fermentation

MDPI

Review

Bioactive Compounds Produced by Macromycetes for Application in the Pharmaceutical Sector: Patents and Products

Walter José Martinez-Burgos [1,*], Everaldo Montes Montes [2], Roberta Pozzan [3], Josilene Lima Serra [4], Diego Ocán Torres [1], Maria Clara Manzoki [1], Ricardo Luiz Vieira [1], Guilherme Anacleto dos Reis [1], Cristine Rodrigues [1], Susan Grace Karp [1] and Carlos Ricardo Soccol [1,*]

[1] Department of Bioprocess Engineering and Biotechnology, Federal University of Paraná, Centro Politécnico, Curitiba 81531-990, PR, Brazil; diego.ocan@ufpr.br (D.O.T.); mariamanzoki@ufpr.br (M.C.M.); imycena@gmail.com (R.L.V.); guillerme.anacleto@ufpr.br (G.A.d.R.); cristiner@ufpr.br (C.R.); susan.karp@ufpr.br (S.G.K.)
[2] Research Group on Food Properties and Processes (GIPPAL), Department of Food Engineering, Universidad de Córdoba, Montería 230002, Colombia; everaldomontes@correo.unicordoba.edu.com
[3] Laboratory of Cell Toxicology, Department of Cell Biology, Federal University of Paraná, Centro Politécnico, Curitiba 81531-908, PR, Brazil; robertapozzan03@gmail.com
[4] Federal Institute of Maranhão, São Luís 65095-460, MA, Brazil; josilene.serra@ifma.edu.br
* Correspondence: walter.burgos@ufpr.br (W.J.M.-B.); soccol@ufpr.br (C.R.S.)

Abstract: It is widely known that mushrooms present several properties with applications in the medicinal and pharmaceutical sectors, including antimicrobial, immunomodulatory, antioxidant, hypotensive, neuroprotective, and anti-inflammatory activities. This article aims to review examples of the bioactive metabolites responsible for those activities, such as polysaccharides, phenols and polyphenols, terpenes, peptides, alkaloids, and steroids, which are produced by several relevant mushroom species. It also discusses their production through solid-state fermentation and submerged fermentation, as well as the processes of obtention of mushroom bioactive extracts and considerations on their stability aiming industrial applications. In addition, the article examines the patent landscape surrounding mushroom-derived bioactives, shedding light on the intellectual property history and innovations driving this field forward. Examples of recently deposited patents in the field are highlighted, as well as the main depositors. China and the United States are the major depositor countries in this field (52% and 35% of patents, respectively), and the principal compounds on the patents are polysaccharides and alkaloids. The article also provides insights into the current market landscape, showcasing mushroom-derived products in the pharmaceutical field available to consumers. From dietary supplements to skincare formulations, the market offerings reflect the growing interest in harnessing the health benefits of mushroom bioactives.

Keywords: mushroom; bioactive compound; fermentation; pharmaceutical; macromycete; products; patents

Citation: Martinez-Burgos, W.J.; Montes Montes, E.; Pozzan, R.; Serra, J.L.; Torres, D.O.; Manzoki, M.C.; Vieira, R.L.; dos Reis, G.A.; Rodrigues, C.; Karp, S.G.; et al. Bioactive Compounds Produced by Macromycetes for Application in the Pharmaceutical Sector: Patents and Products. *Fermentation* **2024**, *10*, 275. https://doi.org/10.3390/fermentation10060275

Academic Editors: Guojian Zhang and Fu Yan

Received: 28 April 2024
Revised: 17 May 2024
Accepted: 19 May 2024
Published: 23 May 2024

1. Introduction

Bioactive compounds are beneficial to human health due to their ability to positively influence various physiological processes. The health conditions that mostly affect the world population nowadays, namely cardiovascular disease, cancer, and COVID-19 (FastStats—Leading Causes of Death (cdc.gov)), can be prevented or their effects can be minimized by the use of bioactive molecules along with conventional treatments. Antioxidant compounds, for example, neutralize free radicals in the body and reduce oxidative stress, thus helping to prevent cell damage and lowering the risk of chronic diseases like cancer and neurodegenerative disorders. There are also bioactive molecules that can directly inhibit cancer cell proliferation, induce apoptosis, and modulate signaling pathways

involved in cancer development [1,2]. Anti-inflammatory compounds can prevent inflammation through different routes, like the inhibition of pro-inflammatory pathways by blocking enzymes such as cyclooxygenase and lipoxygenase, or by the downregulation of the expression of pro-inflammatory cytokines. This can be beneficial to individuals suffering from inflammation of various causes. Inflammation can be a chronic condition caused by environmental stress, inflammatory diets, autoimmune disorders, and infections, among other causes. Even when the causes are multiple, complementary treatments with bioactive compounds can be of great value to improve life quality [3].

Macromycetes, commonly known as mushrooms, are important sources of bioactive compounds used in traditional medicine and nutrition for thousands of years [4]. They are low in calories and fat but rich in nutrients, containing essential vitamins and minerals such as vitamin D, vitamin B complex (riboflavin, niacin, and pantothenic acid), potassium, selenium, and copper. Some varieties of mushrooms also provide protein and dietary fiber, making them an important source of alternative proteins for human nutrition [3]. They contain antioxidants and immunomodulators such as polyphenols, flavonoids, beta-glucans, and polysaccharides. Compounds like beta-glucans and lovastatin, found especially in oyster mushrooms, may help lower LDL cholesterol levels and improve lipid profiles, reducing the risk of cardiovascular disease. Their fiber content can be a source of prebiotics for the beneficial gut microbiota. Additionally, mushrooms can present antimicrobial activity against various microorganisms, including bacteria, viruses, and fungi [5]. This antimicrobial activity is attributed to the presence of bioactive compounds such as polysaccharides, peptides, terpenoids, phenolic compounds, and lectins found in different mushroom species [4].

This manuscript presents an overview of macrofungi as sources of bioactive compounds, focusing on the health benefits of polysaccharides, including glucans, glycans, and exopolysaccharides, peptides, phenols and polyphenols, terpenes, alkaloids, and sterols. Studies demonstrating their in vitro and in vivo effects and mechanisms of action are presented, together with methods to obtain such biomolecules from fungal biomass. A patent search was also carried out in the Derwent Innovations Index database, focusing on the application of macromycetes and their bioactive compounds in the pharmaceutical area. Finally, commercial products derived from mushrooms and their claimed properties are presented, showing the potential of fungal bioactive metabolites in various segments of the pharmaceutical market.

2. Macromycetes as Sources of Bioactive Compounds

Macromycetes are superior fungi that, under certain conditions, are capable of forming visible structures. They are divided into two phyla—Ascomycota and Basidiomycota [6]. The first contains mycelia with septa and generally their cells exist as diploids, while the second is characterized by a dolipore septum with pincer connections. Macromycetes are eukaryotic and heterotrophic organisms with chitin-based cell walls. It is estimated that there are between 2.2 and 3.8 million fungi, of which around 120,000 have been identified and around 2000 have been classified as edible or medicinal [7,8].

Mushrooms are of great importance to the population due to the edible and pharmaceutical value of these organisms. According to Valverde et al. [4], mushrooms have several properties with around 100 medicinal functions, including antimicrobial (antifungal, antibacterial, antiviral), immunomodulatory, antioxidant, digestive, antitumor, hypotensive, neuroprotective, antidepressant, antithrombotic, anti-inflammatory, hepatoprotective, antiallergic, cytotoxic, antidiabetic, nephroprotective, and osteoprotective, among others [9,10].

The therapeutic properties of mushrooms are mainly due to the wide range of bioactive compounds that they produce or synthesize in their metabolism, either in the fruiting bodies when the biomass is produced by solid fermentation, or in the mycelium or fermentation broth when the biomass is produced via submerged fermentation. Among the metabolites produced by mushrooms are high-molecular-weight compounds, such as carbohydrates,

proteins (peptides), and lipids in low proportions. While low-molecular-weight metabolites are terpenes, phenols, sterols, and alkaloids among others (Figure 1).

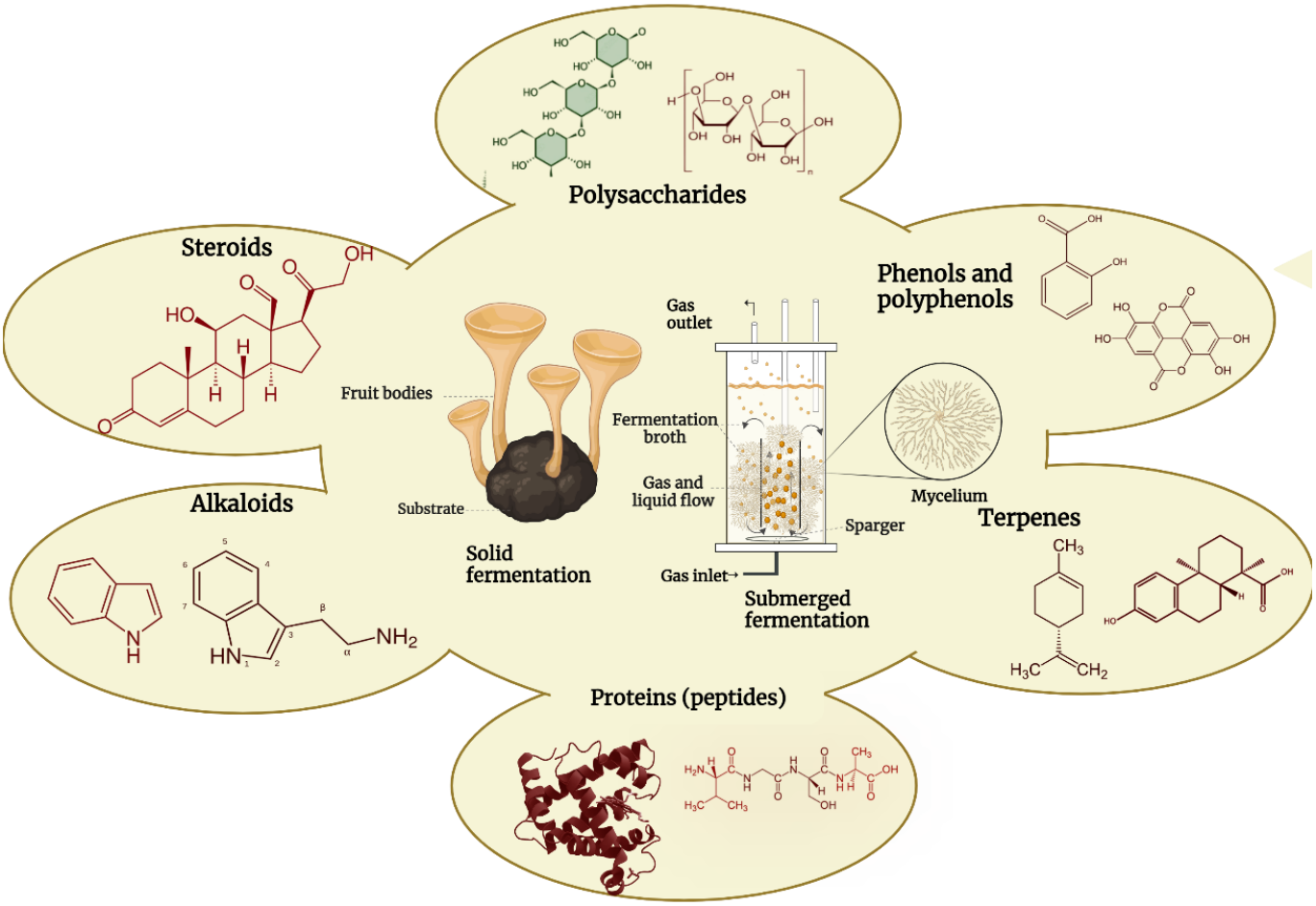

Figure 1. Biometabolites with biological activity produced by mushrooms.

3. Polysaccharides from Mushrooms

Polysaccharides are carbohydrate polymers composed of more than one sugar, which can be either a single type of monosaccharide (homopolysaccharide) or at least two different types of monosaccharides (heteropolysaccharide) [11]. In macromycete fungi, polysaccharides play an important role as they can be structural components, as in the case of chitin at the cell wall level; or functional, such as exopolysaccharides (EPS) and glycans, which in turn can form complexes with proteins or lipids [12].

Macrofungal polysaccharides such as glucans (β-glucans and α-glucans), glycans (galactans, fucans, xylans, and mannans), chitin and EPSs have a wide range of applications, including their capacity as bioactive components for antitumor treatments, antimicrobial, antiviral, immune system regulators, among others (Figure 2). This makes them compounds of broad pharmaceutical interest [13–15].

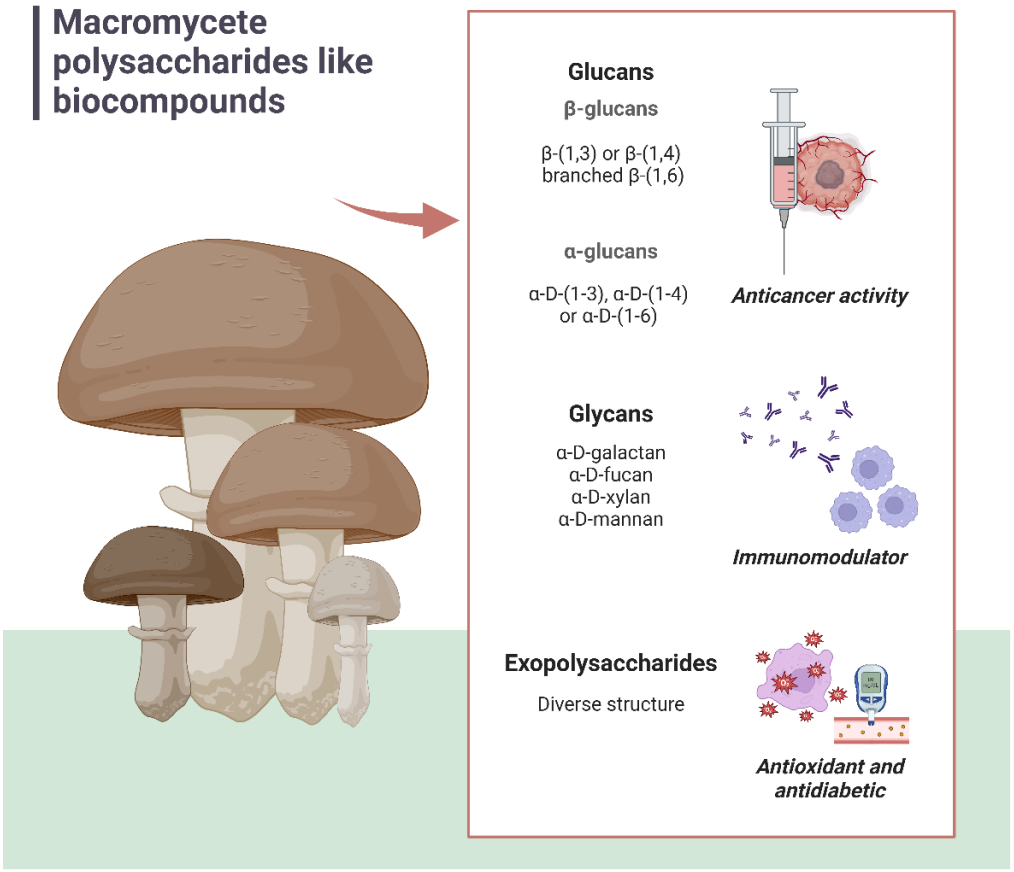

Figure 2. Variety of polysaccharides produced by macromycete fungi with pharmaceutical bioactive potential.

3.1. Glucans

Glucans are the most abundant polysaccharides in macromycete fungi and make up the majority of their cell wall, representing approximately 50–60% of their dry weight mass [16]. These compounds are mainly composed of glucosyl residues that can be substituted by a wide variety of glycosyl residues. They can also be classified into α-glucans, β-glucans, and α-β-glucans, presenting a homopolymeric or heteropolymeric structure of various chain lengths, whose structural diversity depends directly on the species of fungus [17].

The biological synthesis of these compounds begins with the synthesis of nucleotide sugars at the cytoplasmic level which are transferred in sequence to a lipid carrier to form assembled repeating units and continue with their subsequent export through the polysaccharide or Wzx/Wzy-dependent pathway [18].

These compounds have several functions, mainly structural, and have been studied as antioxidants, immunoregulators and antitumor agents [19], especially those of the β-glucan type, which have been the subject of study because of these bioactive properties.

3.1.1. β-Glucans

β-glucans are long- or short-chain glucose polymers that typically consist of a backbone of glucose residues linked by β-(1,3) or β-(1,4) bonds, or with branched β-(1,6) side chains [20,21]. Likewise, β-glucans typically exhibit a triple helix conformation, which differentiates them in terms of their glycosidic bonds, molecular weight, and branching points, among other characteristics, across the various compounds within this group [22]. There are different species of widely distributed macromycetes, which produce bioactive compounds widely studied in drug design [23], among which the species *Schizophyllum commune*, *Lentinula edodes*, *Pleurotus ostreatus* and *Grifola fondosa* stand out for their production of schizophyllan, lentinan, pleuran and grifolan, respectively [24–27].

Schizophyllan is a water-insoluble nonionic homopolysaccharide composed of a primary β-(1,3)-glucan structure with β-(1,6)-glucopyranosyl side chains on every third or fourth residue of the main chain. This fungal polymer has been noted due to its great capacity as an antitumor and immunobiological agent since [28] first discovered that an aqueous solution of this compound exhibited antitumor activity against sarcoma 180. Schizophyllan was found to activate NK cells, spleen cells, lymphoid cells, and bone marrow cells and increase the production of antitumor cytokines [29]. Recent studies such as that of [30] showed a gene silencing effect by the formation of a schizophyllan-mRNA complex, resulting in the suppression of the growth of human lung adenocarcinoma cells. Likewise, the combination of technologies such as the use of nanoparticles for the formation of complexes is being investigated, as in the case of schizophyllan-qutine encapsulated with ellagic acid in the treatment of breast adenocarcinoma in MCF-7 cells, generating a cytotoxic effect [31,32].

Another example of β-glucan is lentinan, which is composed of a main structure of β-(1-3)-glucopyranoside with two branches of β-(1-6)-glucopyranoside for every five positions [33]. Extracted from the fungus known as shiitake, this polymer has presented several applications as a bioactive product over the years. Among these, its anticancer and immunomodulatory activity stands out, as evidenced by the activation of macrophages and dendritic cells and increased activity of cytotoxic T lymphocytes and NK cells [34–36]. In more recent trials, Park et al. [37] confirmed the anticancer potential of lentinan in colon and gastric cancer cells, slowing their proliferation in AGS cells and HT-29 cells by inhibiting the G2/M phase in the cell cycle. In addition to this property, its potential in wound healing, such as those developed in patients affected by diabetes, has also been investigated. Jia et al. [38] developed a hydrogel (GelMA) encapsulated with 10 μM of lentinan, which accelerated wound closure by increasing neovascularization and M2 macrophage proliferation, resulting in a reduction of inflammation. This report strengthens the ability of lentinan to modulate macrophage polarization and angiogenesis through the AMPK/DAF16 pathway, facilitating wound healing.

3.1.2. α-Glucans

Alpha-glucans are another group of linear or branched polysaccharides, which may be linked by α-D-(1-3), α-D-(1-4) or α-D-(1-6) bonds [19]. Pseudonigeran is one of the most studied polymers in this group because it is the most prevalent component of the fungal cell wall; however, there is very limited information about its use as a pharmaceutical biocompound [39]. Pseudonigeran is a linear homopolysaccharide linked by α-D-(1-3) bonds. It is a structural component, unlike β-glucans, which are produced by a wide diversity of species. These include *Cyclocybe cylindracea*, *Ganoderma* spp., *Lentinula edodes*, *Pleurotus* spp. and others. Recent studies have demonstrated that pseudonigeran possesses a high prebiotic potential, as it can stimulate the growth of *Lactobacillus* and *Bifidobacterium*, two microbial groups of significant importance to the native intestinal microbiota [40].

Other α-D-glucans isolated from macromycete fungi have been isolated, but their study has been limited. For instance, Patra et al. [41] isolated an α-(1,3)-(1,4) glucan from the edible mushroom *Favolus grammocephalus* (formerly *Polyporus gramocephalus*), which demonstrated the activation of macrophages, splenocytes, and thymocytes. This glucan thus has the potential to serve as an immunomodulatory agent in the development of drugs to treat pathological conditions associated with diseases such as AIDS, cancer, and autoimmune disorders. A type of α-(1,4)-D-glucan isolated from the mushroom *Albatrellus ovinus* has also been reported [42], although it has also been isolated from the mushrooms *Pleurotus ostreatus* and *Agaricus bisporus* [43,44]. Its properties are poorly understood and have yet to be studied.

3.2. Glycans

Glycans are another type of more complex polysaccharides found in macromycetes, which are characterized by being composed of units other than glucose in its main chain

and are classified according to the type of sugar that composes it, such as galactans, fucans, xylans, mannans or others [12].

