Mushrooms as Promising Therapeutic Resources: Review and Future Perspectives

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Contents

Abstract Several human diseases, such as diabetes, cancer, cardiovascular and neurodegenerative disorders, increasingly affect the adult population worldwide. Therefore, scientists have tried to discover new natural sources of medicines,

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especially from mushrooms, to prevent and treat these diseases. Wild mushrooms and mushrooms growing on solid media or in submerged cultures belong to a large number of genera (*Agaricus*, *Auricularia*, *Ganoderma*, *Grifola*, *Hericium*, *Lentinula*, *Schizophyllum*) and may be used to produce biologically active compounds (lectins, polysaccharides, phenolics, terpenoids, and steroid derivatives) as anti-inflammatory, antimicrobial, antioxidant, antitumor, antiviral, hepatoprotective, hypocholesterolemic, hypoglycemic, immunomodulatory, and neuroprotective agents. Metabolomics and genomic studies of the unexplored biotechnological potential of mushrooms may also assist in the production of mushroom-derived biotech products. High-quality, long-term, randomized, double-blind, placebo-controlled clinical studies have been described as necessary to prove the efficacy of mushroom extracts or isolated compounds. The present review discusses the current state of knowledge and the main findings of previous studies on mycotherapeutics and healthy mycofood. This chapter is an update contribution to modern mycopharmacology and biomedicine.

Keywords Biomedicine · Clinical trials · Mushrooms · Mycopharmaceuticals · Mycotherapy · Nutraceuticals

Abbreviations

AAM	*Auricularia auricula* melanin
ABM	*Agaricus blazei* Murill (ABM)
ABTS	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid
AE	Aqueous extract
AgNPs	Silver Nanoparticles
ALL	Acute lymphoblastic leukemia
AOA	Antioxidant activity
BDNF	Brain-derived neurotrophic factor
BGE	β-D-glucan-enriched
BW	Body weight
CGC	Chitin-glucan complex
CHS	Contact hypersensitivity
cPLA2	Phospholipase A2
CREB	cAMP response element-binding protein
DC	Dendritic cell
DMBA	7,12-Dimethylbenz(a)anthracene
DNFB	Dinitrofluorobenzene
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DW	Dry weight
EAAs	Essential amino acids
EC_{50}	Half maximal effective concentration
EPS	Exopolysaccharide

FABPs	Fatty acid-binding proteins
FDA	Food and Drug Administration
GAL-Am	α-D-Galactan from *Amanita muscaria*
GAs	Ganoderic acids
GATA4	GATA binding protein 4
GC-MS	Gas chromatography - mass spectroscopy
GDH	Glutamate dehydrogenase
GLC-Am	β-D-Glucan from *Amanita muscaria*
GLF	*Ganoderma lucidum* fruiting body
GLS	*Ganoderma lucidum* spores
GLSF	*Ganoderma lucidum* spores and fruiting bodies
βgPp	β-Glucan-rich *Pleurotus pulmonarius*
HCC	Hepatocellular carcinoma
HDL	High density lipoprotein
HFD	High-fat diet
HMM	High molecular mass
HUVEC	Human umbilical vein endothelial cells
IC_{50}	Half-maximal inhibitory concentration
IL-2	Interleukin-2
INF-γ	Interferon-γ
IOP	*Inonotus obliquus* polysaccharides
IPS	Intracellular polysaccharide
LC-MS	Liquid chromatography-mass spectrometry
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LP-7A	Latcripin-7A
LPS	Lipopolysaccharide
LX2	Human hepatic stellate cells
MDR	Multidrug-resistant
ME	Methanolic extract
MIC	Minimum inhibitory concentration
MMP	*Macrolepiota procera* mycelium polysaccharides
M^{pro}	Main protease
MS	Multiple sclerosis
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NDD	Neurodegenerative diseases
NLRP3	Nod-like receptor protein 3
NO	Nitric oxide
NP	Nonylphenol
NPE	Neuroprotective effect
OPG	Osteoprotegerin
OSi	Oxidative stress index
oxLDL	Oxidized low density lipoprotein

PC3	Prostate cancer cell line
PF-L	Lectin purified from *Pleurotus flabellatus*
PoPE	*Pleurotus ostreatus* polar extract
RANkL	Receptor activator of nuclear factor kappa B ligand
ROS	Reactive oxygen species
S1PR1	Sphingosine-1-phosphate receptor 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCFA	Short-chain fatty acids
TAS	Total antioxidant status
TCM	Traditional Chinese medicine
Thel	Thelephoric acid
TLR4	Toll-like receptor 4
TNFα	Tumor necrosis factor-α
TOS	Total oxidant status
TrkB	Tropomyosin receptor kinase B
TST	Tail suspension test
WHO	World Health Organization

1 Introduction

Global food production faces many challenges, including environmental impacts, climate change, water crisis, land degradation, and cultural and socioeconomic changes (Thornton et al. 2018; Pérez-Moreno et al. 2021; Vogt-Schilb et al. 2022). These challenges require research into non-traditional natural sources of human food and medicine, including plants and mushrooms collectively referred to as macrofungi (Chang and Wasser 2012; Badalyan et al. 2019; Elkhateeb et al. 2021b; Khatua and Acharya 2021; Li et al. 2021a).

Mushrooms taxonomically belong to phyla Basidiomycota (class Agaricomycetes) and Ascomycota (class Pezizomycetes) of the subkingdom Dikarya. Of the estimated number of fungal species, 0.5-(1.5)-(5.1) million, about 140,000–160,000 species are mushrooms, from which around 10% (14,000–16,000) have been taxonomically identified (Hawskworth 2012; Hibbet and Taylor 2013; Peay et al. 2016). More than 54,000 basidiomycete species will be discovered by 2030, showing a huge gap between the described and unknown mushroom diversity (He et al. 2022).

Out of about 7000 known species of mushrooms possessing varying degrees of edibility, more than 3000 species in 231 genera have been considered first-order edible fungi. About 3% of known species (at least 170, currently about 500) are poisonous, while about 700 species of 2000 known as safe mushrooms have medicinal properties (Wasser 2011, 2014; Chang and Wasser 2012; Badalyan et al. 2019; Niego et al. 2021; Gopal et al. 2022).

Edible mushrooms belonging to different ecological groups possess nutraceutical potential due to their low-fat content, unsaturated fatty acids, and high amount of dietary fiber. They are rich in proteins, vitamins, and minerals and are considered promising next-generation healthy food due to their nutritional value, attractive gourmet taste, and aroma (Chang and Wasser 2012; Badalyan and Zambonelli 2019, 2023; Włodarczyk et al. 2022).

The contents of vitamins A, C, D_2, and E (α-tocopherol), macroelements, and trace elements of hymenochaetoid wild mushrooms *Fuscoporia torulosa*, *Inonotus pachyphloeus*, *Phellinus allardii*, *Ph. fastuosus*, *Ph. gilvus*, and *Ph. sanfordii* collected from India have been recently reported (Azeem et al. 2022). This study showed that *Ph. gilvus* contained the highest number of the chemical elements. The mushrooms were rich in microelements, including Ca (80–2610 mg/kg), Cl (39.63–240 mg/kg), K (246.7–2620 mg/kg), Mg (96.6–500 mg/kg), Na (9.56–56 mg/kg), P (39.5–126.7 mg/kg), and S (69.37–170 mg/kg) in terms of dry weight (DW). Many trace elements (Co, Cr, Cu, Fe, Mn, Mo, Ni, Si, V, and Zn) and some non-essential elements (Al, Ba, Br, Rb, Sr, Ti, and Zr) were also detected in the tested species. The vitamins C (9.32 mg/100 g DW) and D_2 (1.55 mg/100 g DW) were mostly found in *F. torulosa*, while the lowest amounts were detected in *Ph. fastuosus* and *Ph. allardii*. These results will be beneficial in the formulation of mushroom-derived nutraceutical and pharmaceutical products (Azeem et al. 2022).

Medicinal mushrooms synthesize different bioactive compounds (alkaloids, lactones, polysaccharides, polyphenolics, sterols, triterpenes, terpenoids, eritadenine, chitosan, fatty acids, etc.), which are beneficial for human health (Badalyan 2012, 2016; Badalyan et al. 2019; Badalyan and Rapior 2021a, b). Fungal polysaccharides, *β*-glucans, and polysaccharide-protein complexes possess therapeutic properties, such as antiviral, antioxidant, antitumor, anti-obesity, hypocholesterolemic, hepatoprotective, immunomodulatory, anti-aging, and others. The bioactive ingredients may be extracted from edible and medicinal mushrooms and incorporated into health-enhancing functional food products and supplements to prevent or treat several human diseases (Badalyan and Zambonelli 2019, 2023; Badalyan et al. 2019; Badalyan and Rapior 2021a, b; Haq et al. 2022).

Since ancient times, several edible agaricomycete and ascomycete mushrooms, belonging to the genera *Agaricus*, *Boletus*, *Flammulina*, *Lyophyllum*, *Lentinula*, *Morchella*, *Pleurotus*, *Tuber*, and others with worldwide distribution, have been reported as a valuable food with healing properties (Badalyan 2012; Badalyan et al. 2019; Kües and Badalyan 2017; Badalyan and Rapior 2021a, b; Li et al. 2021a).

Ganoderma species have been used in traditional Chinese medicine (TCM) for more than six millennia for strengthening the immune system, treatment of hypertension, arthritis, bronchial asthma, anorexia, gastritis, hemorrhoids, hepatitis, vascular problems, cancer, and other disorders (Wasser 2017; Badalyan et al. 2019; Xu et al. 2021). Polysaccharides and triterpenes are the main bioactive ingredients isolated from *Ganoderma* species, particularly from *Ganoderma lucidum* (Kües and Badalyan 2017; Badalyan et al. 2019; Badalyan and Rapior 2020). These compounds have shown positive synergetic antitumor effect when used in combination with radiotherapy and chemotherapy. The analysis of complex molecules

derived from *G. lucidum* for future cancer therapy has been recently reported (Xu et al. 2021).

The well-known medicinal polyporoid mushroom *Fomitopsis officinalis* has been used by humans as medicine for over 5000 years. The chemical structure of therapeutically active compounds (triterpenoids, polysaccharides, organic acids, coumarins, and phenolics) with anti-inflammatory, cytotoxic, and antimicrobial effects from fruiting bodies of this polypore (Muszyńska et al. 2020). Agaricoid species *Auricularia auricula-judae* possess anti-inflammatory, antioxidant, and other health-enhancing effects due to substantial amounts of phenolics, flavonoids, carbohydrates, β-glucans, melanin derivatives, 5'-nucleotides, vitamin D_2, ergosterol, and ergothioneine. The available data may provide a basis for formulation of different mushroom-derived healthy biotech products from this fungus (Islam et al. 2022).

The Ascomycetes species from the genus *Cordyceps* (Ophiocordycipitaceae, Hypocreales) has been used in Asian countries for longevity and healthy life. The fruiting bodies of these entomophagous fungi develop and erupt from the head of larva and adult stages of other insect species. Numerous *Cordyceps* species were described in *Materia Medica* and used in TCM for more than 2000 years. Among these species, *Cordyceps sinensis* (syn. *Ophiocordyceps sinensis*), with various hosts, including *Hepialus armoricanus,* is the most widely used fungus. *Cordyceps militaris,* the orange caterpillar fungus, has a similar chemical composition and biological activities to *C. sinensis.* Although many *in vitro* and *in vivo* studies of *Cordyceps* species have been performed, it is still debatable whether they are healthy food supplements or therapeutics. Nonetheless, the *Cordyceps* industry has significantly advanced and offers thousands of products commonly available worldwide (Elkhateeb and Daba 2022b; Mapook et al. 2022). Nowadays, the major *Cordyceps*-based companies are ALOHA MEDICINALS (USA, https://www.alohamedicinals.com); DOCTORS BEST (USA, https://www.drbvitamins.com); HOSTDEFENSE MUSHROOMS (USA https://hostdefense.com); HERBSENS (China, https://www.herbsens.com); RealHerbs (USA http://www.irealherbs.com); TEREZIA (Czech Republic, https://www.terezia.eu); ZEINPHARMA (Germany, https://www.zeinpharma.com); THE REALLY HEALTHY (UK, https://www.healthy.co.uk) and others.

Thus, mushrooms possess unexplored potential to develop different mycoproducts, such as pharmaceuticals, nutraceuticals, nutriceuticals, and cosmeceuticals (Badalyan et al. 2019, 2022; Badalyan and Rapior 2021a, b; Elkhateeb and Daba 2022a). The sustainable approach for using nutritional values and health benefits of bioactive metabolites of edible and medicinal mushrooms will assist in their further biomedical and biotechnological applications (Badalyan 2012; Kües and Badalyan 2017; Badalyan et al. 2019; Badalyan and Rapior 2021a, b; El-Ramady et al. 2022; Badalyan et al. 2022). However, extensive pre-clinical and clinical studies are warranted to explore the economic sustainability of different mushroom species and evaluate their potential applications in biomedicine. New nano-technological approaches, such as nano-biofortification, nano-emulsion techniques, and usage of silver nanoparticles (AgNPs), are needed to supply edible

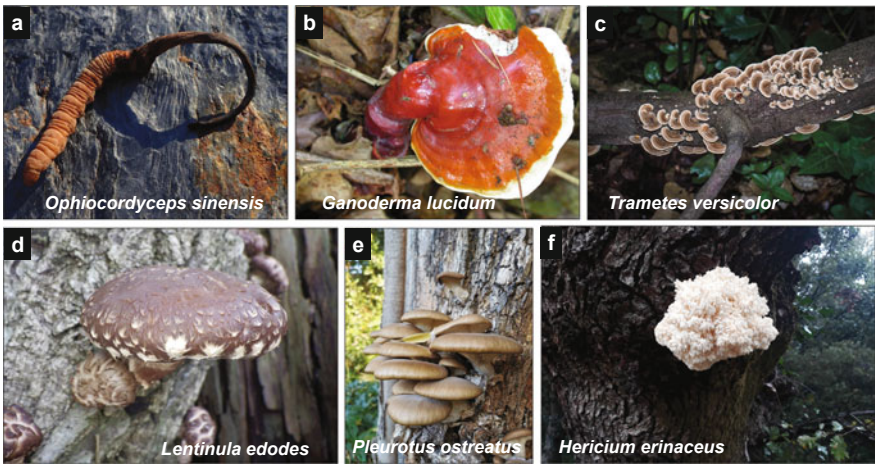

Fig. 1 (**a**–**f**) The fruiting bodies of wild-growing medicinal mushrooms used as therapeutic agents: (**a**) *Ophiocordyceps (=Cordyceps) sinensis* (Courtesy of Rioult JP), (**b**) *Ganoderma lucidum* (Courtesy of Rioult JP), (**c**) *Trametes versicolor* (Courtesy of Nespoulous D), (**d**) *Lentinula edodes* (Courtesy of Nebel RE), (**e**) *Pleurotus ostreatus* (Courtesy of Nespoulous D), (**f**) *Hericium erinaceus* (Courtesy of Bessière JM)

mushrooms with essential nutrients and increase their bioactive ingredients (Badalyan et al. 2019; Kaplan et al. 2021; Chandrawanshi et al. 2022; El-Ramady et al. 2022; Mishra and Kaladhar 2022). Further metabolomic and genomic studies of unexplored biotechnological potential of mushrooms may assist in the production of novel mushroom-derived biotech products for human welfare (Chaturvedi et al. 2018, 2019; Badalyan and Zambonelli 2019, 2023; Bolaniran et al. 2021; Kaplan et al. 2022).

