Review

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Pharmaceutical and Nutraceutical Importance of Bioactive Metabolites from Macrofungi

Mehmoona Sharif[1], Aneela Nawaz[1], Shayan Naeem[1], Umme Habiba Saeeda[1], Arshad Farid[2], Numan Saleh Zada[1], Aamer Ali Shah[1], Malik Badshah[1], Mohanned Talal Alharbi[3], Muyassar Khaled Tarabulsi[3], Samy Selim[4,*], Samiullah Khan[1,*]

[1]Department of Microbiology, Faculty of Biological Sciences, Quaid-i-Azam University, 45320 Islamabad, Pakistan
[2]Gomal Center of Biochemistry and Biotechnology, Gomal University, 29050 Dera Ismail Khan, Pakistan
[3]Department of Medical Microbiology and Parasitology, Faculty of Medicine, University of Jeddah, 23218 Jeddah, Saudi Arabia
[4]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, 72388 Sakaka, Saudi Arabia
*Correspondence: sabdulsalam@ju.edu.sa (Samy Selim); samikhan@qau.edu.pk (Samiullah Khan)
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Mushrooms emerge as fascinating organisms within the vast expense of the natural world. They have been rapidly expanding in demand due to their popularity among consumers for their delightful taste, distinctive odor, and nutritional value. They are regarded as functional foods, that confer nutritional benefits and enhance health. Macrofungi exhibit a diverse array of bioactive compounds, categorized as secondary metabolites. Mushrooms are the richest source of proteins, polysaccharides, polysaccharide-protein complexes, phenolic compounds, sterols, triterpenes, triterpenoids, and vitamins. Mushroom extracts have great medicinal uses for human well-being as they possess numerous properties such as anticancer, antimicrobial, antidiabetic, antioxidant, antiobesity, antilipidemic, antiaging, immunomodulatory, hepatoprotective, and neuroprotective properties. This review highlights the nutraceutical and therapeutic potential of various macrofungi. Furthermore, it serves as a valuable resource for researchers, enabling them to access existing knowledge on the ethnopharmacological activities of bioactive compounds extracted from macrofungi and other useful compounds that could be the source for the discovering novel drugs with better pharmaceutical and therapeutic properties.

Keywords: medicinal macrofungi; bioactive metabolites; nutraceuticals; therapeutic applications

Introduction

Macrofungi are derived from the Greek word macros, which means large. Macrofungi encompass Phylum Basidiomycota and some Ascomycota species with morphologically distinct fruiting bodies growing above or below ground [1]. They are distributed worldwide, and 14,000 species of macrofungi have been identified so far. About 2000 edible and medicinally important mushroom species have been characterized [2]. Edible mushrooms cultivated all around the world include *Agaricus bisporus* (button mushroom), *Flammulina velutipes* (enoki mushroom), *Auricularia auricula* (wood ear macro mushroom), *Lentinula edodes* (shiitake mushroom), *Volvariella volvacea* and *Pleurotus* spp. (oyster mushroom) [3]. Medicinal mushrooms cultivated worldwide include *Ganoderma lucidum*, *Cordyceps sinensis*, *Lentinula edodes*, *Inonotus obliquus*, *Phellinus linteus*, *Antrodia cinnaomea* and *Xylaria nigripes* [1]. The most researched medicinal mushrooms are *Antrodia cinnamomea*, *Ganoderma lingzhi*, *G. sichuanense*, *Ophiocordyceps sinensis*, *Phellinus linteus*, and *Xylaria nigripes* [4]. Some of the common medicinal macrofungi named *Hericium erinaceus*, *Inonotus obliquus*, *Lentinula edodes*, *Trametes versicolor*, and *Ganoderma lucidum* are gaining attention as a novel function food [5]. These fungi are distinguished by their high content of bioactive compounds, including β-d-glucans recognized as dietary fibre, triterpenes, terpenoids, sterols, and phenolic compounds [5–7]. Notable for their potential health benefits, these macrofungi contribute to overall well-being and nutritional enrichment. The bioactive compounds found in macrofungi exhibit a broad spectrum of therapeutic potential, encompassing anticancer, antioxidant, antimicrobial, anti-inflammatory, antidiabetic, and immunomodulatory properties [5–7]. Furthermore, these macrofungi play a role in enhancing metabolism, aiding in the fight against obesity, and contributing to the anti-ageing process due to their robust antioxidant properties [5]. Consequently, the consumption of these macrofungi is increasingly recognized for their positive impact on holistic health and vitality. In *Inonotus obliquus* (Chaga mushroom) case, three compounds were identified: betulin, betulinic acid, and inotodiol showing biologically activity against different cancer cells [8]. *Ganoderma lucidum* also exhibits diverse bioactive compounds, including triterpenoids, sterols, polysaccharides,

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Table 1. Nutritional value of some of the most common macrofungi.

Macrofungi	Local Name	Moisture g/100 g	Ash g/100 g	Protein g/100 g	Fat g/100 g	Carbohydrate g/100 g	Energy kcal/100 g	References
Agaricus bisporus	White button	90.0	9.2	24.4	3.1	53.1	325.0	[18]
Agaricus campestris	Field or Meadow	88.1	23.1	18.5	0.1	58.1	238.0	[19]
Auricularia auricula-judae	Wood ear	89.0	3.2	56.9	3.5	18.6	327.7	[20]
Auricularia polytricha	Wood ear, Jelly ear	82.0	8.4	42.0	0.8	16.0	347.0	[20]
Flammulina velutipes	Enoki	5.0	8.3	23.4	2.1	1.2	467.0	[21]
Ganoderma lucidum	Lingzhi	5.1	1.0	9.2	1.1	83.6	394.0	[21]
Grifola frondosa	Maitake	4.8	4.7	18.3	5.4	67.0	290.0	[21]
Lentinula edodes	Shiitake	7.3	5.1	18.5	0.9	68.4	387.0	[20]
Pleurotus ostreatus	Oyster	8.2	7.7	20.0	8.6	60.3	416.0	[22]
Pleurotus eryngii	King Trumpet/King oyster	28.3	3.5	28.8	3.1	52.2	421.0	[23]
Tricholoma imbricatum	Matsutake	82.4	6.4	50.4	1.8	41.2	383.7	[24]
Tricholoma giganteum	Matsutake	81.2	5.1	16.2	4.4	70.2	383.6	[21]
Tremella fuciformis	White Brain Jelly	5.5	0.4	4.6	0.3	94.8	-	[21]
Volvariella volvacea	Paddy straw	72.2	12.6	30.2	6.3	50.9	374.2	[3]

Ash, inorganic impurities.

terpenes, peptides, alkaloids, and phenols [9,10]. Among them, triterpenoids and polysaccharides emerge as main constituents due to their abundant presence, diverse structures, and noteworthy bioactive properties [9,10]. More than 300 compounds have been identified and isolated from the fruiting body of *G. lucidum* [9]. Ganoderic acids A, C2, D, F, DM, X and Y isolated from *G. lucidum* are currently in clinical trials for their immunomodulatory and anticancer activities [11]. Ganoderic acid A can potentially alleviate the lipid metabolic disorders and positively alter gut microbiota composition [12].

Macrofungi possess therapeutic properties due to the secretion of various secondary metabolites [13]. These secondary metabolites are the low molecular mass bioactive molecules produced due to stress for survival but are not necessary for macrofungal growth and development. It has been reported from various studies that these bioactive compounds not only activate the immune response but also interfere with specific transduction pathways to modulate specific cellular responses [14]. Macrofungi are extremely safe to eat but a few mild to moderate gastrointestinal complications such as nausea, vomiting, dizziness, cramping, and diarrhea are associated with its poisoning [15]. Only limited studies reported the side effects of mushrooms. For example, *Psilocybe* spp. commonly known as "magic mushroom" contain hallucination causing chemicals such as psilocybin or psilocin. The average concentration of psilocybin required to induce hallucination is 40–500 µg/kg body weight [16]. Consequently, to achieve the desired recreational effect, approximately 1 g of dried magic mushrooms or 10 g of fresh magic mushrooms is considered the minimum amount needed [17].

Nutritional Value of Macrofungi

Mushrooms have increased in popularity due to their delicious taste and valuable health benefits. Table 1 (Ref. [3,18–24]) shows they serve as a valuable reservoir of nutrients and bioactive molecules that improve human physical and physiological conditions and prevent and treat various diseases [25]. They are the richest source of proteins that contain essential amino acids and unsaturated fatty acids, for example, linoleic and oleic acids, which are essential for the optimal functioning of the body. The fruiting bodies of macrofungi contain 50–60% carbohydrates and mannitol accounts for 80% of the total carbohydrates [26]. They also contain essential minerals that are necessary for the proper metabolism of various metabolic pathways. The main minerals in macrofungi are K, P, Na, Ca, and Mg, and trace elements are named Cu, Zn, Fe, Mo, and Cd [27]. They also contain fibre, especially soluble fiber glucan, and vitamin B complex, such as vitamin B5, which helps to release energy from carbohydrates, proteins, and lipids [13]. The macrofungi contain 70–95% moisture depending on the environmental conditions and harvest time [13]. Therefore, macrofungi have the potential to serve as valuable sources of functional foods with low-calorie content.

Nutraceuticals

Nutraceuticals are compounds used more as food and less as medicines, so they can be considered an adjunct to treat various diseases effectively. In 1989, the word nutraceutical was coined by Stephen De Felice, founder and chair of the Foundation for Innovation in Medicine [28]. It refers to products that have health benefits and are used to prevent and treat various diseases. Some mushrooms are the source of basic amino acids, carbohydrates, and fibre

Table 2. List of food based on Mushrooms.

