum*, *P. ostreatus*, *L. sulphureus,* etc.); (v) stimulation of neurotrophins' synthesis and neuronal differentiation (extracts of *Sarcodon* spp., *G. frondosa*, *Pleurotus giganteus*, *C. militaris* and *H. erinaceus*, etc.) (Kawagishi et al. 1997; Wang et al. 2004, 2012; Marcotullio et al. 2006, 2007; Nishina et al. 2006; Jung et al. 2008; Lai et al. 2008; Mori et al. 2008; Dai et al. 2010; Lee et al. 2011; Tel et al. 2011; Phan et al. 2012; Knežević et al. 2018; Ćilerdžić et al. 2019).

The efficiency of mushrooms depends on species/strain, development phase (mycelium/fruiting body), extract type, and concentration of the active metabolites. Thus, for example, *P. ostreatus* extracts showed higher reduction potential than *P. citrinopileatus* ones (Jayakumar et al. 2009; Alam et al. 2010; Lee et al. 2007). Lee et al. (2007) reported that the highest amount of active compounds from *P. citrinopileatus* fruiting bodies was extracted with hot water and that basidiocarp extract was a more efficient reduction agent than mycelium one. On the other hand, Ćilerdžić et al. (2015) obtained the highest extraction yield from *P. ostreatus* with 96% ethanol and similar free radical reduction capacity of basidiocarp and mycelium extracts.

Previous reports showed that extracts of a few fungal species produce compounds that inhibit AChE activity (Patocka 2012; Janjušević et al. 2017). Patocka (2012) and Jamila et al. (2015) emphasized that phenols, terpenoids, and alkaloids were responsible for this activity. *Trametes* species showed higher efficiency in AChE inhibition than *Emericella unguis* (El-Hady et al. 2014a; Knežević et al. 2018), and their potential of tyrosinase activity inhibition was even higher than in commercial inhibitors, i.e., kojic acid (El-Hady et al. 2014b), which can be explained by synergistic interaction of numerous compounds of the crude extracts (Şenol et al. 2010). *P. ostreatus* and *L. sulphureus* extracts were good AChE and tyrosinase inhibitors. However, *P. ostreatus* was a significantly better anti-Alzheimer's agent (Ćilerdžić et al. 2019).

H. erinaceus is another mushroom highly effective in slowing down dementia progression and increasing cognitive function. Ma et al. (2010) found that metabolites hericenones C, D, E, F, G, and H were very effective in patients with dementia and mild cognitive impairment. However, patients returned to the former stage only during treatment, i.e., after the termination of their usage.

7 Antihyperglycemic Activity

According to the World Health Organization report, over 220 million people, or 7.8% of the world's population, suffer from diabetes. The International Diabetes Federation predicts that the number of patients in Europe will likely increase by 20% and in Africa by 98%. This number will be about 366 million in 2030 (Wild et al. 2004). Diabetes is the seventh death causal agent in the United States, sixth in Great Britain, and fifth in Taiwan. Although this is an irreversible disease that cannot be cured, glycemic control is necessary to prevent accompanying complications and reduce mortality. Antihyperglycemic agents delay the absorption of carbohydrates, increase the expression of insulin-sensitive glucose transporters, reduce gluconeogenesis in the liver, and stimulate pancreas beta cells to secrete insulin resulting in increased sensitivity to it (Lo and Wasser 2011).

However, many of the agents can cause side effects in the gastrointestinal tract and should be avoided in patients with heart failure and liver and kidney dysfunctions. Nowadays, numerous national and international programs focus on the prevention or disposal of diabetes occurrence as well as its chronic complications. Diet control, increased physical activity, healthy sleep, and weight reduction are the parts of the most effective strategies. Numerous in vitro and in vivo studies have shown that many mushrooms have a high antihyperglycemic potential, but only a few clinical trials have been done (Table 1). One of them showed that the consumption of Ganopoly (a preparation based on *G. lucidum* polysaccharide) significantly reduced the amount of glycosylated hemoglobin in patients with type 2 diabetes (Wińska et al. 2019). Hsu et al. (2007) observed significantly lower insulin resistance and higher blood adiponectin levels in 536 patients with type 2 diabetes whose conventional therapy was enriched with the *A. brasiliensis* extract at a daily dose of 1500 mg. Usage of *C. comatus* also reduces blood glucose, cholesterol, and triglyceride levels in patients with diabetes without any side effects on the function of the liver and kidneys and changes in body weight (Lo and Wasser 2011).