A number of fungal species are known to produce glycans, with α-D-galactan (GAL-Am) being isolated from *Amanita muscaria*. This presented a structure composed of a main chain of galactan (Gal*p*) linked by α-(1-6) bonds and branched at O-2 by terminal Gal*p* units. Moreover, it was demonstrated that this compound exhibited a selective reduction in B16-F10 melanoma cells and their clonogenic capacity, without affecting non-tumor cells. This may prove to be a crucial feature in the treatment of cancer [2]. Similarly, more complex glycans formed by the combination of multiple sugars have been described. Michorini et al. [45] isolated a fucogalactan from the giant fungus *Macrocybe titans*. This glycan exhibited a primary α-(1-6)-Galp chain, partially substituted at O-2 by non-reducing terminal units of Fuc*p* residues (Fucan) in the side chain. Additionally, it demonstrated the capacity to reduce melanoma cell migration by 40% (100 μg/mL) through the reduction of cellular activity.

A glycan isolated from *Isaria cicadae* (formerly *Cordyceps cicadae*) has been described. It is called galactoglucomannan (C-0-1) and is composed of galactose, glucose, and mannose in a 5:1:4 ratio. Its central structure is α-(1,2)-D-Man*p* and O-6 branches. The polysaccharide contains α-(1,4)-D-Glc*p*, β-(1,2)-D-Gal*f*, β-(1,2,6)-D-Gal*f*, and β-Gal*f* terminal in the side chains [46]. Additionally, it exhibits immunomodulatory activity, enhancing the production of nitric oxide synthase and several crucial inflammatory cytokines. Furthermore, it activates macrophages through the mannose receptor. This activity and similarity in polysaccharide structure were also reported in the *Ophiocordyceps sinensis* (formerly *Cordyceps sinensis*) strain [47].

An additional report is that of Chen et al. [48], which presents a GFP-N glycan isolated from the maitake mushroom *Grifola frondosa*. This glycan is composed of L-arabinose, D-mannose, and D-glucose, with a structure consisting of α-(2,6)-D-Manp, α-(1,4)-L-Araf-C1, and β-(3,6)-D-Glcp. This polymer demonstrated the capacity to activate insulin receptor substrate, phosphatidylinositol-3-kinase, and glucose transporter 4, while inhibiting c-Jun N-terminal kinase 1/2. These findings suggest that this compound may have potential as a hypoglycemic agent at the level of intestinal microflora in vivo in mouse assays.

3.3. Exopolysaccharides

Exopolysaccharides (EPSs) represent another type of polysaccharides that are synthesized and secreted to the outside of the cell. These EPSs may be attached to the cell surface or may remain in the extracellular medium. Likewise, their chemical structure can be composed of simple sugars or sugar derivatives [14].

EPSs exhibit a remarkable degree of diversity, varying according to the species of macromycetes. Additionally, their quality and quantity are influenced by external conditions, such as environmental conditions or the micronutrients supplied during their growth [19]. In this context, EPSs are presented as a promising alternative for their application in various fields of bioproducts, with a particular emphasis on the pharmaceutical sector and clinical therapy [49,50]. This has also led to a surge in research activity over the past decade, as evidenced by a simple search in the ScienceDirect database using the keywords “exopolysaccharides” and “mushrooms”.

Sonawane et al. [51] evaluated the hypoglycemic and anticataract activity of a solution of crude EPSs isolated from *Phellinotus badius* (formerly *Phellinus badius*) in streptozotocin (STZ)-induced diabetic rats. The EPS solution demonstrated a reduction in blood glucose (37.2%) and body weight gain (47.4%), as well as a reduction in triglycerides, cholesterol and aspartate aminotransferase activities. Additionally, the EPS solution reduced the risk of cataract formation in goat eyes. Other studies have demonstrated a significant hepatoprotective and antioxidant capacity against diethylnitrosamine (DEN)/carbon tetrachloride (CCL 4) induced damage in rats by an exopolysaccharide-peptide complex extracted from *Pleurotus ostreatus* [52]. Similarly, its antioxidant activity has been demonstrated through radical scavenging, reducing capacity and transition metal catalysis chelation in ex-

opolysaccharides extracted from the medicinal mushroom *Ganoderma sichuanense* (formerly *Ganoderma lingzhi*) [1].

4. Peptides from Mushrooms

Macrofungi are rich in proteins and can be notable sources of natural bioactive peptides, which can be extracted from their mushrooms or mycelia, whether fresh, dried, frozen and/or freeze-dried. These peptides, called MBPs (Mushroom Bioactive Peptides), are small fragments (2 to ~50 amino acids) produced endogenously or isolated from macrofungal proteins, and which have several beneficial effects on the physiology and health of other living beings, including humans [3].

Peptides are composed of at least two amino acids in which the carboxyl group of the first amino acid connects to the amino group of the next amino acid in the chain through a covalent bond called, in this case, a peptide bond. Sequence-specific polypeptides with more than ~50 residues are called proteins, although there are discrepancies in the literature about when to start adopting this term [53]. The bioactive activities of MBPs appear to depend on the composition, structure and sequence of amino acids (especially in relation to their acid–base behavior, determined by free α-amino and α-carboxylic groups and side groups), the length of the amino acid chain (which reflects in its molecular weight), and its electrical charge [54].

Due to their small size, bioactive peptides can be entirely absorbed by the intestine and, consequently, by the bloodstream, being distributed to the body's systems in an intact form, which expands their benefits in various organs and physiological activities [55]. Furthermore, bioactive peptides have great morphofunctional stability, tissue-specific affinities, low toxicity and high pharmacological capacity. All these characteristics make these biomolecules excellent candidates for the composition of functional foods and medicines [5].

Proteins can encode and generate a wide variety of bioactive peptides, which can be released without losing their bioactive properties. In fact, peptides from proteins seem to have enhanced bioactivity compared to the properties of whole proteins, mainly because their smaller size increases their ability to cross biological barriers, such as cell membranes, and then be absorbed by cells [56].

There are two main procedures for obtaining MBPs. The first is based on the extraction of endogenous bioactive peptides from macromycetes, which have an intrinsic origin and are synthesized through specific pathways, generally in response to environmental conditions. Their biological structures and functions are generally species-specific and vary depending on the environment in which they live [3]. The second method is based on obtaining bioactive peptides that are encoded in the proteins they constitute, forming these macromolecules. These peptides can be released through lysis using peptidases, in processes such as enzymatic hydrolysis, or using basic or acidic solutions, a process called chemical hydrolysis [57–59].

The first step in extracting peptides from fungi is to disrupt the cellular structure, especially the cell wall, which is generally accomplished through maceration of the fruiting body and/or mycelium, with an aqueous diluent or lysis buffer. After preliminary bioactivity tests, which can be carried out with enzymatic tests, peptide purification techniques are then carried out via ultrafiltration and/or chromatographic methods based on the physicochemical characteristics of these biomolecules, such as isoelectric point, polarity, molecular mass, solubility, interactions, etc. [60]. After purification, identification and characterization of the peptides can be carried out using spectrometric and electrophoretic techniques, for example [61].

The obtaining of MBPs is still largely unexplored and, therefore, knowledge about their bioactive and pharmaceutical properties and obtaining and purification methodologies is still scarce. However, the literature reports provide data supporting several benefits of MBPs that corroborate their pharmaceutical potential, as described below.

For example, there are MBPs that inhibit the angiotensin-converting enzyme (ACE), the central component of the renin–angiotensin system, which makes it possible to control

blood pressure by regulating the volume of fluids in the body. ACE converts angiotensin I to angiotensin II, a vessel constrictor. In other words, these ACE-inhibiting peptides can be used to control, prevent and/or reduce high blood pressure, replacing drugs that have several undesirable side effects. The action mechanisms of MPBs in inhibiting ACE are not totally unveiled. They appear to act mainly by inhibiting the synthesis of nucleic acids and proteins involved in ACE activation [62]. The fungi *Grifola frondosa*, *Agaricus bisporus*, *Pleurotus cornucopiae* and *Pleurotus cystidiosus* are macromycetes known to inhibit ACE, with great pharmaceutical potential for the treatment of hypertension [63–66].

An analysis carried out by Landy et al. [54] regarding data on antihypertensive MBPs suggests that ACE inhibitors have short chains (3 to 17 amino acid residues), with a molecular weight between 301 and 2037.26 Da. These data suggest that MBPs could also inhibit ACE in a direct way, by binding themselves to active sites of the enzyme, and that larger peptides may have less capacity to bind to active sites from ACE. Furthermore, most of them present lysine and/or proline in their C-terminal part, which indicates that MBPs with these amino acid residues are more effective in inhibiting ACE. The authors' analysis also suggests that there is a prevalence of hydrophilic characteristics in these peptides and that pentameric and hexameric forms are the most abundant, with their isoelectric points varying from 5.52 to 9.75 [54].

Some MBPs also have antioxidant activity, that is, they help the endogenous antioxidant system to remove free radicals that cause cellular oxidative stress, which can lead to premature aging and severe health problems, such as cancer and degenerative diseases. Most of these peptides can act in limiting the production of reactive species (donating protons, electrons and chelating metals), and in modulating enzymes and pathways of the antioxidant system [67]. The majority of this class of MBPs appears to consist of hydrophobic amino acids, which facilitate cellular uptake into different organs through cell membranes, and negatively charged amino acids, which enable the donation of electrons to free radicals, functioning as scavengers and, consequently, inactivating them. Benzene rings of some aromatic amino acids of MBPs (e.g., Phe, Met, Tyr, Lys, Trp, Cys and His) have the ability to stabilize reactive radicals by donating electrons to these molecules and at the same time can maintain their own electrical stability [5].

The basidiomycete *Ganoderma lucidum* has very efficient antioxidant properties. A bioactive peptide fraction, called GLP (from *Ganoderma lucidum* peptide), isolated from this fungus appears to act in different ways in the antioxidant system, increasing the levels of glutathione (GSH) and the enzyme superoxide dismutase (SOD), leading to a decrease in lipid peroxidation in the liver, which in turn inhibits the formation of malondialdehyde (MDA), which can trigger a series of inflammatory processes [68–70].

Macromycetes also synthesize proteins and peptides with antimicrobial action, endogenously, to combat possible fungal, viral and bacterial infections originating from the environment. Some of these peptides can function as very specific and effective natural antibiotics, with low toxicity compared to synthetic ones. Its antimicrobial properties are possibly due to the amphipathic and cationic characteristics of its structure, which enable it to bind to the negatively charged membranes of microorganisms [71]. Antimicrobial MBPs appear to act in different pathways, such as inhibiting the synthesis of nucleic acids, inhibiting protein synthesis, in pathways that cause hyperpermeabilization of biological membranes, inhibiting the activity of some important enzymes and activating apoptotic pathways, processes that lead to death or unviability of microorganisms [72].

Some antibacterial MBPs appear to be positively charged, which, when combined with the negative charges of chemokine receptors on the surface of bacterial cells, cause their depolarization through electrostatic interactions, leading to cell rupture and, consequently, death of the microorganism [56]. This mechanism hinders the development of so-called bacterial resistance to antibiotics, which increases their pharmaceutical potential [3].

Plectasin is a bioactive peptide produced by *Pseudoplectania nigrella*, which has very specific bactericidal properties, without causing toxicity to eukaryotic cells infected by bacteria. Its potential for treating bacterial infections of the nervous system has been studied, especially as it is highly absorbable by cerebrospinal fluid [73].

Some MBPs also have antitumor and immunostimulating properties, causing a significant increase in the production of macrophages and phagocytosis processes that inhibit the growth of various types of cancer (e.g., breast, leukemia) and help fight infections caused by pathogens [74,75]. MBPs can increase the cytotoxicity of immune system defense cells, the phagocytic capacity of macrophages and the production of immune cells, and can enhance the activation of immune system pathways and the production of antibodies, thus improving the body's defense against pathogens and inhibiting inflammatory responses [76]. Some peptides have been shown to be cytotoxic in treatments against tumor cell lines, reduce cell proliferation rates in mitochondrial pathways and promote expression of tumorigenesis-suppressing caspases in certain types of cancer. These characteristics make them powerful candidates for use as adjuvant agents in conventional treatments (e.g., immunoconjugates or linked to chemotherapeutic agents) or even as alternative medicines to aggressive anti-tumor treatments [54,56].

Pleurotus ostreatus produces two peptides with very promising pharmaceutical characteristics *Pleurotus ostreatus* peptide (POP) and pleurostrin. POP inhibits protein synthesis and pleurostrin appears to have antifungal properties, and, together, they act to inhibit the growth of fungi, in addition to reducing cell proliferation in some cancer types [77,78].

Furthermore, there are MBPs capable of chelating metals due to residues of some specific amino acids (e.g., Cys, His, Gln), which have the property of chelating divalent mineral metals, such as zinc and calcium. These properties can be exploited to increase the bioavailability of minerals in the body. Other MBPs may also act like analgesics or opioids, improve memory and slow cognitive deterioration in nerve cells [79].

Other MBPs have shown other potential bioactivities, such as antithrombotic activities by inhibiting platelet aggregation, antidiabetic activities by inhibiting α-glucosidase and α-amylase (reducing plasma glucose) and antihypercholesterolemic activities (inhibiting enzymes involved in cholesterol biosynthesis and decreasing the synthesis and secretion of triglycerides and cholesterol through increased bile secretion, modulation of hormone and cholesterol receptors, and increasing hepatic lipid metabolism) [80,81]. Some examples of MBPs and their pharmaceutical potential that have demonstrated promising results in studies are shown in Table 1.

Table 1. General characteristics and pharmaceutical potential of some MBPs previously reported.

Species	Peptide	N′-Terminal Sequence	Molecular Mass (Da)	Pharmaceutical Potential	Mechanism of Action	Reference
Hypsizygus marmoreus	No name	LSMGSASLSP	567.3	antihypertensive	Non-competitive inhibition of ACE activity	[82]
Macrocybe gigantea (formerly *Tricholoma giganteum*)	No name	GQP	301	antihypertensive	Competitive inhibition of ACE	[83]
Pholiota adiposa	No name	GQGGP	414	antihypertensive	Competitive inhibition of ACE	[84]
Tricholoma matsutake	TMP	WALKGYK	679.53	antihypertensive	Non-competitive inhibition of ACE activity	[85]

Table 1. *Cont.*

Species	Peptide	N′-Terminal Sequence	Molecular Mass (Da)	Pharmaceutical Potential	Mechanism of Action	Reference
Ganoderma lucidum	QLVP	QLVP	456	antihypertensive	Inhibition of ACE through interaction with Gln242 and Lys472 of ACE via a hydrogen bond and a salt bridge	[62]
Ganoderma lucidum	GLP Fraction	Not found	<10,000	antioxidant	Inhibition of lipid peroxidation; increase of hepatic SOD and GSH	[69]
Pleurotus eryngii	PEMP	Not found	Not found	antioxidant; immunomodulatory; antitumor	Scavenging of reactive species; inhibition of cell proliferation; stimulation of macrophage production	[86]
Pleurotus eryngii	Eryngin	ATRVVYCNRR SGSVVGGDDT VYYEG	10,000	antifungal	Not specified	[87]
Neofavolus alveolaris (formerly *Polyporus alveolaris*)	Alveolarin	GVCDMADLA	14,000	antifungal	Inhibition of mycelial growth	[88]
Pleurotus ostreatus	Pleurostrin	VRPYLVAF	7000	antifungal	Inhibition of mycelial growth	[78]
Cordyceps militaris	Cordymin	AMAPPYGYRTPDAAQ	10,906	antifungal; antiviral; antitumor	Inhibition of mycelial growth; inhibition of HIV virus reverse transcriptase; decrease in cell proliferation	[89]
Pseudoplectania nigrella	Plectasin	GFGCNGPWDE DDMQCHN-HCK SIKGYKGGYC AKGGFVCKCY	4398.80	anti-bacterial	Inhibition of bacterial growth; mechanisms not very well elucidated	[73]
Ganoderma lucidum	GLF and GLM Fractions	Not found	Not found	anti-bacterial	Generation of reactive oxygen species and induction of intracellular protein leakage	[71]
Russula paludosa	SU2	KREHGQHCEF	4500	antiviral	Inhibition of HIV virus reverse transcriptase	[90]

Notes: ACE = Angiotensin-converting enzyme; A = Alanine; R = Arginine; N = Asparagine; D = Aspartic acid; C = Cysteine; E = Glutamic acid; Q = Glutamine; G = Glycine; H = Histidine; I = Isoleucine; L = Leucine; K = Lysine; M = Methionine; F = Phenylalanine; P = Proline; S = Serine; T = Threonine; W = Tryptophan; Y = Tyrosine; V = Valine. Each letter in the "N′-terminal Sequence" column represents an amino acid, so if the sequence has the letters "KREH", it means that it has 4 amino acids in its composition.

5. Phenols and Polyphenols from Mushrooms

Phenols and polyphenols are organic compounds found abundantly in nature, particularly in plants and certain macromycetes. In those organisms, phenols and polyphenols act on various biological activities and physiological functions. They are involved in processes such as defense mechanisms against pathogens and predators, regulation of growth and development, and adaptation to environmental stressors. In macromycetes, those compounds

can inhibit the growth of bacteria and other microorganisms, thus protecting the mushroom from diseases, predation and decay. However, the action of phenols and polyphenols is not only limited to those benefits for the fungi but is also extended to biological activities of interest in human health [91–93].

Phenolic compounds are characterized by the presence of at least one aromatic ring (C_6) and one or more hydroxyl (OH) groups in the molecule. The structures of these compounds can extend from simple molecules to complicated polymers [92,94]. The total phenolic content of medicinal mushrooms is around 6.0 mg per gram of dried matter, with phenolic acids, flavonoid compounds, tannins, and tocopherols being the principal classes. Even if many different compounds are identified inside those classes, the content of phenolic compounds in mushroom species has not been as precisely characterized as in the case of plants, especially concerning phenolic acids [92].

The most prevalent phenolic acids discovered in mushroom species include *p*-coumaric, cinnamic, p-hydroxybenzoic, benzoic, ferulic, and gallic acids. Phenolic acids are divided into two principal classes, benzoic acid derivatives (with a C1–C6 backbone) and cinnamic acid derivatives (with a C3–C6 backbone). In the study by Çayan et al., 26 fungal species were analyzed concerning the phenolic acid compounds, and fumaric acid was found to be the most abundant in 16 out of 26 mushrooms. Catechin hydrate, a polyphenol, was identified as the major phenolic compound in the other species. Higher phenol content was identified on the mushroom species *Suillus granulatus* (71.79 μg/g) and *Lepista nuda* (currently *Collybia nuda*) (68.38 μg/g) [95].

The class of polyphenols known as flavonoids can also be present on mushrooms, at quantities of up to 3.0 mg per gram of dried matter. Homogentisic acid, benzoic acid (4-OH-benzoic, vanillic, protocatechuic, salicylic) and cinnamic acid derivatives (caffeic, ferulic, p-coumaric, myricetin and catechin) are some of the principal flavonoids reported in mushroom species [96]. However, some researchers affirm that edible mushrooms lack the enzymes necessary for synthesizing flavonoids, and studies have not found significant flavonoid absorption in cultivated fruiting bodies or mycelia grown in flavonoid-rich environments. Flavonoids detected in mushrooms could arise from sample contaminations or procedural issues, and at the moment there is still no consensus about this topic. Employing appropriate analytical methods for flavonoid detection can further help the understanding of flavonoid synthesis in mushroom cells [97,98].

Tannins are other significant secondary mushroom metabolites, and are categorized into hydrolyzable and condensed types. Hydrolyzable tannins consist of esters of gallic acid or ellagic acid with glucose, while condensed tannins are polymers of flavan-3-ols or flavan-3,4-diols. The structures of hydrolyzable tannins vary due to the different oxidative bonds formed through intermolecular oxidation reactions, typically appearing as oligomers with a molecular weight of 2000–5000 Daltons. Condensed tannins, also referred to as procyanidins, can be converted into anthocyanins through acid-catalyzed reactions. Tannin contents from mushroom samples from the *Pleurotus* genus are highly reported, being in the range of 36 to 40 mg/g. Those substances can accelerate wound healing, aid in cancer prevention, and assist in treating inflamed mucous membranes and ulcerated tissues [99,100].

Among mushroom polyphenols, tocopherols can also be cited. Those compounds comprise a 6-chromanol ring and a saturated side chain, whereas if the compound features a geranyl side chain and three double bonds, it is termed tocotrienol. They are present in mushrooms such as *Agaricus silvicola*, *Agaricus silvaticus*, *Agaricus bresadolanus* (formerly *Agaricus romagnesii*), *Agaricus arvensis*, and *Agaricus bisporus*, *Laccaria laccata*, *Mycena rosea*, *Clitopaxillus alexandri* (formerly *Clitocybe alexandri*), *Paralepista flaccida* (formerly *Lepista inversa*) and *Laccaria laccata* [92,93]. Besides the phenolic compounds discussed above, other phenolic compounds found in mushrooms include lignans, stilbene, and pyrogallol [93].