Macrofungi	Food items		Function	References
Lentinus sajor-caju (Oyster mushroom), *Agaricus bisporus*	Baked food	Biscuit	Increase dietary fiber, level of β-glucan and protein in biscuit and enhance glycemic response	[38]
Agaricus blazei, *Hericium erinaceus*, *Pleurotus plumonariu*		Bread	Increase dough volume, level, protein, and nutritional value, decreasing the loss of moisture	[39]
Pleurotus eryngii (King Oyster)		Cookie	Increase dough volume and beneficial effect on health	[40]
Lentinus edodes		Muffin	Beneficial effect on health	[41]
Pleurotus sapidus	Sausage	Vegan sauce	Replace commercial vegetable proteins	[36]
Lentinus edodes		Brown sauce	Enhance flavor	[39]
Tricholoma matsutake		Apple dressing	Enhance flavor	[39]
Agaricus bisporus	Meat substituent		Improve texture	[36]
Lentinus edodes	Pork patties		Improve texture and increase juiciness and beneficial ingredients	[42]
Agaricus bisporus	Beef burger		Enhance flavor and fat replacer	[43]
Ganoderma lucidum	Drink	Beer	Enhance biological potential	[44]
Pleurotus ostreatus		Wine	Preventive effect against cancer	[45]
Grifola frondosa, Ganoderma lucidum	Fermented products	Fermented tea	Enhance sensory flavor and therapeutic effect	[37]
Lentinus edodes (shiitake)		Beverages	Use as a source of nitrogen	[37]
Flammulina velutipes	Preservatives	Apple juice	Prevent browning of apple juice	[45]
Flammulina velutipes, *Pleurotus eryngii*		Processed fish meat	Stabilization of color	[46]
Bachu mushroom		Compound beverages	Beneficial effect on health	[45]

Table 3. The pharmaceutical potential of various bioactive compounds from macrofungi.

Pharmaceutical potential	Macrofungi	Bioactive compounds	Mechanism	References
Anticancer	*Grifola frondosa*	Polysaccharides	➢ Decrease cell viability	[3,49–51]
	Ganoderma lucidum	Polysaccharides	➢ Increase apoptotic rate	
	Ophiocordyceps sinensis	Polysaccharides	➢ Induce mitochondrial dysfunction	
	Calocybe indica	Calocyban		
	Agaricus blazei	Ergosterol		
	Lentinus edodes	Lentinan		
	Lentinus edodes	Vitamin D		
Antioxidant	*Sanghuangporus sanghuang*	Triterpenoid	➢ Block the production of free radical	[25,53,74,79]
	Agaricus bisporus	Polysaccharides Vitamin B2	➢ Scavenging of oxidants ➢ Convert toxic free radicals into less toxic compounds	
	Pleurotus citrinopileatus	Ergothioneine		
	Auricularia auricula	Melanin Vitamin		
	Oudemansiella radiata	Polysaccharides		
Antimicrobial	*Lentinula edodes*	Lentinamycin	➢ Inhibiting the growth of microorganisms	[54,81,82]
	Pleurotus species	Phenol Flavonoid	➢ Prevent replication	
	Ganoderma lucidum	Polysaccharides		
	Cordyceps militaris	Cordycepin		
Antiviral	*Pleurotus ostreatus*	β-glucan pleuran	➢ Enhance host antiviral defense	[55–57]
	Ganoderma lucidum	Triterpenes Triterpenoids	➢ Disrupt virus particles ➢ Stimulate the production of cytokine	
	Pleurotus ostreatus	Polysaccharides	➢ Activate natural killer cells and T lymphocytes	
	Lentinula edodes	Polysaccharides		
	Lentinula edodes, Lignosus rhinocerus, Flammulina velutipes	Ergosterol, heliantriol F, velutin		
Antihyperglycemic	*Trametes pubescens*	Polysaccharides	➢ Enhancing the activity of insulin	[58–60]
	Calvatia gigantean	Polysaccharides	➢ Inhibiting alpha-amylase enzyme	
	Ganoderma lucidum	Polysaccharides Terpenoids	➢ Inhibiting alpha-glucosidase ➢ Enhancing the insulin signaling pathway	
	Coprinus comatus	Terpenoids		
Antiobesity	*Pleurotus citrinopileatus*	Polysaccharides	➢ Improving glucose tolerance	[61,80,83,84]
	Cordyceps sinensis	Polysaccharides	➢ Modifying gut microbiota	
	Pleurotus florida	Polysaccharides	➢ Regulate the expression of the gene for lipid metabolism	
	Grifola frondosa	Polysaccharides		
	Cordyceps militaris	Cordycepin		

Table 3. Continued.

Pharmaceutical potential	Macrofungi	Bioactive compounds	Mechanism	References
Antiaging	*Agaricus bisporus* *Agrocybe aegerita* *Grifola frondosa* *Ganoderma lucidum* *Hericium erinaceus*	Polysaccharides Polysaccharides Polysaccharides Polysaccharides Polysaccharides	➢ Enhance the activity of the antioxidant enzyme ➢ Decrease peroxidation of lipid ➢ Remit the metabolism of lipid	[62,63,85]
Antiinflammatory	*Lentinula edodes* *Echinodontium tinctorium* *Ganoderma lucidum* *Pleurotus* spp.	Polysaccharides Polysaccharides Triterpenes Polysaccharides, Peptides Amino acids Phenolics, Terpenes	➢ Reducing levels of Blood urea nitrogen, Creatinine, and Uric acid ➢ Slow down lipid peroxidation ➢ Decreasing level of TNF-α, IL-6, IL-1β	[52,64,65,86]
Antihypertensive	*Pleurotus cornucopiae* *Trametes versicolor* *Tricholoma matsutake* *Hypsizygus marmoreus* *Pleurotus eryngii*	D-mannitol Polysaccharides Peptides Peptides Polysaccharides	➢ Inhibit angiotensin I converting enzyme (ACE) and vascular receptors ➢ Reduce the total level of cholesterol in the blood, low-density lipoprotein in serum ➢ Vasodilation	[66,67]
Antiasthmatic	*Grifola gargal* *Flammulina velutipes* *Lignosus rhinocerotis*	Polysaccharides Proteins Polysaccharides	➢ Reduce the level of Th2 cytokines in BALF ➢ Decrease IgE in serum ➢ Stop infiltration of leucocytes and mucus production	[68–70]
Neuroprotective	*Pleurotus eryngii* *Ganoderma lucidum* *Cordyceps sinensis*	Polysaccharides Polysaccharides Polysaccharides Proteins Cordycepin	➢ Modulate anti-acetylcholinesterase activity ➢ Stimulation of neurite outgrowth ➢ Synthesis of nerve growth factor ➢ Boosting function of mitochondria ➢ Reduce neuroinflammation	[71,72,87]
Hepatoprotective	*Hericium erinaceus* *Agaricus bisporus* *Oudemansiella radiata* *Pleurotus ostreatus* *Ganoderma lucidum* *Antrodia cinnamomea*	Polysaccharides Polysaccharides Polysaccharides Polysaccharides Polysaccharides, Triterpenoids Polysaccharides, Triterpenoids	➢ Decreasing the expression of TGF-β1/Smad signaling pathway ➢ Decreasing enzymes such as ALT, AST, and AP in serum ➢ Boosting the action of hepatic antioxidant enzymes	[73–75]
Immunomodulatory	*Naematelia aurantialba* *Craterellus cornucopioides* *Cordyceps sinensis* *Flammulina velutipes* *Pleurotus* spp. *Grifola frondosa* *Lentinula edodes*	Polysacchharide (glucuronoxylomannan) Polysaccharide Polysaccharide Polysaccharide Polysaccharides, Peptides Polysaccharide (Grifolan) Lentinan	➢ Stimulate the secretion of nitric oxide, TNF-α, and IL-1β from macrophages ➢ Overexpress the TLR4 receptors of cell membrane ➢ Downstream product of protein kinase by the activation of toll-like receptor 4-nuclear transcription factor kappa B (TLR4-NFκB) pathway ➢ Enhance the number of CD4^{+} T cells and SCFAs	[76–78,88]

SCFAs, short-chain fatty acids; IL-1β, interleukin-1β; IL-6, interleukin-6; TGF-β1, transforming growth factor-β1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TLR4, toll-like receptor 4; AP, alkaline phosphatase.

[29]. Some nutraceutical molecules macrofungi produce include bioactive polysaccharides, proteins, sterols, triterpenoids, and antioxidants. In this way, they could be an integral part of a balanced diet and utilized in the clinical management of different degenerative diseases. These bioactive compounds have both additive and synergistic potential [30]. The fruiting bodies and mycelia of mushrooms contain various beneficial compounds such as beta-glucans, lectins, terpenoids, polyphenols, tocopherols with immunomodulatory and anticancer properties, low molecular weight compounds (LMW) such as terpenes, steroids, quinones, derivatives of benzoic acid and quinolones, and high molecular weight compounds (HMW) such as peptides and proteins with antimicrobial activity [31].

The mushrooms exhibiting medicinal properties are mostly referred to as mushroom nutraceuticals. These nutraceuticals are taken as dietary supplements using tablets or capsules obtained from the extract, dried biomass, or fruiting bodies of edible mushrooms. About 270 varieties of mushrooms have medicinal properties, but only a few are considered nutraceuticals. Species most commonly utilized as dietary supplements are *Agaricus bisporus* (button mushroom), *Ganoderma lingzhi* (reishi), *Ophiocordyceps sinensis* (cordyceps), *Grifola frondosa* (maitake), *Hericium* erinaceus (lion's mane), *Lentinula edodes* (shiitake), and *Trametes versicolor* (turkey tail) [32]. Many studies have described these fungi as small pharmaceutical factories for biologically active compounds [13,33,34]. The noteworthy findings have sparked interest in using fungi as a biologically active ingredient in functional foods that could improve the nutritional value of these products [35]. The annual per capita consumption of mushrooms is approximately 5 kg, and it is anticipated to rise in the future [32].

Recently, macrofungi have been researched to improve the taste and nutrition of foods. Table 2 (Ref. [36–46]) shows the industrial value of macrofungi [30]. Currently, mushrooms are mainly used in flour-based products, including bread and biscuits. They increase the antioxidant and nutritional value of pasta and decrease the digestibility of starch, ultimately decreasing the glycemic response [47]. The proteins derived from mushrooms can replace thermal proteins in vegan sausage production and also act as an alternative to meat [36]. The phosphates used in sausage emulsions could be replaced with mushroom powder to overcome the peroxidation of lipids and improve the aroma, flavor, and accessibility of the product [48]. Mushrooms also make novel tea beverages, fermented rice dishes, beer, and healthy wine [37].