The advancements in the study of mushrooms as promising therapeutic resources and perspectives for their biotechnological and biomedical application are discussed in this Chapter. Selected wild-growing fruiting bodies of medicinal mushrooms used as therapeutic agents are shown in Fig. 1a–f.

2 Mushroom-Derived Biomolecules and Mycopharmacology

The mushrooms-derived biomolecules mainly belong to polysaccharides, polyphenolics, sterols, terpenoids, proteins, and alkaloids which can be a source for developing novel health-enhancing formulations used in mycotherapy (Da Silva de Souza et al. 2017; Badalyan et al. 2019; Badalyan and Rapior 2021a, b; Girometta 2019; Elsayed et al. 2021; Das et al. 2022b; Elkhateeb and Daba 2022a; Kuo et al. 2022; López-Hortas et al. 2022; Meade et al. 2022) (Table 1). Identification of bioactive molecules is necessary to assess their pharmaceutical potential, safety, and efficacy.

Table 1 Therapeutic potential of mushroom-derived bioactive molecules

Species	Bioactive compound(s)	Therapeutic effect(s)	References
Amanita muscaria	α-D-Galactan (GAL-Am), *β*-D-Glucan (GLC-Am)	Antitumor	Zavadinack et al. (2021)
Amylosporus cf. *graminicola* and *Amylosporus* cf. *campbelii*	Colletochlorin B -amylosporanes derivatives	Antibacterial, cytotoxic	Kemkuignou et al. (2022); Hamad et al. (2022)
Astraeus hygrometricus	Astrakurkurone	Cytotoxic	Dasgupta et al. (2019)
Auricularia auricula	Melanin	Antioxidant, hypolipidemic, hepatoprotective	Chen et al. (2014); Hou et al. (2021)
Calocybe gambosa	α-Tocopherol, organic and fatty acids	Antioxidant with moderate antimicrobial potential	Petrović et al. (2022)
Cordyceps sinensis	Cordymin, Cordycepin, adenosine, *β*-(1-3)-D-glucan, ergosterol, mannitol	Hypoglycemic, antitumor, anti-inflammatory, antioxidant, antimicrobial	Elkhateeb and Daba (2022b)
Cordyceps militaris	Cordycepin, mannitol	Anti-inflammatory, hypolipidemic, antitumor	Chen et al. (2014); Phull et al. (2022); Elkhateeb and Daba (2022b)
Cortinarius sp.	Polyketides rufoolivacin E viocristin B	Antioxidant	Song et al. (2022a)
Fomitopsis (=*Laricifomes*) *officinalis*	Chlorinated coumarins from mycelia and lanostane triterpenoids from basidiomes	Antiviral, antibacterial, trypanocidal	Girometta (2019)
Fomitopsis palustris	Polyporenic acid B, palustrisolides A, C, and G	Cytotoxic	Zhao et al. (2018)
Fomitopsis pinicola	Lanostane triterpenoids, pinicopsic acid F, 16-α-hydroxy-3-oxolanosta-7,9 (11),24-trien-21-oic acid	Anti-inflammatory	Liu et al. (2022)
Favolaschia calocera	Ergostane triterpenoid favolon, favolon C, norergostane laschiatrion	Antifungal	Palasarn et al. (2022)
Ganoderma lucidum	Triterpenes and aromatic meroterpenoids	Antioxidant, neuroprotective	Badalyan et al. (2019); Badalyan and Rapior (2021a, b); Wang et al. (2019)
Ganoderma resinaceum	Branched mannogalactan [O-2-*β*-D-mannosyl-(1→6)-*α*-D-galactan] and highly branched *β*-D-glucan (1→3) (1→4)(1→6)-*β*-D-glucan	Antitumor, immunomodulatory	Badalyan et al. (2019); Badalyan and Rapior (2021b); Bleha et al. (2022);

(continued)

Table 1 (continued)

Species	Bioactive compound(s)	Therapeutic effect(s)	References
Ganoderma tsugae	Tsugaric acid F, palmitamide	Cytotoxic	Lin et al. (2016)
Hericium erinaceus	Terpenoid erinacine A	Neuroprotective, antioxidant, antitumor, anti-aging, hypolipidemic, gastroprotective	Badalyan and Rapior (2021b); Kuo et al. (2022)
Inonotus nidus-pici	Citropremide, 3,4-dihydroxybenzalacetone, lanosterol, ergost-6,8,22-trien-3β-ol, and ergosterol peroxide	Antimicrobial, antioxidant, anti-proliferative	Garádi et al. (2021)
Inonotus obliquus	Inotodiol, trametenolic acids, polysaccharides IOP	Cytotoxic, hepatoprotective	Zhang et al. (2018b); Li et al. (2019); Khoroshutin et al. (2021); Lee et al. (2021)
Isaria sinclairii	Amino acid myriocin	Immuno-suppressive	Ayzenberg et al. (2016); Chiba (2020); Cuello-Oderiz and McGraw (2022)
Lentinula edodes	Peptide latcripin 7A (LP-7A)	Antitumor, proapoptic	Din et al. (2020)
Neonothopanus nimbi	Phenolic scaffolds neonambiterphenyls-A	Antiviral, anti-COVID-19, anti SARS-CoV-2	Sen et al. (2022)
Ophiocordyceps gracilis (anamorph *Paraisaria dubia*)	Polysaccharides	Antioxidant	Tong et al. (2022)
Phellinus orientoasiaticus	Cyclohumulanoids of illudane-, sterpurane-, and tremulane-type scaffolds	Anti-inflammatory	Pham et al. (2022)
Piptoporus betulinus	Piptolinic acid A	Cytotoxic	Tohtahon et al. (2017)
Pleurotus flabellatus	Lectin PFL-L	Antibacterial	Murugesan and Gunasagaran (2021)
Polyozellus multiplex	Phenolics and flavonoids	Antiviral (anti-COVID-19)	Sen et al. (2022)
Polyozellus multiplex	Terphenylquinone pigment thelephoric acid (Thel)	Enhance alkaline phosphatase activity and bone matrix mineralization in pre-osteoblasts, cell adhesion, and migration in osteoblast differentiation	Park et al. (2022)

(continued)

Table 1 (continued)

Species	Bioactive compound(s)	Therapeutic effect(s)	References
Taiwanofungus camphoratus	Triterpenoids, phytosterols, antcin A, B, C, H, and K, dehydroeburicoic and dehydrosulphurenic acids	Hepatoprotective inducing hepatocellular carcinoma apoptosis, antitumor	Hsieh et al. (2011); Huang et al. (2012); Lu et al. (2020); Du et al. (2012); Wang et al. (2022a)
Trametes versicolor	Protein musarin	Anti-proliferative, cytotoxic	He et al. (2021b)
Tricholoma pardinum	Pardinols A–H, saponaceol B	Anti-inflammatory, cytotoxic	Zhang et al. (2018a, b)
Wolfiporia cocos (=*Poria cocos*)	Poricoic acid GM, lanostane triterpenoids	Anti-inflammatory, antioxidant, immunomodulatory	Bao et al. (2022)
Xylaria sp.	Eremophilanes, xylariones A1−B2 (2,5-diarylcyclopentenones), xylaripyone A-G (α-pyrone derivatives), xylaripyone H (γ-pyrone, derivative), diketopiperazine cyclo-(L-Leu-N-ethyl-L-Glu)	Antitumor, antioxidant anti-proliferative, anti-inflammatory antibacterial, anti-obesity, antiviral	Yuyama et al. (2017); Song et al. (2022b)
Xylodon flaviporus	Drimane-type sesquiterpene	–	Pham et al. (2022)

Evaluation of bioactive metabolites is also required to avoid the risk of post-market withdrawal of different bioproducts, including mycoproducts.

2.1 Polysaccharides

Despite advancements in cancer treatment, including chemotherapy, radiotherapy, hormonal therapy, and surgery, researchers are pursuing novel bioactive compounds to treat malignancy to avoid adverse side effects. Fungal polysaccharides have shown a huge therapeutic potential in this field of clinical research (Jin et al. 2012; Aras et al. 2018; Dasgupta et al. 2019; Daba et al. 2020; Din et al. 2020; He et al. 2021a, b; Xu et al. 2021; Chandrawanshi et al. 2022; Mishra and Kaladhar 2022).

Polysaccharides are classified according to their structure (linear and branched), sugar composition (homo- and hetero-polysaccharides), and type of bonds between monomers, such as β-(1→3), β-(1→6), or α-(1→3), etc. Fungal polysaccharides mainly belong to β-glucans with a backbone of glucose residues linked by β-(1→3)-glycosidic bonds and an attached β-(1→6) branch. The antitumor activities of fungal polysaccharides mainly depend on their molecular mass, degree of branching, conformation, and structure modification. The polysaccharides isolated particularly

from medicinal mushrooms *G. lucidum* (Reishi or Lingzhi), *Grifola frondosa* (Maitake), *Trametes versicolor,* and *Schizophyllum commune* exert their antitumor effect through their immunomodulatory activity (Ferreira et al. 2015; Wasser 2017; Badalyan et al. 2019). Higher molecular weight and low degree of branching of polysaccharides increase immunomodulatory effect of these molecules. The role of primary structures (sidechain length, branching) and conformations (single helix, triple helix, or random coil) is important for this activity and remain to be clarified (Han et al. 2020).

Polysaccharides isolated from the aqueous extracts (AE) of *Ganoderma resinaceum* contain two main polysaccharides: mannogalactan, a branched *O*-2-*β*-D-mannosyl-(1→6)-*α*-D-galactan and a highly branched (1→3)(1→4)(1→6)-*β*-D-glucan. Mannogalactan predominated in cold-water extract, whereas *β*-D-glucan was the main product of hot-water extract. Three sub-fractions from the hot-water soluble fraction contained branched *β*-D-glucans. The alkaline extract contained a linear (1→3)-*α*-D-glucan and a weakly branched (1→3)-*β*-D-glucan having terminal *β*-D-glucosyl residues attached to *O*-6 of the backbone. Following all extractions, the insoluble part of extract was identified as a polysaccharide complex containing chitin and *β*-D-glucans (Bleha et al. 2022).

The antitumor potential of *α*-D-galactan (GAL-Am) and *β*-D-glucan (GLC-Am) chemically characterized and purified from fruiting bodies of *Amanita muscaria* have been studied using B16-F10 murine melanoma and non-tumorigenic fibroblast BALB/3T3 clone A31 cell line. Both polysaccharides showed a selective reduction in proliferation against melanoma cells and did not affect non-tumorigenic fibroblast cells. GAL-Am or GLC-Am did not modulate the adhesion of B16-F10 cells. They selectively reduced melanoma cell viability and proliferation, suggesting further investigation to evaluate their anti-melanoma properties (Zavadinack et al. 2021).

The administration of polysaccharides extracted from edible medicinal oyster mushroom *Pleurotus ostreatus* showed anti-cancer and anti-ascitic effects in *in vivo* and *in vitro* experiments. They significantly decreased the tumor cell metastasis and increased survival in mouse models of H22 malignant ascites. The downregulation of regenerative genes Foxp3 and Stat3 and secretion of immunological factors IL-2, TNF-α, and INF-γ were observed after treatment with the extracted and partially purified polysaccharide derived from *P. ostreatus*. Consistent with tumor suppression hypothesis *in vivo*, polysaccharides decrease invasion and migration capabilities and induce the chain of gene regulation processes leading to apoptosis in the hepatocellular carcinoma (HCC) cell line (Khinsar et al. 2021).

It has been shown that sulfated *P. ostreatus*-derived polysaccharides revealed a stronger anticoagulant activity *in vitro* than in other conditions in the intrinsic pathway, which indicate that they significantly improved the plasma clot formation inhibitory activity by intrinsic and extrinsic pathways compared to native polysaccharides. Moreover, the cytotoxicity of polysaccharides against two normal cell lines was reduced. These findings suggest that *P. ostreatus*-derived polysaccharides may be an alternative to anticoagulant therapy (Rizkyana et al. 2022).

The method for enhancing intracellular polysaccharide (IPS) production by the anamorph (*Paraisaria dubia*) of *Ophiocordyceps gracilis* has been developed. The highest IPS and exopolysaccharides (EPS) yield in a 5 L bioreactor reached 83.23 ± 1.4 mg/mL and 518.50 ± 4.1 mg/L, respectively. Both IPS and EPS showed high antioxidant activity (AOA) (Tong et al. 2022).

The effects of polysaccharides isolated from medicinal mushrooms, *Lentinus edodes* and *Agaricus blazei* Murill (ABM), on the gelation process of the Pluronic® F127 copolymer have been evaluated. Their structural characterization revealed a *β*-glucan from *L. edodes* and a proteoglycan complex from ABM. Both possess rheological properties to develop pharmaceutical formulations with AOA and low cytotoxicity against human neutrophils (Menezes et al. 2022).

The dietary supplements obtained from mycelial extracts of *Lentinus* (*Pleurotus*) *sajor-caju* may improve their beneficial properties by increasing the amount of proteins or polysaccharides about 3.5- and 4.5-fold, respectively. *In vitro* antioxidant and anticancer activities against human normal colon epithelial cells (CCD 841 CoTr) and colorectal cancer cells (HT-29, SW948, and LS 180) have been reported. The viability of cancer cells was reduced along with pro-apoptotic and NO (nitric oxide)-secreting effects of their extracts. However, the mechanisms for this activity remain to be elucidated. This study suggests that polysaccharides have multiple nutritional and anticancer properties and may be used as a source of therapeutic biomolecules or functional foods (Zając et al. 2021).