The biological activities of mushroom phenolic compounds are wide ranging, including antioxidant, antitumor, anti-inflammatory, antihyperglycemic, antimicrobial, anti-osteoporotic and anti-tyrosinase activities [92]. Reactive oxygen species (ROS) are key

catalysts for oxidation in vivo and in vitro, associated with numerous diseases and aging processes. Excessive ROS accumulation damages lipids, proteins, carbohydrates, and DNA, inducing oxidative stress, cell dysfunction, and cell death. These processes are prevalent in various diseases like cancer, inflammation, atherosclerosis, and cardiovascular issues. Phenols and polyphenols have been demonstrated to have antioxidant potentials, neutralizing ROS, through different pathways, including the inactivation of metals, acting as oxygen scavengers, or inhibiting free radicals [101].

In a study by Guo et al., a positive linear correlation between total antioxidant capacities and total phenolic contents was observed in 49 edible macro-fungi. Macro-fungi like *Thelephora ganbajun*, *Boletus edulis*, *Volvariella volvacea*, *Butyriboletus regius* (formerly *Boletus regius*), *Suillus bovinus* and *Agaricus blazei* display high antioxidant capacities and total phenolic contents, being important sources of natural antioxidants for the prevention of diseases caused by oxidative stress [102].

Numerous terpenes and terpenoids (terpenes with the addition of functional groups, usually oxygen-containing) can be obtained from medicinal mushrooms, and are responsible for their antioxidant, anti-inflammatory, anticancer activities, and immunomodulatory [96]. The mushroom extracts from *Hypsizygus tessullatus* (brown and white varieties) and *Flammulina velutipes*, for example, showed good antiproliferative activities against human breast cancer cell lines (CF-7 and MDA-MB-231 cell lines). This anticancer activity was attributed principally to the phenolic compounds quantified on the sample, which included significant flavonoid compounds [103].

Furthermore, the ability of natural polyphenols to scavenge reactive oxygen species (ROS) positions these compounds as valuable candidates for the production of anti-aging lotions or creams in the cosmetic industry [92]. In the study by Ziemlewska et al., water extracts from the mushrooms *Grifola frondosa* (Maitake), *Hericium erinaceus* (Lion's Mane) and *Ganoderma lucidum* (Reishi) were assessed for antioxidant properties, bioactive content, and skin effects. Maitake extract exhibited the highest levels of flavonoids and phenols, along with efficient scavenging of radicals. Importantly, all extracts mitigated skin irritation, increased skin hydration, and reduced transepidermal water loss. Furthermore, the incorporation of mushroom extracts into washing gels decreased skin irritation and intracellular production of free radicals compared to a cosmetic base. Overall, these findings highlight the potential of mushroom extracts in enhancing cosmetic formulations [104].

Phenolic compounds have also been shown to be useful in the treatment of COVID-19. *Ganoderma lucidum*, a common mushroom in Chinese medicine, produces luteolin and quercetin, phenolic compounds that were screened for anti-COVID-19 action [105,106]. *Ganoderma lucidum* extract has also been applied in skincare products, as well as *Pleurotus ostreatus* extract, showing promising cosmeceutical potential [107].

Concerning the process of extraction of phenol compounds from the mushrooms, this depends strongly on the effectiveness and efficiency of the selected extraction method. Conventional methods for phenol compound extraction from mushrooms include maceration and Soxhlet method of lipid extraction. Those methodologies are simple and depend principally on the solvent and external factors such as temperature, time, and agitation, which are adjusted to improve the solubility of the compounds. Nevertheless, those techniques demand long extraction periods and high solvent volumes and may lead to low extraction yields. Novel methods of extraction, which are green, economical, and faster, have been researched, however. One example is Ultrasound-Assisted Extraction (UAE), applied in the article by Machado-Carvalho et al. for the extraction of phenolic compounds from the mushroom *Inonotus hispidus*. A total phenolic content of 219.01 μg/g (dry weight) was identified on the extract, with hispidin as the main polyphenol. The extract demonstrated potential as a source of antioxidant compounds, with possible industrial, pharmaceutical, and food applications [108].

After extraction, the application of those mushroom phenols and polyphenols in industry faces some challenges, especially related to their stability, solubility, bioavailability, and bioactivity, especially during storage and processing. These challenges restrict

their utilization in both food and medicinal contexts. Sensitivity to storage conditions like temperature, oxidation, and light, along with gastrointestinal conditions such as pH and enzyme interactions, complicates their incorporation into dietary supplements. Furthermore, exposure to alkaline environments can prompt the formation of undesirable derivatives, while metabolites with a bitter taste present additional hurdles for integration into food products. However, research and technologies have been developed to encounter those challenges and expand the application of those compounds, utilizing strategies that include novel drug delivery systems and encapsulation or nanoencapsulation of the mushroom extracts with success.

6. Terpenes from Mushrooms

Terpenes and terpenoids are a class of fungal secondary metabolites that possess chemical structure diversity and a broad range of biological activities. The terpenoids are classified into different classes based on the number of linked isoprene units as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), and polyterpenes (longer chains of C_5) [109].

The biosynthesis of terpene originates from the mevalonate pathway, and mevalonic acid is the main precursor from isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). The monoterpenes are formed from geranyl diphosphate (GPP, C_{10}), resulting in the phosphorylation of mevalonic acid. The GPP combined with IPP produces the farnesyl diphosphate (FPP, C_{15}), a precursor molecule from sesquiterpenes. The diterpenes are produced by condensation of the FFP and IPP to form geranylgeranyl diphosphate (GGPP, C_{20}). FPP and GGPP are molecules precursors from triterpenoids (C_{30}) and tetraterpenoids (C_{40}) [110,111].

Macromycete fungal species contain a variety of bioactive terpenes that have potential pharmacological applications. These terpenes include sesquiterpenes, diterpenes, triterpenes, monoterpenes, and polyketides (Table 2). Terpene biosynthesis for higher fungi depends on the type of terpene synthase produced, which is a peculiar characteristic of each fungal species and its bioactivity [110].

Ten species of mushrooms are producers of sesquiterpenes, including *Agrocybe salicaceicola*, *Anthracophyllum* sp., *Flammulina velutipes*, *Pleurotus cornucopiae*, *Montagnula donacina*, *Neonothopanus nambi*, *Russula rosea* (formerly *Russula lepida*), *Russula amarissima*, *Stereum hirsutum* and *Strobilurus ohshimae*. Mushroom sesquiterpenes are bioactive compounds and have antimicrobial [112–114], anti-cancer [115], antimalarial [112], antimycobacterial [116], antioxidant [115], anti-inflammatory [117], and cytotoxic activities [112]. However, sesquiterpenes obtained from some species of mushrooms, such as *Agrocybe salicaceicola*, *Russula rosea* (formerly *Russula lepida*), *Russula amarissima*, *Stereum hirsutum*, and *Strobilurus ohshimae*, have not demonstrated biological activity [118–121].

Five species of mushrooms are producers of diterpenes including *Cyathus africanus*, *Pleurotus eryngii*, *Hydnellum scabrosum* (formelly *Sarcodon scabrosus*), *Hydnellum glaucopus* (formerly *Sarcodon glaucopus*) and *Sarcodon cyrneus*. Some of these diterpenes possess a strong to moderate cytotoxic [122,123], antibacterial [124], anti-inflammatory [125,126] and neuritogenic activity [127,128]. Some terpenes with their biological properties are presented in Table 2.

In the triterpene class, five mushroom species are important producers, including *Astraeus odoratus*, *Ganoderma pfeifferi*, *Ganoderma lucidum*, *Ganoderma orbiforme*, and *Hypholoma fasciculare* (formerly *Naematoloma fasciculare*). Many of these compounds exhibit antibacterial and cytotoxic, antiviral, antimycobacterial and acetylcholinesterase inhibitory activities [129–134].

The monoterpenes are rarely isolated from filamentous fungi, such as *Aspergillus*. Among the mushrooms, the production of monoterpenes was reported by only three species, including *Agaricus bisporus*, *Pleurotus cornucopiae*, and *Pleurotus ostreatus*. Many of these monoterpenes possess antioxidant and anti-inflammatory activities [117,135].

Table 2. Biological properties of terpenes obtained from mushrooms.

Species of Macromycetes	Class	Terpenoids	Pharmaceutical Properties	References
Astraeus odoratus	Triterpenes	Astraodoric acids A–D, 5-hydroxyhypaphorine	Antibacterial and cytotoxic activities	[129]
Anthracophyllum sp.	Sesquiterpenes	Anthracophyllic acid, anthracophyllone, aurisins A, G, K, nambinones A, C, axinysones A, and B	Antimalarial, antibacterial, citotoxicity activities	[112]
Agaricus bisporus	Monoterpenes	m-Xylene, β-Myrcene, DL-Limonene, Styrene, β-Terpinene, (E)-Limonene oxide, Dihydromyrcenol, Linalool, D-Carvone	Antioxidant activity	[135]
Cyathus africanus	Diterpenes	Neosarcodonin O, cyathatriol, 11-O-acetylcyathatriol, cyathins D–H	Cytotoxicity activity	[122]
Dentipellis fragilis	Diterpenes	Dentipellin, erinacines A-C	Antibacterial and antifungal activities	[136]
Ganoderma lucidum	Triterpenes	Ganoderate A acetonide and n-butyl ganoderate H	Inhibitor of acetylcholinesterase	[132]
Ganoderma orbiforme	Triterpenes	Ganorbiformins A–G	Antimycobacterial activity	[133]
Flammulina velutipes	Sesquiterpenes	Enokipodins A and B	Antimicrobial activity	[113]
Flammulina velutipes	Sesquiterpenes	Enokipodins E–J, sterpurols A and B	Antibacterial, antifungal anticancer and antioxidant activities	[115]
Panus strigellus formerly *Lentinus strigellus*	Polyketides	Lentinoids A–D	Antibacterial activity	[137]
Pleurotus eryngii	Diterpenes	Eryngiolide A	Cytotoxicity activity	[123]
Pleurotus cornucopiae	Monoterpenes and Sesquiterpenes	Monoterpenoids and Sesquiterpenoids	Inhibitory activity against nitric oxide	[138]
Pleurotus ostreatus	Monoterpenes	m-Xylene, β-Myrcene, DL-Limonene, Styrene, (E)-Limonene oxide, Dihydromyrcenol, Linalool, (E)-Caryophyllene, α-Humulene, γ-Muurolene, (E)-Carveol, (Z)-Carveol	Antioxidant activity	[135]
Montagnula donacina	Sesquiterpenes	Donacinolides A and B, donacinoic acids A and B, donacinols AeC and a meroterpenoid (Z)-4-hydroxy-3-(3-hydroxy-3-methylbut-1-en-1-yl)benzoic acid	Antibacterial activity	[114]
Neonothopanus nambi	Sesquiterpenes	Nambinones A-D, 1-epi-nambinone B, aurisin K	Antimalarial and antimycobacterial activities	[116]
Tapinella atrotomentosa	Sesquiterpenes	5-hydroxy-hex-2-en-4-olide, spiromentins C and B	Antibacterial and antioxidant activity	[139]
Hydnellum scabrosum (formely *Sarcodon scabrosus*)	Diterpene	Neosarcodonin O, 19-O-linoleoyl, 19-O-oleoyl and 19-O-stearoyl derivatives of sarcodonin	Anti-inflammatory activity	[125]
Hydnellum glaucopus (formerly *Sarcodon glaucopus*)	Diterpene	Glaucopine C	Anti-inflammatory acitvity	[126]
Hydnellum scabrosum (formely *Sarcodon scabrosus*)	Diterpene	Scabronines H, K, L and sarcodonins G, A, M	Neurite activity	[128]
Strobilurus ohshimae	Sesquiterpenes	Strobilols A–D	Not showed antibacterial activity	[120]

7. Alkaloids from Mushrooms

Different groups of mushrooms are known to be potential producers of high-molecular-weight bioactive compounds, such as alkaloids [140]. Alkaloids are secondary metabolites, some of which are produced by macrofungi; these compounds exert protective activities on the organism, for example, to combat pathogen attacks. They also act to mediate inter-species communication, acquisition of nutrients against competitors, and act in symbiotic interactions [141].

Among the main alkaloids produced by macrofungi are indoles. These compounds are some of the main nitrogen-containing secondary metabolites, characterized by a structure containing the indole nucleus or derivatives (Figure 3A).

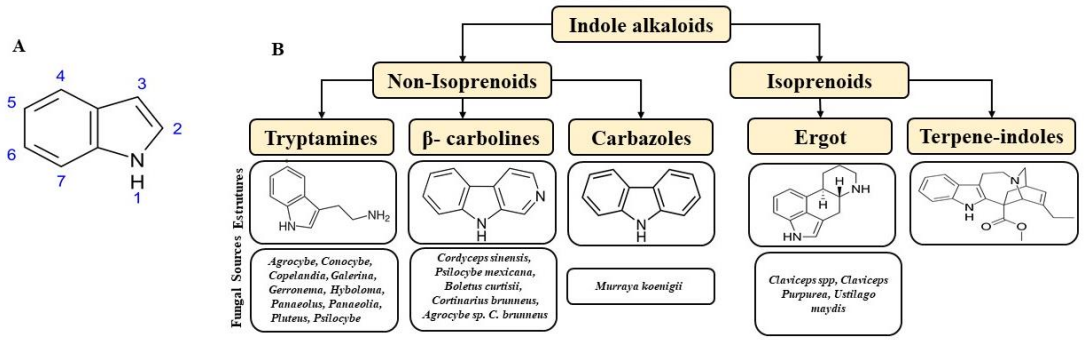

Figure 3. (**A**) Indole nucleus; (**B**) classification of indole alkaloids.

Indole alkaloids are derived from the amino acid tryptophan, which is obtained via the shikimate route [141,142]. The synthesis of indole alkaloids begins with chorismate in the shikimic acid pathway and involves the intermediates anthranilate (AT) and indole-3-glycerol-phosphate (IGF). The IGF intermediate is transformed into indole, which can couple with serine to form tryptophan (Trp). The Trp can be decarboxylated and converted to tryptamine (TPT), or prenylated at C4 to produce 4-dimethylallyl tryptophan (4-DMAT). The compounds Trp, IGF, TPT and 4-DMAT can serve as precursors for the synthesis of fungal indole alkaloids [141–143].

Indole alkaloids from mushrooms have a wide range of biological properties, which is why the pharmaceutical sector has shown great interest in these compounds as a more efficient alternative to synthetic drugs currently used for neuropsychiatric diseases, such as depression, anxiety, post-mortem stress, traumatic stress, obsessive–compulsive disorders, depressive disorders, bipolarity and schizophrenia, among others [144,145].

According to Plazas et al., Charlson et al., and Leichsenring et al. [145–147], neuropsychiatric diseases currently represent a challenge for global health systems due to their constant growth in number of cases and the lack of medicine and effective treatments. Furthermore, currently used psychiatric medications have unpleasant side effects and reduced tolerability, impacting patients' quality of life [145].

The use of macrofungi with hallucinogenic effects constitutes a ceremonial tradition of Mesoamerican indigenous cultures. These fungi have compounds characterized by the ability to induce neurotrophic effects, mental changes, and even hallucinations after being ingested [148,149]. One of the first indole alkaloids consumed by man was psilocin (500-200 BC), obtained mainly from *Psilocybe mexicana*. This compound is a substance analogous to serotonin and acts as an agonist of serotonin 5-HT receptors, which can cause psychic effects (altered states of consciousness, synesthesia, increased introspection) [150].

Indole alkaloids can be classified into two groups: (i) non-isoprenoids, among which are tryptamines, β-carbolines, carbazoles; and (ii) isoprenoids, such as ergot and terpene-indoles (Figure 3B). Non-isoprenoids are phenolic lipids derived from the polyketide pathway and can have varied and diverse structures that do not follow the isoprene unit pattern. Differently, the isoprenoids are molecules synthesized through condensations of the five-carbon compound isopentenyl diphosphate (IPP) and dimethylallyldiphosphate

derived from the mevalonate pathway [141,148]. Tryptamines are known as simple alkaloids derived from indole formed by a benzopyrrole with an ethylamine-type side chain at C-3 and substituents at positions C-4 and C-5 on the indole nucleus [141,148,151]. This type of compound has psychotropic activity by modulating serotonin receptors [152]; examples of this group of alkaloids are psilocybin, aeruginasin, and bufotenine [145].

The β-carbolines are organic amines with multi-target pharmacological activities by modulating enzymes and receptors involved in depressive disorders monoamine oxidases. Examples of these compounds are β-carboline-1-propanoic acid, brunnein A, etc. These compounds also intercalate into DNA, inhibit CDK, topoisomerase and monoamine oxidase and interact with benzodiazepine receptors and 5-hydroxyserotonin receptors. Furthermore, these biometabolites also have sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic and antimicrobial properties [153,154].

Carbazoles have a tricyclic structure, consisting of two six-membered benzene rings fused on each side of a ring. One side of a ring contains five-membered nitrogen [155]. Examples of this group are carquinostatin, koenimbin, and koenigicine, among others. Some of these compounds have biological properties against diseases such as ischemia-reperfusion, atherosclerosis, inflammation, autoimmune diseases and cancer [151,156]. Finally, ergot is an indole alkaloid that shares a common tetracyclic system formed biosynthetically by condensation of tryptophan and dimethylallyl pyrophosphate (Figure 3B); lysergol and ergonovine are part of this group [145].

8. Sterols from Mushrooms

Steroids are fat-soluble compounds that have a basic structure of 17 carbon atoms arranged in rings linked together. One of the most important steroids is ergosterol, which is a sterol that makes up the cell membranes of fungi and some protists [157]. This sterol is a precursor to vitamin D_2 [158]. Ergosterol is transformed into viosterol by the action of ultraviolet light and is subsequently converted into ergocalciferol, which is a form of vitamin D [159].

Steroids are essential eukaryotic constituents, are secondary metabolites of mushroom metabolism and are biosynthesized through triterpenoids [157]. According to Rangsinth et al. and Baker et al. [159,160], the main sterol in mushrooms is ergosterol. These compounds are increasingly relevant in the pharmacological sphere due to their health benefits, mainly due to their antioxidant properties, immunological activity, and effects against diabetes and cancer. Among the ergosterol-producing mushrooms, the following stand out: *Agaricus bisporus*, *Tuber melanosporum*, *Lentinula edodes*, and *Agaricus blazei* [161].

The ergosterol content in mushrooms varies between species and between different parts of the mushroom, for example, in button and morel mushrooms, the ergosterol content can reach concentrations of 3.52 mg/g and 0.45 mg/g, respectively [162]. Regarding the ergosterol content in mushroom capsules, this can reach concentrations of 3.76 mg/g and 4.56 mg/g for white and brown mushrooms [163].

Ergosterol has properties similar to some medicines. However, the main advantage of this biometabolite is that it does not cause hepatotoxicity or skin allergy. Its average lethal dose in rats is extremely high—2.05 mol/kg. In addition, ergosterol was considered a non-mutagenic and non-carcinogenic compound [159,164].

Ergosterol is an effective antioxidant agent that acts in different ways depending on the type of free radical. According to [165], this biometabolite is capable of neutralizing free radicals induced by terbutyl hydroperoxide. Furthermore, ergosterol also reacts with the hydrogen peroxide radical (H_2O_2), whereby it inhibits or prevents lipid oxidation. The authors in [166] demonstrated that ergosterol-rich extracts obtained from *Auricularia nigricans* (formerly *Auricularia polytricha*) present a significant defense against neurotoxicity induced by oxidative stress.

On the other hand, ergosterol also has anti-inflammatory properties. According to Yoo et al. [167] this metabolite inhibits inflammation induced by lipopolysaccharides in conjunction with the phosphorylation of p38, extracellular signal-regulated protein kinase

and mitogen-activated proteins. According to Huan et al. [168], ergosterol suppresses the expression of inflammatory mediators through different signaling pathways, including the Janus kinase signal transducer and the JAK-STAT interaction chain, routes that are related to inflammation, cell division and death. Nallathamby et al. [169] found that *Cordyceps militaris* extract enriched with ergosterol exerts neuroprotective effects by attenuating radical production activated by lipopolysaccharide.