Pharmaceutical Properties of Bioactive Metabolites from Macrofungi

Secondary metabolites are well-documented in medicinal mushrooms and are known for their biological activities. Various studies have described the pharmaceutical properties of macrofungi such as anticancer, immunomodulatory, antioxidant, antihemolytic, cardiovascular protective, antihypercholesterolemic, antihyperlipidemic, antiviral, antifungal, antibacterial, antiparasitic, antiobesity, hepatoprotective and hypoglycemic (Table 3, Ref. [3,25,49–88]) [34,89–91]. Various polysaccharides or polysaccharide-protein complexes exhibit antitumor activities in animals and humans by enhancing the body's innate and cell-mediated immune response. Recently, it has been reported that phenolic compounds such as chlorogenic and syringic acids derived from fungi have antiangiogenic properties and restrict blood vessel development by inhibiting vascular endothelial growth factor (VEGF) [92]. Some mushrooms also possess various bioactive components, for example, lovastatin, gamma-aminobutyric acid (GABA), and-ergothioneine with antihypercholesterolemic, antineuroinflammatory, antihypertensive, antioxidant, and cytoprotective properties [93]. In addition, fungi may also significantly regulate the human gut microbiome [92].

Macrofungi with Anticancer Properties

Cancer ranks among the primary causes of death globally. It is commonly treated with chemotherapy but has various side effects namely leukopenia, thrombocytopenia, vomiting, etc. Addressing the side effects requires an immediate requirement for alternative strategies. Recently, macrofungi have garnered significant interest as a potent reservoir of physiologically functional foods and drugs because of their therapeutic importance. Bioactive components of macrofungi, such as polysaccharides and polysaccharide-protein complexes, have medicinal properties and they do not cause harm or additional burden to the body, but help the body adapt to biological and environmental stresses [94]. Polysaccharides from *Grifola frondosa* have been reported to have promising antitumor properties. In China, a drug based on *G. frondosa* polysaccharide has been developed and authorized as an alternative therapeutic approach for cancer treatment [49]. *Ganoderma lucidum* polysaccharides slow myeloid suppressor cell (MDSC) accumulation via the CARD9-NF-B-IDO pathway, thereby preventing the development of lung cancer [50]. Polysaccharide (DTX-AA-CSP) from *Ophiocordyceps sinensis* shows antitumor activity against human liver cancer cells (HepG2) and colon cancer cells (SW480) *in vivo*, surpassing the efficacy of currently available docetaxel injection (Taxotere) [51]. Furthermore, calocyban extracted from *Calocybe indica* showed anti-proliferative and apoptotic effects on pancreatic cancer PANC-1 and MIAPaCa2 cell lines *in vitro* [3]. In 2020, El-Sharkawy and Malki [52] declared vitamin D and its analogues as anticancer drugs. Numerous clinical studies have explored the therapeutic potential of various mushroom species in phase I and phase II clinical trials, with a primary focus on their applications in breast cancer (19%), along with col-

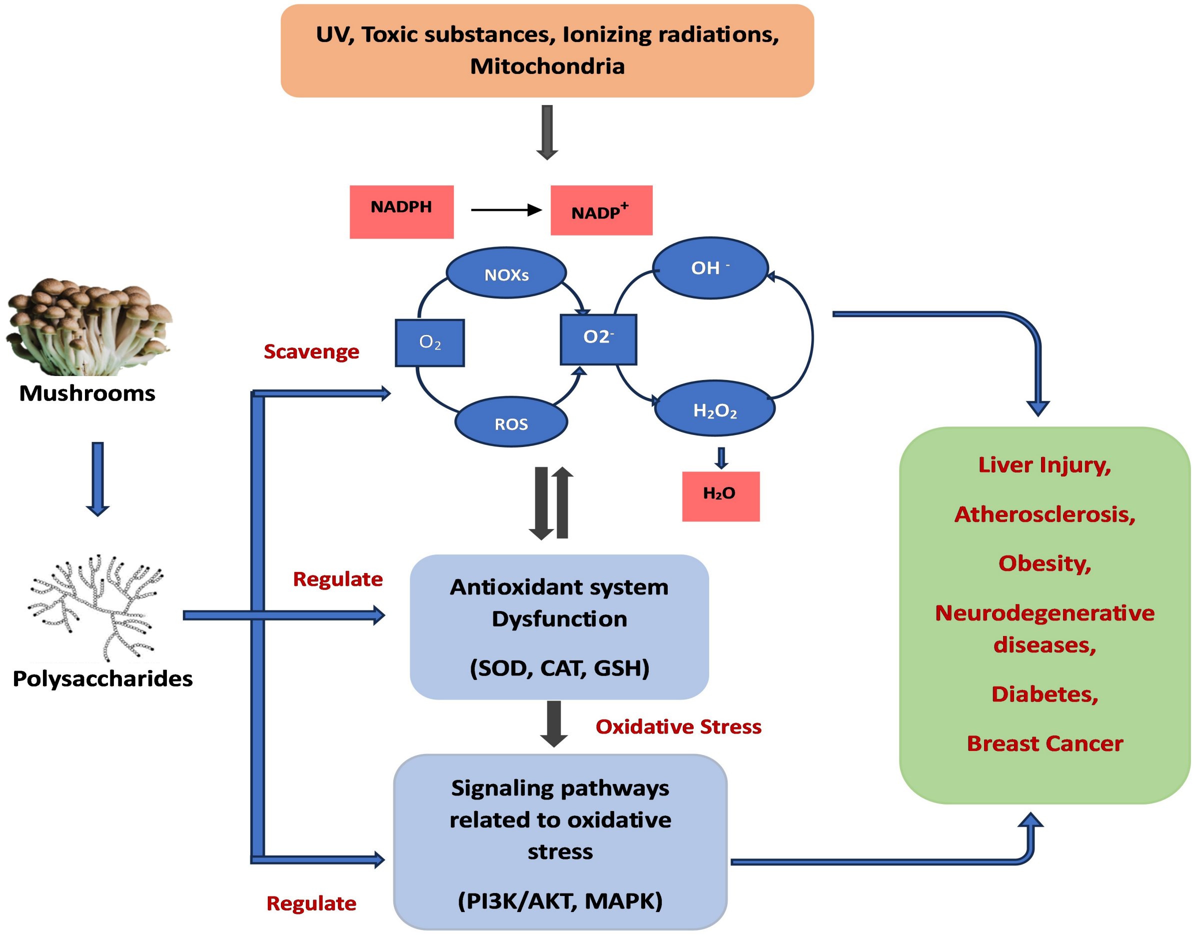

Fig. 1. Mechanism of antioxidant activity showing bioactive compounds that neutralize free radicals to prevent cell and tissue damage (Created using Adobe Illustrator, version 2020, Adobe Inc, San Jose, CA, USA).

orectal (14%) and prostate (12%) cancers [95–97]. The most commonly investigated mushrooms were *Lentinula edodes* (23%), *Coriolus versicolor*, (14%), and *Ganoderma lucidum* (14%), while *Agaricus bisporus* (11%) and *Grifola frondosa* (11%) were also studied [95]. The present evidence allows only a preliminary conclusion that mushrooms exhibit the potential to control the proliferation of cancerous cells and can be used to treat cancer. Interestingly, various *in vitro* studies reported the most potent anticancer compounds, including but not limited to lentinans, schizophyllan, krestin, etc. [95]. These studies aimed at elucidating the mechanisms of action have clearly shown immunomodulating effects such as the proliferation of lymphocytes and changes in immunoglobulins and cytokines, among other factors [95]. In our laboratory, we extensively investigated mushroom extracts to unravel their cytotoxic potential by using a Brine shrimp lethality assay to elucidate their potential role in cancer treatment. Notably, our findings showed a significant cytotoxic potential against brine shrimps at a very low concentration of 1 mg/mL (Unpublished data). Overall, there are various *in vitro* and *in vivo* studies highlighting the anticancer properties of mushrooms but the scientific clinical evidence suggesting their efficacy in cancer treatment is still constrained. Therefore, additional studies with proper standardization, a sufficient number of patients, adequate treatment duration, and more details regarding the mode of administration and dosage will need to be investigated.

Macrofungi with Antioxidant Properties

Oxidative stress is a consequence of disrupted metabolism and an abundance of reactive oxygen species (ROS), leading to various health problems in humans. Various synthetic antioxidants can successfully enhance defense mechanisms, but natural products are preferred due to their antagonistic toxic effects under certain conditions. Therefore, the need for an alternative natural source of antioxidants in macrofungi and the mechanical activity underlying their antioxidant properties has expanded rapidly [98]. Currently, researchers are intrigued by the antioxidant potential of mushrooms because of the presence of antioxidant compounds such as polyphenols, ascorbic acid, polysaccharides, ergosterols, carotenoids, and tocopherols [99] (Fig. 1). Triterpenoid extracted from *Sanghuangporus sanghuang* possesses antioxidant activity against hydroxyl radicals 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free radicals [53]. The study performed by Liu and his coworker [100] showed that polysaccharides from *Agaricus bisporus in vitro* had a scavenging effect on hydroxyl and DPPH free radicals at a concentration of 1000 μg/mL *in vitro* Ergothioneine, an amino acid present in *Agaricus bisporus* and *Pleurotus citrinopileatus*, showed antioxidant and cytoprotective effects *in vitro*. Machado-Carvalho and his coworker [101] reported that the best antioxidant activity was showed by *A. bisporus* (56%), followed by *B. edulis* (28%), *L. edodes* (15%), and then by *P. ostreatus* (12%). The antioxidant potential of mushroom compounds has undergone extensive research, revealing well-documented effects such as suppression of lipid peroxidation and malondialdehyde (MDA), reduction in low-density lipoprotein (LDL) in humans, chemical free radical scavenging activity, and various other factors [102]. Among the diverse compounds, polysaccharides are recognized as the main contributor to the observed antioxidant potential [103]. The assessment of the antioxidant potential of the extracts from various mushrooms by DPPH free radical scavenging assay was also carried out in our laboratory. The results revealed robust antioxidant activity at 1mg/mL (unpublished data). After reviewing numerous *in vitro* and *in vivo* studies, it becomes evident that bioactive compounds from mushrooms have the potential to enhance the antioxidant system and mitigate oxidative stress. That suggests that they could serve as a viable alternative therapy for managing the complications accompanied by oxidative stress.