S. commune is a source of chitin-glucan complex (CGC) with biodegradable, biocompatible, antioxidant, and antibacterial properties. It is also considered a powerful agent in wound-healing therapy. The optimization of CGC nanofibers by electrospinning showed that CGC/PVA/gelatin nanofibers inhibited the growth of *Escherichia coli* and *Staphylococcus aureus* by 25% and 78% after 24 h, respectively. These nanofibers are non-toxic to fibroblast cells and improve their proliferation and adhesion. *S. commune* CGC nanofibers showed 86% wound-healing effect in Wistar rats (Zeynali et al. 2022).

In vitro antioxidant and immunomodulatory potential of a crude polysaccharide obtained from *Termitomyces medius* has been previously reported using cell proliferation, stimulation of phagocytosis, NO release capacity, and reactive oxygen species (ROS) production in murine macrophage cell line RAW 264.7. However, *in vivo* trials are required for the development of pharmaceutical applications and to study medicinal properties of these polysaccharides (Mitra et al. 2021).

2.2 Terpenoids, Steroids, Sterols, and Lipids

Since ancient times, humans have been interested in natural products derived from plants and fungi. Mushrooms are considered sources of different terpenoids, steroids, sterols, and lipids with antioxidant, antibacterial, antimitotic, neuroprotective, anti-inflammatory, cytotoxic, immunomodulatory, and other pharmacological effects (Corrêa et al. 2017; Wasser 2017; Morel et al. 2018, 2021; Badalyan et al.

2019; Badalyan and Rapior 2021a, b; Wang et al. 2019; Akiba et al. 2020; Diallo et al. 2020, 2021).

However, mushrooms, as a source of bioactive terpenoids, have not been sufficiently investigated; mushroom-derived terpenoids and their therapeutic properties have been used in pre- and post-clinical trials (Badalyan et al. 2019; Dasgupta and Acharya 2019).

Ganoderma species possess two main types of biomolecules: polysaccharides with antioxidant and immunomodulatory activities and lanostane-type triterpenoids, such as ganoderic acids (GAs) with antimicrobial, anticancer, antiviral, and immunomodulatory effects. Triterpenoids constitute more than 0.5% of *Ganoderma* fruiting bodies on a DW basis. At least 561 triterpenoids have been isolated from *Ganoderma* mushrooms, particularly from *G. lucidum, G. lingzhi, G. sinense*, and *G. leucocontextum*. The *Ganoderma* triterpenoids are structurally different. Among these GAs, ganoderiols, lucidones, lucidenic acids, and ganolucidic acids are considered the most important for their bioactivity (Kües and Badalyan 2017; Angulo-Sanchez et al. 2022).

GAs are highly oxygenated triterpenoids with different functional groups attached to the lanostane skeleton, allowing new drugs to be developed to treat multiple illnesses, including cancer. Cytotoxic effects of GAs have been associated with inhibitory activity of specific targets, such as STAT3, to induce apoptosis and increase NK-cell activity. Due to the bioactivity of *Ganoderma* terpenoids, novel strategies are developing for their synthesis. The current knowledge on *Ganoderma* triterpenoids and their production, biosynthesis, pharmacological properties, gene expression in liquid culture, and their pharmacological potential has been reported (Angulo-Sanchez et al. 2022). According to the authors, the investigation of mechanisms of action of GAs is still warranted despite extensive information about their bioactivities, particularly in cancer, as well as their pharmacokinetic and toxicological properties to advance their application in clinical models. Moreover, it is necessary to characterize different phases of the life cycle (primary and secondary mycelia and fruiting bodies) of strains since biotic and abiotic ecological factors, combined with genetic intraspecies variability, play a significant role in the synthesis of bioactive compounds.

Around 431 secondary metabolites, 380 terpenoids, 30 steroids, and other bioactive compounds have been isolated from 22 *Ganoderma* species (Baby et al. 2015). The structure-activity relationship of these molecules has been revealed (Castellano and Torrens 2015).

Cancer chemopreventive agents, such as a new lanostanoid named tsugaric acid F and a new palmitamide with weak antioxidant and cytotoxic activities against PC3 cells (human prostate cancer cell line) were isolated and characterized from *Ganoderma tsugae* (Lin et al. 2016).

Fourteen lanostane triterpenoids, nine *Ganoderma* acids, and five *Ganoderma* alcohols were isolated from *Ganoderma hainanense* fruiting bodies. Reviewing *G. hainanense*, a species similar to *G. lucidum* and *Ganoderma sinense*, containing lanostane triterpenoids, the former might also have a broad spectrum of activities, especially as an anticancer agent against HL-60, SMMC-7721, A-549 and MCF-7

(Peng et al. 2015). Three undescribed lanostane triterpenoids, ganoellipsic acids A-C, and seven known *Ganoderma* lanostanoids have been isolated from cultivated fruiting bodies of *Ganoderma ellipsoideum*. The chemical structures of these compounds have been elucidated (Sappan et al. 2022).

Seven secondary metabolites, including a new lanostane triterpene, two known aromatic meroterpenoids, and four known triterpenes, were isolated from the fruiting bodies of *G. lucidum.* They showed *in vitro* AOA and neuroprotective effect (NPE) against H_2O_2 and aged Aβ-induced cell death in SH-SY5Y cells (thrice-subcloned cell line derived from the SK-N-SH neuroblastoma cell line). Therefore, *G. lucidum*-derived meroterpenoids may be suggested as potential antioxidants and neuroprotective functional food ingredients to prevent the development of neurodegenerative diseases (NDD) (Wang et al. 2019).

Terpenoid erinacine A extracted from the mycelial biomass of russuloid mushroom *Hericium erinaceus* was intravenously and *per os* administered to Sprague-Dawley rats. The bioavailability of erinacine A in rats after *per os* administration at 2.381 g/kg body weight (BW), *H. erinaceus* mycelium extract (equivalent to 50 mg/kg BW of erinacine A) was 24.39%. These preclinical studies initially showed that erinacine A could pass the blood-brain barrier of rats by passive diffusion. Further studies of metabolomic profiles of erinacine A to develop *H. erinaceus* mycelium-based neuroprotective drugs are warranted (Tsai et al. 2021).

Thirteen undescribed lanostane triterpenoids, including six C25–C27 nor-lanostane derivatives and nine known derivatives, were isolated from fruiting bodies of *Fomitopsis pinicola*. Anti-inflammatory assays indicated that pinicopsic acid F and 16α-hydroxy-3-oxolanosta-7,9(11),24-trien-21-oic acid showed moderate inhibitory effects against lipopolysaccharide (LPS)-induced NO production in RAW 264.7 cells, with IC_{50} values of 24.5 and 25.7 μM, respectively (Liu et al. 2022).

Fifteen undescribed lanostane-like C31-triterpenoid derivatives and five known derivatives (palustrisoic and polyporenic acids) were isolated from the hydro-alcoholic extract of cultivated *Fomitopsis palustris* fruiting bodies. Polyporenic acid B demonstrated strong cytotoxicity against cell lines HCT116, A549, and HepG2, while weak cytotoxicity of palustrisolids A, C, and G was shown (Zhao et al. 2018).

The chemical study of cultivated edible medicinal mushroom *Wolfiporia cocos* (= *Poria cocos*) revealed 46 lanostane triterpenoids containing 17 new compounds. Evaluation of anti-inflammatory activities of these compounds showed that poricoic acid GM significantly inhibited NO production in LPS-induced RAW264.7 murine macrophages ($IC_{50} = 9.73$ μM). Moreover, poricoic acid GM induced HO-1 protein expression, inhibited iNOS and COX2 protein expression, and released PGE2, IL-1β, IL-6, TNF-α, and ROS in murine macrophages. The poricoic acid GM suppressed IκBα protein phosphorylation to regulate antioxidant genes. The lanostane triterpenoids proved to be the key compounds responsible for anti-inflammatory properties of *W. cocos* (Bao et al. 2022).

Isolation and structure elucidation of three new meroterpenoids and seven known compounds from chloroform extracts of agaricomycete fungus *Albatrellus*

yasudae and their Aβ-aggregation inhibitory activity have been reported. Apart from known grifolin, grifolic acid, neogrifolin, confluentin, 2-hydroxyneogrifolin, daurichromenic acid, and a cerebroside derivative, three novel compounds were identified (Akiba et al. 2020).

The steroids and polysaccharides isolated from the sclerotia of *Polyporus umbellatus* play an important role in diuresis and nephroprotection. The metabolic pathways indicated that steroids, fatty acids, and carbohydrates were actively produced when *P. umbellatus* sclerotia was infected by *Armillaria mellea*. The contents of ergosterol, polyporusterone A, and B are increased by 32.2%, 75.0%, and 20.0%, respectively. The comprehensive metabolomic and transcriptomic information will contribute to studying the mechanisms of *P. umbellatus* sclerotial formation infected by *A. mellea* (Xing et al. 2021).

Eight undescribed lanostane triterpenoids, pardinols A-H, and a previously reported lanostane triterpenoid saponaceol B were isolated from *Tricholoma pardinum* fruiting bodies. Pardinols B and E-H demonstrated inhibitory effects on NO production with an IC_{50} value ranging from 5.3 to 14.7 mM. The cytotoxicity against five human cancer cell lines with IC_{50} values less than 40 mM was also shown (Zhang et al. 2018a).

According to Tohtahon et al. (2017), a lanostane triterpenoid piptolinic acid A isolated from methanolic extract (ME) of *Piptoporus betulinus* exhibited both cytotoxic activity against human promyelocytic leukemia cell line HL-60 and human acute monocytic leukemia cell line THP-1 (IC_{50} = 1.77 mM and IC_{50} = 8.21 mM, respectively). Lanostane and ergostane triterpenoids have also been identified in the medicinal mushroom *Antrodia cinnamomea* (Qiao et al. 2015).

Bioactive eremophilane-type sesquiterpenes with a broad spectrum of bioactivity, including antibacterial, anti-inflammatory, anti-obesity, antiviral and cytotoxic, have been observed in several macrofungi, especially from the ascomycete genus *Xylaria* (Yuyama et al. 2017).

A bis-epoxide ergostane triterpenoid favolon, its undescribed derivative favolon C, and a biogenetically related norergostane laschiatrion were isolated from the cultures of agaricoid species *Favolaschia calocera*. The study initially described the stereochemistry of favolon and its derivatives (Palasarn et al. 2022).

Further chemical screening of mushrooms allows the discovery of new pharmacologically promising terpenoids, steroids, and sterols with therapeutic effects.

2.3 Phenolics

Phenolics represent a diverse group of bioactive compounds, including flavonoids, phenolic acids, quinones, tocopherols, tannins, etc. Mushroom-derived phenolics are known for their various therapeutic effects, including anti-inflammatory, antioxidant, analgesic, and neuroprotective (Badalyan et al. 2019; Dhakal et al. 2019; Badalyan and Rapior 2021a, b). Phenolic compounds, flavonoids, ascorbic acid, β-carotene, and lycopene have been detected in fruiting body extracts of

G. frondosa, S. commune, Volvariella volvacea (Acharya et al. 2015, 2016; Yao et al. 2016; Butkhup et al. 2018).

The study of total phenolic content, as well as antioxidant, antimicrobial, and inhibitory effects against cholinesterase, tyrosinase, α-amylase, and α-glucosidase activities of ME and AE obtained from *Ganoderma applanatum* suggest that they may be considered a source of new food supplements and represent a model for the development of new drug formulations (Zengin et al. 2015).

Studies of AOA of cultivated edible mushrooms *A. bisporus* and *P. ostreatus,* as well as several wild-growing edible species, such as *Boletus edulis*, *Cantharellus cibarius, Russula alutacea,* and *Trametes* species, identified them as sources of phenolics and flavonoids (Buruleanu et al. 2018). The total phenolic contents (coumarins, flavanols, flavonols, isoflavonoid derivatives, phenolic acids) and AOA of *T. versicolor* and *T. gibbosa* were evaluated using ME and AE. The highest AOA was observed in ME, whereas the highest polyphenol and flavonoid contents were detected in AE (Pop et al. 2018).

Recently, Psurtseva et al. (2022) analyzed three *Sparassis crispa* strains on various agar and liquid media for growth and production of phenolic compounds, such as sparassol (methyl-2-hydroxy-4-methoxy-6-methylbenzoate), methyl ester of sparassol, and methyl ester of orsellinic acid. The strain LE-BIN 2902 of *S. crispa* was considered promising for the production of sparassol.

2.4 Amino Acids and Proteins

A natural immunosuppressive product, myriocin—a complex amino acid, was isolated from culture broths of ascomycete fungus *Isaria sinclairii.* After extensive chemical modification and pharmacological evaluation, a highly potent immunosuppressor, fingolimod, was developed. Fingolimod is a sphingosine-1-phosphate receptor 1 (S1PR1) modulator used as a therapeutic agent for treatment of multiple sclerosis (MS) and autoimmune diseases of the central nervous system. The analysis of mechanism of action of fingolimod revealed its molecular target as S1PR1, which plays an essential role in lymphocyte circulation. Phosphorylated fingolimod acted as an antagonist of S1PR1, modulates lymphocyte circulation, and shows potent immunosuppressive activity (Chiba 2020). Previous studies have showed that fingolimod significantly reduced the relapse rate of MS and has been approved as a new medicinal product in many countries (Kappos et al. 2015; Derfuss et al. 2016).

The unphosphorylated fingolimod reduces the ability of cytotoxic CD8 T-cells to kill their target cells which can increase susceptibility to viral infections and enhance therapeutic efficacy in MS. Fingolimod modulates the proliferation of anti-inflammatory M2 phenotype macrophages, their morphology, and ability to release cytokines. It has been reported to be a cannabinoid receptor antagonist, a phospholipase A2 (cPLA2) and a ceramide synthase inhibitor, it also stimulated the repair processes of glial cells and glial precursor cells after injury. Preclinical and clinical

data have revealed NPE of fingolimod, which may open a perspective for future therapeutic approaches and diagnosis of NDD, such as stroke, Alzheimer's, and other diseases (Ayzenberg et al. 2016; Chiba 2020; Cuello-Oderiz and McGraw 2022).

The development of effective chemotherapeutic drugs with few side effects is still continuing. The peptide latcripin-7A (LP-7A), extracted from *L. edodes*, causes apoptosis and autophagy of MCF-7 and MDA-MB-231 breast cancer cells by inducing their growth arrest at G_0/G_1 phase and decreasing mitochondrial membrane potential without adverse effects on MCF-10A normal breast cells (Din et al. 2020).

The amino acids, protein, mineral, and fatty acid composition and nutritional values of uncooked and pressure-cooked gasteroid fungus *Astraeus hygrometricus* have been studied. The results have shown that all samples possess nutritional values with sufficient protein, high carbohydrate and fiber contents, and low-fat amount with antioxidant properties (Pavithra et al. 2018).