Ergosterol and its derivatives also have biological activity against cancer. This disease still remains one of the most common causes of morbidity and mortality in the world [170]. Compounds of natural origin with chemopreventive and chemotherapeutic properties have led to a new era in the research of medicines to combat cancer and its lethal malignancies, due to which current treatments are insufficient especially when this disease is in advanced stages [159]. Chen et al. found that ergosterol fractions obtained from *Ganoderma lucidum* exhibited potent cytotoxicity against MDA-MD-231 and HepG2 cell lines, while for normal cells, the biometabolite had no effect. Rangsinth et al. [159] reported that ergosterol derivatives such as 5,6-dehydroergosterol and ergosterol peroxide also possess anticancer activity specifically in breast and cancer-related cells. Martínez-Montemayor et al. [171] showed that ergosterol also inhibits the expression of the enzymes ATK1, ATK2, etc., which attenuates the invasion of cancer into organisms. Li et al. [172] found that the *Sanguinoderma rude* (formerly *Amauroderma rude*) stratum rich in ergosterol inhibits melanoma B16 cancer cells. According to researchers, the inhibition of cancer by ergosterol occurs mainly because ergosterol positively regulates multiple tumor suppressors such as pro-apoptotic genes, including FasL, Bad, Bim and Trail. Yazawa et al. [173] found that a diet with an ergosterol content between 0.01 and 0.1% inhibits bladder carcinogenesis and that the inhibition of cancer cells occurs by blocking androgenic signaling. Other examples of the anticancer properties of ergosterol are summarized in Table 3.

Other biologically important properties of ergosterol are its antidiabetic and antimicrobial activity. Regarding the first, Xiong et al. [174] demonstrated that treatment with ergosterol obtained from *Pleurotus ostreatus* in mice reduced blood glucose with type 2 diabetes, in addition, ergosterol stimulated the expression of GLUT4 modulated by the PI3K pathway. Furthermore, according to Rangsinth et al. [159], ergosterol also increases glucose uptake due to which it positively regulates the activity of glucose transporter 4 and the phosphorylation of Akt and PKC in muscle cells as well as tissues.

Regarding antimicrobial activity, according to [175], steroids such as stigmasterol, sitosterol and ergosterol exhibit potent antimicrobial activity against a broad spectrum of microorganisms. For example, ergosterol has antifungal properties demonstrated against filamentous fungi such as *Aspergillus flavus*, *Penicillium digitatum*, among others [159]. In fact, Li et al. [176] showed that ergosterol inhibits the growth of *Helicobacter pylori*, the main etiological agent associated with chronic gastritis and duodenal ulcers [177]. Ergosterol also affects the growth of *Trypanosoma cruzi*, the etiological agent that causes Chagas disease, as ergosterol permeabilizes the plasma and mitochondrial membranes, causing the death of the parasite. Finally, ergosterol also has antiviral properties against the COVID-19 virus.

Table 3. Biological properties of ergosterol.

Compounds/Origin	Biological Property	Type of Disease	Model	Dose (Ergosterol)	Mechanism	Reference
Ergosterol (*Monascus anka*)	Antioxidant	-	H_2O_2-induced fibroblast	200 mg/mL and 400 mg/mL	Inhibition of lipid peroxidation	[178]
Industrial-Ergosterol	Antioxidant	-	In vitro assay	11 µM	Ergosterol is involved in yeast resistance to tert-butyl hydroperoxide and protects lipids against oxidation in liposomes	[165]

Table 3. *Cont.*

Compounds/Origin	Biological Property	Type of Disease	Model	Dose (Ergosterol)	Mechanism	Reference
Ergosterol (*Amaouroderma rude*)	Anticancer	Carcinoma	MDA-MB-231 cancer cells	In vitro test with MCF-7 cells with IC50 of 43.51 µg/mL	Ergosterol isolate inhibits the growth of MDA-MB-231 cancer cells through apoptotic pathways by increasing FOXO3 expression	[179]
Industrial-Ergosterol	Anticancer	Bladder cancer	Rats were given an N-butyl-N-(4-hydroxybutyl) nitrosamine	Oral and intraperitoneal administration (15 µg/kg/day, for 21 days)	Inhibition of androgen signaling pathways	[180]
Industrial-Ergosterol	Anticancer	Chronic obstructive pulmonary disease	Rats were exposed 5 days a week to main smoke from five cigarettes, four times a day with a 10 min smoke session.	The mice were treated with doses of 25 mg/kg/day and 50 mg/kg/day, intragastric administration, for 4 weeks	Ergosterol inhibited pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) in serum and lung	[168]

9. Patents: Technological Development and Innovation

Patent applications related to macrofungi and bioactive compounds have been increasing worldwide in recent years. A patent search in the Derwent Innovations Index database identified patent applications in many areas, whether for human or animal pharmaceuticals, agriculture, polymer extraction methods, and biochemical compounds. Products such as encapsulates, tablets, extracts, liquid compositions, alternative supplements, probiotic foods and nutraceuticals, supplementary human and animal nutrition ingredients, etc., were identified in the patent documents.

With the aim of finding patent documents in the field of pharmacology, an International Patent Classification (IPC) code group A61K-31/* was selected, where class A61 (medical or veterinary science), subclass A61K (preparations for medical, dental, or hygienic purposes), and group A61K-31 (medicinal preparations containing organic active ingredients) were chosen. Along with this IPC, the names "macromycet*", "macro$fung*", and "mushroom" were added. This resulted in the final search algorithm: A61K-031* AND (macromycet* OR macro$fung* OR mushroom*).

With this algorithm, 1237 patent documents were retrieved from the Derwent Innovations Index database. These documents were considered in the analysis of the historical technological development of the segment and in the evaluation of the number of patent publications per year (Figure 4b). By refining the search, selecting documents related to the areas "Pharmacology Pharmacy" and "Biotechnology Applied Microbiology", excluding the areas "Food Science Technology" and "Agriculture", and restricting to patents filed in the last five years, 176 patent documents were found. By reading the titles and abstracts of these documents, 174 were selected for being related to the pharmaceutical or therapeutic field (Figure 4a,c).

The first patent was filed in Japan in 1982 (JP57047482-A). The patent was assigned by the General Electric Company and Zh Biseibutsu Kagaku Ken. The invention refers to producing an antibiotic using a macromycete fungus species, *Leucoagaricus leucothites* (currently *Leucocoprinus leucothites*). This bioproduct, a carcinostatic substance, has the therapeutic potential to help treat leukemia. Patented by the assignee, the cultivated macromycetes of the genus *Leucoagaricus* had their metabolic liquors of interest extracted using solvents such as (m)ethanol, butanol, ethyl acetate, butyl acetate, ether, diozane and acetone. The carcinostatic compound acts to inhibit cancer cells from spreading [181].

In the Derwent Innovations Index database, Japanese patents were the most numerous and prominent until the early 2000s, with important contributions of the assignee Kagome

Co Ltd. According to the company's website, its mission is to provide quality food to solve social issues [182].

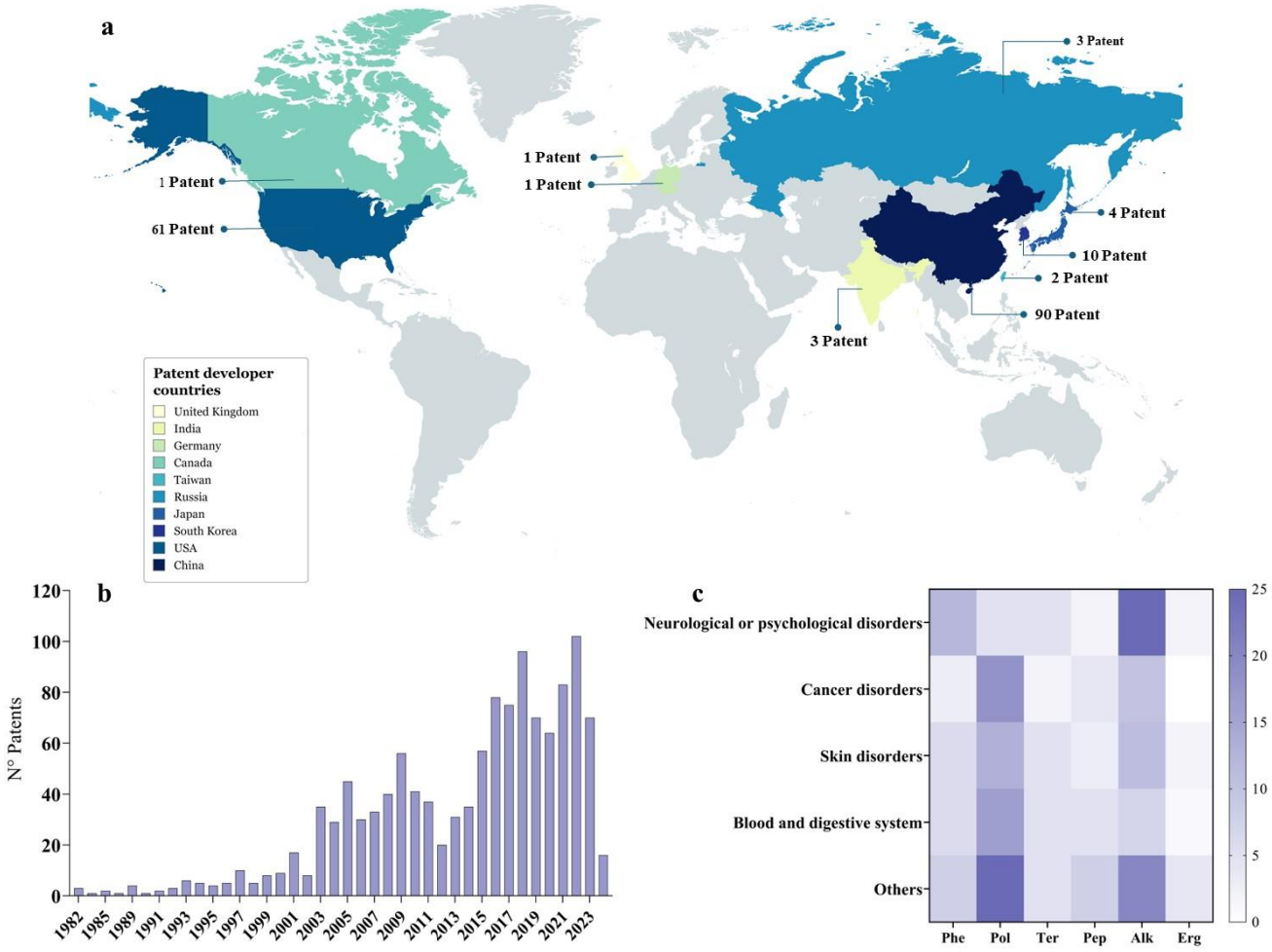

Figure 4. (**a**) The map with the countries' respective patent numbers over the last five years. (**b**) The graph showing the number of published patents per year, retrieved from the Derwent Innovations Index database, related to macromycete fungi in pharmacology and applied microbiological biotechnology. (**c**) The number of patents registered in the last five years is classified according to their applications and bioactive compounds. The numbers of the bioactive compounds may overlap, as some patents have more than one compound in their formulation. Phe—Phenol and Polyphenols; Pol—Polysaccharides; Ter—Terpenes and terpenoids; Pep—Peptides; Alk—Alkaloids; Erg—Ergosterol.

Of the six patents filed by Kagome Co., Ltd. up to the 2000s, two, JPH09235224A and JPH09235226A, were designed to help treat ischemic brain diseases linked to memory disorders. The bioactive compounds (phenols, palmitic acid, stearic acid, and linoleic acid) are extracted from the *Hericium erinaceus* mushroom as reported in both patent documents. The compounds of interest are extracted from *Hericium erinaceus* with a homogeneous solvent system consisting of water and an organic solvent. The dried solid is subsequently treated by fractional chromatography and then fractionated to isolate each of the three compounds. The final product can be formulated into an oral agent, such as a tablet, granules, powder preparation, or capsule. The only difference between one patent and the other concerns the derivatives used for the formulation. While the first (JPH09235224A) contains benzyl alcohol derivatives, the second (JPH09235226A) has chroman derivatives [183].

Over time, in the 1980s and 1990s, the focus of patent applications continued to be on the anti-tumor properties of bioactive fungal compounds. In 1983, Noda Shokukin Kogyo

Co., Ltd. patented an anti-cancer agent derived from a glycoprotein of xylose produced by a mycelium belonging to Basidiomycetes (*Lentinula edodes*). Using membrane filtration and freeze-drying methods, the powder obtained from the mushroom was subjected to ethanol extraction, and the precipitate was separated by fractionation chromatography. When the patent was filed, they did not know which bioactive compound was responsible for the anti-cancer effect. Still, they knew that the action of the extracted anti-cancer substance was to increase immunity [184].

In 1989, Nichirei Corp., using ergosterol (*Agaricus* sp.), patented a method of extracting this compound with organic solvents to treat uterine cancer. An organic solvent, such as methanol, ethanol, acetone, ethyl acetate, chloroform, etc., extracts the compound. The extract obtained is subjected to solid–liquid separation by filtration, centrifugation, or a combination. Finally, the extract is put under adsorption chromatography for further purification. This produces three ergosterol derivatives with a remarkable cytocidal effect on cancer cells. The patent states that the destructive impact acts on the membranes of cancer cells, breaking them down through a biochemical reaction [185].

In 1995, New Oji Paper Co., Ltd. patented a method for hydrolyzing proteins from the mycelium of Basidiomycetes (*Pleurotus sajor-caju*, (currently *Lentinus sajor-caju*)) to prevent or treat hypertension. Its mechanism of action is a substance that acts as an angiotensin-converting enzyme inhibitor. Through extraction with a water-soluble solvent such as acetone or ethyl acetate, a protein extract is obtained from the mycelium of the fungus. By freeze-drying and then precipitating again with acetone, a mixture of converting enzyme-inhibiting peptides is obtained, which can be administered orally or parenterally [186].

In the 2000s, several patents with applications against cancer, neurological and psychological problems, dermatological problems, and many others gained focus in the Western market. As an example of applications against cancer, the Japanese patent JP2000159682A can be cited, the aim of which is to strengthen the anti-tumor activity contained in the β-glucan polysaccharides of mushrooms (*Agaricus* sp.) by irradiating them with infrared rays, which increase the amount of lipoperoxides in their composition, increasing their anti-tumor activity proportionally [187]. Another good example, filed by Nagatomo Yakuhin KK, another Japanese company, concerns a method for extracting the anti-tumor polysaccharide β-glucan from *Pachyma hoelen* (currently *Wolfiporia hoelen*) mushrooms. By boiling the sample at 100 °C for 5 to 6 h, the macropolysaccharide β-glucan is extracted efficiently [188].

Regarding innovative applications of neurological treatments, the international patent WO2010124089A2 of Synosia Therapeutics Inc. can be mentioned, the aim of which is to help treat people with an addiction to illicit drugs such as cocaine. One of the active alkaloid ingredients (ketamine) comes from the Ergot fungus (*Claviceps purpurea*). The invention relates to the use of imidazol-alkylamine inhibitors of dopamine β-hydroxylase. Their mechanism of operation consists of inhibiting plasma esterases to slow down the elimination of cocaine, which can result in elevations in plasma cocaine levels, increasing at least one negative subjective symptom of cocaine abuse and dependence, such as irritability, agitation, and extreme suspicion [189]. A more recent example is the patent CA3186405A1, granted by Optimi Health Corp., the aim of which is to provide a drug composed of indole-alkylamines for the treatment of depression and anxiety through their psychoactive properties. The alkaloid compounds (baeocystine, norbaeocystine, N, N-dimethyltryptamine, 5-hydroxytryptamine (serotonin), 5-hydroxytryptophan, psilocybin and psilocin) found in mushrooms such as *Psilocybe cyanescens* can be extracted using a deep eutectic solvent composed of choline chloride, sugar, an allylene glycol, a diol and an acid, xylitol or proline [190].

Another field of activity extensively explored in patent documents was dermatological treatments. The patent JP2005089391A, granted to Kanebo Cosmetics Inc., created a pharmaceutical composition with an active ingredient obtained from the mushroom *Tricholoma orirubens* to treat dry skin caused by the degradation of hyaluronic acid. The active compound acts on fibroblasts, inhibiting the degradation of hyaluronic acid. The compound's name was not mentioned, but it is known to have phenols in its composition [191]. Another

example, patent JP2005068061A, filed by Kao Corp., developed a pharmaceutical product capable of inhibiting the apoptosis of melanocytes, making it effective in preventing the appearance of gray hair and vitiligo. By extracting a lanostane-type terpenoid from the fungus *Ganoderma lucidum* with organic solvents such as methanol, ethanol, propanol, 1,3-butanediol, acetone, tetrahydrofuran, it is possible to obtain a product in the form of injections, inhalants, suppositories, oral preparations, ointments, creams, lotions, emulsions, gels, etc. [192].

In addition to the conventional applications listed above, there are also diverse and pioneering fields of application. Patent US20020127243A1, filed by Sun Farm Corp., created a dietary supplement with the therapeutic functions of helping against viral infections and low immunity. The active compounds (phytoestrogens, β-glucans, saponins, inositol hexaphosphate, and lectins) extracted from mushrooms, such as *Lentinula edodes*, help by increasing immune activity, such as increasing the production of lymphocytes, immunoaccelerators, immunopotentiators and immunomodulators [193]. Another diverse application example is patent US20080200429A1, filed by ImmuDyne Inc., where β-glucan compounds are extracted from *Agaricus blazei* mushrooms to treat bone loss or low bone density conditions. This happens through the inhibition of osteoclasts and the maturation of osteoblasts by β-glucans, leading to decreased bone resorption and increased bone formation, making β glucans ideal agents for treating diseases such as osteoporosis. The method of obtaining such compounds mainly involves enzymatic hydrolysis of fungal cells or biomass [194].

The growth of this sector in the 21st century shows that the market is awakening to this branch of biotechnology, especially about the therapeutic applications of bioactive fungal compounds. As can be seen in Figure 4a, the main countries with technology for producing or obtaining pharmaceutical products from mushrooms are China, the United States, South Korea and Japan, with 52%, 35%, 6.0% and 2% of patents, respectively. Therefore, it is clear that the most prominent researchers and producers of products with bioactive compounds derived from fungi in the last five years have been in North America and Asia, according to the Derwent Innovations Index database. This phenomenon can be explained by a linear increase in the global market trend, mainly in emerging countries such as China, to transform abundant and cheap substrates and natural resources into value-added products through bioprocesses. In this way, a resource that is easy, quick, and cheap to grow, such as mushrooms, becomes a raw material for high-value products in the pharmaceutical natural products market [195].

On the other hand, moving forward to the 21st century, the peak of publications related to the topic was more specifically in the last five years, with the highest peak of patent filings identified in the year 2022, post-pandemic. However, in the last two years, the number of patents applied to the pharmaceutical sector has decreased (Figure 4b). This could be due to the post-pandemic period, where concerns about collective health have reduced, and the trend has advanced towards environmental, climate, and sustainable development concerns [196].

The main patent depositors in the last five years were Hunan Ansen Biotechnology Co., Ltd. (Zhuzhou, China), Changde Jizhi Biotechnology Ltd., Co. (Hunan, China), and Shanghai Cheermore Biotechnology Co., Ltd. (Shanghai, China). Both companies develop food products or medicines linked to pharmaceutical and medicine manufacturing, dietetic foods adapted for medical purposes, or high-quality international food raw materials and related application technologies [197].

The patent CN114887052A assigned to the company Changde Jizhi Biotechnology Ltd., Co. claims several components to assist in the treatment of cardiovascular diseases through a multivitamin complex composed of several compounds, including *Cordyceps sinensis* (currently *Ophiocordyceps sinensis*) leaves and *Agaricus* sp. peptides. The multivitamin can improve the medicinal effect of cardiovascular disease treatments by increasing immunity, quickly balancing nutrition, and supplementing energy [198].

Hunan Hanzhen Biotechnology Co., Ltd.'s patent CN112315973A refers to developing anticancer drugs with the selenoside-III polysaccharide specific to the colon cancer-resistant

mushroom *Pleurotus ostreatus*. The polysaccharide selenoside-III can kill cancer cells and simultaneously does not damage normal cells by specifically promoting apoptosis of HCT116 cells [199].

Shanghai Cheermore Biotechnology Co., Ltd.'s patent CN110638687A concerns polysaccharides from the mushroom *Lentinula edodes*. Such a composition, a paste or aqueous gel, prevents inflammation and skin aging. Its mechanism of action focuses on improving the skin's water retention properties, increasing collagen content in the cortex, and improving skin elasticity [200].

As can be seen in Figure 4c, the patents filed in the last five years have been divided into applications for disorders of the nervous system; therapy against multiple types of cancer; treatments against dermatological problems and anti-aging; and treatment for problems of the digestive and blood systems and numerous others, such as treatment against respiratory diseases, inflammation, immune diseases, obesity, influenza, COVID-19, cardiovascular diseases, etc.

In addition to the pharmacological applications, the presence of bioactive compounds in each patent was also analyzed, making it possible to see the predominance of certain compounds in relation to a specific pharmacological application. For example, bioproducts used to treat neurological and psychological disorders predominantly use alkaloids, like indole-alkylamines, in the form of pharmacological compositions in paste, encapsulated, liquid, or tablet form. Meanwhile, for treating cancerous disorders, polysaccharides, like β-glucan, make up the vast majority in the same formats as above or fungal extracts. For dermatological disorders, polysaccharides and alkaloids are used the most in gels, ointments, or fungal extracts.