Macrofungi with Antimicrobial Potential

Antibiotic resistance is the world's most severe and threatening problem. 70% of antibiotic resistance is increasing in South Asia, posing a global threat [104]. In recent years, multi-drug resistance and widespread drug resistance have been reported in Pakistan, which will pose a serious global threat [105]. The antibiotic resistance crisis is due to the misuse and overuse of antibiotics and the lack of interest from pharmaceutical companies in developing new antibiotics due to demanding regulatory requirements and reduced economic incentives. To address the resistance problem, there is an urgent need to explore natural compounds with novel structural templates. Recent research has focused on finding new bioactive compounds from macrofungi with antimicrobial potential. Kosanić *et al.* (2019) [106] reported that *Craterellus cornucopioides* acetone extract showed potent antibacterial potential against gram-positive bacteria named *Staphylococcus aureus*, *Bacillus subtilis*, and *Bacillus cereus* and gram-negative bacteria named *Escherichia coli* and *Proteus mirabili*s. The methanolic extract of *P. ostreatus* exhibited outstanding activity against the tested isolates of *S. aureus*, *E. coli*, and *N. gonorrhoeae* at the lowest concentration of 1×10^{-3} mg/mL [107]. Numerous phenolic compounds with antimicrobial potential, such as 4-hydroxybenzoic acid, p-hydroxyphenylacetic acid, protocatechuic acid, and gallic acid, could be produced from the extraction process [107]. Similarly, Fukushima-Sakuno [54] reported antimicrobial compounds in *Lentinula edodes* filtrate, termed octa-2,3-dien-5,7-diyn-1-ol (lentinamycin), and antifungal activity against various fungi such as *Aspergillus niger*, *Aspergillus flavus*, *ustilago maydis Mucor mucedo*, *Penicillium niotatum*, *Moniliella tomentosa*, *Pyricularia setariae*, *Trichophyton fischeri*, *Colletotrichum horii*, *Helminthosporium oryzae*, *Candida rugosa*, *Chaetomium globosum*, *Saccharomyces cerevisiae*, and *Cyberlindnera jadinii*. In 2022, the methanolic extract of another medicinal mushroom *T. camphoratus* exhibited potent antifungal activity against *A. fumigatus* and *C. albicans* [108]. Similar results were obtained from the studies performed in our laboratory, in which mostly the extract from polar solvents such as ethyl acetate, acetonitrile, and methanol exhibited antibacterial activity against bacterial strains such as *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*, and fungal strains like *C. albicans*, *A. niger*, and *A. flavus* (Unpublished data). For the selection of solvent for extracting the compounds, unlike non-polar solvents, polar solvents can easily pass through the matrix within the fungal cell wall. Polar solvent extracts possessed the best antimicrobial activities [109]. These findings were supported by the results recorded by Stojković *et al.* [110] that a high flavonoid content was extracted in hot water polar solvent. By increasing the polarity of solvents, the extraction of bioactive compounds has increased, leading to an increase in antimicrobial potential. In the present study, Gram-negative bacteria, including *K. pneumonia*, appeared to be more resistant to the macrofungal crude extracts than Gram-positive bacteria. Like the previous studies, it was confirmed that Gram-positive bacteria showed more sensitivity towards the crude extracts. Gebreyohannes and his colleagues concluded that the extracts of different mushrooms were more susceptible to Gram-positive bacteria than Gram-negative bacteria [109]. Past studies have also indicated that the difference between the susceptibility of gram-positive and gram-negative bacteria towards bioactive metabolites is predominantly because of their structural differences. Gram-negative bacteria possess lipopolysaccharides in their outer membrane making the cell wall impermeable to lipophilic compounds [111]. Overall, phenolic acids, quinones, and p-coumaric acid exhibit antibacterial activity by disrupting cell membrane permeability through changing cytoplasmic pH, binding capacity of DNA, and interference with the overall functions of cells [112]. Furthermore, the antimicrobial potential of organic compounds includes the interaction with polypeptides of bacterial cell walls, surface-exposed adhesion, and inhibition of enzymes, resulting in cell death [113].

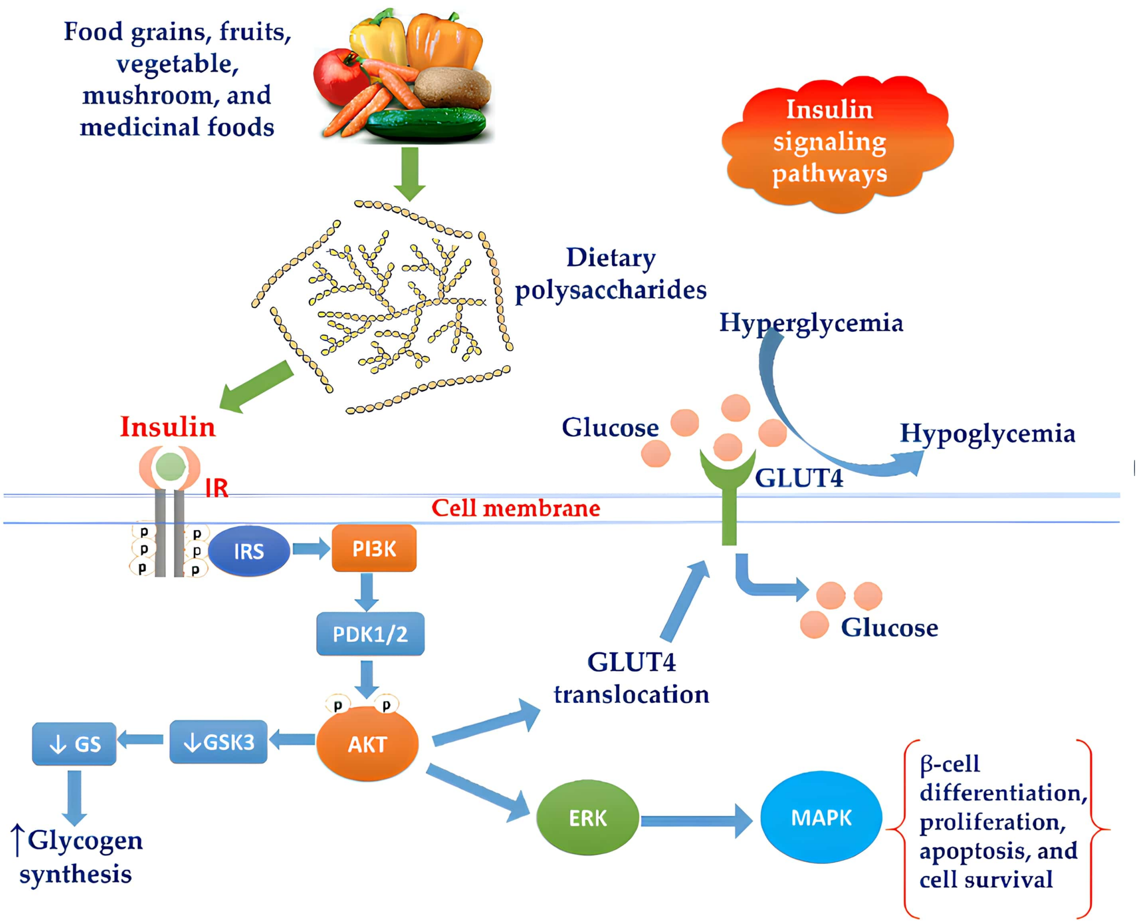

Fig. 2. Activation of insulin signaling pathways by macrofungal polysaccharides. Polysaccharide enhancement of insulin receptor substrate (IRS)/phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/glucose transporter type 4 (GLUT4) cascade signaling and blockade of glycogen synthase kinase-3/glycogen synthase (GS), eventually stimulate the secretion of glycogen. AKT activates the signaling pathways of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and thus stimulates various mechanisms such as cell differentiation, proliferation, and apoptosis (Reproduced with permission from [Ganesan K, Xu B.], [Molecules]; published by [MDPI (Basel, Switzerland)], [2019] [121]).

Macrofungi with Antiviral Activity

Viruses are the cause of major outbreaks across all continents, resulting in severe symptoms, a high mortality rate, and a huge financial drain on society. Furthermore, the continuous emergence of new serotypes with a high mutation rate and low commitment to viral replication poses additional challenges in confronting these viral infections. Therefore, there is a need for both vaccines and antivirals to combat viral infections. Therefore, it is a great challenge to develop a new vaccine against emerging viral serotypes, and vaccines against a few viruses are available today. In addition, vaccines cannot help if viral infections are already present in the system. Since then, today's focus has shifted to developing various antivirals against numerous viruses, targeting a common but crucial viral function [114]. However, the bioactive compounds extracted from biological natural sources offer an endless and untapped variety of chemical structures. Of particular importance in the discovery of new drugs was a bioactive compound derived from fungi. Ethanol, hexane, ethyl acetate and aqueous extracts prepared from fungi such as *Lignosus rhinocerotis*, *Pleurotus ostreatus*, *Hericium erinaceus*, *Schizophyllum commune*, and *Ganoderma lucidium* showed antiviral activities against dengue virus serotype 2 [55]. Furthermore, the β-glucan pleuran extracted from *Pleurotus ostreatus* showed antiviral activity against herpes simplex virus type 1 (HSV-1) by directly inhibiting virus particles or indirectly enhancing the host antiviral defense system [56]. Several bioactive compounds have been described as anti-HIV proteases. Recently, these anti-coronavirus compounds have been repurposed with potential activity against proteases of COVID-19 [57]. In 2022, it was found that three possible hits named Kynapcin-12 (M_78), Kynapcin-28 (M_82), and Kynapcin-24 (M_83) were present in edible mushroom *Polyozellus multiplex* that might be employed as a COVID-19 treatment [115]. *In vitro*, cytotoxic activity performed in our laboratory demonstrated that the macrofungi could be used as a promising source of antiviral agents. Additional experiments to evaluate their efficacy against viral diseases are essential for a more comprehensive understanding of their antiviral potential. These preliminary investigations lay the foundation for subsequent detailed analysis to elucidate mushroom compounds' full spectrum of antiviral capabilites. Bioactive compounds of mushrooms known for their antiviral potential include polysaccharides, carbohydrate-binding proteins, proteins like lectin, and lentin, as well as peptides, enzymes such as laccase, tyrosinase, etc., polyphenols, triterpenoids, and triterpenes [116]. These compounds reportedly exhibit an inhibitory effect by targeting various stages such as viral entry, duplication, production of viral enzymes, expression of proteins, and enhancement of immunity [117]. Furthermore, polysaccharides and peptides have shown relieving effects against different viruses such as Herpes simplex virus, influenza virus, and human immunodeficiency virus [116]. While the antiviral mechanisms of mushroom compounds are well-elucidated against the enveloped viruses, further assessment is needed for their effectiveness against non-enveloped viruses, such as norovirus and enterovirus. In conclusion, based on *in vitro* and *in vivo* studies, bioactive compounds from macrofungi hold a potential as antiviral candidates against both DNA and RNA viruses [118].