Mechanisms of mushroom hypoglycemic action can differ depending on how diabetes occurs. Namely, Lo and Wasser (2011) emphasized that diabetes was a result of pancreas beta cells damage, which can occur in several ways: (i) by free radicals which affect the cells inhibiting synthesis and secretion of insulin and inducing their apoptosis and development of accompanying complications; (ii) by infection when NF-κB activates leading to increase the production of inflammatory mediators (cytokines and NO) and at the end to the death of beta cells; (iii) by abnormal fatty acid metabolism. Namely, according to the so-called glucocytotoxic hypothesis, the increased presence of free fatty acids and hyperglycemia act synergistically in causing damage to beta cells.

Numerous studies have shown that compounds originating from mushrooms affect antidiabetic activity on glucose absorption, regeneration of pancreas beta cells, regulation of insulin secretion and metabolisms of carbohydrates and fat, neutralization of free radicals, and anti-inflammatory action (Lo and Wasser 2011). Gray and Flatt (1998) and Yang et al. (2008) observed that water-soluble fibers and polysaccharides of *A. campestris*, *T. versicolor*, *C. sinensis,* and *Fomes fomentarius* increased the viscosity of the gastrointestinal content and reduced the nutrient flow, which led to decrease in glucose absorption and its level in plasma. The high content of dietary fibers in *A. bisporus* and *I. obliquus* can also inhibit the activity of α-amylase and α-glucosidase, enzymes that catalyze the hydrolysis of carbohydrates, thus reducing glucose levels in the blood (Lu et al. 2010). The mushrooms' antihyperglycemic effect can also be based on (i) increase of SOD, CAT and GPx activity (*A. bispotus*, *A. brasiliensis*, *Phellinus baumii*, *T. versicolor* and *Tremella aurantia*) (Wei et al. 1996; Yuan et al. 1996; Hwang et al. 2007; Zhang et al. 2009; Yamac et al. 2010); (ii) protection of beta cells from the cytotoxic effect of hyperglycemic agents (polysaccharides of *P. citrinopileatus* and *Agrocybe chaxingu* and exobiopolymers of *C. sinensis* and *F. fomentarius*) (Hwang et al. 2005); (iii) reparation of beta cells damages to a certain degree (*L. edodes*) (Yang et al. 2002b); (iv) stimulation of the insulin synthesis and secretion (*A. bisporus*, *A. brasiliensis*, *A. campestris*, *C. militaris*, *C. sinensis*, *G. applanatum*, *G. lucidum*, *G. frondosa*, *Ph. linteus* and *Tremella fuciformis*) (Lo and Wasser 2011); (v) inhibition of the production of NO, ILs (1β and 6) and TNF-α in lipopolysaccharide-activated macrophages (*G. frondosa* fraction and cordicepine from *C. militaris*) (Shin et al. 2009); (vi) increase in the content of glucose 2 transporter (GLUT-2) in the liver and GLUT-4 in the muscles (*C. militaris*) (Choi et al. 2004); (vii) increase the activity of glucokinase, hexokinase and glucose-6-phosphate dehydrogenase in the liver (*C. sinensis* and *T. aurantia*) (Kiho et al. 1996, 2000); (viii) stimulation of glucose oxidation and incorporation into glycogen (*A. campestris*) (Gray and Flatt 1998); (ix) increase glycogenesis and reduction of glycogenolysis (*C. militaris*, *C. comatus* and *G. lucidum*) (Choi et al. 2004; Gao et al. 2004; Lv et al. 2009); (x) improving sensitivity to insulin by regulating peroxisome proliferator-active receptor-γ (PPAR-γ) and further lipid metabolism (*Ph. baumii*, *Ph. linteus*, *Poria cocos* and *T. fuciformis*) (Cho et al. 2007; Lee et al. 2008; Li et al. 2011).