Another point worth highlighting is that some patents, precisely 56, include more than one bioactive compound in their formulations, showing that joint action can be more efficient and effective than just one active ingredient. Patent US2023293610-A1, whose field of action is to treat a person with an inflammatory disease, has alkaloids (indole-alkylamines), phenols (mycophenolic acid), and terpenes (isopulegol) in its formulation. Of the most diverse mushrooms used, *Agaricus* sp. was the most prominent. The patent comprises methods of administering doses with at least one edible or medicinal mushroom or extract thereof, a cannabinoid, a terpene, a curcuminoid, and a flavonoid. Treating inflammation in this way involves the application of combined corticosteroids to suppress the immune response and slow the inflammation process [201].

Another great example is patent US2022331344-A1, deposited by Resurgent Biosciences Inc. The patent comprises a botanical extract of a psychotropic macrofungus in the case of several species and genera, such as *Agrocybe*, *Amanita*, *Conocybe*, *Panaeolus* (formerly *Copelandia*), *Coprinus*, *Entoloma*, and *Galerina*. The aim is to create a soluble tablet with a combination of psychoactive compounds such as psilocybin, psilocin, norpsilocin, baeocystin, norbaeocystin, aeruginascin, serotonin, bufotenine, β-carboline alkaloids, muscarine, muscimol, muscazone and ibotenic acid extracted from one or more psychotropic fungi. This pharmaceutical formulation can be used to treat drug addiction, obsessive–compulsive disorder, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, etc. Its active ingredient consists of cholinesterase inhibitors [202].

Another point that deserves attention is the most cited patent documents. Patent US2022304980-A1, which has 22 citations, relates to a measured dosage composition for treating neurological conditions such as anxiety, post-traumatic stress disorder, attention deficit disorders, depression, memory loss, dementia, cognitive dysfunction, hearing loss, vision loss, neurological pain, insomnia, erectile dysfunction, physiological pain or discomfort, or a combination thereof. Its active compounds include psilocybin, psilocin, baeocystin, norbaeocystin, salts and isomers, and combinations. Patented by Sw Holdings Inc., the active compounds were extracted from mushrooms of the genera *Panaeolus*, *Copelandia*, and *Psilocybe*. Its operating mechanism includes alkaloids acting on the central nervous system, altering brain function, and resulting in temporary changes in perception, mood, consciousness, and behavior [203].

The patent US2022273680-A1, which has ten citations, also refers to a method through a liquid mixture with serotonin for preventing or treating various psychological disorders, such as depression, psychotic disorders, schizophrenia, and bipolar I disorder, among others. Its active biocompounds are psilocybine, psilocin, baeocystine, norbaeocystine, lysergide (LSD), dimethyltryptamine, carboxamidotryptamine, ibogaine, and 3,4-methylenedioxy-methamphetamine. Patented by the University of Maryland in Baltimore, psychoactive substances can be extracted from numerous species of mushrooms, including the genera *Psilocybe*, *Gymnopilus*, *Panaeolus*, *Copelandia*, *Hypholoma*, *Pluteus*, *Inocybe*, *Conocybe*, *Panaeolina*, *Gerronema*, *Agrocybe*, *Galerina*, and *Mycena*. Its mechanism of action consists of acting on serotonin receptors in the nervous system of the person being treated and can be ingested via pill, tablet, or liquid [204].

Finally, the patent US2023021957-A1 has nine citations. It has a scope of functions for treating compulsive eating disorders, aiding or causing weight loss, or treating obesity or a complication associated with obesity. Its active ingredients are indole alkylamines with their psychoactive effects. Patented by Neonmind Biosciences Inc., its alkaloid compounds come from mushrooms of the genus *Psilocybe*, where the active ingredients such as psilocin, psilocybin, and their analogs are manufactured through dry mushroom powder and an analog of psilocin or purified psilocybin is manufactured synthetically, 4-thiol-dimethyltryptamine, 1-methylpsilocin, 4-fluoro-N, N-dimethyltryptamine, O-acetylpsilocin, 4-hydroxy-N-methyl-N-isopropyltryptamine or 4-hydroxy-N-methyl-N-ethyltryptamine. This alkaloid will act on selected serotonin receptors [205].

10. Commercial Products with Pharmaceutical Properties Obtained from Macromycetes

Mushrooms have a long history of use in traditional medicine, particularly in Asian countries. They have been found to possess a wide range of medicinal properties. Mushrooms are a rich source of bioactive compounds, with over 100 medicinal functions identified. Further research is needed to explore the full range of applications of mushrooms as a source of pharmaceuticals [206].

A number of products have been developed for therapeutic and commercial use, primarily comprising polysaccharides, with β-glucans being a particularly prominent example. These include polysaccharide peptide (PSP) and krestin (PSK) from *Trametes versicolor*; lentinan isolated from *Lentinula edodes*; schizophyllan (also known as Sonifilan, Sizof), and so on. Iran, or SPG, is derived from *Schizophyllum commune*; Befungin is extracted from *Inonotus obliquus*; D-fraction is derived from *Grifola frondosa*; GLPS polysaccharide fraction is derived from *Ganoderma lucidum*; and active hexose correlated compound and other substances are also present [207].

Pandey et al. [208] presented the results of their investigation into commercial mushroom-derived pharmaceutical products. These include *Ganoderma lucidum*, which has been produced in three different forms, including a product with wound-healing and anti-inflammatory activity, produced by *CV Skinlabs*. The first product is Abs, U.S., which contains anti-oxidative properties. It is produced by *La Bella Figura* Gentle Enzyme Cleanser, Italia. The second product is called California Gold, and the last is called Immune Duo. Both products contain immune-system-strengthening activity and are derived from *Agaricus bisporus*.

Another mushroom utilized in the production of the product known as "Krestin" (β-glucan derived) is *Coriolus versicolor* (currently *Trametes versicolor*). This product is prescribed as an adjuvant in cancer and antitumor treatment and is produced by the Japanese company Sankio, Kureha. A product derived from *L. edodes*, produced by the Chinese company ShenYuan ChemPharm Co., Ltd. C. (Xiaogan, China), with the commercial brand XiaoGan [209], is a multifunctional anti-cancer, anti-oxidative, wound-healing, and immunomodulating agent.

Once more, two commercial products are presented as examples of immune-strengthening activity. The first is a product called *Mushroom 8-Plex Powder*, produced by Zhou Nutrition and containing fermented and organic mushrooms. The second is a product produced by

Source Naturals, called Mushroom Immune Defense, which contains a combination of 16 mushroom mycelia biomass. Finally, we consider a product with antioxidant properties that contains beta glucan derived from *Schizophyllum commune*, a fungus native (cosmopolitan) to the Czech Republic. This product is manufactured by *Contipro* A.S. [208].

The beneficial compounds found in mushroom types such as Reishi, Shiitake, Turkey tail, Chaga, and Maitake are causing a stir in the food world because they help regulate blood sugar and heart health. Because of their umami flavor and potential health advantages, these mushrooms are utilized in a variety of products, including capsules, powders, tinctures, and infused goods like coffee and tea. In order to satisfy customer needs and adhere to product registration and clearance procedures for medicinal or supplement goods in the food and beverage, dietary supplement, and pharmaceutical applications, the sector is also concentrating on sustainability and organic practices [210,211].

Another area of pharmacological interest is the use of mushroom-derived bioactive compounds. These include neurotrophic substances, which are synthesized from tryptophan as a secondary metabolite in some mushroom species. The most well-known and researched example is psilocybin. There has been a recent resurgence of interest in this molecule as a potential treatment for a range of common psychiatric disorders, including major depression and obsessive–compulsive disorder [212]. Currently, several developed countries, including the United States and Australia, have approved the use of psilocybin as an alternative treatment for mental illnesses [213]. Table 4 provides a summary of other products, their active ingredients, characteristics, and the companies that produce them.

The market for medicinal mushrooms is expected to expand by USD 5.94 billion at a compound yearly growth rate of 9.96% between 2022 and 2027. Several key factors contribute to the growth of the medicinal mushroom market [214]. One such factor is the growing need for goods produced from mushrooms, which is being driven by factors such as changing customer preferences and growing awareness of their health benefits [215]. The industry is also benefiting from the rising acceptance of online purchasing, which has made these products more accessible to a wider clientele. The industry is growing faster as a result of its development into uncharted territory. A significant proportion of therapeutic mushroom claims are derived from the extrapolation of cell cultures.

A significant number of businesses had previously received warnings for using the term "medical mushrooms" and making health claims for their products that contain mushrooms [214]. Despite the existence of compelling evidence for the health benefits of certain mushroom products, the industry is constrained by a number of factors: (a) the extensive array of nutraceuticals currently available on the market; (b) the absence of standardized production and testing protocols that are necessary to guarantee product quality; and (c) the fact that the majority of medicinal products derived from mushrooms do not contain a single chemically defined molecule that is employed in conventional pharmacological treatments, rendering them neither pharmaceuticals nor nutraceuticals (food/functional food).

While some mushrooms, such as *Ganoderma lucidum*, are believed to hold the key to curing all human diseases, such assertions are exaggerated [214]. No known treatment has this ability, not even conventional or alternative medicine. While it is inaccurate to view products made from mushrooms as a replacement for contemporary medications, they do occupy a unique category. In certain instances, they enhance overall health and act in conjunction with other therapies [216,217].

A significant number of nations have conducted research into the medicinal properties of mushrooms. However, most of these studies have focused on pre-clinical investigations, which involve the use of chemicals, enzymes, and animal models to screen for bioactivity. A considerable number of these investigations have been conducted using human cells in culture, but many are still in the pre-clinical phase or have not yet reached clinical trial stages I, II, or III [214]. To demonstrate the safety and efficacy of medicinal mushrooms, high-quality, long-term, randomized, double-blind, placebo-controlled clinical

studies—including sizable population studies—are essential for producing statistically significant results.

Table 4. Biological properties of mushrooms.

Compounds/Origin	Biological Property	Type of Disease	Model	Company	Reference
Mico Rei	Food supplement with the highest concentration of active ingredients from Reishi (*Ganoderma lucidum*), "the mushroom of eternal youth".	-	The product contains alpha, beta and D-glucans, triterpenoid compounds, ergosterol, ganoderic acids (A, F, C2 and D) and alpha-linolenic acid C18:3n6.	Hifas da Terra (E.U)	[218]
Mico-Five	Food supplement with the highest concentration of active ingredients from Chaga, Reishi, Maitake, Shiitake and Sun Mushroom.	Greater activation of host cell receptors (high concentration of immunomodulatory compounds).	The product contains organic extract, *Ganoderma lucidum*, *Lentinula edodes*, *Grifola frondosa*, *Agaricus blazei*, *Inonotus obliquus*.	Hifas da Terra (E.U)	[219]
Mico-Mix	Powerful formula of organic Shiitake, Reishi and Maitake extracts. This product supplement has alpha, beta and D-glucans, ergosterol, ganoderic acid, grifolan and lentinan.	Mico-Mix supported a phase of insulin resistance, bringing it under control well.	The product has alpha, beta and D-glucans, ergosterol, ganoderic acid, grifolan and lentinan.	Hifas da Terra (E.U)	[220]
The Real Thing—Medical Mushrooms 60s	-	The product helps boosting immunity, assists in providing cyto protective activity and helps maintain healthy cellular function.	The product has *G. lucidum*, *A. blazei*, *C. versicolor*, *L. edodes*, *G. frondosa*, *I. obliquus*, *C. militaris*, *H. erinaceus*, *P. linteus*, *A. auricula*, *P. eryngii*, *P. ostreatus*	Wellness-Warehouse	[221]
Agarikon.1	Myko San has been the leader in producing high-quality medicinal mushroom supplements for promoting health. Our expert-developed, scientifically-tested medicinal mushroom extract blends feature the most important medicinal mushrooms, including shiitake (*Lentinula edodes*), reishi (*Ganoderma lucidum*), maitake (*Grifola frondosa*), turkey tail (*Trametes versicolor*) and many others.	Agarikon.1 is a potent medicinal mushroom extract blend scientifically formulated for patients with cancer and other critical conditions.	The product contains extracts from edible and medicinal mushrooms *Ganoderma lucidum* (reishi), *Lentinula edodes* (shiitake), *Grifola* frondosa (maitake), *Agaricus blazei* Murill (=*A. brasiliensis* = *A. subrufescens*), *Trametes versicolor* (turkey tail) and *Pleurotus ostreatus* (oyster mushroom). The addition of immunity-boosting vitamin C enhances the absorption of the mushroom extracts in Agarikon.1.	Mykosan	[222]

11. Conclusions

Mushrooms have been considered as true natural pharmaceutical factories since ancient times. Many recent studies over the last 50 years have proven the production and characterization of these compounds produced by macromycetes cells. Many medicinal effects of these bioactive compounds have been proven by research at a preliminary, preclinical level in animal models and in in vivo and ex vivo studies. Some clinical studies have already been carried out, but modern science cannot yet categorically state that these effects are similar to modern medicine and its treatments. Despite this, there has been a growing interest in mushrooms as medicines, nutraceuticals and cosmeceuticals in recent

years, both due to the marketing carried out by certain segments and the dissemination of information via the internet. This has generated a significant number of patents in the field, as well as a market worth billions of dollars around the world, which will only grow in the coming years. If we take into account the number of classes of compounds, their plurality of described molecules, and the immense diversity of mushroom species not yet explored, we can conclude that this market is still only in its infancy. Robust studies in clinical and (meta)population trials, with effective and safe methods, as well as modern, cheap and effective in silico molecular analysis tools will allow for exponential growth of discoveries and their diverse applications as new drugs of interest.

Author Contributions: W.J.M.-B.: conceptualization, writing—original draft preparation and editing; E.M.M.: writing—original draft preparation; R.P.: conceptualization, writing—original draft preparation; J.L.S.: writing—original draft preparation; D.O.T.: writing—review and editing; M.C.M.: writing—original draft preparation; R.L.V.: conceptualization, writing—original draft preparation; G.A.d.R.: writing—original draft preparation; C.R.: conceptualization, writing—original draft preparation; S.G.K.: writing—original draft preparation and editing; C.R.S.: conceptualization, resources, supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the National Council of Technological and Scientific Development (CNPq) (grant number: 440138/2022-1) and the Coordination for the Improvement of Higher Education Personnel (CAPES), PNPD Program.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Si, J.; Meng, G.; Wu, Y.; Ma, H.F.; Cui, B.K.; Dai, Y.C. Medium Composition Optimization, Structural Characterization, and Antioxidant Activity of Exopolysaccharides from the Medicinal Mushroom Ganoderma Lingzhi. *Int. J. Biol. Macromol.* **2019**, *124*, 1186–1196. [CrossRef] [PubMed]
2. Zavadinack, M.; de Lima Bellan, D.; da Rocha Bertage, J.L.; da Silva Milhorini, S.; da Silva Trindade, E.; Simas, F.F.; Sassaki, G.L.; Cordeiro, L.M.C.; Iacomini, M. An α-D-Galactan and a β-D-Glucan from the Mushroom Amanita Muscaria: Structural Characterization and Antitumor Activity against Melanoma. *Carbohydr. Polym.* **2021**, *274*, 118647. [CrossRef] [PubMed]
3. Zhou, J.; Chen, M.; Wu, S.; Liao, X.; Wang, J.; Wu, Q.; Zhuang, M.; Ding, Y. A Review on Mushroom-Derived Bioactive Peptides: Preparation and Biological Activities. *Food Res. Int.* **2020**, *134*, 109230. [CrossRef] [PubMed]
4. Valverde, M.E.; Hernández-Pérez, T.; Paredes-López, O. Edible Mushrooms: Improving Human Health and Promoting Quality Life. *Int. J. Microbiol.* **2015**, *2015*, 376387. [CrossRef] [PubMed]
5. Kimatu, B.M.; Fang, D.; Zhao, L.; Hu, Q. *Agaricus bisporus* Peptide Fractions Confer Cytoprotective Ability against Hydrogen Peroxide-Induced Oxidative Stress in HepG2 and Caco-2 Cells. *J. Food Meas. Charact.* **2020**, *14*, 2503–2519. [CrossRef]
6. Pilafidis, S.; Diamantopoulou, P.; Gkatzionis, K.; Sarris, D. Valorization of Agro-Industrial Wastes and Residues through the Production of Bioactive Compounds by Macrofungi in Liquid State Cultures: Growing Circular Economy. *Appl. Sci.* **2022**, *12*, 11426. [CrossRef]
7. Hawksworth, D.L.; Lücking, R. Fungal Diversity Revisited: 2.2 to 3.8 Million Species. *Fungal Kingd.* **2017**, 79–95. [CrossRef]
8. Meenu, M.; Xu, B. Application of Vibrational Spectroscopy for Classification, Authentication and Quality Analysis of Mushroom: A Concise Review. *Food Chem.* **2019**, *289*, 545–557. [CrossRef]
9. Gargano, M.L.; van Griensven, L.J.L.D.; Isikhuemhen, O.S.; Lindequist, U.; Venturella, G.; Wasser, S.P.; Zervakis, G.I. Medicinal Mushrooms: Valuable Biological Resources of High Exploitation Potential. *Plant Biosyst.* **2017**, *151*, 548–565. [CrossRef]
10. Rathore, H.; Prasad, S.; Sharma, S. Mushroom Nutraceuticals for Improved Nutrition and Better Human Health: A Review. *PharmaNutrition* **2017**, *5*, 35–46. [CrossRef]
11. Sun, X.; Zhang, J. Bacterial Exopolysaccharides: Chemical Structures, Gene Clusters and Genetic Engineering. *Int. J. Biol. Macromol.* **2021**, *173*, 481–490. [CrossRef] [PubMed]
12. Moradali, M.F.; Mostafavi, H.; Ghods, S.; Hedjaroude, G.A. Immunomodulating and Anticancer Agents in the Realm of Macromycetes Fungi (Macrofungi). *Int. Immunopharmacol.* **2007**, *7*, 701–724. [CrossRef] [PubMed]
13. Yang, D.; Zhou, Z.; Zhang, L. An Overview of Fungal Glycan-Based Therapeutics. *Prog. Mol. Biol. Transl. Sci.* **2019**, *163*, 135–163. [CrossRef] [PubMed]
14. Choudhary, S. Characterization and Applications of Mushroom Exopolysaccharides. In *New and Future Developments in Microbial Biotechnology and Bioengineering: Recent Advances in Application of Fungi and Fungal Metabolites: Environmental and Industrial Aspects*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 171–181. [CrossRef]