2.5 Lectins and Other Compounds

Lectins, also known as hemagglutinins, are proteins that specifically and reversibly bind to certain carbohydrates and are involved in various biological processes at the level of recognition between cells.

Lectins are largely distributed in mushrooms and account for their potential medicinal properties, including antitumor, mitogenic/antimitogenic, nematocidal, entomocidal, immunomodulatory, antiviral, and other effects (Sabotič et al. 2016; Kües and Badalyan 2017; Singh et al. 2017; Badalyan et al. 2019; Badalyan and Rapior 2021a, b). The antibacterial effect of 18 kDa lectin purified from *Pleurotus flabellatus* (PF-L) has been reported against Gram-positive (*Bacillus subtilis, and S. aureus*) and Gram-negative (*Pseudomonas aeruginosa, E. coli, and Klebsiella pneumoniae*) human pathogens. PF-L also possesses a potent antioxidant effect (Murugesan and Gunasagaran 2021).

The mushroom-derived alkaloids and related compounds have recently been described by Zorrilla and Evidente (2022). The authors classified five subgroups as β-carboline alkaloids, pyrroloquinoline alkaloids, pyrrole alkaloids, indole alkaloids, and miscellaneous alkaloids. The isolation, structure, biological activities, and pharmacological potential of fungal alkaloids to develop drugs and agrochemicals have been reported. Among bioactive indole alkaloids, psilocybin and psilocin are two the most studied hallucinogenic compounds (Dinis-Oliveira 2017). Moreover, psilocin-containing mushrooms, as viable chemotherapeutic agents against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), have recently been proposed (Khan et al. 2022) (**see Part 3.5**).

3 Mushrooms as Therapeutics

The literature data, case studies, and information derived from traditional medicine and ethno-mycological data show that mushrooms possess promising pharmacological potential (anti-allergic, antibacterial, anti-depressant, antifungal, anti-inflammatory, antioxidant, antiviral, cardio-, hepato- and neuroprotective, cytotoxic, hypotensive, immunomodulatory, etc.). Therefore, they can be considered promising sources for developing new mycopharmaceuticals and functional food with health-enhancing effects (Wasser 2011, 2014; Özcan and Ertan 2018; Sharma et al. 2018, 2022a, b; Badalyan and Zambonelli 2019; Badalyan et al. 2019; Badalyan and Rapior 2021a, b).

The traditional usage of mushrooms and a growing scientific interest due to their valuable chemical composition, nutritional value, and therapeutic properties allow considering them as natural source for the development of mushroom-derived bioproducts, including healthy food, pharmaceuticals, nutraceuticals, and cosmeceuticals (Chang and Wasser 2012; Badalyan and Zambonelli 2019, 2023; Badalyan et al. 2019, 2022; Badalyan 2020; Badalyan and Gharibyan 2020; Badalyan and Rapior 2021a, b; Bolaniran et al. 2021; Cateni et al. 2021; Elkhateeb et al. 2021b; Elkhateeb and Daba 2022a; El-Ramady et al. 2022) (Table 1).

Isolation, purification, identification, and characterization of bioactive compounds from edible mushrooms, the study of their chemical and biological properties, extraction techniques, and food applications have recently been updated (López-Hortas et al. 2022).

The chemical composition (13 minerals, 23 polyphenols, 11 organic acids, 22 carbohydrates) and medicinal properties (antimicrobial, antioxidant, hypoglycemic, neuroprotective, and cytotoxic) of methanolic and acetone extracts of edible giant polypore *Meripilus giganteus* have been reported (Petrović et al. 2022). According to authors, the antimicrobial activity of tested extracts ranged from 0.002 to 20 mg/mL. The AOA was detected by DPPH assay as a half maximal inhibitory concentration (IC_{50}) was 673.42 and 712.31 μg/mL for methanolic and aceton extracts, respectively, and by reducing power assay from 0.042 to 0.099 mg/mL. The total phenolic content was determined as 4.86 mg gallic acid equivalents (GAE)/g for the ME and 5.06 mg GAE/g for the aceton extract. The hypoglycemic effects of tested extracts ranged from 30.66% to 38.67% and 11.06% to 17.08%, respectively. The NPE of *M. giganteus* tested by acetylcholinesterase inhibition assay ranged from 4.54% to 9.31%, while the cytotoxic activity revealed by microtetrazolium assay—196.24 μg/mL to 322.8 μg/mL. Based on obtained data, *M. giganteus* extracts were considered natural sources of therapeutic compounds without side effects (Petrović et al. 2022).

The edible medicinal mushroom *H. erinaceus* is known for its nutraceutical and pharmaceutical properties, particularly, antioxidant, antitumor, anti-aging, hypolipidemic, and anti-inflammatory. Erinacine A has been reported as the main bioactive compound in the mycelium of *H. erinaceus* as a potential source of functional food widely used to treatment of neurological diseases. The consumption

of erinacine A-enriched mycelium has shown significant nutraceutical effects in Alzheimer's and Parkinson's diseases, ischemic stroke, and other NDDs (Badalyan and Rapior 2021a; Kuo et al. 2022).

For the first time, the metabolic process of erinacine A and identification of its metabolites from the rat and human liver S9 fraction were described. The results have shown that 75.44% of erinacin A was metabolized within 60 min in rats and 32.34% within 120 min in humans. Five major metabolites of erinacin A were detected and identified. A better understanding of metabolic process of erinacin A and creation of a database on its metabolic profile may facilitate further nutraceutical application and discovery of related biomarkers of this unique bioactive molecule (Kuo et al. 2022).

The exotic edible fungus *Dictyophora indusiata* (= *Phallus indusiatus*) is known for its numerous medicinal properties. Comprehensive reviews of chemistry, pharmacology and potential therapeutic applications of extracts and compounds obtained from *D. indusiata* have been published (Habtemariam 2019). The chemistry of polysaccharides, as major bioactive compounds (β-(1→3)-D-glucan with side branches of β-(1→6)-glucosyl units) are discussed, whereas low molecular weight compounds include terpenoids and alkaloids. The biochemical and cellular mechanisms of different therapeutic actions, such as antioxidant and anti-inflammatory, were reported along with potential applications in cancer therapy, immunotherapy, and NDDs (Habtemariam 2019).

The medicinal mushroom *Leucocalocybe mongolica* possesses high nutritional, pharmaceutical, and therapeutic values. It has been used in a wide range of chronic diseases in TCM. Around 100 compounds (polysaccharides, sterols, lectins, laccase, amino acids, and volatiles) with significant pharmacological effects (antitumor, antiproliferative, hypoglycemic, hepatoprotective, and hypotensive) have been identified in this fungus. Since polysaccharides can increase NO production, they may also have an strong hypotensive effect. However, further studies are needed to assess the pharmacological potential of *L. mongolica* (Zaki et al. 2022).

Bioactive molecules extracted from edible and inedible bracket mushrooms show favorable biological potential and can be used to develop various health care bioproducts (Barros et al. 2008; Heleno et al. 2015a, b; Reis et al. 2017; Badalyan et al. 2019; Badalyan and Zambonelli 2023).

Chen et al. (2010) reported induction of ovulation in women with polycystic ovary syndrome by Maitake (*G. frondosa*) extract. In addition, amino acids, aromatic acids, flavones, polysaccharides, triterpenes, and other bioactive molecules isolated from the inedible bracket *Phelllinus linteus* exhibited anticancer, anti-inflammatory, antioxidant and hypoglycemic properties and contributed to the regulation of the immune system (Chen et al. 2016).

3.1 Antitumor and Immunomodulatory

Cancer is a leading cause of morbidity and mortality worldwide. Chemotherapy has been extensively used to treat certain types of cancer; however, side effects and drug resistance are the drawbacks of these agents. Therefore, the development of new strategies with minimal adverse effects, including natural compound therapy, is required.

Cancer cells reprogram their metabolism to meet the demands of uncontrolled proliferation and survival. This re-programming of lipid metabolism supports tumor growth, cancer metastasis, and therapy resistance. Therefore, targeting this process is regarded as a potential therapeutic strategy.

Bioactive molecules from plants and mushrooms have not been used as first-line therapy in oncology. The main anticancer and cytotoxic substances of fungal origin are polysaccharides, particularly immunomodulatory β-D-glucans and triterpenoids, such as ganoderic acids, the antagonists of growth factor receptors and inhibitors of cyclin-dependent kinase. However, the anticancer effects of mushrooms were typically demonstrated *in vitro* and *in vivo* models, and clinical studies conducted in humans are limited. Evaluation of the efficacy of adjuvant therapy with mushroom-derived molecules in combination with evidence-based medicine, as well as precisely designed experimental and clinical studies, could be an effective therapeutic approach (Joseph et al. 2018; Zmitrovich et al. 2022).

The anticancer activities of mushroom extracts tested *in vitro*, *in vivo,* and *in silico* experimental models were recently prospected using scientific electronic databases (Nowakowski et al. 2021a, b). The extracts obtained from 92 species, using 12 different solvents, reduced the viability of 38 various cancers (breast, cervical, colorectal, gastric, lung, ovarian, prostate etc.), and 61 extracts showed cytotoxicity against breast cancer in a broad spectrum of experimental models. Various anticancer mechanisms of action of mushroom extracts have been reported, as well (Nowakowski et al. 2021a).

Different signaling pathways, particularly WNT, SHH, TGF-β/Smad, and JAK/STAT, have been shown to modulate cancer development and progression. There is a growing evidence that genetic/epigenetic mutations and loss of apoptosis also require a "multi-molecular" perspective for development of cancer therapy. An overview of mushrooms' regulation of different signaling pathways and their bioactive compounds were reported (Aras et al. 2018). The regulation of WNT and JAK-STAT pathways by mushrooms has been extensively reviewed. However, information on the regulation of TGF-β /Smad, Notch, and TRAIL-induced signaling pathways is lacking due to superficial data. The mechanisms of modulation of oncogenic and tumor suppressor microRNAs by mushrooms in different cancers have not been sufficiently investigated, yet. Therefore, a detailed insight related to targeting multiple pathways by mushroom extracts or their bioactive compounds will be useful to fill the knowledge gap and transform medically valuable bioactive molecules into clinically effective therapy (Aras et al. 2018).

Mushroom-derived compounds also impact cancer cells, terminating the cell cycle and inhibiting proliferative signaling pathways PI3K/AKT, Wnt-CTNNB1, and NF-κB. Therefore, mushroom-derived bioactive molecules and extracts as therapeutic agents may be used in studies of multiple pathways (Joseph et al. 2018).

Gastric cancer (GC) is the fourth most commonly diagnosed cancer and the second leading cause of death worldwide. The medicinal fungus *Phellinus igniarius* is used in traditional medicine as an anticancer agent. The ethanolic extract of *Ph. igniarius* was studied against five human tumor cell lines HepG-2, AGS, SGC-7901, Hela, and A-549. The extract was the most cytotoxic against SGC-7901 cells *in vitro* and strongly inhibited tumor growth in xenografted nude mice *in vivo*. After treatment, typical morphological changes due to cell apoptosis, including chromatin condensation and nuclear fragmentation with the formation of apoptotic bodies, were observed. Fungal extract blocked the SGC-7901 cell cycle at G0/G1 phase and induced apoptosis by downregulating cyclin D1 expression. It caused a remarkable decrease in mitochondrial membrane potential and induced mitochondrial-dependent apoptosis by triggering the activation of caspases 9 and 3 and cleavage of PARP in SGC-7901 cells. Furthermore, *Ph. igniarius* extract increased Bax/Bcl-2 ratio in SGC-7901 cells *in vitro* and *in vivo*. Thus, *Ph. igniarius* may be a promising therapeutic agent for prevention and treatment of GC, as it may induce apoptosis of cancer cells through a mitochondria-dependent pathway (Wang et al. 2018).

Medicinal bracket fungus *Sanghuangprous vaninii* (= *Phellinus vaninii*) is used to treat vaginal bleeding, leucorrhea, and abdominal pain in patients with different gynecological tumors. The antitumor potential of a hydro-ethanolic extract derived from *S. vaninii* was evaluated *in vitro* on three human cancer cell lines: human gastric cancer cells (SGC7901), human ovarian cancer cells (SK-OV-3), and human cervical cancer cells (SiHa), as well as on a 4-week-old BALB/c *in vivo* female mice. The results have shown that the extract possesses anticancer activity by inducing apoptosis of SiHa cells. According to the results, *S. vaninii* was suggested as a potential antitumor agent against cervical cancer (He et al. 2021a).

Recent literature on the medicinal properties of the Chaga mushroom (*Inonotus obliquus)* and its usage as a supplementary medicine for cancer therapy have been updated (Khoroshutin et al. 2021).

Breast cancer is among the most common cancers causing the death of women worldwide. The cytotoxic effect of ethanolic extract of *I. obliquus* was observed after *per os* administration in 4T1 tumor-bearing *BALB/c* mice. The lanostane triterpenoid inotodiol and trametenolic acids have been identified as the main cytotoxic constituents of *I. obliquus* (Lee et al. 2021). The effect of inotodiol on breast cancer was also reported in streptozotocin (STZ)-induced diabetic rats. The results have shown that inotodiol lowered blood glucose levels, reduced plasma levels of cholesterol, triglyceride, and high-density lipoprotein (HDL), and induced apoptosis via downregulation of β-catenin signaling in rats (Zhang et al. 2018b).

Thus, *I. obliquus* as an anticancer agent may be recommended as a preventive medicine for treatment of breast cancer, particularly in diabetic patients (Zhang et al. 2018b; Lee et al. 2021).

The mycochemical study of the methanol extract of *Inonotus nidus-pici*, a relative species of *I. obliquus,* revealed five compounds (citropremide, 3,4-dihydroxybenzalacetone, lanosterol, ergost-6,8,22-trien-3β-ol, and ergosterol peroxide) which exhibited moderate antimicrobial activities against Gram-positive (*B. subtilis* subsp. *spizizenii*, and *Rhodococcus fascians)* and Gram-negative (*Pseudomonas syringae* pv. *maculicola*, and *Aliivibrio fischeri*) bacteria, as well as an AOA in DPPH assay, an anti-proliferative potential on A431 human skin-derived and epidermoid carcinoma cell lines (Garádi et al. 2021).

A novel 12-kDa protein musarin, purified from *T. versicolor* hot-water extract has shown a strong anti-proliferative potential against human colorectal cancer stem cell-like CD24+CD44+HT29 and demonstrated tyrosine kinase-inhibitory activity *in vitro*. As a promising new drug, musarin may be used in colorectal cancer therapy (He et al. 2021b).