Macrofungi with Antihyperglycemic Effect

Diabetes is a persistent disease that causes serious health problems worldwide. Diabetes mellitus, commonly known as diabetes, constitutes a cluster of metabolic disorders identified by elevated blood glucose levels due to an insulin imbalance. In 2015, it was shown that beta-glucans and polysaccharides from macrofungi could rejuvenate the ability of pancreatic juice by enhancing insulin secretion from beta cells that lower blood glucose levels [119]. *Trametes pubescens*, a medicinal mushroom, has also been reported to lower blood glucose levels and increase insulin activity [120]. Fungal polysaccharides are also reported to trigger insulin signaling and activate the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway by enhancing the expression of the insulin receptors, insulin receptor substrate 1 (IRS1), PI3K and AKT in animal models of type 2 diabetes [58] (Fig. 2, Ref. [121]). Currently, *Calvatia gigantean* possesses anti-diabetic properties by inhibiting the alpha-amylase enzyme, which is 90 times more potent than the standard drug, acarbose [59]. Another study found that polysaccharides extracted from mushrooms inhibit glucose uptake, increase pancreatic beta cell mass, and improve insulin signaling, lowering blood sugar levels. Similarly, terpenoids have demonstrated antihyperglycemic properties by inhibiting alpha-glucosidase in animal models [60]. Numerous studies have demonstrated the significant blood glucose-lowering effects of mushrooms, particularly *Pleurotus* spp., *Grifola frondosa*, *Agaricus bisporus*, *Hericium erinaceus*, and *Ganoderma lucidum*, as they slow down the absorption of glucose and thus improve hyperglycemia [122]. The bioactive compounds isolated from mushrooms exhibit antidiabetic potential in animal and human models through extensive *in vitro* and *in vivo* studies. Polysaccharides, dietary fibers, vitamin D, proteins, and other compounds contribute to the prevention of diabetes [123]. Notably, mushroom polysaccharides (β-glucans) can restore pancreatic tissue function, thereby increasing the insulin production of β-cells and reducing the glucose level in the blood [124]. Other mechanisms involve inhibiting α-glucosidase enzyme, facilitating the function of glucose transporter 4, and mitigating the inflammatory factors to enhance insulin resistance and fat metabolism [124]. The potential of medicinal mushrooms for developing novel antidiabetic treatments is promising, however, due to intricate signaling pathways in the glucose metabolism system, further exploration of the mechanisms of action of these bioactive compounds is crucial and needs rigorous research and clinical investigations. Animal studies have provided compelling evidence of the therapeutic potential of mushrooms [125]. While, the establishment of these compounds for the prevention and treatment of diabetes requires more extensive clinical studies such as *in vivo* animal studies, *in vitro* enzyme inhibition assays (targeting amylase, α-glucosidase, lipase, and DPP4-dipeptidyl peptidase 4), human trials, pilot studies, and both prospective and retrospective studies. Special attention should be given to investigating the linkage between vitamin D and insulin resistance and exploring the enzyme inhibition assay and its potential impacts. Overall, drawing any conclusion without comprehensive investigation is challenging, therefore the necessity for expanded clinical investigations is underscored.

Macrofungi with Antiobesity Properties

Obesity is one of the major health problems worldwide and has also been associated with the onset of numerous other metabolic disorders including diabetes mellitus, hypercholesterolemia, and atherosclerosis due to accumulation of excess fat in adipose tissue. *Pleurotus florida* showed promising anti-obesity activity by inhibiting weight gain, lowering cholesterol, low-density lipoprotein and triglycerides, and reducing the deposition of fats in the body of high-cholesterol diet mice [126]. Currently, another study was conducted on obese rats, in which *Pleurotus citrinopileatus* water extract showed an anti-obesity effect by reducing the weight of mice, improving glucose tolerance, and lowering triglycerides, cholesterol, and LDP [61]. Polysaccharides isolated from *Cordyceps sinensis* prevented weight gain by modifying gut microbiota in high-fat-consuming mice [127]. It was found that the intake of bioactive compounds from mushrooms reduces obesity-related parameters such as body weight gain, epididymal adipocyte cells, markers responsible for adipogenesis, lipogenesis, inflammation, glucose level, endotoxin, and lipopolysaccharide level [128]. These compounds also regulate intestinal integrity and alter the intestinal microbiota by decreasing the ratio of Firmicutes to Bacteroidetes which is related to high energy accumulation, fat deposition, and intestinal balance [128]. These compounds include polysaccharides, alkaloids, peptides, flavonoids, phenols, terpenes, terpenoids, glycoproteins, steroids, etc. [129]. Edible mushroom polysaccharides exhibit anti-obesity properties by suppressing the expression of mRNA in 3T3-L1 adipocytes [130]. In summary, preclinical and clinical trials on bioactive compounds of mushrooms demonstrate significant anti-obesity properties. Furthermore, the efficient extraction and separation methods, deep understanding of its mechanisms of lipid regulation within the body, and distinct strategies based on objectives. These endeavors serve as vital assurances for the development of an anti-obesity functional food industry associated with edible mushrooms.

Macrofungi with Antiageing Potential

Ageing is an irresistible, natural, and physiological phenomenon characterized by dysregulation of the immune system, a decrease in body functions, wrinkling of the skin, and a decrease in the size of body parts. It also increases the likelihood of other age-related diseases such as diabetes, heart attack, cancer, and neurological disorders [131]. *In vitro,* analysis of alkali-extractable polysaccharides from *Agaricus bisporus* showed an anti-ageing effect by improving the antioxidant potential and lipid metabolism. It has also been suggested that polysaccharides may be a source of dietary supplements to mitigate ageing and prevent other associated diseases [132]. Likewise, the acid-extractable polysaccharides from *Agaricus bisporus* positively affect liver and kidney protection by improving the activity of enzymes, antioxidant properties, biochemical content, and lipid levels in consumers [62]. Another study showed that water-extractable and enzyme-extractable polysaccharides were promising antioxidant and anti-ageing compounds, enhancing the activities of antioxidant enzymes, decreasing fatty acid peroxidation, and reducing lipid metabolism [63]. Apparoo and his coworker [133] demonstrated the anti-ageing effects of a hydrophilic molecule, ergothioneine (EGT) isolated from mushrooms. As a traditional reservoir of natural bioactive components, macrofungi are currently exploited for their capability as an ingredient in the cosmetics industry. Various mushrooms and their extracts are utilized or patented in cosmetics products, offering benefits including anti-oxidant, antiageing, anti-wrinkle effect, skin lightening, and moisturization [134]. The bioactive compounds of mushrooms with potential anti-ageing applications include terpenoids, terpenes, polyketides, polyphenols, ergothioneine, ceramides, etc. [135]. Going beyond conventional cosmetics, Systemic Aesthetic Medicine primarily focuses on preventing and treating skin diseases and related cutaneous symptoms. Noteworthy properties attributed to mushrooms in this context encompass hydration, antioxidant effects, accelerated skin cell turnover, skin biorepair stimulation, antiseptic qualities, and immunomodulation [135].

Macrofungi with Anti-Inflammatory Action

In the human body, inflammation is a multistep, complicated biological response to remove injuries and adverse stimuli, such as pathogens, damaged cells, or irritation. At a systemic level, this response leads to numerous physical side effects such as fever, pain, and inflammation, but at a cellular level, it can cause blood vessel dilation and include blood vessel leaking. In 2018, the enzymatic residue of polysaccharide from *Lentinula edodes* was reported as an anti-inflammatory agent that inhibits the function of creatine kinase isoenzyme, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, lipid peroxidation and blood urea nitrogen (BUN), creatinine (CRE) and uric acid (UA) in serum [64]. Polysaccharides extracted from *Lentinula edodes* showed anti-inflammatory activity by lowering serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-6, interleukin-1, slowing down lipid peroxidation and also lowering blood urea nitrogen levels (BUN), creatinine (CRE) and serum uric acid (UA) [65]. Mushrooms have become recognized as a valuable biosource of potent anti-inflammatory properties. The bioactive compounds found in macrofungi include polysaccharides, terpenes, peptides, steroids, fatty acids, and phenolic compounds that exhibit notable efficacy in inhibiting pro-inflammatory biomarkers and interlinked pathways [136]. Studies have indicated that mushroom extracts caused a reduction in the LPS-induced expression of inflammatory markers such as nitric oxide, interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), TNF-α, and prostaglandin E2 [137]. *In vitro* and *in vivo* studies also reported that mushroom compounds exhibit anti-inflammatory properties by modulating the inflammatory pathways. One such pathway includes nuclear factor-kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory genes [136]. The mitogen-activated protein kinase (MAPK) signaling pathway also helps produce inflammatory cytokines. Mushroom compounds inhibit the activation of these pathways, thereby reducing the expression of pro-inflammatory genes and cytokine production [136].

Macrofungi against Cardiovascular Diseases

Cardiovascular disease is associated with elevation in low-density lipoprotein (LDP) and reduction in high-

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density lipoprotein (HDL). The main reason for the rising levels of total cholesterol and triglycerides in the blood is trans fats. The risk factors for cardiovascular disease are hypertension, hyperglycemia, and hyperlipidemia. Medicinal mushrooms such as *Grifola frondosa* (Maitake), *Pleurotus eryngii* (Eringi), and *Hypsizygus tessulatus* (Bunashimeji) contain bioactive compounds that lower total blood cholesterol levels. When 30% dried mushroom is orally administered to atherosclerotic mice, it lowers total blood cholesterol [138]. *Tricholoma matsutake* crude extract possesses bioactive peptide chains that inhibit the function of angiotensin, a factor contributing to hypertension and cardiovascular disease [66]. In 2020, Huang and his colleagues [67] reported that the intracellular and extracellular polysaccharides extracted from *Trametes versicolor* remarkably reduced total cholesterol, triglycerides, serum low-density lipoprotein, and atherosclerosis index of hyperlipidemic mice. Several studies have explored the impact of mushroom consumption on metabolic markers associated with cardiovascular diseases like LDL cholesterol, HDL cholesterol, total cholesterol, tri glycerol, blood pressure, homocysteine, homeostatic function, and oxidative and inflammatory changes [139]. Key nutritional aspects of mushrooms associated with their health benefits include a high content of fiber, low fat with isomers of unsaturated fatty acids, and a low amount of sodium [139]. Macrofungi contain important compounds like eritadenine, phenols, sterols (like ergosterol), chitosan, and triterpenes, which are crucial for preventing cardiovascular diseases [140]. The hypocholesterolemic effects of mushrooms are attributed to various mechanisms, including the reduction of very-low-density lipoproteins (LDL), improvement of lipid metabolism, and the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase activity), thereby preventing the development of atherosclerosis [140]. Additionally, antioxidant and anti-inflammatory compounds in mushrooms further lower the risk of atherosclerosis. Nevertheless, comprehensive scientific efforts are necessary to fully understand the underlying mechanisms and identify and characterize the specific bioactive compounds responsible for these health benefits. Long-term clinical studies are also imperative to provide thorough insights into the sustained effects of mushroom consumption on cardiovascular health.