15. Vetter, J. The Mushroom Glucans: Molecules of High Biological and Medicinal Importance. *Foods* **2023**, *12*, 1009. [CrossRef] [PubMed]
16. Bowman, S.M.; Free, S.J. The Structure and Synthesis of the Fungal Cell Wall. *BioEssays* **2006**, *28*, 799–808. [CrossRef] [PubMed]
17. Ruiz-Herrera, J.; Ortiz-Castellanos, L. Cell Wall Glucans of Fungi. A Review. *Cell Surf.* **2019**, *5*, 100022. [CrossRef] [PubMed]
18. Liu, J.J.; Hou, Y.K.; Wang, X.; Zhou, X.T.; Yin, J.Y.; Nie, S.P. Recent Advances in the Biosynthesis of Fungal Glucan Structural Diversity. *Carbohydr. Polym.* **2024**, *329*, 121782. [CrossRef] [PubMed]
19. Araújo-Rodrigues, H.; Sousa, A.S.; Relvas, J.B.; Tavaria, F.K.; Pintado, M. An Overview on Mushroom Polysaccharides: Health-Promoting Properties, Prebiotic and Gut Microbiota Modulation Effects and Structure-Function Correlation. *Carbohydr. Polym.* **2024**, *333*, 121978. [CrossRef] [PubMed]
20. Kim, Y.T.; Kim, E.H.; Cheong, C.; Williams, D.L.; Kim, C.W.; Lim, S.T. Structural Characterization of β-d-(1→3, 1→6)-Linked Glucans Using NMR Spectroscopy. *Carbohydr. Res.* **2000**, *328*, 331–341. [CrossRef]
21. Han, B.; Baruah, K.; Cox, E.; Vanrompay, D.; Bossier, P. Structure-Functional Activity Relationship of β-Glucans from the Perspective of Immunomodulation: A Mini-Review. *Front. Immunol.* **2020**, *11*, 658. [CrossRef]
22. Du, B.; Meenu, M.; Liu, H.; Xu, B. A Concise Review on the Molecular Structure and Function Relationship of β-Glucan. *Int. J. Mol. Sci.* **2019**, *20*, 4032. [CrossRef]
23. Ruiz-Herrera, J. Biosynthesis of β-Glucans in Fungi. *Antonie Leeuwenhoek* **1991**, *60*, 73–81. [CrossRef]
24. Klaus, A.; Kozarski, M.; Niksic, M.; Jakovljevic, D.; Todorovic, N.; Van Griensven, L.J.L.D. Antioxidative Activities and Chemical Characterization of Polysaccharides Extracted from the Basidiomycete Schizophyllum Commune. *LWT-Food Sci. Technol.* **2011**, *44*, 2005–2011. [CrossRef]
25. Rasmy, G.E.; Botros, W.; Kabeil, S.S.; Daba, A. Preparation of Glucan from Lentinula Edodes Edible Mushroom and Elucidation of Its Medicinal Value. *Aust. J. Basic Appl. Sci.* **2010**, *4*, 5717–5726.
26. Cha, Y.J.; Alam, N.; Lee, J.S.; Lee, K.R.; Shim, M.J.; Lee, M.W.; Kim, H.Y.; Shin, P.G.; Cheong, J.C.; Yoo, Y.B.; et al. Anticancer and Immunopotentiating Activities of Crude Polysaccharides from Pleurotus Nebrodensis on Mouse Sarcoma 180. *Mycobiology* **2012**, *40*, 236–243. [CrossRef]
27. Masuda, Y.; Togo, T.; Mizuno, S.; Konishi, M.; Nanba, H. Soluble β-Glucan from Grifola Frondosa Induces Proliferation and Dectin-1/Syk Signaling in Resident Macrophages via the GM-CSF Autocrine Pathway. *J. Leukoc. Biol.* **2012**, *91*, 547–556. [CrossRef]
28. Komatsu, N.; Okubo, S.; Kikumoto, S.; Kimura, K.; Saito, G.; Sakai, S. Host-Mediated Antitumor Action of Schizophyllan, a Glucan Produced by Schizophyllum Commune. *GANN Jpn. J. Cancer Res.* **1969**, *60*, 137–144. [CrossRef] [PubMed]
29. Zhang, L.; Guang Li, C.; Liang, H.; Reddy, N. Bioactive Mushroom Polysaccharides: Immunoceuticals to Anticancer Agents. *J. Nutraceuticals Food Sci.* **2017**, *2*, 1–5.
30. Sasaki, S.; Izumi, H.; Morimoto, Y.; Sakurai, K.; Mochizuki, S. Induction of Potent Cell Growth Inhibition by Schizophyllan/K-Ras Antisense Complex in Combination with Gemcitabine. *Bioorg. Med. Chem.* **2020**, *28*, 115668. [CrossRef]
31. Negahban, Z.; Shojaosadati, S.A.; Hamedi, S. A Novel Self-Assembled Micelles Based on Stearic Acid Modified Schizophyllan for Efficient Delivery of Paclitaxel. *Colloids Surf. B Biointerfaces* **2021**, *199*, 111524. [CrossRef]
32. Pirzadeh-Naeeni, S.; Mozdianfard, M.R.; Shojaosadati, S.A.; Khorasani, A.C.; Saleh, T. A Comparative Study on Schizophyllan and Chitin Nanoparticles for Ellagic Acid Delivery in Treating Breast Cancer. *Int. J. Biol. Macromol.* **2020**, *144*, 380–388. [CrossRef]
33. Wang, K.P.; Wang, J.; Li, Q.; Zhang, Q.L.; You, R.X.; Cheng, Y.; Luo, L.; Zhang, Y. Structural Differences and Conformational Characterization of Five Bioactive Polysaccharides from Lentinus Edodes. *Food Res. Int.* **2014**, *62*, 223–232. [CrossRef]
34. Chihara, G.; Hamuro, J.; Maeda, Y.Y.; Shiio, T.; Suga, T.; Takasuka, N.; Sasaki, T. Antitumor and Metastasis-Inhibitory Activities of Lentinan as an Immunomodulator: An Overview. *Cancer Detect. Prev. Suppl.* **1987**, *1*, 423–443. [PubMed]
35. Goodridge, H.S.; Reyes, C.N.; Becker, C.A.; Katsumoto, T.R.; Ma, J.; Wolf, A.J.; Bose, N.; Chan, A.S.H.; Magee, A.S.; Danielson, M.E.; et al. Activation of the Innate Immune Receptor Dectin-1 upon Formation of a 'Phagocytic Synapse'. *Nature* **2011**, *472*, 471–475. [CrossRef] [PubMed]
36. LeibundGut-Landmann, S.; Osorio, F.; Brown, G.D.; Sousa, C.R.E. Stimulation of Dendritic Cells via the Dectin-1/Syk Pathway Allows Priming of Cytotoxic T-Cell Responses. *Blood* **2008**, *112*, 4971–4980. [CrossRef] [PubMed]
37. Park, G.S.; Shin, J.; Hong, S.; Gopal, J.; Oh, J.W. Anticarcinogenic Potential of the Mushroom Polysaccharide Lentinan on Gastric and Colon Cancer Cells: Antiproliferative, Antitumorigenic, Mu-2-Related Death-Inducing Gene, MUDENG Ramifications. *J. Ind. Eng. Chem.* **2024**, *135*, 122–130. [CrossRef]
38. Jia, Z.; Chen, L.; Gu, D.; Li, X.; Wen, T.; Li, W. Lentinan-Loaded GelMA Hydrogel Accelerates Diabetic Wound Healing through Enhanced Angiogenesis and Immune Microenvironment Modulation. *Int. J. Biol. Macromol.* **2024**, *264*, 130716. [CrossRef] [PubMed]
39. Grün, C.H. Structure and Biosynthesis of Fungal α-Glucans. Ph.D. Thesis, Universiteit Utrecht, Utrecht, The Netherlands, 2003.
40. Reddy Shetty, P.; Batchu, U.R.; Buddana, S.K.; Sambasiva Rao, K.R.S.; Penna, S. A Comprehensive Review on α-D-Glucans: Structural and Functional Diversity, Derivatization and Bioapplications. *Carbohydr. Res.* **2021**, *503*, 108297. [CrossRef]
41. Patra, S.; Maity, P.; Chakraborty, I.; Sen, I.K.; Ghosh, D.; Rout, D.; Bhanja, S.K. Structural Studies of Immunomodulatory (1→3)-, (1→4)-α Glucan from an Edible Mushroom Polyporus Grammocephalus. *Int. J. Biol. Macromol.* **2021**, *168*, 649–655. [CrossRef]
42. Samuelsen, A.B.C.; Rise, F.; Wilkins, A.L.; Teveleva, L.; Nyman, A.A.T.; Aachmann, F.L. The Edible Mushroom Albatrellus Ovinus Contains a α-l-Fuco-α-d-Galactan, α-d-Glucan, a Branched (1→6)-β-d-Glucan and a Branched (1→3)-β-d-Glucan. *Carbohydr. Res.* **2019**, *471*, 28–38. [CrossRef]

43. Palacios, I.; García-Lafuente, A.; Guillamón, E.; Villares, A. Novel Isolation of Water-Soluble Polysaccharides from the Fruiting Bodies of *Pleurotus ostreatus* Mushrooms. *Carbohydr. Res.* **2012**, *358*, 72–77. [CrossRef] [PubMed]
44. Smiderle, F.R.; Sassaki, G.L.; Van Arkel, J.; Iacomini, M.; Wichers, H.J.; Van Griensven, L.J.L.D. High Molecular Weight Glucan of the Culinary Medicinal Mushroom *Agaricus bisporus* Is an α-Glucan That Forms Complexes with Low Molecular Weight Galactan. *Molecules* **2010**, *15*, 5818–5830. [CrossRef] [PubMed]
45. Milhorini, S.d.S.; Smiderle, F.R.; Biscaia, S.M.P.; Rosado, F.R.; Trindade, E.S.; Iacomini, M. Fucogalactan from the Giant Mushroom Macrocybe Titans Inhibits Melanoma Cells Migration. *Carbohydr. Polym.* **2018**, *190*, 50–56. [CrossRef] [PubMed]
46. Gao, F.; Luo, L.; Zhang, L. A New Galactoglucomannan from the Mycelium of the Medicinal Parasitic Fungus Cordyceps Cicadae and Its Immunomodulatory Activity In Vitro and In Vivo. *Molecules* **2023**, *28*, 3867. [CrossRef] [PubMed]
47. Chen, P.X.; Wang, S.; Nie, S.; Marcone, M. Properties of Cordyceps Sinensis: A Review. *J. Funct. Foods* **2013**, *5*, 550–569. [CrossRef] [PubMed]
48. Chen, Y.; Liu, D.; Wang, D.; Lai, S.; Zhong, R.; Liu, Y.; Yang, C.; Liu, B.; Sarker, M.R.; Zhao, C. Hypoglycemic Activity and Gut Microbiota Regulation of a Novel Polysaccharide from Grifola Frondosa in Type 2 Diabetic Mice. *Food Chem. Toxicol.* **2019**, *126*, 295–302. [CrossRef] [PubMed]
49. Devi, P.V.; Islam, J.; Narzary, P.; Sharma, D.; Sultana, F. Bioactive Compounds, Nutraceutical Values and Its Application in Food Product Development of Oyster Mushroom. *J. Future Foods* **2024**, *4*, 335–342. [CrossRef]
50. Hamza, A.; Mylarapu, A.; Krishna, K.V.; Kumar, D.S. An Insight into the Nutritional and Medicinal Value of Edible Mushrooms: A Natural Treasury for Human Health. *J. Biotechnol.* **2024**, *381*, 86–99. [CrossRef]
51. Sonawane, H.; Arya, S.; Ghole, V.; Apte, K.; Shelke, D.; Chaskar, M. Hypoglycemic and Anticataract Activity of Crude Exopolysaccharides of Medicinal Mushroom Phellinus Badius on Streptozotocin-Induced Diabetic Rats and Goat Eye Lenses Respectively. *Bioact. Carbohydr. Diet. Fibre* **2020**, *24*, 100241. [CrossRef]
52. Abdel-Monem, N.M.; El-Saadani, M.A.; Daba, A.S.; Saleh, S.R.; Aleem, E. Exopolysaccharide-Peptide Complex from Oyster Mushroom (*Pleurotus ostreatus*) Protects against Hepatotoxicity in Rats. *Biochem. Biophys. Rep.* **2020**, *24*, 100852. [CrossRef]
53. Lidbecq, C. IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) Nomenclature and Symbolism for Amino Acids and Peptides—Recommendations 1983. *Eur. J. Biochem.* **1984**, *138*, 9–37.
54. Landi, N.; Clemente, A.; Pedone, P.V.; Ragucci, S.; Di Maro, A. An Updated Review of Bioactive Peptides from Mushrooms in a Well-Defined Molecular Weight Range. *Toxins* **2022**, *14*, 84. [CrossRef] [PubMed]
55. Wang, B.; Shi, Y.; Lu, H.; Chen, Q. A Critical Review of Fungal Proteins: Emerging Preparation Technology, Active Efficacy and Food Application. *Trends Food Sci. Technol.* **2023**, *141*, 104178. [CrossRef]
56. Li, H.; Gao, J.; Zhao, F.; Liu, X.; Ma, B. Bioactive Peptides from Edible Mushrooms—The Preparation, Mechanisms, Structure—Activity Relationships and Prospects. *Foods* **2023**, *12*, 2935. [CrossRef] [PubMed]
57. Dong, Y.; Qi, G.; Yang, Z.; Wang, H.; Wang, S.; Chen, G. Preparation, Separation and Antioxidant Properties of Hydrolysates Derived from Grifola Frondosa Protein. *Czech J. Food Sci.* **2015**, *33*, 500–506. [CrossRef]
58. Kimatu, B.M.; Zhao, L.; Biao, Y.; Ma, G.; Yang, W.; Pei, F.; Hu, Q. Antioxidant Potential of Edible Mushroom (*Agaricus bisporus*) Protein Hydrolysates and Their Ultrafiltration Fractions. *Food Chem.* **2017**, *230*, 58–67. [CrossRef] [PubMed]
59. Farzaneh, P.; Khanahamadi, M.; Ehsani, M.R.; Sharifan, A. Bioactive Properties of *Agaricus bisporus* and *Terfezia claveryi* Proteins Hydrolyzed by Gastrointestinal Proteases. *LWT* **2018**, *91*, 322–329. [CrossRef]
60. Agyei, D.; Ongkudon, C.M.; Wei, C.Y.; Chan, A.S.; Danquah, M.K. Bioprocess Challenges to the Isolation and Purification of Bioactive Peptides. *Food Bioprod. Process.* **2016**, *98*, 244–256. [CrossRef]
61. Ulug, S.K.; Jahandideh, F.; Wu, J. Novel Technologies for the Production of Bioactive Peptides. *Trends Food Sci. Technol.* **2021**, *108*, 27–39. [CrossRef]
62. Wu, Q.; Li, Y.; Peng, K.; Wang, X.L.; Ding, Z.; Liu, L.; Xu, P.; Liu, G.Q. Isolation and Characterization of Three Antihypertension Peptides from the Mycelia of Ganoderma Lucidum (Agaricomycetes). *J. Agric. Food Chem.* **2019**, *67*, 8149–8159. [CrossRef]
63. Choi, H.S.; Cho, H.Y.; Yang, H.C.; Ra, K.S.; Suh, H.J. Angiotensin I-Converting Enzyme Inhibitor from Grifola Frondosa. *Food Res. Int.* **2001**, *34*, 177–182. [CrossRef]
64. Lau, C.C.; Abdullah, N.; Shuib, A.S.; Aminudin, N. Novel Angiotensin I-Converting Enzyme Inhibitory Peptides Derived from Edible Mushroom *Agaricus bisporus* (J.E. Lange) Imbach Identified by LC-MS/MS. *Food Chem.* **2014**, *148*, 396–401. [CrossRef] [PubMed]
65. Jang, J.H.; Jeong, S.C.; Kim, J.H.; Lee, Y.H.; Ju, Y.C.; Lee, J.S. Characterisation of a New Antihypertensive Angiotensin I-Converting Enzyme Inhibitory Peptide from Pleurotus Cornucopiae. *Food Chem.* **2011**, *127*, 412–418. [CrossRef] [PubMed]
66. Lau, C.C.; Abdullah, N.; Shuib, A.S. Novel Angiotensin I-Converting Enzyme Inhibitory Peptides Derived from an Edible Mushroom, Pleurotus Cystidiosus O.K. Miller Identified by LC-MS/MS. *BMC Complement. Altern. Med.* **2013**, *13*, 313. [CrossRef] [PubMed]
67. Feng, Q.; Lu, X.; Yuan, G.; Zhang, Q.; An, L. Effects of Agaricus Blazei Polypeptide on Cell Senescence by Regulation of Keap1/Nrf2/ARE and TLR4/NF-KBp65 Signaling Pathways and Its Mechanism in D-Gal-Induced NIH/3T3 Cells. *J. Funct. Foods* **2020**, *72*, 104037. [CrossRef]
68. Sun, J.; He, H.; Bi, J.X. Novel Antioxidant Peptides from Fermented Mushroom Ganoderma Lucidum. *J. Agric. Food Chem.* **2004**, *52*, 6646–6652. [CrossRef] [PubMed]

69. Shi, Y.; Sun, J.; He, H.; Guo, H.; Zhang, S. Hepatoprotective Effects of Ganoderma Lucidum Peptides against D-Galactosamine-Induced Liver Injury in Mice. *J. Ethnopharmacol.* **2008**, *117*, 415–419. [CrossRef] [PubMed]
70. He, H.; He, J.-P.; Sui, Y.-J.; Zhou, S.-Q.; Wang, J. The Hepatoprotective Effects of Ganoderma Lucidum Peptides against Carbon Tetrachloride-Induced Injury in Mice. *J. Food Biochem.* **2008**, *32*, 628–641. [CrossRef]
71. Mishra, J.; Rajput, R.; Singh, K.; Puri, S.; Goyal, M.; Bansal, A.; Misra, K. Antibacterial Natural Peptide Fractions from Indian Ganoderma Lucidum. *Int. J. Pept. Res. Ther.* **2018**, *24*, 543–554. [CrossRef]
72. Bondaryk, M.; Staniszewska, M.; Zielińska, P.; Urbańczyk-Lipkowska, Z. Natural Antimicrobial Peptides as Inspiration for Design of a New Generation Antifungal Compounds. *J. Fungi* **2017**, *3*, 46. [CrossRef]
73. Mygind, P.H.; Fischer, R.L.; Schnorr, K.M.; Hansen, M.T.; Sönksen, C.P.; Ludvigsen, S.; Raventós, D.; Buskov, S.; Christensen, B.; De Maria, L.; et al. Plectasin Is a Peptide Antibiotic with Therapeutic Potential from a Saprophytic Fungus. *Nature* **2005**, *437*, 975–980. [CrossRef] [PubMed]
74. Lam, Y.W.; Ng, T.B.; Wang, H.X. Antiproliferative and Antimitogenic Activities in a Peptide from Puffball Mushroom Calvatia Caelata. *Biochem. Biophys. Res. Commun.* **2001**, *289*, 744–749. [CrossRef] [PubMed]
75. Ngai, P.H.K.; Zhao, Z.; Ng, T.B. Agrocybin, an Antifungal Peptide from the Edible Mushroom Agrocybe Cylindracea. *Peptides* **2005**, *26*, 191–196. [CrossRef] [PubMed]
76. Yu, Y.; Hu, Q.; Liu, J.; Su, A.; Xu, H.; Li, X.; Huang, Q.; Zhou, J.; Mariga, A.M.; Yang, W. Isolation, Purification and Identification of Immunologically Active Peptides from Hericium Erinaceus. *Food Chem. Toxicol.* **2021**, *151*, 112111. [CrossRef] [PubMed]
77. Ye, X.Y.; Ng, T.B. A Novel Peptide with Ribonuclease and Translation-Inhibitory Activities from Fruiting Bodies of the Oyster Mushroom *Pleurotus ostreatus*. *J. Pept. Sci.* **2002**, *8*, 235–240. [CrossRef] [PubMed]
78. Chu, K.T.; Xia, L.; Ng, T.B. Pleurostrin, an Antifungal Peptide from the Oyster Mushroom. *Peptides* **2005**, *26*, 2098–2103. [CrossRef] [PubMed]
79. Wang, J.; Liu, Y.M.; Cao, W.; Yao, K.W.; Liu, Z.Q.; Guo, J.Y. Anti-Inflammation and Antioxidant Effect of Cordymin, a Peptide Purified from the Medicinal Mushroom Cordyceps Sinensis, in Middle Cerebral Artery Occlusion-Induced Focal Cerebral Ischemia in Rats. *Metab. Brain Dis.* **2012**, *27*, 159–165. [CrossRef] [PubMed]
80. Zhang, Q.; Wu, C.; Wang, T.; Sun, Y.; Li, T.; Fan, G. Improvement of Biological Activity of Morchella Esculenta Protein Hydrolysate by Microwave-Assisted Selenization. *J. Food Sci.* **2019**, *84*, 73–79. [CrossRef] [PubMed]
81. Feng, T.; Wu, Y.; Zhang, Z.; Song, S.; Zhuang, H.; Xu, Z.; Yao, L.; Sun, M. Purification, Identification, and Sensory Evaluation of Kokumi Peptides from *Agaricus bisporus* Mushroom. *Foods* **2019**, *8*, 43. [CrossRef]
82. Kang, M.G.; Kim, Y.H.; Bolormaa, Z.; Kim, M.K.; Seo, G.S.; Lee, J.S. Characterization of an Antihypertensive Angiotensin I-Converting Enzyme Inhibitory Peptide from the Edible Mushroom Hypsizygus Marmoreus. *Biomed. Res. Int.* **2013**, *2013*, 283964. [CrossRef]
83. Lee, D.H.; Kim, J.H.; Park, J.S.; Choi, Y.J.; Lee, J.S. Isolation and Characterization of a Novel Angiotensin I-Converting Enzyme Inhibitory Peptide Derived from the Edible Mushroom Tricholoma Giganteum. *Peptides* **2004**, *25*, 621–627. [CrossRef] [PubMed]
84. Koo, K.-C.; Lee, D.-H.; Kim, J.-H.; Yu, H.-E.; Park, J.-S.; Lee, J.-S. Production and Characterization of Antihypertensive Angiotensin I-Converting Enzyme Inhibitor from Pholiota Adiposa. *J. Microbiol. Biotechnol.* **2006**, *16*, 757–763.
85. Geng, X.; Tian, G.; Zhang, W.; Zhao, Y.; Zhao, L.; Wang, H.; Ng, T.B. A Tricholoma Matsutake Peptide with Angiotensin Converting Enzyme Inhibitory and Antioxidative Activities and Antihypertensive Effects in Spontaneously Hypertensive Rats. *Sci. Rep.* **2016**, *6*, 24130. [CrossRef] [PubMed]
86. Sun, Y.; Hu, X.; Li, W. Antioxidant, Antitumor and Immunostimulatory Activities of the Polypeptide from Pleurotus Eryngii Mycelium. *Int. J. Biol. Macromol.* **2017**, *97*, 323–330. [CrossRef]
87. Wang, H.; Ng, T.B. Eryngin, a Novel Antifungal Peptide from Fruiting Bodies of the Edible Mushroom Pleurotus Eryngii. *Peptides* **2004**, *25*, 1–5. [CrossRef] [PubMed]
88. Wang, H.; Ng, T.B.; Liu, Q. Alveolarin, a Novel Antifungal Polypeptide from the Wild Mushroom Polyporus Alveolaris. *Peptides* **2004**, *25*, 693–696. [CrossRef] [PubMed]
89. Wong, J.H.; Ng, T.B.; Wang, H.; Sze, S.C.W.; Zhang, K.Y.; Li, Q.; Lu, X. Cordymin, an Antifungal Peptide from the Medicinal Fungus Cordyceps Militaris. *Phytomedicine* **2011**, *18*, 387–392. [CrossRef]
90. Wang, J.; Wang, H.X.; Ng, T.B. A Peptide with HIV-1 Reverse Transcriptase Inhibitory Activity from the Medicinal Mushroom Russula Paludosa. *Peptides* **2007**, *28*, 560–565. [CrossRef] [PubMed]
91. Ngai, P.H.K.; Wang, H.X.; Ng, T.B. Purification and Characterization of a Ubiquitin-like Peptide with Macrophage Stimulating, Antiproliferative and Ribonuclease Activities from the Mushroom Agrocybe Cylindracea. *Peptides* **2003**, *24*, 639–645. [CrossRef]
92. Abdelshafy, A.M.; Belwal, T.; Liang, Z.; Wang, L.; Li, D.; Luo, Z.; Li, L. A Comprehensive Review on Phenolic Compounds from Edible Mushrooms: Occurrence, Biological Activity, Application and Future Prospective. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 6204–6224. [CrossRef]
93. Zhou, Y.; Chu, M.; Ahmadi, F.; Agar, O.T.; Barrow, C.J.; Dunshea, F.R.; Suleria, H.A.R. A Comprehensive Review on Phytochemical Profiling in Mushrooms: Occurrence, Biological Activities, Applications and Future Prospective. *Food Rev. Int.* **2024**, *40*, 924–951. [CrossRef]
94. Michalak, A. Heavy Metals Toxicity Phenolic Compounds and Their Antioxidant Activity in Plants Growing under Heavy Metal Stress. *Pol. J. Environ. Stud.* **2006**, *15*, 523–530.