Yamac et al. (2010) showed that enrichment of the diet of rats with induced diabetes with *A. bisporus* extract significantly increased the number of beta cells in Langerhans pancreas islands, primarily due to increased activity of antioxidative enzymes, increased insulin level by 78.5%, and reduced level of glucose in serum by 29.7%. Significant reduction in blood glucose level was also caused by extracellular *A. brasiliensis* β-glucans and glycoproteins that increased insulin levels in plasma and antioxidative activity as well as expressed GLUT-4 in the fatty tissue (Oh et al. 2010). Extract of this species in the dose of 400 mg/kg of body weight had a similar efficiency to 500 mg of the commercial drug (metformin) per kg of body weight. *P. eryngii* and *P. citrinopileatus* also cause a significant reduction in blood glucose levels by increasing sensitivity to insulin and reduction of Langerhans islands damage, respectively (Hu et al. 2006b; Kim et al. 2010). Extracellular exopolymer of *L. edodes* (200 mg/kg) also remarkably repaired the damage of pancreas beta cells, increased insulin synthesis by 22.1%, and consequently reduced glucose level in plasma by 21.5% (Yang et al. 2002b). High efficiency in the prevention and treatment of induced diabetes in mice was also shown by neutral water-soluble polysaccharides and the acidic polysaccharides from *A. auricula-judae* fruiting bodies (Yuan et al. 1998).

The exopolysaccharides of *T. fuciformis* fruiting bodies improve the sensitivity to insulin by regulating lipid metabolism and, therefore present good hypoglycemic agents or functional food whose usage is suggested for the treatment of type 2 diabetes (Cho et al. 2007). Acidic heteropolysaccharides from *T. mesenterica* fruiting bodies also can significantly reduce the level of glucose in the blood. At the same time, its fibers and other compounds prevent macrovascular complications in diabetes (Lo et al. 2006). Significant reparation of damaged pancreas beta cells, an increase in insulin secretion, and a reduction in glucose level were noted in rats with induced diabetes after 3 weeks of therapy with *G. applanatum* exopolymer and *G frondosa* fruiting bodies (Kubo et al. 1994; Yang et al. 2007). According to Lo and Wasser (2011), *G. frondosa*'*s* hypoglycemic action was based on antioxidative and immunomodulating activity, i.e., inhibiting macrophage proliferation and decreasing the synthesis of factors destructive to beta cells (NO and IL-1). *I. obliquus,* polysaccharides from *T. versicolor* fruiting bodies and β-glucan-protein complex from its mycelium also base strong antidiabetic activity on high antioxidative capacity, i.e., on the increase of SOD and GPx activities (Wei et al. 1996; Lu et al. 2010). Extremely high efficiency in reduction of glucose level in plasma of rats with induced diabetes, as high as 52.3%, was caused by consumption of *P. baumii* exopolysaccharides, while metabolites of *Ph. linteus* (hispidin and its derivatives) as good antioxidants prevented accompanying complications (Cho et al. 2007; Lee et al. 2008). *C. militaris* metabolites, cordycepin, and acarbose (0.2 mg/kg and 10 mg/kg, respectively), were also highly effective in rats with induced diabetes since they reduced glucose levels in the blood by 48.4% and 37.5%, respectively (Yun et al. 2003).