Macrofungi against Respiratory Infections

Asthma is a chronic inflammatory airway disease that occurs through exposure to allergens. *Grifola gargal* extract was found to be effective in the prevention and treatment of allergic bronchial asthma by reducing airway hyperreactivity, pulmonary eosinophilic infiltration, pulmonary interleukin IL-13 expression and IgE-Reduced plasma levels, and also increased interleukin IL-10 Plasma [68]. It was also shown that when *Lignosus rhinocerotis* (tiger milk mushroom) extract was administered by intranasal injection, it remarkably reduced the number of inflammatory cells in the bronchoalveolar lavage fluid and the amount of CD4+ T cells in the lymph nodes draining the lungs. It also suppressed the level of Th2 cytokines in bronchoalveolar lavage fluid and serum IgE [69]. In addition, another study was conducted in 2021 showing that administration of tiger milk mushroom (*Lignosus rhinocerus*) extract significantly reduced levels of interleukin 1, interleukin 8, malondialdehyde, and symptoms of respiratory diseases [70]. The antitubercular activity of ethanolic extract from fungi such as *G. lucidum*, *S. hirsutum*, *H. fasciculare*, *R. capensis*, *S. commune*, *P. ostreatus*, *G. junonius*, *L. elegans* and *P. sanguineus* has also been reported in the literature. Similarly, Didloff screened the ethyl alcohol and aqueous extract of *A. campestris*, *P. baudoni*, *P. ostreatus*, *L. sulfurous*, *G. penetrans*, *C. molybdites*, and *H. erinaceus* for antitubular activity [141]. Hetland *et al*. [142] suggest that basidiomycetes mushrooms could be useful against asthma, lung infections, and prophylactic measures for COVID-19 infection. Medicinal macrofungi represent a large reservoir of unexplored bioactive compounds and their widespread utilization in the human diet worldwide underscores the potential for discovering novel bioactive molecules. The pursuit of compounds to prevent tuberculosis and malaria underscores the need to explore novel sources equipped with advanced genetic systems capable of generating drug leads resistant to antibiotic resistance. TB and malaria active compounds primarily consist of terpenes, terpenoids, phenols, steroids, polyketides, polyacetylenes, etc. [143]. Both *in vitro* and *in vivo* studies on models demonstrated that consumption of medicinal macrofungi significantly reduced lung toxicity by decreasing lactate dehydrogenase activity, oxidative stress, malondialdehyde level, infiltration of inflammatory cells, and enhanced histopathological conditions [144]. In conclusion, there is a pressing need to enhance taxonomical efforts to accurately characterize the edibility of mushrooms, as many species remain unrecognized despite their potential to produce effective molecules against respiratory infections. The presence of numerous active components suggests that even the existing list of edible mushrooms merits further investigation to isolate potential drug leads.

Macrofungi against Neurodegenerative Diseases

Neurodegenerative diseases are untreatable and disabling conditions that result in the degeneration and death of neurons. It can also lead to conditions such as ataxia (lack of muscle control that impairs movement), dementia (loss of memory), and other common conditions (Alzheimer's disease, Parkinson's disease, and Huntington's disease) [145]. The anti-neurodegenerative potential of different fungi was investigated in different animal models and cell lines. Apart from their free-radical scavenging and anti-inflammatory capabilities, mushroom extracts have been documented to mitigate neurotoxicity through additional neuroprotective mechanisms such as anti-acetylcholinesterase activity, stimulation of neurite protrusion, synthesis of nerve growth factor, enhancement of mitochondrial function, and reduction of stress in the endoplasmic reticulum [71]. Similarly, the polysaccharide extracted from *Pleurotus eryngii* showed neuroprotective activity against beta-amyloid-induced neurotoxicity by modulating calcium levels, attenuating beta-amyloid-mediated cell apoptosis, increasing cell viability, and downregulating molecules involved in inflammation [72]. In the 5$\times$FAD mouse model, ergothioneine has been shown to exhibit neuroprotective properties that can decrease Aβ plaques, and oxidative stress, improve glucose metabolism, and slow the onset of Alzheimer's disease [146]. In neurodegenerative research, mushroom compounds have gained a lot of attention. Various studies over the past decades underscore the advantages of macrofungi in influencing diverse disease conditions. Recently, mushroom bioactive compounds have been explored as regulators of neuroinflammation, providing a valuable tool for unraveling the molecular mechanisms contributing to disease pathogenesis. These mushrooms can help mitigate neuroinflammation-induced cell death, enhance the clearance of abnormal proteins, and promote anti-neuroinflammatory effects in animal and cell models without causing cytotoxicity [147]. A wide range of compounds but not limited to these that are prominent in neurodegenerative research include polysaccharides, phenolic compounds, alkaloids, and a variety of triterpenoids such as di-, tri-, sesqui-, and lanostane-based triterpenoids [148]. Furthermore, neuroinflammation is persistent throughout the process of neurodegeneration, therefore, the best target for drug discovery and development is the neuroinflammatory pathway named NLRP3 (nucleotide-binding domain, leucine-rich containing family, pyrin domain-containing 3) inflammasome that is a crucial element of innate immunity facilitate the activation of caspase-1 and release of pro-inflammatory cytokines 1L-1β or IL-18 [147]. In conclusion, the isolated compounds from macrofungi are recognized for the potential to alleviate neurotoxicity through a diverse range of molecular mechanisms that confer neuroprotection. These mechanisms include inhibiting acetylcholinesterase, stimulating neurite outgrowth, promoting the synthesis of the nerve growth factor (NGF) for neurotrophic effects, enhancing the function of mitochondria, alleviating endoplasmic reticulum stress, and providing antioxidant and anti-inflammatory effects [149]. As a result, mushrooms emerge as valuable therapeutic agents for the prevention, management, and treatment of neurodegenerative diseases.

Macrofungi with Hepatoprotective Effect

The liver plays a crucial function in metabolic processes and detoxification, decreasing susceptibility to chemical contaminants like drugs in the course of diseases in the body. Bioactive compounds extracted from macrofungi such as phenolic compounds, steroids, terpenes, and cell wall constituents protect against liver dysfunction. Alkaline-extractable polysaccharides from *Agaricus bisporus* have been shown to have hepatoprotective potential by reducing serum liver enzyme activities and also reducing liver lipid levels [132]. Another study suggested that *Agaricus bisporus* polysaccharides have hepatoprotective potential against CCl4-caused liver damage by reducing the expression of the transforming growth factor (TGF)-1/Smad signaling pathway [73]. *In vitro*, hepatoprotective effects of polysaccharides extracted from *Oudemansiella radiata* using enzymes have been reported and decreased the levels of various serum enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, and also decreased total cholesterol (TC) and triacylglycerols in the liver [74]. In another study, phosphorylated polysaccharide was derived from naturally occurring polysaccharide of *Pleurotus ostreatus*, which showed hepatoprotective activity against liver damage by reducing serum levels of enzymes such as alanine aminotransferase, Serum Glutamic Oxaloacetic Transaminase, alkaline phosphatase along with total cholesterol, glycerin trilaurin, and LDL-cholesterol and increasing HDL-lower cholesterol and blood albumin and malondialdehyde and increase the effect of hepatic antioxidant enzymes [75]. The hepatoprotective potential was also demonstrated by a polysaccharide extracted from *Schizophyllum commune*, which inhibited lipid peroxidation and increased the level of glutathione against damage caused by H_2O_2 [150]. Mushroom compounds safeguard the liver through a diverse array of mechanisms. These include modulation of liver enzymes, reducing the levels of liver malondialdehyde (MDA), lactate dehydrogenase (LDH), and hydrogen peroxide (H_2O_2), enhancing the activity of antioxidant enzymes like glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and alcohol dehydrogenase (ADH) [151]. They also exhibit suppression of β-glucuronidase, antifibrotic and antiviral actions, regulating the production of nitric oxide (NO), and maintaining Ca homeostasis of hepatocytes [151]. Additionally, they possess immunomodulatory activity by reducing the expression of inflammatory cytokines such as TNF-α, transforming growth factor-β (TGF-β), IL-1β, and IL-6, while simultaneously increasing the expression of the protective IL-10 cytokine [152]. Among the bioactive compounds, polysaccharides and terpenoids exhibit a broad range of hepatoprotective effects in various liver diseases such as hepatitis B, liver fibrosis, nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ARLD), and hepatic cancer

[151]. In conclusion, these studies provide valuable insight into the mechanisms responsible for hepatoprotective effects. Further studies employing isolated pure compounds are desirable to understand better the exact therapeutic potential of mushrooms for clinical applications.