95. Çayan, F.; Deveci, E.; Tel-Çayan, G.; Duru, M.E. Identification and Quantification of Phenolic Acid Compounds of Twenty-Six Mushrooms by HPLC–DAD. *J. Food Meas. Charact.* **2020**, *14*, 1690–1698. [CrossRef]
96. Sommano, S.R.; Suksathan, R.; Sombat, T.; Seehanam, P.; Sirilun, S.; Ruksiriwanich, W.; Wangtueai, S.; Leksawasdi, N. Novel Perspective of Medicinal Mushroom Cultivations: A Review Case for 'Magic' Mushrooms. *Agronomy* **2022**, *12*, 3185. [CrossRef]
97. Pukalski, J.; Latowski, D. Secrets of Flavonoid Synthesis in Mushroom Cells. *Cells* **2022**, *11*, 3052. [CrossRef] [PubMed]
98. Gil-Ramírez, A.; Pavo-Caballero, C.; Baeza, E.; Baenas, N.; Garcia-Viguera, C.; Marín, F.R.; Soler-Rivas, C. Mushrooms Do Not Contain Flavonoids. *J. Funct. Foods* **2016**, *25*, 1–13. [CrossRef]
99. Sifat, N.; Lovely, F.; Zihad, S.M.N.K.; Hossain, M.d.G.; Shilpi, J.A.; Grice, I.D.; Mubarak, M.S.; Uddin, S.J. Investigation of the Nutritional Value and Antioxidant Activities of Common Bangladeshi Edible Mushrooms. *Clin. Phytosci.* **2020**, *6*, 88. [CrossRef]
100. Ogidi, O.I.; Oguoma, L.M.O.; Adigwe, P.C.; Anthony, B.B. Phytochemical Properties and In-Vitro Antimicrobial Potency of Wild Edible Mushrooms (*Pleurotus ostreatus*) Obtained from Yenagoa, Nigeria. *J. Phytopharm.* **2021**, *10*, 180–184. [CrossRef]
101. Hwang, B.S.; Lee, I.K.; Yun, B.S. Phenolic Compounds from the Fungus Inonotus Obliquus and Their Antioxidant Properties. *J. Antibiot.* **2016**, *69*, 108–110. [CrossRef]
102. Guo, Y.J.; Deng, G.F.; Xu, X.R.; Wu, S.; Li, S.; Xia, E.Q.; Li, F.; Chen, F.; Ling, W.H.; Li, H. Bin Antioxidant Capacities, Phenolic Compounds and Polysaccharide Contents of 49 Edible Macro-Fungi. *Food Funct.* **2012**, *3*, 1195–1205. [CrossRef]
103. Ukaegbu, C.I.; Shah, S.R.; Hamid, H.A.; Alara, O.R.; Sarker, M.Z.I. Phenolic Compounds of Aqueous and Methanol Extracts of *Hypsizygus tessellatus* (Brown and White Var.) and *Flammulina velutipes* Caps: Antioxidant and Antiproliferative Activities. *Pharm. Chem. J.* **2020**, *54*, 170–183. [CrossRef]
104. Ziemlewska, A.; Wójciak, M.; Mroziak-Lal, K.; Zagórska-Dziok, M.; Bujak, T.; Nizioł-Łukaszewska, Z.; Szczepanek, D.; Sowa, I. Assessment of Cosmetic Properties and Safety of Use of Model Washing Gels with Reishi, Maitake and Lion's Mane Extracts. *Molecules* **2022**, *27*, 5090. [CrossRef] [PubMed]
105. Ekiz, E.; Oz, E.; Abd El-Aty, A.M.; Proestos, C.; Brennan, C.; Zeng, M.; Tomasevic, I.; Elobeid, T.; Çadırcı, K.; Bayrak, M.; et al. Exploring the Potential Medicinal Benefits of Ganoderma Lucidum: From Metabolic Disorders to Coronavirus Infections. *Foods* **2023**, *12*, 1512. [CrossRef] [PubMed]
106. Xu, J.; Gao, L.; Liang, H.; Chen, S. dong In Silico Screening of Potential Anti–COVID-19 Bioactive Natural Constituents from Food Sources by Molecular Docking. *Nutrition* **2021**, *82*, 111049. [CrossRef]
107. Taofiq, O.; Rodrigues, F.; Barros, L.; Barreiro, M.F.; Ferreira, I.C.F.R.; Oliveira, M.B.P.P. Mushroom Ethanolic Extracts as Cosmeceuticals Ingredients: Safety and Ex Vivo Skin Permeation Studies. *Food Chem. Toxicol.* **2019**, *127*, 228–236. [CrossRef] [PubMed]
108. Machado-Carvalho, L.; Martins, T.; Aires, A.; Marques, G. Optimization of Phenolic Compounds Extraction and Antioxidant Activity from Inonotus Hispidus Using Ultrasound-Assisted Extraction Technology. *Metabolites* **2023**, *13*, 524. [CrossRef] [PubMed]
109. Ge, J.; Liu, Z.; Zhong, Z.; Wang, L.; Zhuo, X.; Li, J.; Jiang, X.; Ye, X.Y.; Xie, T.; Bai, R. Natural Terpenoids with Anti-Inflammatory Activities: Potential Leads for Anti-Inflammatory Drug Discovery. *Bioorg. Chem.* **2022**, *124*, 105817. [CrossRef] [PubMed]
110. Wawrzyn, G.T.; Bloch, S.E.; Schmidt-Dannert, C. Discovery and Characterization of Terpenoid Biosynthetic Pathways of Fungi. In *Methods in Enzymology*; Academic Press Inc.: Cambridge, MA, USA, 2012; Volume 515, pp. 83–105.
111. Trepa, M.; Sułkowska-Ziaja, K.; Kała, K.; Muszyńska, B. Therapeutic Potential of Fungal Terpenes and Terpenoids: Application in Skin Diseases. *Molecules* **2024**, *29*, 1183. [CrossRef]
112. Intaraudom, C.; Boonyuen, N.; Supothina, S.; Tobwor, P.; Prabpai, S.; Kongsaeree, P.; Pittayakhajonwut, P. Novel Spiro-Sesquiterpene from the Mushroom Anthracophyllum Sp. BCC18695. *Phytochem. Lett.* **2013**, *6*, 345–349. [CrossRef]
113. Ishikawa, N.K.; Fukushi, Y.; Yamaji, K.; Tahara, S.; Takahashi, K. Antimicrobial Cuparene-Type Sesquiterpenes, Enokipodins C and D, from a Mycelial Culture of *Flammulina velutipes*. *J. Nat. Prod.* **2001**, *64*, 932–934. [CrossRef]
114. Zhao, Z.Z.; Zhao, K.; Chen, H.P.; Bai, X.; Zhang, L.; Liu, J.K. Terpenoids from the Mushroom-Associated Fungus Montagnula Donacina. *Phytochemistry* **2018**, *147*, 21–29. [CrossRef]
115. Wang, Y.; Bao, L.; Yang, X.; Li, L.; Li, S.; Gao, H.; Yao, X.S.; Wen, H.; Liu, H.W. Bioactive Sesquiterpenoids from the Solid Culture of the Edible Mushroom *Flammulina velutipes* Growing on Cooked Rice. *Food Chem.* **2012**, *132*, 1346–1353. [CrossRef] [PubMed]
116. Kanokmedhakul, S.; Lekphrom, R.; Kanokmedhakul, K.; Hahnvajanawong, C.; Bua-Art, S.; Saksirirat, W.; Prabpai, S.; Kongsaeree, P. Cytotoxic Sesquiterpenes from Luminescent Mushroom Neonothopanus Nambi. *Tetrahedron* **2012**, *68*, 8261–8266. [CrossRef]
117. Wang, S.J.; Bao, L.; Han, J.J.; Wang, Q.X.; Yang, X.L.; Wen, H.A.; Guo, L.D.; Li, S.J.; Zhao, F.; Liu, H.W. Pleurospiroketals A-E, Perhydrobenzannulated 5,5-Spiroketal Sesquiterpenes from the Edible Mushroom Pleurotus Cornucopiae. *J. Nat. Prod.* **2013**, *76*, 45–50. [CrossRef] [PubMed]
118. Clericuzio, M.; Cassino, C.; Corana, F.; Vidari, G. Terpenoids from Russula Lepida and *R. amarissima* (Basidiomycota, Russulaceae). *Phytochemistry* **2012**, *84*, 154–159. [CrossRef] [PubMed]
119. Liu, L.Y.; Li, Z.H.; Dong, Z.J.; Li, X.Y.; Su, J.; Li, Y.; Liu, J.K. Two Novel Fomannosane-Type Sesquiterpenoids from the Culture of the Basidiomycete Agrocybe Salicacola. *Nat. Prod. Bioprospect* **2012**, *2*, 130–132. [CrossRef]
120. Hiramatsu, F.; Murayama, T.; Koseki, T.; Shiono, Y. Strobilols A-D: Four Cadinane-Type Sesquiterpenes from the Edible Mushroom Strobilurus Ohshimae. *Phytochemistry* **2007**, *68*, 1267–1271. [CrossRef] [PubMed]
121. Yun, B.S.; Lee, I.K.; Cho, Y.; Cho, S.M.; Yoo, I.D. New Tricyclic Sesquiterpenes from the Fermentation Broth of Stereum Hirsutum. *J. Nat. Prod.* **2002**, *65*, 786–788. [CrossRef] [PubMed]

122. Han, J.; Chen, Y.; Bao, L.; Yang, X.; Liu, D.; Li, S.; Zhao, F.; Liu, H. Anti-Inflammatory and Cytotoxic Cyathane Diterpenoids from the Medicinal Fungus Cyathus Africanus. *Fitoterapia* **2013**, *84*, 22–31. [CrossRef]
123. Wang, S.J.; Li, Y.X.; Bao, L.; Han, J.J.; Yang, X.L.; Li, H.R.; Wang, Y.Q.; Li, S.J.; Liu, H.W. Eryngiolide A, a Cytotoxic Macrocyclic Diterpenoid with an Unusual Cyclododecane Core Skeleton Produced by the Edible Mushroom Pleurotus Eryngii. *Org. Lett.* **2012**, *14*, 3672–3675. [CrossRef]
124. Shibata, H.; Irie, A.; Morita, Y. New Antibacterial Diterpenoids from the Sarcodon Scabrosus Fungus. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2450–2452. [CrossRef] [PubMed]
125. Kamo, T.; Imura, Y.; Hagio, T.; Makabe, H.; Shibata, H.; Hirota, M. Anti-Inflammatory Cyathane Diterpenoids from Sarcodon Scabrosus. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1362–1365. [CrossRef] [PubMed]
126. Marcotullio, M.C.; Pagiotti, R.; Campagna, V.; Maltese, F.; Fardella, G.; Altinier, G.; Tubaro, A. Glaucopine C, a New Diterpene from the Fruiting Bodies of Sarcodon Glaucopus. *Nat. Prod. Res.* **2006**, *20*, 917–921. [CrossRef]
127. Marcotullio, M.C.; Pagiotti, R.; Maltese, F.; Oball-Mond Mwankie, G.N.; Hoshino, T.; Obara, Y.; Nakahata, N. Cyathane Diterpenes from Sarcodon Cyrneus and Evaluation of Their Activities of Neuritegenesis and Nerve Growth Factor Production. *Bioorg. Med. Chem.* **2007**, *15*, 2878–2882. [CrossRef] [PubMed]
128. Shi, X.W.; Liu, L.; Gao, J.M.; Zhang, A.L. Cyathane Diterpenes from Chinese Mushroom Sarcodon Scabrosus and Their Neurite Outgrowth-Promoting Activity. *Eur. J. Med. Chem.* **2011**, *46*, 3112–3117. [CrossRef] [PubMed]
129. Arpha, K.; Phosri, C.; Suwannasai, N.; Mongkolthanaruk, W.; Sodngam, S. Astraodoric Acids A-D: New Lanostane Triterpenes from Edible Mushroom Astraeus Odoratus and Their Anti-Mycobacterium Tuberculosis H37Ra and Cytotoxic Activity. *J. Agric. Food Chem.* **2012**, *60*, 9834–9841. [CrossRef]
130. Mothana, R.A.A.; Ali, N.A.A.; Jansen, R.; Wegner, U.; Mentel, R.; Lindequist, U.; Kreisel, H. Antiviral Lanostanoid Triterpenes from the Fungus Ganoderma Pfeifferi. *Fitoterapia* **2003**, *74*, 177–180. [CrossRef]
131. Niedermeyer, T.H.J.; Lindequist, U.; Mentel, R.; Gördes, D.; Schmidt, E.; Thurow, K.; Lalk, M. Antiviral Terpenoid Constituents of Ganoderma Pfeifferi. *J. Nat. Prod.* **2005**, *68*, 1728–1731. [CrossRef]
132. Lee, I.S.; Ahn, B.R.; Choi, J.S.; Hattori, M.; Min, B.; Bae, K.H. Selective Cholinesterase Inhibition by Lanostane Triterpenes from Fruiting Bodies of Ganoderma Lucidum. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6603–6607. [CrossRef]
133. Isaka, M.; Chinthanom, P.; Kongthong, S.; Srichomthong, K.; Choeyklin, R. Lanostane Triterpenes from Cultures of the Basidiomycete Ganoderma Orbiforme BCC 22324. *Phytochemistry* **2013**, *87*, 133–139. [CrossRef]
134. Kim, K.H.; Moon, E.; Choi, S.U.; Kim, S.Y.; Lee, K.R. Lanostane Triterpenoids from the Mushroom Naematoloma Fasciculare. *J. Nat. Prod.* **2013**, *76*, 845–851. [CrossRef] [PubMed]
135. Selli, S.; Guclu, G.; Sevindik, O.; Kelebek, H. Variations in the Key Aroma and Phenolic Compounds of Champignon (*Agaricus bisporus*) and Oyster (*Pleurotus ostreatus*) Mushrooms after Two Cooking Treatments as Elucidated by GC–MS-O and LC-DAD-ESI-MS/MS. *Food Chem.* **2021**, *354*, 129576. [CrossRef] [PubMed]
136. Ha, L.S.; Ki, D.W.; Kim, J.Y.; Choi, D.C.; Lee, I.K.; Yun, B.S. Dentipellin, a New Antibiotic from Culture Broth of Dentipellis Fragilis. *J. Antibiot.* **2021**, *74*, 538–541. [CrossRef] [PubMed]
137. Vásquez, R.; Rios, N.; Solano, G.; Cubilla-Rios, L. Lentinoids A–D, New Natural Products Isolated from Lentinus Strigellus. *Molecules* **2018**, *23*, 773. [CrossRef] [PubMed]
138. Wang, S.; Bao, L.; Zhao, F.; Wang, Q.; Li, S.; Ren, J.; Li, L.; Wen, H.; Guo, L.; Liu, H. Isolation, Identification, and Bioactivity of Monoterpenoids and Sesquiterpenoids from the Mycelia of Edible Mushroom Pleurotus Cornucopiae. *J. Agric. Food Chem.* **2013**, *61*, 5122–5129. [CrossRef] [PubMed]
139. Béni, Z.; Dékány, M.; Kovács, B.; Csupor-Löffler, B.; Zomborszki, Z.P.; Kerekes, E.; Szekeres, A.; Urbán, E.; Hohmann, J.; Ványolós, A. Bioactivity-Guided Isolation of Antimicrobial and Antioxidant Metabolites from the Mushroom Tapinella Atrotomentosa. *Molecules* **2018**, *23*, 1082. [CrossRef]
140. Badalyan, S.M.; Rapior, S. Perspectives of Biomedical Application of Macrofungi. *Curr. Trends Biomed. Eng. Biosci.* **2020**, *19*, 556024.
141. Xu, W.; Gavia, D.J.; Tang, Y. Biosynthesis of Fungal Indole Alkaloids. *Physiol. Behav.* **2015**, *176*, 100–106. [CrossRef]
142. Byrne, K.M.; Smith, S.K.; Ondeyka, J.G. Biosynthesis of Nodulisporic Acid A: Precursor Studies. *J. Am. Chem. Soc.* **2002**, *124*, 7055–7060. [CrossRef]
143. Dunn, M.F.; Niks, D.; Ngo, H.; Barends, T.R.M.; Schlichting, I. Tryptophan Synthase: The Workings of a Channeling Nanomachine. *Trends Biochem. Sci.* **2008**, *33*, 254–264. [CrossRef]
144. Cristino, A.S.; Williams, S.M.; Hawi, Z.; An, J.Y.; Bellgrove, M.A.; Schwartz, C.E.; Costa, L.D.F.; Claudianos, C. Neurodevelopmental and Neuropsychiatric Disorders Represent an Interconnected Molecular System. *Mol. Psychiatry* **2014**, *19*, 294–301. [CrossRef]
145. Plazas, E.; Faraone, N. Indole Alkaloids from Psychoactive Mushrooms: Chemical and Pharmacological Potential as Psychotherapeutic Agents. *Biomedicines* **2023**, *11*, 461. [CrossRef] [PubMed]
146. Charlson, F.; van Ommeren, M.; Flaxman, A.; Cornett, J.; Whiteford, H.; Saxena, S. New WHO Prevalence Estimates of Mental Disorders in Conflict Settings: A Systematic Review and Meta-Analysis. *Lancet* **2019**, *394*, 240–248. [CrossRef] [PubMed]
147. Leichsenring, F.; Steinert, C.; Ioannidis, J.P.A. Toward a Paradigm Shift in Treatment and Research of Mental Disorders. *Psychol. Med.* **2019**, *49*, 2111–2117. [CrossRef]
148. Guerra-Doce, E. Psychoactive Substances in Prehistoric Times: Examining the Archaeological Evidence. *Time Mind* **2015**, *8*, 91–112. [CrossRef]