8 Antimicrobial Activity

Viral, bacterial, and fungal infections are among the most serious threats to human health and quality of life and present a significant challenge to modern medicine. Although the arsenal of antimicrobial drugs constantly expands, it does not meet the increasing requirements for the successful treatment of various infections due to the alarming increase in microbial resistance. Therefore, developing novel natural antimicrobial agents with improved modes of action and higher efficiency are the main requirements of modern society. Mushrooms, as producers of numerous intra- and extracellular antimicrobial metabolites, could be an excellent basis for preparations for successful treatments of human and animal diseases (Table 1). In vitro studies have shown that numerous mushrooms, their extracts, and compounds can potentially inhibit the growth of Gram+ and Gram- bacteria. However, Gram+ bacteria are more susceptible to mushroom extracts than Gram- ones due to the absence of lipoproteins in the cell wall (Kosanić and Ranković 2011). Ćilerdžić et al. (2014) showed that phenols were the main carriers of the mushrooms' antibacterial activity, which was confirmed by the high correlation between phenols content and the inhibitory activity of *G. lucidum* and *G. applanatum* extracts against *Staphylococcus aureus* and *Bacillus* sp. Rare in vivo studies showed the indirect antibacterial effect of mushrooms based on the improvement of the immune system. Thus, *A. brasiliensis* fraction rich in polysaccharides increases host resistance to some infectious agents by stimulating macrophage activity, while *A. blazei* extract by stimulation of TNF-α synthesis (Stajić 2015). This antimicrobial-immunomodulatory activity is also the basis of the antifungal and antiviral effects of mushrooms' extracts and metabolites.

The most potent antifungal compounds are phenols and polysaccharides. However, proteins, peptides, terpenoids, and numerous low molecular mass compounds act as inhibitors of pathogen development and virulence, activators of pathogens' autolytic system, and immunomodulators (Yamaç and Bilgili 2006). Thus, *G. lucidum* methanol extract and gallic acid originated from *Clitocybe subconnexa* inhibit virulence of *Aspergillus niger* and *A. fumigatus*, respectively, by demelanization of conidiophores and vesicle (Stajić et al. 2017). Highly effective natural agents against *Aspergillus* spp. were also *I. obliquus* and *G. lucidum* ethanol extracts, which were even better than the commercial fungicide Ketoconazole (Ćilerdžić et al. 2014). *Aspergillus, Penicillium* spp., *Candida albicans, and Trichoderma viride were* sensitive to *Cordyceps militaris* extracts, *G. applanatum,* and *G. carnosum* mycelial extracts and fermentation filtrates (Ćilerdžić et al. 2016b). These are just some examples of mushrooms' antifungal activity that are extensively reviewed (Stajić et al. 2017).

Antiviral activity of mushroom extracts and metabolites is expressed in two modes: (i) direct by inhibition of viral enzymes or virus absorption by the host cell and (ii) indirect by stimulation of the host immune system (Stajić 2015). This author emphasized that proteins, peptides, polysaccharides, and triterpenoids were the carriers of this activity. There are numerous examples of mushroom efficiency in combat against various viruses. Thus, *G. frondosa* is highly effective against hepatitis B virus and herpes simplex virus type 1 owing to its ability to stop their replication, while its activity against influenza A virus is based on virus growth inhibition as well as immune response improvement (Nishihira et al. 2017; Wu et al. 2021). Influenza A and B viruses were also sensitive to triterpenoids from *Ganoderma* spp., phenol compounds from *Inonotus hispidus*, and herpes simplex virus type 1 to krestin and PSP (Stajić 2015). This author reported that inhibition of HIV-1 reverse transcriptase was due to the activity against the HIV-1 virus and can be caused by *G. lucidum* and *G. colossum* triterpenoids, lentinan, *P. ostreatus* protein, *P. nebrodensis* terpenoid, *A. bisporus* lectin, *I. obliquus* water-soluble metabolites, as well as *F. velutipes* ribosome-inactivating protein. On the other hand, krestin and PSP affect anti-HIV-1 activity on immune system stimulation and prevention of virus binding for the cell receptor (Lindequist et al. 2005; Rodríguez-Valentín et al. 2018). Brandler et al. (2020) showed that the activity of some mushrooms against COVID-19 was also based on immunostimulatory and anti-inflammatory effects.

9 Other Activities

Besides the above-mentioned activities of mushroom extracts and compounds, several other less-studied effects have been recorded. For example, the ethanol extract and proteoglycan isolated from *Ph. linteus*, as well as methanol extract of the *Pleurotus florida* fruiting bodies and ganoderic acids A, B, G, and H, isolated from *G. lucidum,* have anti-inflammatory effect in arthritis, which can be stronger than the effects of diclofenac and acetylsalicylic acid (Kim et al. 2003; Jose et al. 2004; Stajić 2015). Numerous studies have shown that this effect is associated with mushrooms' antioxidative and immunomodulatory properties.