Macrofungi with Immunomodulatory Effect

The immune system comprises a network of cells, tissues, and organs collaborating to safeguard the body from foreign pathogen attacks [153]. When the pathogens overcome the physical barriers such as skin and mucosa, the body's next line of defense such as granulocytes and monocytes are activated and operate as antigen-presenting cells (APCs). These antigen-presenting cells synthesize and release lipid mediators like prostaglandins and cytokines, serving as messengers to modulate the immune response and induce acquired immunity. Natural killer cells can identify the infected and abnormal cells such as cancerous cells and eliminate them through apoptosis or by secreting cytokines like interferon-gamma (IFN-γ). It is widely acknowledged that the human immune system is regulated through food, supplements, and bioactive compounds [153]. Various types of immunomodulators have been extracted from medicinal macrofungi. Bioactive polysaccharides from fungi are mostly described as modifiers of the immune system. The main component of macrofungal polysaccharides is homopolysaccharide (beta-glucan) which has different physiological functions [76]. Glucan regulates adaptive and inherent immunity (Fig. 3) and has indirect antitumor activity. In 2020, the major polysaccharide glucuronoxylomannan TAP-3 from *Naematelia aurantialba* was reported to enhance immune system activity and stimulate secretion of nitric oxide, tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1) from macrophages [77]. In addition, another study was conducted in which the polysaccharide CCP extracted from *Craterellus cornucopioides* demonstrates macrophage phagocytic activity, enhances the cytokines expression, overexpresses the cell membrane receptors named toll-like receptor 4 (TLR4), and downregulates the production of protein kinase by activating toll-like receptor 4-nuclear transcription factor kappa B (TLR4-NFκB) signaling pathway [154]. A polysaccharide from *Cordyceps sinensis* increases the number of CD4+ T cells, increases the secretion of interleukins17 and 21, and stimulates the expression of transcription factors (retinoic acid-related orphan receptor (ROR)-t). In addition, they regulate the composition of the gut microbiota and increase SCFA levels [78]. The extract of *Ganoderma lucidum* boosted the production of nitric oxide (NO) and reactive oxygen species (ROS) by the stimulation of peritoneal macrophages (PMs) through TLR4 and improved the potential of monocyte-derived dendritic cells (MoDCs) to polarize Th1 and allostimulatory cells [155]. In general, macrofungi possess active components that activate both innate and adaptive immune systems, hinder inflammation and regulate the function of immune cells such as neutrophils, eosinophils, basophils, and monocytes through different inflammatory pathways named Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol-3-kinase (PI3K), and MAPK pathways [136]. The bioactive components including peptides, polysaccharides, terpenes, steroids, fatty acids, and phenolic compounds exhibited notable effectiveness in suppressing major pro-inflammatory biomarkers and pathways associated with inflammation in both *in vitro* and *in vivo* conditions [156]. It was reported that mushroom extracts stimulate the synthesis of cytokines that produce important interleukins, confirming their immunomodulatory effects [157].

Macrofungi Modulate the Gut Microbiota

The gut microbiota could be a fundamental moderator to keep up with human health. There are various functions of the gut microbiota which include the production of various bioactive compounds such as vitamins and short-chain fatty acids (SCFs), maintenance of the barrier of epithelial cells, suppression of adhesion of pathogens to the gut surface, and deterioration of the original gut microflora and non-digestible carbon sources such as polysaccharides as well the regulation and proper development of the immune system [98]. Alterations within the gut microbiota are associated with various chronic infections such as obesity, atherosclerosis, kidney infections, type II diabetes mellitus, myocardial infarction and hypertension. Various bioactive metabolites extracted from macro fungi alter gut microbiota and improve health status. Indigestible polysaccharides of macrofungi can act as prebiotics and reduce pathogens' proliferation by increasing the growth of probiotics in the digestive tract [158]. *Ganoderma lucidum*, *Grifola frondosa*, *Hericiumerinaceus*, and *Lentinula edodes* are the most commonly identified edible macrofungi that can regulate gut microbiota [159]. Mushrooms are a rich source of indigestible polysaccharides, including chitin, hemicellulose, beta-glucan, alpha-glucan, mannans, xylans, galactans and polysaccharide peptide complexes. Human/animal digestive enzymes do not easily break down ingested polysaccharides, however, they are not absorbed in the upper gastrointestinal tract. After entering the colon, they are broken down by active enzymes (CAZymes) produced by gut microbiota, e.g., *Bacteriodes* spp., which are hydrolyzed to short-chain fatty acids (SCFAs) [160]. SCAFs, which include acetate, propionate, butyrate, and valerate, are important in protecting the colonic epithelium. The short-chain fatty acids are important for the microbiota-gut-brain crosstalk and affect the immune system. Short-chain fatty acids strengthen the immune system, protect against cancer, protect the nervous system, and improve humoral functions as shown in Fig. 4 [161].

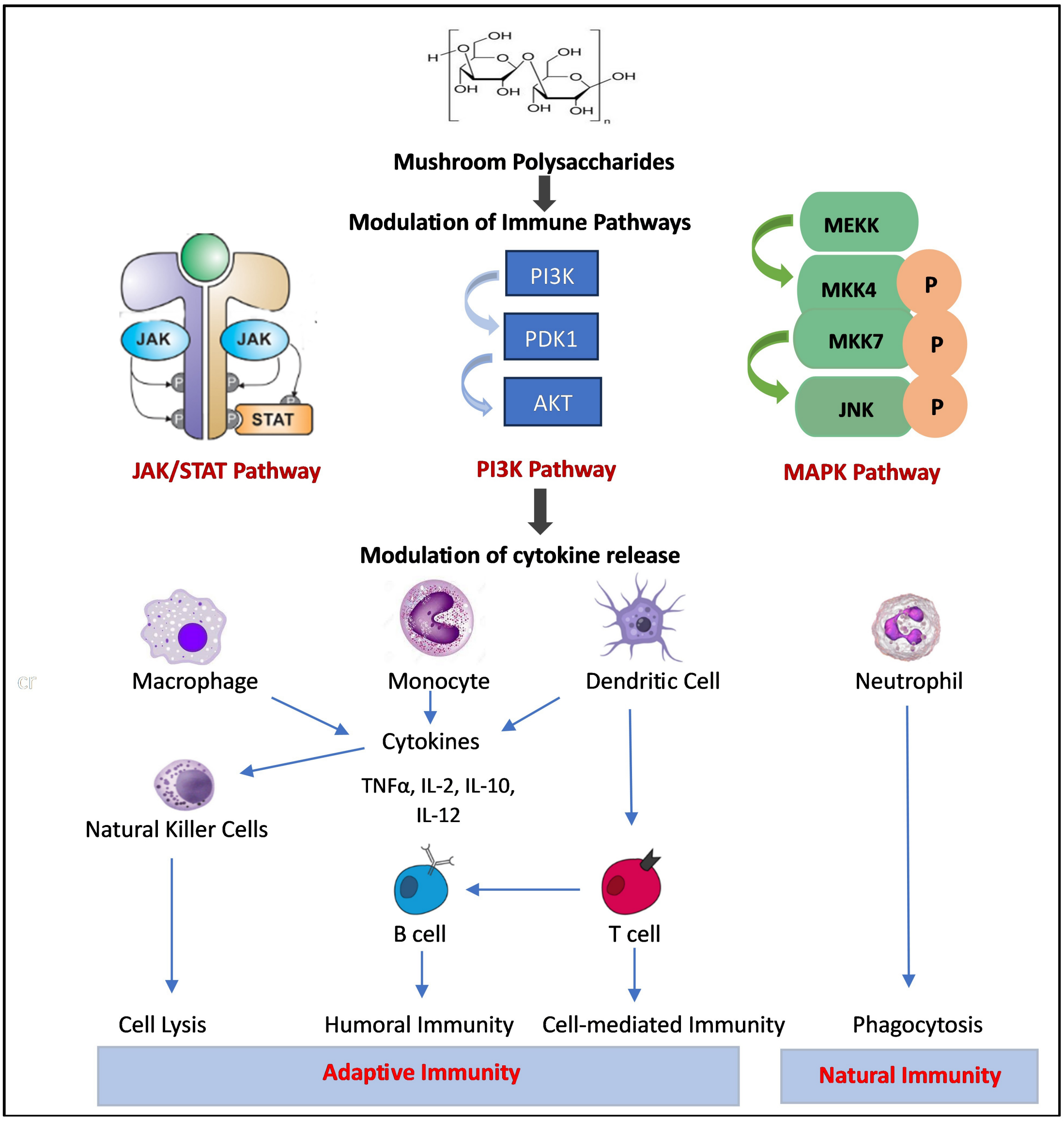

Fig. 3. Immunomodulatory mechanism of fungal-derived glucan. Polysaccharide glucans regulate natural and adaptive immunity by modulating various signaling pathways such as Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol-3-3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) pathways and activating immune cells including macrophages, neutrophils, natural killer cells, monocytes, dendritic cells, B and T cells. In addition, the secretion of cytokines, tumor necrotic factor-alpha (TNF-α), and interleukins (ILs) is also stimulated by beta-glucans (Created using Adobe Illustrator,version 2020, Adobe Inc, San Jose, CA, USA). Keys: PDK1, phosphoinositide-dependent kinase 1; MEKK, mitogen-activated protein kinase kinase; MKK4, mitogen-activated protein kinase kinase 4; MKK7, mitogen-activated protein kinase kinase 7; JNK, c-Jun N-terminal kinase.

These polysaccharides overexpress occludin and zonula occludens protein 1 (ZO-1) within the epithelium of the gut. These polysaccharides can also control the permeability of epithelial cells and the integrity of the intestinal mucosa. They also block the release of pro-inflammatory endotoxins from bacteria into the blood. Therefore, polysaccharides can regulate gut microbiota, lower levels of bacterial endotoxins, and address disturbances in gut microbiota resulting from conditions like obesity, diabetes mellitus, and other issues. Wu *et al*. (2019) [79] demonstrated that high molecular mass (>300 kDa) polysaccharides extracted from *Hirsutella sinensis* were effective in treating obesity-induced gut dysbiosis, leaky gut, inflammation, insulin resistance, and hypercholesterolemia. They can also act as prebiotics, selectively promoting the proliferation of the beneficial gut bacterium *Parabacteroides goldsteinii*, and treat type II diabetes mellitus which are overwhelming factors against obesity. They regulate various genes linked with host metabolism and create a gut microenvironment favourable for colonizing *Akkermansia muciniphila* [80]. Polysaccharides from *Cordyceps sinensis* regulate gut mucosal immune system and microbiota in cyclophosphamide