Novel anticancer triterpene GL22 isolated from *Ganoderma leucocontextum* significantly inhibited the growth of liver cancer cell line Huh7.5 *in vitro* and Huh7.5-derived tumor xenografts *in vivo*, inducing mitochondrial dysfunction and cell death (Liu et al. 2018).

The cytotoxic triterpene astrakurkurone, isolated from a wild edible mushroom *A. hygrometricus* at low doses, was shown to be active against HCC cell lines (Hep 3B and Hep G2) (Nandi et al. 2019). The astrakurkurone acts by inducing apoptosis of cells, disrupting mitochondrial membrane potential, and inducing the expression of Bcl-2 family proteins Bax, caspases 3 and 9. Previous molecular study predicted a direct interaction of the drug with anti-apoptotic proteins, Bcl-2 and Bcl-xL. Thus, astrakurkurone can be suggested as a promising therapeutic agent for cancer treatment (Dasgupta et al. 2019).

The selenium (Se)-enriched EPS fraction, isolated from *L. edodes,* mainly consists of a highly branched 1-6-α-mannoprotein (molecular weight 4.5×10^6 Da). It significantly improves cell viability when incubated with human umbilical vein endothelial cells (HUVEC) absent from human cervical HeLa cells. The Se-EPS fraction also possesses antioxidant and immunosuppressive activities. At concentrations of 10–100 μg/mL, it inhibited mitogen-induced T-cell proliferation without revealing a significant effect on B cells (Górska-Jakubowska et al. 2021).

The aqueous, 70% and 95% ethanolic extracts derived from *C. cibarius, Coprinus comatus, Lactarius deliciosus,* and *Lycoperdon perlatum* were investigated for their anticancer effect on U87MG, LN-18 glioblastoma, and SVGp12 normal human astroglial cell lines. *C. comatus* and *L. deliciosus* demonstrated the greatest anticancer effects. The activities of ethanolic extracts were higher than those of aqueous extracts. The anti-glioma mechanism of *C. comatus,* based on the inhibition of cancer cell proliferation and induction of apoptosis, was associated with the termination of subG1 or G2/M phase of the cell cycle and inhibition of metalloproteinase activity (Nowakowski et al. 2021b).

Fifteen compounds from submerged mycelial cultures of *Amylosporus* cf. *graminicola* and *Amylosporus* cf. *campbelii* were isolated. Seven novel amylosporanes' derivatives, five known metabolites, and colletochlorin B have been identified (Kemkuignou et al. 2022). Colletochlorin B showed a

cytotoxic activity against *B. subtilis* (MIC = 2 μg/mL), stronger than oxytetracycline, and cytotoxicity against squamous cancer A431 cells with an IC_{50} value of 4.6 μM (Hamad et al. 2022).

The cold-water extract obtained from freeze-dried *Lignosus rhinocerus* sclerotial powder TM02® was tested on a panel of human oral cancer cell lines. MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) proliferation assay indicated that oral cancer cells ORL-48 (derived from gingiva), ORL-188 (derived from the tongue), and ORL-204 (derived from buccal mucosa) were inhibited by *L. rhinocerus*. A high molecular mass fraction from the cold-water extract induced apoptosis on ORL-204 and arrest G0/G1-phase cell cycle through caspase-3/7 cleavage. These results support the usage of *L. rhinocerus* as a potential dietary compound for cancer prevention and treatment (Yap et al. 2022).

The methanolic and ethyl acetate extracts of agaricomycetous mushrooms, *A. hygrometricus*, *Lentinus* sp., *Serpula* sp., *Tricholoma* sp., and *Phallus* sp. were investigated for their anti-proliferative activities on Jurkat leukemic cell line. A high and more efficient anti-proliferative activity of ME ($IC_{50} = 22.7 \pm 0.23$ μg/mL) was detected compared to ethyl acetate extract of *A. hygrometricus* ($IC_{50} = 68.9 \pm 0.33$ μg/mL) (Pal et al. 2021).

Reishi mushroom (*G. lucidum)* has traditionally been used to treat immunosuppression and cancer. Skin cancer-preventive effects of commercial products containing spore and fruiting bodies of *G. lucidum* have been tested on JB6 cells. The products prevented the development of skin cancer, probably via attenuating UV-induced immunosuppression (Shahid et al. 2022). Silver and titanium dioxide nanoparticles prepared with an AE of medicinal bracket fungus *Fomes fomentarius* revealed a strong cytotoxic effect on HCT-116 human colorectal carcinoma cells (Rehman et al. 2020). Polyphenol-rich and β-glucan-containing aqueous alkali extract obtained from *F. fomentarius* fruiting bodies (FFE) were studied on human colorectal adenocarcinoma (Caco-2) and cutaneous melanoma (COLO-818) cells. Caco-2 cells did not react on FFE, which may indirectly suggest its safety for human intestinal epithelium. The melanoma cells were dose-dependent at 0.01-0.05 mg/mL concentrations of FFE (Storsberg et al. 2022).

Fourteen undescribed compounds including five 2,5-diarylcyclopentenone (xylariaones A1-B2), seven α-pyrone derivatives (xylaripyones A-G), one γ-pyrone derivative xylaripyone H, one diketopiperazine cyclo-(L-Leu-N-ethyl-L-Glu), and two known diketopiperazines, have been isolated from cultures of an endophytic *Xylaria* sp. (Song et al. 2022c). These compounds were also investigated for their potential anti-proliferative effects against PC3 and A549 human tumor cell lines. The authors reported that xylaripyone D exhibited a moderate inhibitory activity against the proliferation of PC3 cell lines with an IC_{50} value of 14.75 μM. In addition, xylariaone A3 and xylaripyone F showed weak inhibitory effects on NO production in RAW 264.7 murine macrophages (IC_{50} of 49.76 and 69.68 μM, respectively).

The AE derived from three ascomycetous species of edible ectomycorrhizal desert truffles (*Terfezia claveryi, T. boudieri,* and *T. olbiensis*) were investigated for their cytotoxic and apoptosis-inducing effects on pancreatic cancer cell line

(PANC-1). The results showed a strong, dose-dependent inhibition of PANC-1 cell growth by inducing apoptosis via upregulation of pro-apoptotic genes BAX, CDKN1A, and TP53 and downregulation of the anti-apoptotic gene *BCL2*. These results suggest that *Terfezia* truffles may be used as a functional food with anticancer effects (Saleh et al. 2022).

Doxorubicin (DOX) is a widely used chemotherapy drug with a cardiotoxic effect. The effect of *Morchella esculenta* extract in attenuating DOX-induced cardiotoxicity *in vitro* by MTT assay using H9c2 cardiomyoblast cells was evaluated. The mushroom extract reduced cytotoxicity at concentrations of 150 and 200 μg ($p < 0.05$ and $p < 0.01$, respectively) and restored near-normal levels of endogenous antioxidants, such as SOD, GPx, and GSH, depleted by DOX administration (Das et al. 2022b).

3.2 Antioxidant

Many chronic diseases, such as cancer and inflammation, develop due to the adverse effect of free radicals (hydroxyl, peroxy-nitrite, nitrite, DPPH, superoxide anion, hydrogen peroxide). As active producers of phenolic compounds and flavonoids, mushrooms are considered a natural source of dietary antioxidants (Huang et al. 2022). Various methods, such as ABTS, DPPH, hydrogen peroxide, and lipid peroxidation, were used to assess the antioxidant potential of edible and medicinal mushrooms. The potential of mushrooms as a source of natural antioxidants and their application in mycotherapy of different diseases have been assessed (Mwangi et al. 2022).

The ethanolic extract of *Trametes hirsuta* was studied for its total antioxidant status (TAS) and total oxidant status (TOS). The oxidative stress index (OSi; ratio of TOS to TAS values) was outlined. The TAS and TOS values of *T. hirsuta* were 3.466 ± 0.148 mmol/L and 13.482 ± 0.234 μmol/L, respectively. The OSi value was estimated to be 0.390 ± 0.018. The most effective antimicrobial activity of ethanolic extract of *T. hirsuta* was detected at concentrations of 100, 200, and 400 μg/mL (Akgul et al. 2021).

The chemical composition of three extracts of *Ganoderma australe*, and the role of IPS in the induction of maturation and activation of bone marrow-derived dendritic cells (DCs), have been studied. Glucose, mannose, and galactose prevailed in all extracts. The IPS extract obtained from fungal mycelia showed a significant AOA, possibly related to high amounts of phenolic compounds. The effect of AE of mycelial polysaccharides derived from *G. australe* on the maturation and activation of mouse DCs and prevention of oxidative processes was originally described in this study (Gallo et al. 2022).

The screening of AOA of decoction, infusion, and hydro-methanolic extracts isolated from edible medicinal *Flammulina velutipes* in *in vitro* ABTS and DPPH assays showed that the decoction extract was capable of better scavenging of radicals followed by the hydro-methanolic extract; in contrast, the infusion extract exhibited

a promising effect on metal ion chelating ability (Sharma et al. 2022a). The amount of phenols in the decoction was the highest (14.85 μg gallic acid equivalent/mg extract), followed by the infusion (12.02 μg gallic acid equivalent/mg extract). Additionally, lycopene (1.4 μg/mg of extract) and ascorbic acid (1.56 μg/mg of extract) were detected in greater quantity in the hydro-methanolic fraction. At 100 μg/mL and 500 μg/mL concentrations, both hydro-methanolic extract and infusion fraction inhibited around 25% and 77% radicals, respectively. The decoction fraction exhibited the best potential by inhibiting more than 32% and 90% radicals, respectively. According to obtained data, *F. velutipes* was considered a source of mycopharmaceuticals with AOA (Sharma et al. 2022a).

A moderate antimicrobial potential and AOA of *Calocybe gambosa* have recently been reported. Based on the chemical analyses of macronutrients, α-tocopherol, free sugars, organic and fatty acids of *C. gambosa*-enriched oatmeal cookies, this mushroom was suggested as a potential functional food with antimicrobial and antioxidant effects (Petrović et al. 2022).

Two new polyketides, rufoolivacin E and viocristin B, a new natural product of 1-hydroxy-3,6,8-trimethoxyanthraquinone, 13 known compounds with inhibitory effects against glutamate dehydrogenase (GDH) and AOA have been isolated and identified from wild growing *Cortinarius* sp. Four compounds exhibited significant AOA with IC_{50} values of 7.0 ± 0.3, 8.6 ± 0.1, 7.5 ± 0.1, and 2.8 ± 0.2 μg mL^{-1}, respectively. Thus, *Cortinarius* sp. may be used in food and drug industries as a natural source of polyketides (Song et al. 2022a, b)

The chemical study of a hydro-ethanolic extract of *Russula pseudocyanoxantha* and its functional secondary metabolites with AOA was performed. The extract was highlighted to be enriched with various phenolic compounds, such as *p*-coumaric acid, cinnamic acid, and pyrogallol, as well as ascorbic acid and carotenoids. A significant *in vitro* radical scavenging effect (hydroxyl, DPPH, and ABTS), ferrous ion chelating capacity, and potency reduction were recorded at EC50 values of 15–2674 μg/mL. Incorporation of *R. pseudocyanoxantha* into daily diet, as a novel mycofood, may provide health benefits. It may be further used in formulating nutraceutical, cosmeceutical, and pharmaceutical bioproducts (Badalyan et al. 2022; Khatua and Acharya 2022).

The chemical screening of therapeutic potential of lignicolous fungus *Lentinus squarrosulus* revealed that AE, hydro-ethanolic, and ethanolic extracts of *L. squarrosulus* were almost free of tannins, poor in the total flavonoids and moderately rich in reducing sugars. The aqueous and ethanolic extracts were rich in total polyphenols, whereas aqueous and hydro-ethanolic extracts—in alkaloids. The AE was rich in saponosides and hydro-ethanolic extract in coumarin derivatives. These results have shown that tested extracts possess low to moderate AOA. The highest activity has demonstrated the ethanolic extract of *L. squarrosulus,* which could be used as an antioxidant agent (Ndong et al. 2021). Evaluation of the nutritional profile and digestion-stimulating effect of *L. squarrosulus* suggested that this fungus promotes the growth of selected probiotic bacteria, especially *Bifidobacterium* strains, and may be used as a functional food to improve gut microflora (Ayimbila et al. 2022). The antioxidant effects of water and ethyl acetate

extracts from the ascomycete mushroom *Morchella steppicola* were also reported (Sarikurkcu et al. 2022).

3.3 Anti-Inflammatory and Antimicrobial

The numbers of human pathogens resistant to antibiotics have increased worldwide. The World Health Organization (WHO) considers resistant antimicrobial infections to be a threat to global health, accounting for a high percentage of annual deaths (https://www.ox.ac.uk/news/2022-01-20-estimated-12-million-people-died-2019-antibiotic-resistant-bacterial-infections) (Prestinaci et al. 2015; Saha and Sarkar 2021; Murray et al. 2022). Particularly, multidrug-resistant ESKAPE pathogens (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* spp.) have become the universal origin of skin and soft-tissue infections in the WHO priority pathogens list (https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Mushrooms are a source of different antimicrobial compounds. The cytokines IL-1β, IL-8, and TGF-β involved in signaling inflammatory processes, which may be produced by HT-29 epithelial cell line, were selected to study *in vitro* anti-inflammatory activity of crude EPS isolated from *T. versicolor*. IL-1β and IL-8 mediate inflammatory processes, whereas TGF-β is the signaling peptide related to the anti-inflammatory processes. The medium, containing 2 mg/mL of crude EPS, significantly reduced the concentration of pro-inflammatory IL-8 and IL-1β cytokines. In contrast, a 2.5-fold increase in TGF-β concentration was related to the anti-inflammatory properties of *T. versicolor* EPS (Angelova et al. 2022).

The antimicrobial potential of different extracts of hymenochaetoid bracket fungi *Phellinus tuberculosus* and *Fuscoporia ferruginosa* against Gram-positive (*S. aureus* ATCC25923, *B. subtilis* ATCC6633, *Streptococcus mutans* ATCC 35,665) and Gram-negative (*P. aeruginosa* ATCC9027, *A. baumannii* BAA-744, and *E. coli* ATCC8739) bacteria, as well as of *Candida albicans* ATCC10231 strains showed that Gram-positive bacteria were more sensitive to fungal extracts compared to Gram-negative bacteria. No activity of fungal extracts against *C. albicans* yeast was found. The activities of methanol and ethanol extracts were similar, while the antibacterial effect of AE was weak. The extracts of *P. tuberculosus* showed the highest antibacterial activity. The methanolic and ethanolic extracts of *F. ferruginosa* were highly resistant to *P. aeruginosa*, whereas *S. mutans* showed the highest sensitivity to these extracts (Dokhaharani et al. 2021). The ethanolic extract of polypore mushroom *Trametes hirsuta* at concentrations of 100, 200, and 400 μg/mL was effective against six bacterial strains (*A. baumannii, Enterococcus faecalis*, *E. coli, P. aeruginosa*, *S. aureus*, and *S. aureus* MRSA), as well as *Candida* species (*C. albicans*, *C. glabrata,* and *C. krusei*) (Akgul et al. 2021).