Extracts of *C. sinensis* are very effective in the treatment of asthma in children during the remission stage. Their activity is based on the inhibition of proliferation and differentiation of Th2 cells, reduction of the expression of the transcription factor involved in the expression of T cell receptors, and rising IL-10 (Stajić 2015).

Extracts of some mushrooms used to treat allergies can suppress immune responses. For example, using the fruiting bodies of *Tricholoma populinum,* the ethanol extracts of *Hypsizygus marmoreus*, *F. velutipes*, *Pholiota nameko,* and *P. eryngii* cause regression of severe allergic symptoms (Stajić 2015). Chen et al. (2015) showed that ganoderic acids C and D, ganoderiol F, ganodermanontriol, and ganodermonondiol from *G. lucidum* caused inhibition of the complement system and release of histamine from the mast cells. Therefore, their usage is primarily recommended after organ transplantation. In vitro studies showed that extracts of fruiting bodies of *Polyporus badius*, *Lactifluus vellereus*, *Heterobasidion annosum*, *T. versicolor,* and *P. betulinus* inhibit the binding of lipopolysaccharides to CD14 receptors on immune cells and release inflammatory mediators and reactive oxygen species, and thereby prevent the appearance of a complex syndrome known as septic shock (Stajić 2015).

In vitro studies showed that triterpenoids isolated from *G. lucidum* basidiocarps (ganoderic acids R and S and ganosporeric acid A) have hepatoprotective activity, which was later confirmed in vivo (Lin et al. 2002). The addition of two triterpenoid fractions to mice's diet protects them from hepatic necrosis, which is probably associated with the ability to activate antioxidative enzymes. Stajić (2015) reported that by use of Ganopoly, 13% of patients who suffered from chronic hepatitis B did not have serum hepatitis B antigen after 6 months, while in patients with chronic hepatitis C positive effect was observed after 8 weeks of oral administration, twice per day. Also, the hepatoprotective effect was noted in patients with chronic hepatitis B and hepatitis C treated with the *A. blazei* extract.

Obstipation is one of the leading gastrointestinal problems of modern humans. Recently, great attention has been given to the importance of diet and the creation of new dietary supplements with probiotic functions. Mushrooms are potential candidates for prebiotics because they contain chitin, hemicellulose, β- and α-glucans, mannans, xylans, and galactanes (Aida et al. 2009). Nondigestible chitin and β-glucans have the role of dietary fibers and represent sources of prebiotics. The proportion of chitin ranges from 68 mg to 102 mg per gram of dried fruiting body (in *Boletus* spp.), while in the case of β-glucan, the values range between only 0.8 mg/g of dried matter (in *A. bisporus*) and even 548.8 mg/g (in *Boletus* spp.) (Manzi et al. 1999, 2004). Fruiting bodies of *Auricularia* spp. contain about 50% more fibers than other species and significantly improve the state of patients who suffer from functional obstipation without any side effects. Aida et al. (2009) showed that *P. ostreatus* and *P. eryngii* extracts stimulated the growth of 4 strains of *Lactobacillus* sp. (Lac A-D), three strains of *Bifidobacterium* sp. (Bifi A-C), and two strains of *Enterococcus faecium* (Ent A and B). *P. eryngii* was more effective, especially in the Lac B and C and Bifi B strains, while *P. ostreatus* extract primarily stimulated the growth of Bifi A. Results demonstrated that strains Lac B and Lac C were the most effective producers of short-chain fatty acids. These authors divided three fractions from *P. ostreatus* and *P. eryngii* fruiting bodies (water- and bases-soluble fractions and insoluble ones) and showed that they were responsible for the activities.