149. Miller, M.J.; Albarracin-Jordan, J.; Moore, C.; Capriles, J.M. Chemical Evidence for the Use of Multiple Psychotropic Plants in a 1000-Year-Old Ritual Bundle from South America. *Proc. Natl. Acad. Sci. USA* **2019**, *166*, 11207–11212. [CrossRef] [PubMed]
150. Madsen, M.K.; Fisher, P.M.; Burmester, D.; Dyssegaard, A.; Stenbæk, D.S.; Kristiansen, S.; Johansen, S.S.; Lehel, S.; Linnet, K.; Svarer, C.; et al. Psychedelic Effects of Psilocybin Correlate with Serotonin 2A Receptor Occupancy and Plasma Psilocin Levels. *Neuropsychopharmacology* **2019**, *44*, 1328–1334. [CrossRef] [PubMed]
151. Kobayashi, M.; Kuzuyama, T. Recent Advances in the Biosynthesis of Carbazoles Produced by Actinomycetes. *Biomolecules* **2020**, *10*, 1147. [CrossRef] [PubMed]
152. Araújo, A.M.; Carvalho, F.; Bastos, M.d.L.; Guedes de Pinho, P.; Carvalho, M. The Hallucinogenic World of Tryptamines: An Updated Review. *Arch. Toxicol.* **2015**, *89*, 1151–1173. [CrossRef] [PubMed]
153. Dai, J.; Dan, W.; Schneider, U.; Wang, J. β-Carboline Alkaloid Monomers and Dimers: Occurrence, Structural Diversity, and Biological Activities. *Eur. J. Med. Chem.* **2018**, *157*, 622–656. [CrossRef]
154. Cao, R.; Peng, W.; Wang, Z.; Xu, A. β-Carboline Alkaloids: Biochemical and Pharmacological Functions. *Curr. Med. Chem.* **2007**, *14*, 479–500. [CrossRef]
155. Ziarani, G.M.; Moradi, R.; Lashgari, N.; Kruger, H.G. Carbazole Dyes. In *Metal-Free Synthetic Organic Dyes*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 109–116. ISBN 9780128156476.
156. Birari, R.; Roy, S.K.; Singh, A.; Bhutani, K.K. NPC Natural Product Communications. *Nat. Prod. Commun.* **2010**, *1*, 9–12.
157. Yaoita, Y.; Kikuchi, M.; Machida, K. Terpenoids and Sterols from Mushrooms. In *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, The Netherlands, 2015; Volume 44, pp. 1–32. ISBN 9780444634603.
158. Hu, Z.; He, B.; Ma, L.; Sun, Y.; Niu, Y.; Zeng, B. Recent Advances in Ergosterol Biosynthesis and Regulation Mechanisms in Saccharomyces Cerevisiae. *Indian J. Microbiol.* **2017**, *57*, 270–277. [CrossRef] [PubMed]
159. Rangsinth, P.; Sharika, R.; Pattarachotanant, N.; Duangjan, C.; Wongwan, C.; Sillapachaiyaporn, C.; Nilkhet, S.; Wongsirojkul, N.; Prasansuklab, A.; Tencomnao, T.; et al. Potential Beneficial Effects and Pharmacological Properties of Ergosterol, a Common Bioactive Compound in Edible Mushrooms. *Foods* **2023**, *12*, 2529. [CrossRef]
160. Baker, M.A.B.; Brown, A.J. A Detour to Sterol Synthesis. *Nat. Microbiol.* **2019**, *4*, 214–215. [CrossRef]
161. Papoutsis, K.; Grasso, S.; Menon, A.; Brunton, N.P.; Lyng, J.G.; Jacquier, J.C.; Bhuyan, D.J. Recovery of Ergosterol and Vitamin D2 from Mushroom Waste—Potential Valorization by Food and Pharmaceutical Industries. *Trends Food Sci. Technol.* **2020**, *99*, 351–366. [CrossRef]
162. Barreira, J.C.M.; Oliveira, M.B.P.P.; Ferreira, I.C.F.R. Development of a Novel Methodology for the Analysis of Ergosterol in Mushrooms. *Food Anal. Methods* **2014**, *7*, 217–223. [CrossRef]
163. Shao, S.; Hernandez, M.; Kramer, J.K.G.; Rinker, D.L.; Tsao, R. Ergosterol Profiles, Fatty Acid Composition, and Antioxidant Activities of Button Mushrooms as Affected by Tissue Part and Developmental Stage. *J. Agric. Food Chem.* **2010**, *58*, 11616–11625. [CrossRef] [PubMed]
164. Rangsinth, P.; Sillapachaiyaporn, C.; Nilkhet, S.; Tencomnao, T.; Ung, A.T.; Chuchawankul, S. Mushroom-Derived Bioactive Compounds Potentially Serve as the Inhibitors of SARS-CoV-2 Main Protease: An in Silico Approach. *J. Tradit. Complement. Med.* **2021**, *11*, 158–172. [CrossRef]
165. Dupont, S.; Fleurat-Lessard, P.; Cruz, R.G.; Lafarge, C.; Grangeteau, C.; Yahou, F.; Gerbeau-Pissot, P.; Abrahão Júnior, O.; Gervais, P.; Simon-Plas, F.; et al. Antioxidant Properties of Ergosterol and Its Role in Yeast Resistance to Oxidation. *Antioxidants* **2021**, *10*, 1024. [CrossRef] [PubMed]
166. Sillapachaiyaporn, C.; Rangsinth, P.; Nilkhet, S.; Ung, A.T.; Chuchawankul, S.; Tencomnao, T. Neuroprotective Effects against Glutamate-Induced Ht-22 Hippocampal Cell Damage and Caenorhabditis Elegans Lifespan/Healthspan Enhancing Activity of Auricularia Polytricha Mushroom Extracts. *Pharmaceuticals* **2021**, *14*, 1001. [CrossRef] [PubMed]
167. Yoo, M.S.; Shin, J.S.; Choi, H.E.; Cho, Y.W.; Bang, M.H.; Baek, N.I.; Lee, K.T. Fucosterol Isolated from Undaria Pinnatifida Inhibits Lipopolysaccharide- Induced Production of Nitric Oxide and pro-Inflammatory Cytokines via the Inactivation of Nuclear Factor-KB and P38 Mitogen-Activated Protein Kinase in RAW264.7 Macrophages. *Food Chem.* **2012**, *135*, 967–975. [CrossRef]
168. Huan, W.; Tianzhu, Z.; Yu, L.; Shumin, W. Effects of Ergosterol on COPD in Mice via JAK3/STAT3/NF-KB Pathway. *Inflammation* **2017**, *40*, 884–893. [CrossRef] [PubMed]
169. Nallathamby, N.; Guan-Serm, L.; Vidyadaran, S.; Malek, S.N.A.; Raman, J.; Sabaratnam, V. Ergosterol of Cordyceps Militaris Attenuates LPS Induced Inflammation in BV2 Microglia Cells. *Nat. Prod. Commun.-NPC* **2015**, *10*, 9–10. [CrossRef]
170. Hassan, S.; Dritsas, S.; O'Dwyer, S.T.; Aziz, O.; Sutton, P.; Wang, X.; Fish, R.; Renehan, A.G.; Wilson, M.; Selvasekar, C.; et al. Open versus Closed Technique for Administration of Heated Intraperitoneal Chemotherapy (HIPEC): Morbidity and Mortality Outcomes from a High-Volume Centre. *Eur. J. Surg. Oncol.* **2023**, *49*, 106924. [CrossRef]
171. Martínez-Montemayor, M.M.; Ling, T.; Suárez-Arroyo, I.J.; Ortiz-Soto, G.; Santiago-Negrón, C.L.; Lacourt-Ventura, M.Y.; Valentín-Acevedo, A.; Lang, W.H.; Rivas, F. Identification of Biologically Active Ganoderma Lucidum Compounds and Synthesis of Improved Derivatives That Confer Anti-Cancer Activities in Vitro. *Front. Pharmacol.* **2019**, *10*, 115. [CrossRef] [PubMed]
172. Li, X.; Wu, Q.; Xie, Y.; Ding, Y.; Du, W.W.; Sdiri, M.; Yang, B.B. Ergosterol Purified from Medicinal Mushroom Amauroderma Rude Inhibits Cancer Growth in Vitro and in Vivo by Up-Regulating Multiple Tumor Suppressors. *Oncotarget* **2015**, *6*, 17832–17846. [CrossRef]

173. Yazawa, Y.; Ikarashi, N.; Hoshino, M.; Kikkawa, H.; Sakuma, F.; Sugiyama, K. Inhibitory Effect of Ergosterol on Bladder Carcinogenesis Is Due to Androgen Signaling Inhibition by Brassicasterol, a Metabolite of Ergosterol. *J. Nat. Med.* **2020**, *74*, 680–688. [CrossRef]
174. Xiong, M.; Huang, Y.; Liu, Y.; Huang, M.; Song, G.; Ming, Q.; Ma, X.; Yang, J.; Deng, S.; Wen, Y.; et al. Antidiabetic Activity of Ergosterol from *Pleurotus ostreatus* in KK-Ay Mice with Spontaneous Type 2 Diabetes Mellitus. *Mol. Nutr. Food Res.* **2018**, *62*, 1700444. [CrossRef]
175. Mbambo, B.; Odhav, B.; Mohanlall, V. Antifungal Activity of Stigmasterol, Sitosterol and Ergosterol from Bulbine Natalensis Baker (Asphodelaceae). *J. Med. Plants Res.* **2012**, *6*, 5135–5141. [CrossRef]
176. Li, Y.; Song, Y.C.; Liu, J.Y.; Ma, Y.M.; Tan, R.X. Anti-Helicobacter Pylori Substances from Endophytic Fungal Cultures. *World J. Microbiol. Biotechnol.* **2005**, *21*, 553–558. [CrossRef]
177. Bu, F.; Song, X.; Zhao, X.; Wang, R.; Xie, Y.; Yu, L.; Yan, X. Advances in Micro/Nanodrug Delivery Systems for the Treatment of Helicobacter Pylori Infection: From Diagnosis to Eradication. *Appl. Mater. Today* **2024**, *37*, 102138. [CrossRef]
178. Yongxia, Z.; Jian, X.; Suyuan, H.; Aixin, N.; Lihong, Z. Isolation and Characterization of Ergosterol from Monascus Anka for Anti-Lipid Peroxidation Properties. *J. Mycol. Medicale* **2020**, *30*, 101038. [CrossRef] [PubMed]
179. Misgiati, M.; Widyawaruyanti, A.; Raharjo, S.J.; Sukardiman, S. Ergosterol Isolated from Agaricus Blazei Murill N-Hexane Extracts as Potential Anticancer MCF-7 Activity. *Pharmacogn. J.* **2021**, *13*, 418–426. [CrossRef]
180. Ikarashi, N.; Hoshino, M.; Ono, T.; Toda, T.; Yazawa, Y.; Sugiyama, K. A Mechanism by Which Ergosterol Inhibits the Promotion of Bladder Carcinogenesis in Rats. *Biomedicines* **2020**, *8*, 180. [CrossRef] [PubMed]
181. Umezawa, H.; Takeuchi, T.; Tanabe, O.; Iinuma, H. Carcinostatic Cpd. Basidalin. JP Patent 57047482A, 18 March 1982.
182. Kagome-Company. Appreciation, Nature and Corporate Openness. Available online: https://www.kagome.co.jp/english/vision.html (accessed on 20 April 2024).
183. Arimoto, Y.; Mori, Y.; Sakamoto, H.; Ishiguro, Y. Ischemic Brain Disease Improving Agent Containing Chroman Derivative as Active Component. JP Patent H09235226A, 29 February 1996.
184. Sugano, N.; Iizuka, C.; Maeda, H. Anticancer Agent Comprising Xylose Based Glycoprotein Obtained from Basidiomycetes Mycelium Incubated in Solid Culture Medium. JP Patent S58118519A, 14 July 1983.
185. Mizuno, T.; Kawagishi, H.; Hagiwara, T.; Nakamura, T. Ergosterol Derivative and Production Thereof. JP Patent 1246299A, 2 October 1989.
186. Ikemizu, S.; Konishi, H.; Hataya, C.; Kishimoto, M. Method for Producing Angiotensin Conversion-Inhibiting Enzyme-Containing Substance Originated from Basidiomycetes. JP Patent 1995238032A, 12 September 1995.
187. Niwa, K. Method of Strengthening Antitumor Activity of Crude Drug, Composition Containing Crude Drug for Strengthening Antitumor Activity, Method of Evaluating Antitumor Effectivity Treated by Crude Drug and Method of Evaluating Antitumor Effectivity of Crud Drug. JP Patent 2000159682A, 13 November 1998.
188. Nagatomo, S. Method for Extracting Antitumor Active Substance of Crude Drug. JP Patent 2008105972A, 24 October 2006.
189. Mulqueen, M.; Moran, M. Methods for Treating Dependence. International Application Published under the Patent Cooperation Treaty (PCT). WO2010124089A2, 28 October 2010.
190. Kirkland, J. Pharmaceutical Composition Useful for Treating Patient Suffering from Anxiety, Depression, and/or Other Mental Health Conditions, Comprises Deep Eutectic Solvent and One or More Active Pharmaceutical Ingredients Derived from Fungal Biomass. CA Patent 3186405A1, 14 July 2023.
191. Yoshida, H.; Sakai, S.; Inoue, S.; Kawagishi, H. Pharmaceutical Composition, Hyaluronic Acid Decomposition Inhibitor, Cosmetic, Chapped Skin or Dried Skin-Preventing Agent Each Comprising Extract of Tricholoma Orirubens, and New Compound Contained in Tricholoma Orirubens and Its Application. JP Patent 2005089391A, 19 September 2003.
192. Sato, T.; Ichinose, S.; Nishizawa, Y.; Kusuoku, H.; Shibuya, Y. Apoptosis Inhibitor. JP Patent 2005068061A, 22 August 2003.
193. Sun, A. Treating Malignancies and Viral Infections and Improving Immune Function Using Dietary Supplement of Soybean, Mushroom and Mung Bean. US Patent 20020127243A1, 10 January 2002.
194. Bahl, A.K.; Vercellotti, S.V.; Vercellotti, J.R.; Klein, E. Purified Beta Glucan Composition Useful for Treating Conditions Associated with Bone Loss or Low Bone Density, Particularly Osteoporosis, Paget's Disease Comprises Water Soluble Beta Glucan. US Patent 20080200429A1, 14 April 2008.
195. Vandenberghe, L.P.S.; Pandey, A.; Carvalho, J.C.; Letti, L.A.J.; Woiciechowski, A.L.; Karp, S.G.; Soccol, V.T.; Martínez-Burgos, W.J.; Penha, R.O.; Herrmann, L.W.; et al. Solid-State Fermentation Technology and Innovation for the Production of Agricultural and Animal Feed Bioproducts. *Syst. Microbiol. Biomanuf.* **2020**, *1*, 142–165. [CrossRef]
196. Rutjes, S.A.; Vennis, I.M.; Wagner, E.; Maisaia, V. Lukas Peintner Biosafety and Biosecurity Challenges during the COVID-19 Pandemic and Beyond. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1117316. [CrossRef] [PubMed]
197. Justia Trademarks. Featured Companies. Available online: https://trademarks.justia.com/ (accessed on 20 April 2024).
198. Xinqiao, H. Steam Equipment Multivitamin for Auxiliary Treatment of Cardiovascular Diseases and Preparation Method and Application Thereof. CN Patent 114887052A, 11 May 2022.
199. Zhong, S.; Zhang, Y.; Zhang, Z.; Deng, Z.; Shen, J. Application of Oyster Mushroom Polysaccharide Selenoside-III Anticancer Active Ingredient in Preparation of Medicine for Resisting Colon Cancer. CN Patent 112315973A, 11 November 2020.
200. Zhu, C.; Li, J. Composition Useful for Preventing Inflammation, Preventing Aging and Preparing Skin Care Composition Comprises Lentinus Edodes Mycelia Polysaccharide and Salvianic Acid A. CN Patent 110638687A, 23 August 2019.

201. Barnhill, S.D. Composition Used for Treating Human Suffering from Inflammatory Disease e.g., Achalasia, Addisons Disease, Adult Stills Disease, Agammaglobulinemia, Alopecia Areata, Comprises One/More Edible/Medicinal Mushrooms, Cannabinoids and Flavonoids. U.S. Patent 2023293610A1, 21 September 2023.
202. Greenbaum, E.; Bueno, J. Oral Formulations of Psychotropic Macrofungus Botanical Extracts with Mouthfeel Experience Enhancers. U.S. Patent 20220331344A1, 20 October 2022.
203. Arnold, C.M.; Bhatt, P.; Hartman, M.S. Metered Dosing Composition for Treating or Mitigating a Neurological, Physiological, or Mental Health Condition Such as Anxiety, Post-Traumatic Stress Disorder, Attention Deficit Disorders, Depression, Comprises Psychedelic Compounds. U.S. Patent 2022304980A1, 29 September 2021.
204. Thompson, S. Preventing or Treating Psychological Disorder, Comprises Administering Serotonin Agonist in Combination with Serotonin Receptor 2A Antagonist. U.S. Patent 2022273680A1, 1 September 2021.
205. White, P. Treating Compulsive Eating Disorder, Comprises Administering a Compound Comprising Psilocin, Psilocybin, or Their Analogs. U.S. Patent 2023021957A1, 26 January 2021.
206. Glamoclija, J.; Sokovic, M. Fungi a Source with Huge Potential for "Mushroom Pharmaceuticals". *Lek. Sirovine* **2017**, *37*, 50–56. [CrossRef]
207. Wasser, S. A Book Review: The Fungal Pharmacy: Medicinal Mushrooms of Western Canada. *Int. J. Med. Mushrooms* **2008**, *10*, 97–100. [CrossRef]
208. Pandey, A.T.; Pandey, I.; Hachenberger, Y.; Krause, B.C.; Haidar, R.; Laux, P.; Luch, A.; Singh, M.P.; Singh, A.V. Emerging Paradigm against Global Antimicrobial Resistance via Bioprospecting of Mushroom into Novel Nanotherapeutics Development. *Trends Food Sci. Technol.* **2020**, *106*, 333–344. [CrossRef]
209. Chem-Pharm Product Categories. 2020, p. 14970. Available online: https://Www.Chemicalbook.Com/ShowSupplierProductsList14970/0_EN.Htm (accessed on 20 April 2024).
210. Feng, T.; Cai, J.L.; Li, X.M.; Zhou, Z.Y.; Li, Z.H.; Liu, J.K. Chemical Constituents and Their Bioactivities of Mushroom Phellinus Rhabarbarinus. *J. Agric. Food Chem.* **2016**, *64*, 1945–1949. [CrossRef] [PubMed]
211. Parashar, U.K.; Kumar, V.; Bera, T.; Saxena, P.S.; Nath, G.; Srivastava, S.K.; Giri, R.; Srivastava, A. Study of Mechanism of Enhanced Antibacterial Activity by Green Synthesis of Silver Nanoparticles. *Nanotechnology* **2011**, *22*, 415104. [CrossRef] [PubMed]
212. Halford, B. Drug Companies Are Investing Big in Psychedelics, but Can They Engineer Out the Trip? 2022. Available online: https://cen.acs.org/pharmaceuticals/drug-development/Drug-companies-investing-big-psychedelics/100/i9 (accessed on 20 April 2024).
213. Chrysanthos, N.; Dow, A. Australia Becomes First Country to Recognise Psychedelics as Medicines. 2023. Available online: https://www.smh.com.au/politics/federal/australia-becomes-first-country-to-recognise-psychedelics-as-medicines-20230203-p5chs6.html (accessed on 20 April 2024).
214. Chang, S.; Buswell, J. Medicinal Mushrooms: Past, Present and Future. In *Biochemical Engineering and Biotechnology of Medicinal Mushrooms*; Springer: Cham, Switzerland, 2022; Volume 1, pp. 1–27.
215. Yadav, D.; Negi, P.S. Bioactive Components of Mushrooms: Processing Effects and Health Benefits. *Food Res. Int.* **2021**, *148*, 110559. [CrossRef] [PubMed]
216. Sheikha, A.F. Nutritional Profile and Health Benefits of Ganoderma lucidum "Lingzhi, Reishi, or Mannentake" as Functional Foods: Current Scenario and Future Perspectives. *Foods* **2019**, *11*, 1030. [CrossRef]
217. Ahmad, R.; Riaz, M.; Khan, A.; Aljamea, A.; Algheryafi, M.; Sewaket, D.; Alqathama, A. Ganoderma Lucidum (Reishi) an Edible Mushroom; a Comprehensive and Critical Review of Its Nutritional, Cosmeceutical, Mycochemical, Pharmacological, Clinical, and Toxicological Properties. *Phytother. Res.* **2021**, *35*, 6030–6062. [CrossRef]
218. Hifas-da-Terra Mico Rei (Reishi Extract) Capsules. 2021, pp. 2021–2025. Available online: https://hifasdaterra.com/en/product/mico-rei-extract-of-reishi/ (accessed on 20 April 2024).
219. Hifas-da-Terra Mico Five (Chaga, Reishi, Maitake, Shiitake, Sun Mushroom Capsules. 2019. Available online: https://hifasdaterra.com/en/product/mico-five-vit-c/ (accessed on 20 April 2024).
220. Hifas-da-Terra Mico Mix (Shiitake, Reishi, Maitake) Capsules. Natassia. 2023. Available online: https://hifasdaterra.com/en/product/mico-mix-extract-of-3-mushrooms/ (accessed on 20 April 2024).
221. Wellness-Warehouse The Real Thing—Medical Mushrooms 60s. Hifas-Da-Terra. 2024, Volume 184. Available online: https://www.wellnesswarehouse.com/the-real-thing-medical-mushrooms-60s-60s-00011120438103 (accessed on 20 April 2024).
222. Myko-San Myko-San. Superior Medicinal Mushrooms Extracts. 2020. Available online: https://mykosan.com/ (accessed on 20 April 2024).