The extracts from culture liquid and mycelial biomass of *Lentinus arcularius* were tested against bacteria (*E. coli*, *P. aeruginosa,* and *S. aureus*) and fungi (*C.*

albicans, Saccharomyces cerevisiae, and *Aspergillus niger*). The best antimicrobial effect revealed ethyl acetate and n-butanol fractions (Yen et al. 2022).

The antimicrobial and anti-biofilm properties of aqueous and methanolic extracts obtained from *Boletus edulis* and *Neoboletus luridiformis* against multidrug-resistant bacteria were revealed. The most relevant antibacterial effect was detected in aqueous and methanolic extracts of *B. edulis* against Gram-positive *S. aureus* and Gram-negative *P. aeruginosa*. At the same time, the highest bacterial biomass-removing ability has shown the AE of *B. edulis* in *S. aureus* and *E. coli* (Garcia et al. 2021).

P. ostreatus polar extract (PoPE) obtained from cultivated fruiting bodies was evaluated for antimicrobial and cytotoxic effects. The extract was characterized by its phenolic and flavonoid contents, which were 6.94 and 0.15 mg/g, respectively. PoPE showed the potent antimicrobial activity against fungal and bacterial pathogens (*C. albicans, S. aureus, Micrococcus luteus,* and *E. coli*). PoPE was found to inhibit phytopathogenic fungi *Fusarium oxysporum* (47%), *F. solani* (28%), and *Rhizoctonia solani* (21%). The extract was 13 times more selective and toxic to MCF-7 cells than Vero normal cells at an IC_{50} value of 4.5 μg/mL, promoting cell cycle arrest in the sub-G1 stage and cell apoptosis. It significantly increased TNF-α production, while decreasing IL-6 levels. The total AOA, lipid peroxide, and glutathione-reductase activity were recorded at 0.14 ± 0.02 mmol/L, 15.60 ± 0.015 nmol/mL, and 9.50 ± 1.30 U/L, respectively (Hamad et al. 2022)

The antibacterial, antifungal, and antioxidant activities were detected in the ethanolic extract derived from the poisonous fungus *Entoloma sinuatum*. The extract was effective against bacteria at concentration 200 and 400 μg/mL and fungi at 50 μg/mL. This fungus was identified as a natural antioxidant and antimicrobial agent (Bal et al. 2022).

The co-cultivation of microbes and fungi is used as a strategy to induce the biosynthesis of desirable bioactive metabolites. Randomized co-culturing of *Phellinus orientoasiaticus* (Hymenochaetaceae) and *Xylodon flaviporus* (Schizoporaceae) showed no antagonistic growth. Three new sesquiterpenes and five known analogues have been isolated and characterized. The LC-MS analysis suggested that cyclohumulanoids of illudane-, sterpurane-, and tremulane-type scaffolds were produced by *P. orientoasiaticus*, whereas a drimane-type sesquiterpene by *X. flaviporus*. None of the isolates exhibited antifungal activity or cytotoxicity. The compounds produced by *P. orientoasiaticus* promoted NO production of LPS-treated RAW276.4 cells ranging from 15.9% to 38.0% at 100 μM (Pham et al. 2022).

Fomitopsis officinalis, also known as *Laricifomes officinalis*, is a medicinal polypore used for millennia (Agarikon) to treat several, particularly pulmonary diseases. There is rich ethno-mycological information; however, isolation and chemical characterization of single compounds and *in vitro* bioactivity tests have only recently been performed (Girometta 2019). According to several reports, a broad-spectrum of antibacterial and antiviral activities of *F. officinalis* against *Mycobacterium tuberculosis, Yersinia pseudotuberculosis*, *S. aureus,* and *Ortopox* virus are available. The chlorinated coumarins derived from mycelia and lanostane

triterpenoids obtained from basidiomes are directly responsible for antiviral, antibacterial, and trypanocidal activities, respectively (Girometta 2019).

The antibacterial activities of 28 extracts from seven Basidiomycota and Ascomycota mushrooms against Gram-positive and Gram-negative bacteria have been evaluated (Morel et al. 2021). The cyclohexane extract of *Rubroboletus lupinus* was active on a methicillin-resistant *S. aureus* (MRSA) (MIC = 125 μg/mL) and mildly active on methicillin-sensitive *S. aureus* (MSSA) and *B. subtilis* (MIC = 250 μg/mL). Cyclohexane extract from *Neoboletus luridiformis* was active against MSSA with MIC=125 μg/mL; while *Gyroporus castaneus* (cyclohexane and chloroform) extracts against MSSA and MRSA (MIC = 125 μg/mL). Among the tested extracts, *Gyromitra esculenta* cyclohexane extract has shown the strongest antibacterial activity with MIC = 31 μg/mL against MSSA, MSSA, and *B. subtilis* strains (Morel et al. 2021).

In the context of antibiotic resistance, the antibacterial potential of 70 extracts from 31 French mushrooms against wild-type and multidrug-resistant (MDR) bacteria *E. faecalis*, *E. coli, P. aeruginosa, Staphylococcus epidermidis*, and *S. aureus*, were screened. The results have shown that 95% of extracts contained antibacterial compounds. The ethyl acetate extracts exhibited more active compounds than ME. All extracts were mainly active against Gram-positive bacterial strains. The most promising mushroom extracts were tested against various MDR-strains of *S. aureus* and *E. coli*. The activity was weaker on MDR strains. However, *F. pinicola* and *Scleroderma citrinum* contained several compounds which inhibited the growth of MDR pathogenic bacteria. The stearic acid was identified as an ubiquitous compound contributing to the antibacterial defense of mushrooms. The results revealed the antibacterial potential of mushrooms. Nevertheless, further assays are needed to consider fungal compounds as therapeutic agents to counter antibiotic resistance (Huguet et al. 2022).

Evaluation of antimicrobial activities of aqueous and hydro-alcoholic extracts from the mycelia of *Ph. linteus* and *Pleurotus albidus* against *Bacillus cereus, B. subtilis, P. aeruginosa*, and *S. aureus* showed that *P. albidus* extracts showed a stronger activity against *Bacillus* strains. In contrast, *Ph. linteus* extract was effective against *S. aureus* and *P. aeruginosa*. The AE of *P. albidus* and 30% hydro-alcoholic extraction for *Ph. linteus* were the best for obtaining bioactive compounds. MS analyses allowed the identification of main chemical compounds, including glutathione oxidase, leucovorin, and riboflavin extracted from the mycelial biomass of these mushrooms. Considering these findings, *P. albidus* and *Ph. linteus* may be used as promising sources of bioactive molecules to develop novel health-enhancing biotech products (Contato et al. 2022).

Two *Morchella* species have been reported to possess a broad spectrum of biological activities against bacterial infections. The antibacterial potential of extracts obtained from *M. esculenta* and *M. conica* were evaluated against *S. aureus,* MRSA, and *Streptococcus pyogenes*. The extracts of *M. conica* inhibited the growth of *S. aureus* with an inhibitory zone ranging from 10.66 ± 0.3 to 21.00 ± 1.5 mm. The MIC of bacterial growth ranged from 3.33 ± 0.6 to 16.0 ± 0 mg/mL. *Morchella* extracts prevent the growth of *S. aureus* at 8-16

mg/mL showing a bactericidal effect and were more effective against MRSA than currently available antibiotics. Therefore, *Morchella* extracts may be suggested as potential antibacterial agents (Haq et al. 2022).

Identification of bioactive constituents of medicinal mushroom *C. militaris*, including cordycepin, essential amino acids, sterols, and polysaccharides with preventive and therapeutic effects in chronic diseases, including cancer, diabetes, and allergies, have been reported (Sharma et al. 2022b). The molecular mechanisms contributing to the anti-inflammatory properties of *C. militaris* have recently been updated (Phull et al. 2022).

3.4 Antiviral

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a highly pathogenic virus that caused a global pandemic which has promoted researchers worldwide to develop of a novel vaccines or small molecular therapeutics for SARS-CoV-2. Although several vaccines have already been discovered, no medication has been previously approved by FDA for the treatment of COVID-19.

Studies have identified promising hits against the main protease (M^{pro}) of SARS-CoV-2 from edible mushrooms. A structure-based virtual screening of 2433 compounds derived from mushrooms was performed with M^{pro} protein 6LU7. New data showed that Kynapcin-12 (M_78), Kynapcin-28 (M_82), and Kynapcin-24 (M_83) are potent inhibitors of M^{pro} protein 6LU7 available in the edible mushroom *Polyozellus multiplex.* These novel phenolic scaffolds may be developed to potential SARS-CoV-2 inhibitors. The identified molecules could be further explored as antiviral therapeutic agent against this virus. Another promising compound, neonambiterphenyls A (M_366), is recently detected in the poisonous mushroom *Neonothopanus nimbi* (Sen et al. 2022).

3.5 Hypoglycemic and Hypocholesterolemic

The polysaccharide (*β*-D-glucan) and vitamin D contents of mushrooms determine medicinal components and prevention of diabetes mellitus. Within the selected 23 macrofungi, only 11 demonstrated *in vivo* or *in vitro* hypoglycemic activities. Although species of genera *Pleurotus*, *Grifola,* and *Ganoderma* were the most studied, *in vivo* and *in vitro* investigations and clinical tests should be performed due to unknown mechanisms of therapeutic action (Das et al. 2022a).

In vivo (inhibition of α-amylase and α-glucosidase) and *in vitro* (oral starch tolerance and glucose tolerance tests) hypoglycemic activities of 70% ethanolic extracts of bracket fungi *Inonotus pachyphloeus* and five *Phellinus* species (*Ph. allardii*, *Ph. fastuosus*, *Ph. gilvus*, *Ph. sanfordii*, and *Ph. torulosus)* have been reported. The extracts of *Ph. fastuosus* (IC_{50} = 27.33 ± 1.45 mg/mL) and *Ph.*

sanfordii (IC_{50} = 30.33 ± 0.88 mg/mL) strongly suppressed of α-amylase and α-glucosidase activities. Their most active extracts (200 and 400 mg/kg BW, respectively) significantly reduced *in vivo* postprandial hyperglycemic peaks in rats. Further pharmacological studies are needed to develop *Ph. fastuosus* and *Ph. sanfordii*-derived and clinically applicable therapeutic agents for the menagement of diabetes (Azeem et al. 2021).

The extracts from cultivated Agaricomycetes mushrooms *S. commune* (IC_{50} = 15.3 mg/mL; hexane extract) and *L. edodes* (IC_{50} = 12.9 mg/mL; ethanolic extract), as well as wild mushrooms *Phaeogyroporus portentosus* (IC_{50} = 15.7 mg/mL; ethanolic extract) and *Craterellus aureus* (IC_{50} = 25.9 mg/mL; ethanolic extract) have shown potent anti-amylase and anti-glucosidase activities. Both inhibitory enzyme activities are associated with diabetes and obesity. Furthermore, 80% of ethanolic extracts (v/v) had an anti-lipase activity as for *L. edodes* (IC_{50} = 8.85 mg/mL) and *P. portentosus* (IC_{50} = 33.6 mg/mL). These findings promote mushroom consumption in maintaining good health, as well as controlling diabetes and obesity by enzyme inhibitions (Wunjuntuk et al. 2022).

Cholesterol absorption inhibitors, statins, and fibrates are the main therapeutics to reduce a high level of blood lipids. In TCM, herbs and mushrooms as healthy food (i.e., Pu-erh tea, *Crataegus, A. auricula-judae*) are used to treat hyperlipidemia. Cordycepin obtained from *C. militaris* revealed a weak regulatory activity on the level of blood plasma lipids but more significant hepatoprotective effect (Chen et al. 2014; Badalyan et al. 2019).

A randomized, controlled, double-blind clinical trial was performed for eight weeks on volunteers from 18 to 65 years old (n = 52) with untreated mild hypercholesterolemia (Morales et al. 2021). The subjects consumed a *β*-D-glucan-enriched (BGE) mixture (10.4 g/day) obtained from shiitake mushroom (*L. edodes*) equivalent to 3.5 g/day of fungal *β*-D-glucans or a placebo incorporated in three various commercial creams. No inflammatory or immunomodulatory effects were shown, and no changes in IL-1β, IL-6, TNF-α, or oxLDL levels were detected. Although the BGE mixture showed a hypocholesterolemic effect *in vitro* in animal studies, it did not significantly reduce the cholesterol level compared to placebo. The BGE mixture modulated the gut microbiota compared to placebo. Further clinical trials are warranted to reveal an association between BGE administration and cholesterol metabolism or microbiota (Morales et al. 2021).

3.6 Neuroprotective

Depression is a serious neuropsychiatric disorder that affects more than 260 million people worldwide. There are many recognized mental health conditions or mental illnesses. Mushrooms with NPE may be used in anti-depressive therapy (Badalyan and Rapior 2021a, b). An animal model has shown an anti-depressant-like effects of AE of *H. erinaceus* injected intraperitoneally at 10 and 25 mg/kg for 4 weeks against chronic restraint stress (CRS). The potential mechanisms of neurogenesis were

elucidated. The results revealed the anti-depressant-like effects by promoting hippocampal neurogenesis and reducing neuro-inflammation by enhancing the BDNF-TrkB-CREB signaling pathway (Chong et al. 2021).

Several mushrooms (*Amanita muscaria*, *Claviceps purpurea*, *H. erinaceus*, *Pleurotus cornucopiae*, and *Psilocybe* species) are considered producers of bioactive compounds with neurotrophic effects to treat mental health disorders (addiction, anxiety, anorexia, mood, and psychosis) and pain comorbidities (Badalyan and Rapior 2021a, b). These compounds have chemical structures similar to neurotransmitters and can function as agonists of receptors implicated in psychiatric disorders (Meade et al. 2022).

In a previous study, mice were subjected to a tail suspension test (TST) to simulate sleep disruption. The results have shown that, at a dose of 150 mg/kg, *H. erinaceus* mycelium, containing erinacin A (7.20 mg/g) and erinacin C (3.35 mg/g), had reversed TST-induced sleep disturbances. This *in vivo* study suggests that *H. erinaceus* mycelium has a potential dual role in relieving anxiety and improving sleep. Future clinical trials should address these effects of *H. erinaceus* mycelium with randomized placebo-controlled trials (Li et al. 2021b).