Several mushroom species' extracts and compounds can be used as analgesics. For example, *P. betulinus*, *G. applanatum*, *Fomitopsis pinicola,* and *Daedaleopsis confragosa* have an inhibitory effect on natural endopeptidases and, thus, activity similar to opiates can be used against pains (Stajić 2015). This author has reported that skutigeral from *Scutiger ovinus* has an affinity for dopamine D1 receptors in the brain and can eliminate pain by acting on vanilloid receptors, non-selective cationic channels that can be activated by various exogenous and endogenous physical and chemical stimulants that cause pain.

Fruiting bodies, extracts, and compounds of some mushrooms can increase bone density and prevent osteoporosis. Shimizu et al. (2006) and Stajić (2015) showed that *G. lucidum* and *P. eryngii* ethanol extracts significantly improved bone density in female rats, which was disrupted by removing the ovaries, i.e., by estrogen deficiency, without significant effect on the uterus. In mice where low bone density was induced by feed that was poor in calcium and vitamin D_2, an increase in femur density and tibia thickness, as well as increased duodenal and renal transport of calcium, was recorded after the addition of *L. edodes* fruiting bodies exposed to UV radiation (Lee et al. 2009). These authors also showed that the bioavailability of vitamin D_2 from *L. edodes* fruiting bodies enriched with this vitamin was high, and the consumption of the species increased the level of the vitamin in humans and improved alkaline phosphatase activity in osteoblasts. The activity of alkaline phosphatase, as well as the level of mineralization, were also significantly increased, in comparison with control cells, by in vitro cultivation of human osteosarcoma cells in the medium enriched with *G. frondosa* water extract, which means that this extract induced bone formation (Chaturvedi et al. 2018). Extracts of *P. eryngii* also increased the activity of alkaline phosphatase and stimulated the expression of osteocalcin mRNA in osteoblasts (Kim et al. 2006).

Some mushrooms can play an important role in wound healing in patients with diabetes which is a major clinical problem. Kwon et al. (2009) showed that wound healing in rats with induced diabetes was accelerated significantly by adding *Sparassis crispa* fruiting bodies to their diet. β-glucan, which is synthesized in significant amounts by this species stimulates the migration of macrophages and fibroblasts and the synthesis of collagen type 1. *H. erinaceus* and fractions of *G. lucidum* and *L. edodes* polysaccharides increase the activity of antioxidative enzymes and the levels of IL-2 and TNF-α. They have shown high efficiency in treating rats with ulcers (Stajić 2015).

Nowadays, cataract is a widespread ophthalmological problem commonly treated by surgery. According to World Health Organization data from 2011, in a sample of 100,000 people, 1100 primarily women, surgically removed the cataract from one or both eyes. Extracts of some mushrooms have been found very effective in preventing cataract emergence both in vitro and in vivo. Isai et al. (2009) reported that incubation of lenses damaged by selenite with *P. ostreatus* extracts caused a decrease in lens blurring and maintenance of antioxidative compounds at an almost normal level, and cataracts did not occur in 75% of treated rats.

It is known that the presence of free radicals is associated with aging and the appearance and progression of various diseases and disorders from which a large part of the world population suffers and dies. DNA is the most susceptible macromolecule to oxidative damage that can be induced by various agents, among which H_2O_2 has significant genotoxic potential. In vitro studies have shown that water extracts of *A. bisporus* (at a temperature of 20 °C), *G. lucidum* (at a temperature of 100 °C), and *Agrocybe cylindracea*, as well as ethanol extracts of *T. versicolor*, *T. hirsuta,* and *T. gibbosa,* have protective effects against H_2O_2-induced DNA damage (Knežević et al. 2015; Ćilerdžić et al. 2016a). Thermolabile protein isolated from *A. bisporus*, β-glucans from *A. brasiliensis* and *A. blazei,* and extracts of Se-enriched *G. lucidum* basidiocarps have a similar effect. Stajić (2015) showed that *Agaricus* spp. glucan induced the genoprotective effect on the binding of benzopyrene that induced damage or neutralized free radicals, and *G. lucidum* inhibited lipid peroxidation.