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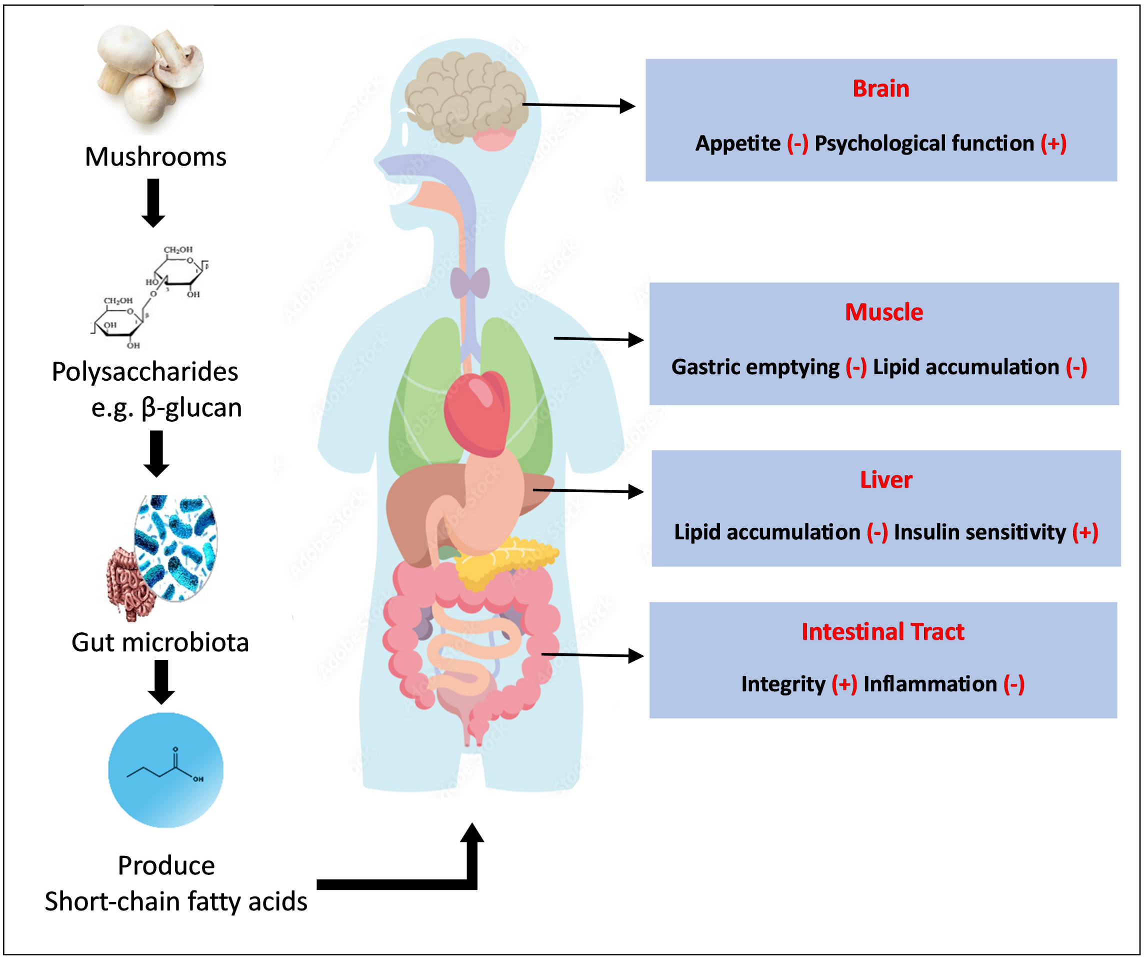

Fig. 4. Role of macrofungi in modulating gut microbiota. The gut microbiota can break down bioactive compounds from macrofungi into short-chain fatty acids that are valuable for human health. A positive sign (+) indicates stimulation, while a negative sign (-) indicates repression (Created using Adobe Illustrator, version 2020, Adobe Inc, San Jose, CA, USA).

(Cy)-induced mice by inducing secretion of cytokines such as IL-12, IFN-γ, IL-4, IL-13, IL-6, IL-17 stimulate. IL-10, TGF-3, TNF-α, IL-2, IL-21 as well as through the production of transcription factors such as T-bet, GATA-3, RORt and Foxp3. In addition, these polysaccharides also regulate the levels of short-chain fatty acids, which are reduced during treatment with cyclophosphamide [162]. In conclusion, the evidence supporting the modulation of intestinal microbiota through the bioactive compounds of mushrooms underscores the relationship between dietary components and microbial community. These compounds play a role in maintaining a homeostatic microbial ecosystem that fosters the growth of beneficial bacteria and inhibits the growth of harmful bacteria. The implications of this modulation extend beyond digestive health, impacting immune function, metabolism, and overall well-being. As our scientific knowledge deepens, the potential application of mushrooms in improving digestive health might lead to innovative dietary approaches, probiotic formulations, and therapeutic strategies aimed at supporting the symbiotic relationship between humans and their gut microbiota.

Discussion

Macrofungi represent a preeminent repository of pharmaceutical compounds and are gaining escalating attention. They are considered healthy food due to their high nutritional value, especially protein, vitamins, minerals, dietary fiber, etc. They have dynamic metabolism and play a significant role in maintaining a balance of ecosystems. In addition, the therapeutic potential of macrofungi is attributed to diverse secondary compounds and metabolites present in the mycelial structure which can act synergistically or independently on various biological functions within the human body. These biologically active compounds include polysaccharides, phenolic compounds, flavonoids, alkaloids, ergosterols, triterpenes, triterpenoids, lectins, and peroxidases, which benefit human health [163].

In the last few years, studies have been conducted on the pharmacological potential of mushrooms. Notably, research on natural products has advanced significantly, uncovering novel compounds with antimicrobial properties. The phytochemical analysis of mushroom extracts has unveiled a range of active secondary and primary metabolites demonstrating promise in treating infectious diseases and controlling pathogens. These metabolites may act via inhibition of bacterial enzymes, disrupting the integrity of cell membranes, or interfering with cellular processes in ways that are not conceivable yet. Understanding these mechanisms is crucial as they may provide invaluable insights into how these extracts target resistance mechanisms which can be manipulated further for in-silico drug synthesis. Recently isolated pharmaceutical compounds from medicinal macrofungi such as triterpenes, lectins, β-glucans, and L-ergothioneine revealed potent and distinctive health-enhancing properties and distributed worldwide [164]. While many of these compounds do not strictly classify as pharmaceuticals, they represent a novel category of dietary supplements or nutraceuticals. These compounds are extracted from fungal mycelia or basidiomata and are also termed functional food, phytochemicals, and biochemopreventatives [164]. These macrofungi have low-fat content quality compared to the other foods, with the fat level ranging from 1% to 15% [165]. That indicated that macrofungi could be a beneficial dietary alternative for individuals with high cholesterol and diabetes [124]. Moreover, edible macrofungi encompass various components, including non-digestible fibre, that enhance digestion [164]. Throughout history, medicinal macrofungi have also been used to treat various diseases, particularly cancer [166]. In the present era, these fungi have gained significant research attention aiming to elucidate the chemical composition and mechanism of action of these bioactive compounds. The multifaced pharmacological and nutraceutical potential of macrofungi can be harnessed by directly inhibiting the cancer-related processes or tumor-specific apoptosis and indirectly, such as immunomodulation, hepatoprotection, and antioxidants [167]. Identifying, demonstrating, and elucidating all these properties primarily relied on *in vitro* tests, which are pivotal in highlighting the therapeutic potential of specific fungi [14]. Subsequently, *in vivo* tests were conducted on animal models to explore the effects of these substances within living cells and systems [163]. Despite the overarching goal of developing drugs and natural products for human healthcare, there is a distinct lack of studies conducted within the more organized realm of clinical trials. This domain remains relatively unorganized, marked by numerous deficiencies and gaps.

The differences in the biological activity of different mushroom extracts are noteworthy. These variations may stem from the choice of extracts, as the extraction method may influence the presence and activities of compounds [14]. Another contributing factor could be ascertaining the concentration of specific metabolites in the extract [14]. Moreover, even when subjected to uniform conditions, the medicinal properties of a given mushroom can fluctuate significantly based on factors such as strain, geographical location, growing conditions, substrate, part of mushrooms, and growth stage during the processing [168]. These factors collectively alter the composition of mushrooms and, consequently, impact their biological potential.

Conclusion

Based on the evaluation of available information and review of scientific research, it can be concluded that macrofungi are renowned for their potential to enhance immune function, regulate metabolism, and mitigate the risk of various infections. The abundance of polysaccharides, polyphenols, alkaloids, flavonoids, amino acids, and vitamins in these macrofungi constitutes a valuable reservoir of bioactive compounds, offering a significant potential to support and maintain the health and well-being of the body. In addition to existing literature, this review offers a distinctive perspective derived from our laboratory investigations into the biological potential of macrofungi. Our studies have contributed valuable insights into macrofungi's antibacterial, antifungal, antioxidant, cytotoxic, and antihemolytic activities. These findings align with the broader framework presented in the reviewed literature, further underscoring the multifaced advantages of mushrooms. We hope that the incorporation of published studies and original contributions from our laboratory aims to enhance the comprehensiveness and depth of understanding regarding the biological attributes of macrofungi. Pakistan's geographic conditions and seasonal variation have yielded a huge diversity of mushrooms used as traditional medicines in many areas of Pakistan. This traditional medicine needed to be further explored for conventional therapies. Understanding structural diversity, natural sources, and the synthetic feasibility of their compounds will help to extend their utilization for the benefit of humankind, animal health, and the environment. Although further studies need to be conducted for further safety and efficacy assessment, these extracts could be used for novel drug development. In addition, toxicity assessment on animal models and clinical settings must be done. The intricate interplay of bioactive compounds and their mechanism of action underpins the necessity to undertake multidisciplinary research to realize these macrofungi's therapeutic potential fully. In short, this review has provided the groundwork for exploring and exploiting natural microbial resources for medicinal purposes.

Availability of Data and Materials

All the data generated and analyzed during this study are included in this article.

Author Contributions

MS, AN, and NSZ participated in the manuscript conceptualization, review, and editing. MS contributed to the writing, original draft preparation, review, and editing of the final version. SN and UHS were responsible for collecting data, writing, rephrasing and reviewing the manuscript. AAS, MB, SK, AF, MTA, SS, and MKT are responsible for conception, design, reviewing, editing, guiding, supervision and analyzing data. All authors have been involved in revising it critically for important intellectual content. All the authors read and approved the final manuscript. All the authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Arshad Farid is serving as one of the Guest Editor of the JBRHA journal. We declare that Arshad Farid had no involvement in the peer review of this article and has no access to information regarding its peer review.

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