Obesity may cause changes in behavior, while maternal obesity can contribute to metabolic disorders or metabolic syndrome in children. The effect of β-glucan-rich *Pleurotus pulmonarius* (βgPp) on the neurological behavior of female ICR mice, hippocampus and development of its offspring's hippocampus showed that βgPp significantly enhanced short-term object recognition memory in high-fat diet (HFD)-fed mice. βgPp also ameliorated histological alterations, neuronal loss, and increased ionized calcium-binding adaptor molecule-1 (Iba-1)-positive microglia in the hippocampus regions of HFD-fed mice and their male offspring. The rich extract of *P. pulmonarius* improves object recognition memory and hippocampus morphology in mice fed with an HFD. These findings demonstrated that βgPp supplementation attenuated the effects of HFD on object recognition memory, as well as alterations in hippocampal regions of maternal mice and their male offspring (Tarmizi et al. 2022).

3.7 Hepatoprotective

The hepatoprotective effect of medicinal mushrooms has been reported by many studies (Chen et al. 2014; Badalyan et al. 2019; Li et al. 2019; Hou et al. 2021).

Liver fibrosis, among other origins, is caused by non-alcoholic steatohepatitis. Non-alcoholic fatty liver disease is defined as the accumulation of fat in hepatocytes in the absence of excessive alcohol consumption. It is a common chronic liver disease that affects more than 30% of western world population and is associated with many metabolic disorders, such as obesity. Se-enriched AE obtained from *A. bisporus* was evaluated for its potential inhibitory effects on the progression of fibrosis using an *in vitro* model like LX2 cell line (human hepatic stellate cells) and *in vivo* female low-density lipoprotein (LDL) receptor knockout mice. The treatment of LX2 cells with the extract reduced fibrotic and oxidative markers levels and

increased GATA4 gene expression. In LDLR-/- mice with HFD-induced liver fibrosis and inflammation, the progression of fibrosis, oxidative stress, inflammation, and apoptosis were prevented by treatment with the extract. A potential anti-atherogenic effect was also observed in the mouse model. The results have shown expression of toll-like receptor 4 (TLR4) and reduced inflammasome activation of nod-like receptor protein 3 (NLRP3) which suggests that mushroom extract exerts protective effects by alleviating inflammation and oxidative stress during the progression of liver fibrosis (Gallego et al. 2021).

The pre-treatment of human liver L02 cells with ethanol followed by *A. auricula* melanin (AAM) showed a therapeutic effect on alcohol-induced liver injury *in vitro* and *in vivo* based on the elevation of cell viability, amelioration of cell morphology, and reduction of ROS. The effect of AAM on ethanol-induced hepatocyte injury can be used as to develop hepatoprotective drug to treat alcohol liver disease (Hou et al. 2021).

Chaga mushroom (*I. obliquus*) has been traditionally used in Asian folk medicine. *I. obliquus* polysaccharides (IOP) have been shown to reduce tacrine-induced apoptosis in HepG2 cells. Inhibition of tacrine-induced ROS generation, 8-OHdG formation in mitochondrial DNA, and loss of mitochondrial transmembrane potential by IOP were also detected. In addition, IOP decreased the release of tacrine-induced cytochrome C and caspase-3 activation. The consumption of IOP may be an approach to prevent tacrine-induced hepatotoxicity (Li et al. 2019).

The isolation of 21 known compounds and structural elucidation of ten undescribed lanostane triterpenoids from static cultured mycelium of *G. lucidum* have been reported (Zhang et al. 2022). These compounds have been investigated for their hepatoprotective activity on H_2O_2-induced HepG2 cells. The obtained results demonstrated that 12 ganoderic acid derivatives possessed significant hepatoprotective activities based on suppression of ALT, AST, and LDH enzymes and increased levels of GSH in H_2O_2-injured HepG2 cells.

The chemical structure and activity of triterpenoids, including phytosterols, antcins A, B, C, H, and K, as well as dehydroeburicoic and dehydrosulphurenic acids extracted from medicinal fungus *Taiwanofungus camphoratus,* have been intensively studied to assess their hepatoprotective activity (Hsieh et al. 2011; Du et al. 2012; Lu et al. 2020; Wang et al. 2022a). It was reported that *T. camphoratus* contains more triterpenoids than *G. lucidum* and possesses a hepatoprotective effect without genotoxicity. The commercial cultivation of *T. camphoratus* is limited due to the limited resources of the host tree, *Cinnamomum camphora*. As a substrate for *T. camphoratus* cultivation, apple wood was used to study the contents of triterpenoids and the hepatoprotective activity of this fungus. The results showed that apple-wood cultivation is feasible for the commercial cultivation of *T. camphoratus* (Wang et al. 2022a). It should be noted that antcin B causes apoptosis of hepatocellular carcinoma cells by inducing oxidative stress involving reduced nicotinamide adenine dinucleotide phosphate oxidase (Hsieh et al. 2011).

3.8 Other

Various herbal medicines, including mushrooms, are considered useful for the treatment of cardio-metabolic diseases and their risk factors (hypoglycemia, diabetes, dyslipidemia, arterial hypertension, and inflammation) (Badalyan et al. 2021). *G. lucidum* has been used to prevent and treat cardiovascular and cardio-metabolic diseases by targeting their risk factors. It is also a source of antioxidant, hypotensive, hypoglycemic, hypolipidemic, and anti-inflammatory compounds.

Further clinical studies are needed to elucidate the potential health benefits of standardized preparations of *G. lucidum* in the prevention and treatment of cardio-metabolic diseases (Chan et al. 2021).

A terphenylquinone pigment thelephoric acid (Thel) with osteogenic effects on pre-osteoblasts was isolated from wild mushroom *Polyozellus multiplex*. Thel enhanced alkaline phosphatase activity, bone matrix mineralization in pre-osteoblasts, as well as cell adhesion and migration in osteoblast differentiation. These findings indicated that Thel could be used to prevent and treat bone disorders (Park et al. 2022).

Recent data has highlighted the role of gut microbiota and its various metabolites in maintaining bone health, and the usage of prebiotics in fight against degenerative bone diseases. The prebiotic potential of medicinal mushrooms *G. lucidum* and *P. ostreatus* has been studied in healthy and osteopenic women to analyze the impact of mushroom fermentation products on human osteoblasts. The results have shown that treatment with *P. ostreatus* mushroom powder and *G. lucidum* extract had positive effects on gut microbiota and SCFA (*short-chain fatty acid* analyses) production. It decreases the levels of RANkL (receptor activator of nuclear factor-κB ligand) and enhances osteoblastic activity. Thus, *G. lucidum* and *P. ostreatus* products may exert beneficial *in vitro* effects on bone physiology by altering gut microbiota and/or SCFA production (Kerezoudi et al. 2021).

The protective effects of *Macrolepiota procera* mycelium polysaccharides (MMP) on nonylphenol (NP)-induced male reproductive dysfunction have been studied. After nonylphenol (NP) administration, declined sperm count and testis index, increased deformation rate of sperms, aberrant hormone secretion, and testicular pathological injury led to a decrease in reproductive capacity. The MMP therapy reversed the changes in NP-treated mice, decreased oxidative stress, apoptosis, autophagy, inflammatory responses, and suppressed Akt/mTOR signaling pathway in testicular tissues. The results have shown MMP to be a promising therapeutic agent against the biotoxicity of NP (Wang et al. 2022b).

Uric acid is the end product of metabolism of purine compounds. Elevated concentrations of serum uric acid may cause hyperuricemia and lead to the development of gouty arthritis, arterial hypertension, cardiovascular and renal diseases. The association between mushroom consumption and hyperuricemia has been reported. The study of several edible medicinal mushrooms, *L. edodes, A. auricula-judae, P. ostreatus, F. velutipes,* and *A. bisporus* with hyperuricemia has shown that xanthine oxidase inhibitors extracted from mushrooms may alleviate

hyperuricemia. The population-based prospective cohort study has demonstrated that a mushroom-rich diet is associated with a lower incidence of hyperuricemia in adult patient cohorts (Zhang et al. 2021).

4 The Advancements in Biomedical Usage of Mushrooms

4.1 Mushroom-Derived Biotech Products

Since ancient times, mushrooms have been considered an expensive gourmet and valuable food due to their high nutritional and medicinal values (Badalyan 2012; Badalyan and Zambonelli 2019, 2023). Medicinal properties (analgesic, antibacterial, antifungal, antioxidant, antitumor, antiviral, cardioprotective, immunomodulatory, neuroprotective, etc.) have been described in several genera and species of macrofungi, such as *A. bisporus, A. blazei, A. cinnamomea, G. lucidum, G. frondosa, H. erinaceus, L. edodes, P. cornucopiae, P. eryngii, P. ostreatus* and *T. versicolor.* They have also contributed to the development of pharmaceutically active ingredients, healthy and functional foods, and cosmeceutical products (Badalyan and Zambonelli 2019, 2023; Badalyan et al. 2019; 2021; 2022).

Studies on the beneficial effects of wild and cultivated medicinal mushrooms, particularly from the genus *Pleurotus*, on the nutrition and health of humans and animals have been reported (Cateni et al. 2021). An overview of the structure and composition of mycochemicals (phenolic compounds, triterpenoids and sterols, fatty acids and lipids, polysaccharides, proteins, peptides, and lectins), as well as the potential of mushrooms in the production of biotech products, including drugs, nutraceuticals, and functional food, have been discussed (Cateni et al. 2021).

The dietary consumption of biotech products obtained from *A. bisporus, G. frondosa, G. lucidum*, *F. velutipes,* and *L. edodes* in the form of fruiting bodies or extracts may prevent or delay the development of gastric and breast cancers (Wasser 2017).

In vitro evaluation of bioactivities of n-hexane extracts from *D. indusiata, H. erinaceus,* and *Metacordyceps neogunnii* revealed their therapeutic significance. The extract of *D. indusiata* showed the highest AOA (87.8 ± 1.2%), followed by *H. erinaceus* (84.9 ± 1.6%) and *M. neogunnii* (77.3 ± 1.3%). The extract of *M. neogunnii* revealed cytotoxicity (68.6 ± 3.6%) against HCT116 human colon cancer cell lines at a concentration of 100 μg/mL, whereas *H. erinaceus* and *D. indusiata* extracts showed weaker cytotoxic effects at the same concentration (18.3 ± 1.7% and 19.3 ± 3.2%, respectively). The extracts also showed potent *in vitro* hypocholesterolemic effects (100 ± 0%). The GC-MS analyses revealed 22 compounds in *D. indusiata*, 29 in *M. neogunnii*, and 33 in *H. erinaceus* extracts. Most of these compounds were esters of fatty acids. These results suggest that the tested mushrooms can be used as functional foods. However, further *in vivo* studies are needed to evaluate their usage as pharmaceuticals (Daba et al. 2020; Elkhateeb et al. 2021a).

The study of therapeutic potential of orally suitable preparations for infusion and decoction from wild mushrooms *Tremella fuciformis* and *Termitomyces heimii* showed that they contained a noticeable amount of bioactive metabolites, such as phenolics, flavonoids, and carotenoids. Both infusion and decoction possess AOA and have shown anti-inflammatory activities via prevention of protein denaturation. The formulations of *T. fuciformis* and *T. heimii* may be sources of antioxidant-rich healthy beverages (Ghosh et al. 2022).

Truffles are symbiotrophic hypogeous ascomycete mushrooms that have gained scientific attention over the past years for their application in medicine (Badalyan and Zambonelli 2019, 2023). They produce bioactive molecules (phenolics, terpenoids, fatty acids, lectins, ergosteroids, and polysaccharides) with antimicrobial, antiviral, antioxidant, anti-inflammatory, anti-depressant, aphrodisiac, and anti-carcinogenic effects (Badalyan 2012). The distribution, biochemical analysis, nutritional values, and health benefits of truffles have been explored, and recent information on the potential therapeutic usage have been reported (Elkhateeb et al. 2021b; Elsayed et al. 2021; Badalyan and Zambonelli 2023).

4.2 Pre-Clinical and Clinical Studies

Recent advances in research of medicinal mushrooms have approved the traditional knowledge about therapeutic properties of mushroom-derived bioactive compounds and extracts, as well as their usage in mycotherapy (Hapuarachchi et al. 2017; Kües and Badalyan 2017; Badalyan et al. 2019; Badalyan and Rapior 2021a). Clinical trials in European and Asian countries indicate that biotech products derived from mushrooms are used in different preventive and therapeutic strategies and other therapies (Wasser 2011, 2014, 2017; Chaiyasut and Sivamaruthi 2017). Additional data from *in vitro* and *in vivo* studies using experimental animal models have been reported. Recent reviews focused on clinical studies of several macrofungi, such as *G. lucidum, G. frondosa, H. erinaceus,* and *T. versicolor*, in the treatment of oncological, immunological diseases and diabetes mellitus (Wasser 2017; Badalyan et al. 2019). Therefore, systematic clinical trials are required to update comprehensive knowledge on mushrooms' mycopharmacological and mycotherapeutical potential.

Contemporary clinical practices rely on mushroom-derived drugs and dietary supplements to increase the tolerance of patients to cancer therapy (Steimbach et al. 2021; Twardowski et al. 2015; Tanaka et al. 2016; Tsai et al. 2016, 2021; Wasser 2017).

The edible and inedible wild and cultivated mushrooms (*Coriolus versicolor, F. fomentarius, F. officinalis, G. lucidum, G. frondosa, L. edodes, H. erinaceus, I. obliquus, O. sinensis, Ph. linteus, P. betulinus,* and *S. commune*) with pharmacological potential are undergoing clinical studies for the treatment of gastrointestinal disorders, cancer, bronchial asthma, and other diseases (Chen et al. 2016; Wasser 2017; Badalyan et al. 2019).

The bioactive compounds along with their effects and mechanisms *in vitro* and *in vivo* preclinical studies of selected medicinal mushrooms, including *A. bisporus*, *A. blazei*, *A. cinnamomea*, *C.* (=*Trametes*) *versicolor*, *G. lucidum*, *G. frondosa*, *H. erinaceus*, *L. edodes*, and *Pleurotus* spp. have been analyzed (Venturella et al. 2021).

The authors also discussed the pharmacological activities of mushrooms in clinical trials, including cancer and neuronal health, diabetes, hyperglycemia, hyperlipidemia, and cardiovascular diseases. The increasing concern in mycotherapy requires a guarantee from the scientific community to expand clinical trials and provide supplements of safe fungal origin and proven genetic purity (Venturella et al. 2021).