10 Scientific Basis, Problems, and Perspectives for Mushroom-Based Drugs Development

Mushrooms are commonly used as prophylactics, i.e., agents that act as preventive or protective against some diseases or infections. Therefore, they are considered dietary supplements or nutraceuticals that can be administered alone or in combination with commercial medicines. On the world market, there are several mushroom-based products: (i) powdered cultivated fruiting bodies, their extracts or extracts mixtures; (ii) dried and milled substrate, mycelium, and primordia after cultivation; (iii) biomass or extracts of mycelium obtained by submerged cultivation in the reactor and (iv) dried fruiting bodies of wild and cultivated species in the form of capsules or tablets. Under strictly controlled conditions, mushrooms' commercial submerged and solid-state cultivation guarantees genetic uniformity, a significant mass of mycelium, fruiting bodies, and certain stable structure and quality metabolites, and allows checking chemical and microbiological correctness.

Until a few decades ago, immunomodulatory and anticancer mushroom-based drugs were primarily based on lentinan, schizophilan, and krestin, i.e., mushrooms' polysaccharides. However, due to the high molecular weight of these metabolites, they are obtained by extraction from fruiting bodies, mycelium, or medium after cultivation. Contemporary pharmaceutical trends in cancer prevention include the development of new drugs based on mushroom low molecular weight metabolites (Wasser 2010). This author listed the mechanisms of the cytotoxic activity of several mushrooms and their metabolites. *Ph. linteus* and *Marasmius oreades* caffeic acid, cordycepin from *C. sinensis*, panepoxidone from *Panus* spp., and *Xylaria* spp. cycloepoxidone can inhibit NF-kB. Some mushroom compounds can inhibit proteinases, matrix metalloproteinases, cyclooxygenase, DNA topoisomerase, or DNA polymerase. Some others can block cell division by binding to specific receptors, interrupt communication between growth-regulation enzymes and the development of tumor cells, or inhibit angiogenesis around them. At the same time, some of them increase vitamin D levels in serum, owing to the synthesis of ergosterol and ergocalciferol, and thus cytostatically affect some malignant cells.

However, the process of mushroom-based drug development still has several disadvantages. International standards and protocols for their production and quality testing are still lacking. According to Wasser (2010), 90–95% of mushrooms' β-glucans on the world market are considered counterfeit, leading to numerous side effects. Various species of the genus *Ganoderma* such as *G. lucidum* and species of the genus *Stereum,* replace species of the genus *Trametes*, and various species of the genus *Cordyceps* are used instead of *C. sinensis*. Further, there are many questions requiring answers. For example, it is still unknown whether mycelium and basidiocarp crude extracts are more effective than isolated compounds. Which is the more efficient? The extract of single species or a mixture of several species? What doses are safe and effective? Can certain mushroom-based preparations be administered to children safely? Can mushroom-based preparations be used during pregnancy and breastfeeding? In the end, a serious disadvantage is that mushroom-based drug development is costly, time-consuming, and can even last several years.

Despite all these limitations, the latest data from the World Health Organization demonstrate that 80% of the world population relies on traditional medicines based on active herbal and mushroom ingredients. In the USA, more than 100 million people use various dietary supplements as a safe and natural way of food enrichment to maintain good health. Today special attention is paid to finding new, highly effective immunomodulators that can be used as both precursors of drugs and prophylactics. The indicator of their importance in modern wellness industries is the budget set aside for their production. In 2012, it was US$ 145.9 billion, which increased to US$ 259.3 billion in 2017.

Presently, a large number of new drugs are developed and tested every year. Pollack (2009) reported that about 860 drugs against various types of cancer had been clinically tested. If several medications for heart disease and stroke, neurodegenerative disorders, AIDS, and other infectious diseases are added, it would add not only to the variety of preparations on the market but also to the budget set aside for each year for these purposes. A good example is Pfizer, the largest world pharmaceutical company with a 2021 research budget of US$ 13.8 billion.

If the discovery of antibiotics marked the twentieth century, the twenty-first century was already marked by the discoveries of the medical potential of mushrooms as well as the beginning of the construction of "a bridge" between eastern, traditional, and western conventional medicine. Solving the above-mentioned problems, standardization and production of mushroom-based preparations, and education of the population present the main tasks and challenges of the scientific community.

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