Overall, more than 130 medicinal properties of mushrooms (anticancer, antioxidant, antimicrobial, immunomodulating, cardiovascular, etc.) have been described (Panda and Luyten 2022). The clinical studies were conducted on medicinal mushrooms or their mushroom-based preparations but not on isolated bioactive compounds. All clinical trials, including scientific and English names of mushroom species, the type of clinical study, disease or indication, mushroom part used, dosage and duration of treatment, study outcome, and a database identifier number, have been summarized. Overall 91 published clinical trials of 22 species were analyzed. The majority of clinical studies have been carried out with seven species: *L. edodes* (19%), *A. bisporus* (15%), *A. blazei* (14%), *G. lucidum* (9%), *P. ostreatus* (7%), *G. frondosa* (5%) and *Agaricus sylvaticus* (5%). The clinical trials were mainly conducted in humans, six on chickens, one in calves, and one in dogs. Mushrooms have mainly been studied for the treatment of cancer (16%) or for their immunomodulatory effects (14%). Around 11% of trials assessed possible fitness and health benefits, such as antioxidant properties, nutritional value, vitamin content, and food intake. Many of the clinical benefits of mushrooms may be attributed to their effect on immune system. In general, a few phase III clinical trials have been performed, and in many cases, randomized, double-blind trials include a relatively small number of patients (Panda and Luyten 2022).

Medicinal properties of raw mushroom extracts and isolated bioactive molecules should be studied using bioassay-guide purification *in vitro* tests, on different cancer cell lines, or even *in vivo* animal models to test their activities on different cancers (Panda et al. 2022). Most *in vitro* cell studies use breast (43.9%), lung (14%), and colorectal (13.1%) cancer cell lines. In contrast, *in vivo* animal studies are mainly performed in mouse tumor models (58.7%). Preclinical studies may be considered for isolated bioactive molecules, as well as clinical studies, including phases from I to IV. Although around 30 mushroom species are promising for the treatment of cancer, only 11 species appear to have been clinically tested. Several mushrooms have been tested in phases I or II clinical trials, primarily for the treatment of breast (18.6%), colorectal (14%), and prostate (11.6%) cancers. Most clinical studies were performed with five species: *L. edodes* (22.2%), *C. versicolor* (13.9%), *G. lucidum* (13.9%), *A. bisporus* (11.1%) and *G. frondosa* (11.1%), involved a small number of patients and were limited to phases III or IV. Despite the availability of preclinical and clinical data, more convincing results are expected

to approve the therapeutic values of mushrooms in oncology (Wasser 2017; Panda et al. 2022).

In many clinical studies, mushrooms were used as an adjuvant therapy with conventional chemo- or radiotherapy for treatment of different types of cancer (breast, stomach, liver, lung, prostate, ovary, etc.) to reduce side effects (e.g., hair loss, nausea and loss of appetite). However, no evidence has revealed appropriate dosages and duration of treatment for many species, sometimes due to poor study design, non-standardized mushroom preparations, inappropriate statistical methods, etc. (Wasser 2017; Badalyan et al. 2019).

Mycelial and fruiting body extracts, mycelial biomass, β-glucans (e.g., lentinan, Maitake D-fraction, schizophyllan, PSK, or Krestin) have been tested in clinical studies to treat oncological diseases (Ina et al. 2016; Wasser 2017; Badalyan et al. 2019). Future randomized placebo-controlled cross-over studies will elucidate the efficacy of mycotherapy, the effects of mushroom-derived anticancer compounds on long-term survival, tumor response, host immune functions, inflammation, and quality of life of cancer patients (Badalyan et al. 2019).

The oral administration of *G. lucidum*-derived β-glucans has shown a potent immunomodulatory effect *in vitro* and *in vivo*. A randomized, double-blinded, placebo-controlled clinical study was performed on asymptomatic three to five-year-old children (Henao et al. 2018). The results have shown that *G. lucidum*-derived β-glucans increased the number of immune cells in the peripheral blood, which are critical in defence against pediatric infectious diseases. However, these findings warrant clinical trials to prevent infections in healthy children and define their potential to increase lymphoid cell count during various lymphoid immune deficiencies (Henao et al. 2018).

Six preclinical and three clinical studies of the therapeutic effects of *H. erinaceus* in Alzheimer's disease have been reviewed. Preclinical trials conducted from 2011 to 2021 successfully demonstrated that extracts and bioactive compounds obtained from *H. erinaceus* have beneficial effects in improving cognitive function and behavioral deficit in animal models (mice and rats) (Yanshree et al. 2022). Three double-blind placebo-controlled clinical studies have shown similar results to pre-clinical studies (Mori et al. 2009, 2011; Saitsu et al. 2019; Li et al. 2020). Nevertheless, future research on *H. erinaceus* should focus on elucidating specific neuroprotective mechanisms and target sites in Alzheimer's disease.

In a previous study, Vetvicka and Vetvickova (2015) showed that the immunomodulatory effects of β-glucans were used to prevent viral infections; feeding mice infected with the influenza virus for two weeks with a mixture of glucans extracted from fruiting bodies of *G. frondosa* and mycelium of *Agaricus brasiliensis*, *I. obliquus,* and *L. edodes* improved the clinical symptoms of the disease. These results suggested that consumption of dietary glucans could be useful as a complementary or alternative approach for treatment of influenza infection. Further application of β-glucans and study of structure-activity relationship to develop functional food products fortified with β-glucans should be performed to prove this effect.

A randomized, double-blind, placebo-controlled study in pediatric patients with regular respiratory infections has shown that treatment with pleuran, a β-glucan from

P. ostreatus, reduced infection-related symptoms of atopy, associated with increased immune responses to common allergens (Jesenak et al. 2014).

Hapuarachchi et al. (2017) reviewed the medicinal properties of 30 species of *Ganoderma* (except *G. lucidum*) and their secondary metabolites; according to the authors, there is no evidence to support the use of *Ganoderma* species as potential food supplements for treatment of cancer or other diseases in humans, because no preclinical test has been carried out to date.

Preclinical trials have suggested that *G. lucidum* possesses promising anticancer and immunomodulatory properties. Over 250 clinical studies on *G. lucidum* and other *Ganoderma* species have been published (Jin et al. 2012). In this study patients with *G. lucidum* extract in their cancer regimen were 1.27 times more likely to respond to chemotherapy or radiotherapy than those who did not.

The results of a double-blind, randomized, placebo-controlled trial found no significant effect of the administration of 3 g/day *G. lucidum* or a combination of *G. lucidum* with *C. sinensis* for 16 weeks on HbA1c and fasting plasma glucose levels of a small number of patients with type 2 diabetes mellitus (Klupp et al. 2016). *G. lucidum* is also widely used to treat cardiovascular diseases (Badalyan et al. 2021).

According to Tangen et al. (2015), 40 patients with multiple myeloma scheduled to undergo high-dose chemotherapy with autologous stem cell support were randomized to receive adjuvant therapy with Andosan™ mushroom extract containing 82% ABM (19 patients) or placebo (21 patients). Increased quantities of Treg cells and plasmacytoid dendritic cells were found in leukapheresis products harvested after stem cell mobilization from patients receiving Andosan™. The genome microarray demonstrated increased expression of immunoglobulin genes, killer immunoglobulin receptor genes, and HLA genes in the *Agaricus* group. This study was registered in Clinicaltrials.gov NCT00970021 (Tangen et al. 2015).

Ex vivo and *in vivo* investigations have shown anticancer, anti-inflammatory, antimicrobial, antimutagenic, antioxidant, anti-parasitic, hepatoprotective, hypodlycemic, and immunomodulatory activities in *A. blazei* Murrill sensu Heinemann (syn. *A. subrufescens*). At the same time, only 17 clinical studies and two case reports on ABM were found (Therkelsen et al. 2016). A study reported the nutritional and therapeutic properties of ABM with emphasis on its chemical composition (Da Silva de Souza et al. 2017). However, further clinical trials using reliable statistical methods and standardized preparations are needed to evaluate the efficacy of ABM as a therapeutic agent.

The medicinal properties (antitumor, immunomodulatory, anti-coagulatory, anti-inflammatory, antimicrobial, antioxidant, antiviral, neuroprotective, etc.) of *L. rhinocerotis* have been reviewed by Nallathamby et al. (2018). *In vitro* investigations have revealed that fruiting bodies and sclerotia of *L. rhinocerotis* may be considered alternative therapeutic resources in the management of non-communicable diseases. Therefore, further studies, including *in vivo* clinical trials, are needed to scientifically validate the application of chemicals derived from *L. rhinocerotis* as pharmaceuticals and medicines.

A prospective randomized study of 25 patients comparing the efficacy of *H. erinaceus* versus essential oils against *Helicobacter pylori* infection revealed that patients who received *H. erinaceus* had negative Pyloritop® test results in 89.5% of cases versus 33.3% in patients who started with essential oils (Donatini 2014). It has been suggested that *H. erinaceus* could be an alternative to antibiotic therapy for *H. pylori*-associated pathology. Additional randomized clinical trials versus reference therapy should be performed to focus on treatment without adverse effects (Donatini 2014).

A prospective phase II, randomized, simple, double-blind, placebo-controlled trial was conducted using cereal bars made from *L. edodes* (Spim et al. 2021a). Men and women aged 20-65 with at least one biochemical marker of borderline hypercholesterolemia were recruited. Sixty-eight people were randomly assigned to group I (placebo; $n = 32$) or group II (intervention; $n = 36$). Sweetened cereal bars (25 g) containing dry shiitake (3.5 g) have been consumed. A daily concentration of shiitake of 100 mg/kg is safe in a study conducted with ingestion of different concentrations of *L. edodes*. Participants in the intervention group showed a 10% reduction in triglycerides after 66 days of consuming *L. edodes* cereal bars. Moreover, after 33 days of consumption, the AOA on reduced lipid peroxidation was observed. However, the consumption of *L. edodes*-based bars caused dermatitis in 10% of individuals (Spim et al. 2021b). Therefore, this study aimed to analyze the effects of shiitake bars on borderline cholesterol and oxidative stress in humans through a phase II double-blind, randomized trial. The authors of a recent study have shown that the sweet bar 1 (SwB1) had better sensory analysis due to its stability, low production cost, and good acceptance, as well as the flexibility to add other beneficial ingredients, such as shiitake (Spim et al. 2021a).

Clinical studies of a novel bioactive substance, derived from *I. obliquus,* for cancer patients depending on the topography of tumor, disease stage, and patient age, as well as the pharmacokinetics and pharmacodynamics of the compound, were performed. The mechanisms of effects of fungal extracts obtained by different extraction methods were revealed. The recommendations for using *I. obliquus* to improve clinical outcomes in cancer patients were discussed (Khoroshutin et al. 2021).

Recently, Chan et al. (2022) investigated erinacine A-enriched *H. erinaceus* (HE) on hearing degeneration through a double-blind, randomized, placebo-controlled clinical trial: 80 hearing-impaired patients aged 50–79 were randomly divided into two groups. The results demonstrated that treatment with HE mycelium could improve hearing function, especially for high frequencies and speech recognition. This effect was observed in hearing-impaired patients of age ≧65 years.

The triterpenes of *Pleurotus tuber-regium* sclerotium have recently been investigated for their hypolipidemic effects (Wang et al. 2022c). In *in vivo* experiments, the authors showed that zebrafish tolerated total triterpenes of mushroom nuclei at a maximum concentration of 500 μg/mL. In addition, the results demonstrated that total triterpenes derived from mushroom nuclei reduced a dose effect lipid accumulation in zebrafish induced by a high-fat diet.

Based on the results of clinical studies involving medicinal mushrooms, high quality, long-term, randomized, double-blind, placebo-controlled clinical trials should be further pursued.

5 Conclusion and Future Prospects

Mushroom-derived bioactive compounds possess various medicinal properties, including immunomodulatory, anti-cancer, antiviral, antioxidant, anti-inflammatory, etc. In addition, the treatment with conventional anticancer drugs poses tremendous challenges and limitations, such as poor solubility, narrow therapeutic window, and cytotoxicity, which may cause side-effects in cancer patients.

Mushrooms are becoming applicable in nanomedicine; mushroom-derived nanoemulsion has recently been suggested for cancer therapy (Chandrawanshi et al. 2022). The therapeutic potential of AgNPs coupled with natural mushroom extracts has been extensively evaluated in various diseases. The synthesis of AgNPs using *C. versicolor* (CV-AgNPs) and *Boletus edulis* (BE-AgNPs) crude extracts was carried out (Kaplan et al. 2021). Strong antimicrobial activity of AgNPs obtained from both species was reported against Gram-negative (*P. aeruginosa* and *K. pneumoniae*) and Gram-positive (*S. aureus* and *E. faecalis*) bacteria rather than against *Candida* strains (*C. albicans* and *C. utilis*). The anti-proliferative activity of AgNPs has been detected, as well. Both species-derived AgNPs decrease proliferation of MCF-7 (breast adenocarcinoma), HT-29 (colorectal adenocarcinoma) and HUH-7 (hepatocellular carcinoma) cell lines. The synthesized nanoparticles have also shown a wound-healing effect at low concentrations on L929 cells. The obtained data may lead to an efficient nanoparticle system for drug design and delivery in the treatment of infectious diseases and cancer (Kaplan et al. 2021).

The synthesized AgNPs using *Tricholoma ustale* and *Agaricus arvensis* extracts exhibited antibacterial activity against *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, *E. faecalis*, and antifungal activity against *C. albicans* and *C. utilis* strains (Kaplan et al. 2022). The AgNPs showed an anti-proliferative effect on human breast cancer (MCF-7), lung cancer (A549), osteosarcoma (Saos-2), and colon cancer (HT-29) cell lines, as well. The AgNPs stimulated intrinsic apoptotic signaling pathways via up-regulation of Bax/Bcl-2 and decreased pro-Casp9 expression in MCF-7, Saos-2, and HT-29 cells. Thus, the mushroom-derived AgNPs may be a potential metal-based nanoparticle system to treat infectious diseases and cancer (Kaplan et al. 2021, 2022).

Several human diseases, such as diabetes, cancer, cardiovascular and neurodegenerative disorders, affect adult population worldwide. Therefore, scientists have tried to discover novel natural sources of medicines, especially from plants and mushrooms, to prevent and treat these pathological conditions. This review addressed the current state of knowledge and findings of recent studies on mushroom-derived healthy food and therapeutics. Although the list of studied medicinal mushrooms and clinical approval for the application of their bioactive

compounds as therapeutic agents is incomplete, this work represents an updated contribution to modern mycopharmacology, mycotherapy, and biomedicine.

Future interdisciplinary research, involving physicians, biologists, chemists, pharmacologists, and mycologists is warranted to create a basis of scientific and traditional knowledge with biomedical data for further usage of therapeutic potential of mushrooms for human welfare.

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