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Medicinal Mushrooms: A Review of Bioactive Compounds, Pharmacological Mechanisms and the Translational Roadmap to Clinical Therapeutics

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ABSTRACT:

Mushrooms, which have gained intriguing recognition in ethnobotany due to their affordability and eco-friendliness, remain underutilized despite their potential as therapeutic agents. Abundant evidence supports their long-term effectiveness against various health disorders, including immunodeficiency, cancer, and metabolic diseases. However, their clinical applications have faced substantial limitations. We conducted a critical analysis of the existing key findings on mushroom bioactive compounds, such as polysaccharides, terpenoids, and phenolics, and explore the molecular mechanisms underlying their effective immunomodulatory, anticancer, antiviral, and metabolic-modulating activities. While highlighting the significant therapeutic prowess of mushrooms, we also examined the development pathway, identifying the key challenges in standardization, quality control, pharmacokinetics, toxicology, and regulatory frameworks. Our findings highlighted the convincing necessity for tailored research and effective development approaches to reconcile disparities between conventional applications, laboratory studies, and human trials, thus uncovering the rich pharmaceutical prospects of mushrooms for novel, holistic therapeutic models.

KEYWORDS:

Mushroom-derived compounds, Immunomodulation, Pharmacological properties, Therapeutic applications, Clinical translation, Regulatory frameworks

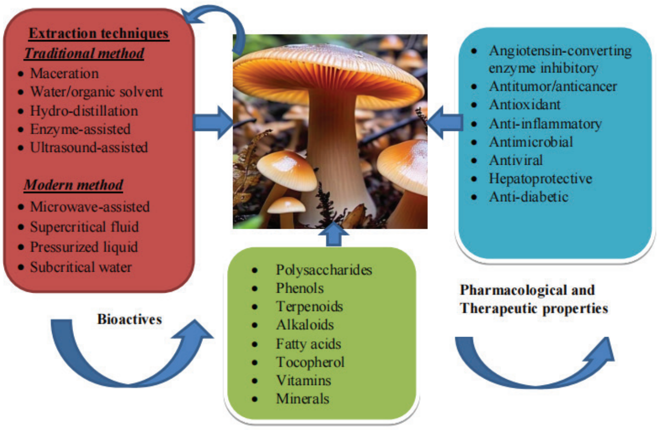

Fig. 1 Graphical abstract of the review

1. Introduction

The global spike in the quest for affordable and eco-friendly panacea for skyrocketing health-threatening diseases has stimulated research interest in novel sources with inherent prospective nutritional, industrial, and pharmaceutical benefits. Mushrooms have gained recognition as a potential source of nutrients and therapeutics due to their unique characteristics and diverse bioactive compounds. Abundant evidence has supported the utilization of mushrooms in traditional medicine for centuries for the treatment of certain human disorders. The recognition and utilization of mushrooms and their products vary globally, with Asian Asian cuisine notably valuing their nutritional and medicinal benefits. Their nutritional richness, including minerals, vitamins, and essential amino acids, accounts for classifying them as "superfoods" [1]. The increasing demand for bioactive foods and nutraceuticals, coupled with the predicted rise in global protein demand, has further spotlighted the prospects of mushrooms

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as a beneficial source for enhancing public health and global wellness. Research has found mushrooms to contain a plethora of bioactive compounds, encompassing diverse polysaccharides, proteins, phenols, terpenoids, and alkaloids, which have been established to show various pharmacological effects, including antioxidant, antidiabetic, antiviral, anti-inflammatory, antimicrobial, antitumor, and anticancer activities [2-4]. The use of mushrooms for medication has grown beyond the traditional aspects, given their notable impacts in the management of various global health maladies, including cardiovascular diseases, viral conditions, and cancer [5-7]. Mushroom-based compounds have been found to exhibit these properties by modulating various biological pathways [8-10]. The significant advantages associated with mushroom production, such as sustainability, simplicity, efficiency, cost-effectiveness, and environmental friendliness, have also strengthened its position as a promising source of nutrition and bioactive ingredients. Mushroom production employs fruiting bodies and fungal biomass cultivation, solvent-assisted methods, precipitation, and novel technologies [1].

Plate 1 Oyster mushroom at Enugu-Ngwo, Enugu North in Enugu State, Nigeria

(A & B = matured mushroom that have been harvested; C = media containing mushroom spores being stacked, D= well-stacked spores inoculated on its media)

2. Methods

A comprehensive literature search was conducted using PubMed, Springer, ScienceDirect, Scopus, and Google Scholar. Peer-reviewed articles published in English between 2018 and 2025 were exclusively searched. Relevant studies were identified by using strategic keyword combinations and phrases, such as "mushroom bioactive compounds," "ethnopharmacology of mushrooms," and "mushroom pharmacology." The search yielded various studies that examined the phytochemical, ethnobotanical, and pharmacological properties of mushrooms. The retrieved articles were meticulously reviewed.

Bioactive chemical composition and nutritional value of mushrooms

Edible mushrooms are promising alternative protein sources, offering high protein levels ranging from 6.60 to 36.87 g/100 g dry weight [4, 11]. However, mushroom protein content depends on several factors like species, strain, maturation stage, substrate, and environmental factors. Compared to other protein sources (animals and plants), some mushrooms have protein values similar to milk, eggs, meat, and fish, while many mushrooms exceed legumes, cereals, nuts, and seeds in protein content. For nutritional value, 100 g of mushrooms can provide 29.41-66.0 % of the recommended dietary allowance (RDA for men and 35.80-80.35 % for women [4]. With respect to protein efficiency ratio (PER), several mushrooms like *Pleurotus ostreatus*, *Agaricus bisporus*, etc., have PER comparable to or exceeding beef jerky and legumes [4, 12]. The nutritional content of mushrooms, which are biologically important, includes: carbohydrate, protein, fat, fatty acid, mineral, vitamins, fiber, etc. [7]. In addition to the nutritional usefulness of mushrooms, many studies have indicated their rich bioactive chemical compositions (Table 1), which are of immense pharmaceutical significance [10]. These bioactive metabolites are polysaccharides, polyketides, terpenes, beta-glucans, polysaccharide-protein complexes, lectins, fungal immunomodulatory proteins (FIP), ribosome-inactivating proteins (RIP), antimicrobial/antifungal proteins, ribonucleases, laccases, and phenolic compounds [4, 13-14]. Wang et al [15] found a new compound (A homogeneous α-glucan (AM-1)) from *Agaricus blazei* coupled with the bioactive compounds previously reported. The advantages of mushrooms as a source of protein and bioactive compounds are worth noting (Figure 2); they can be produced more easily, cheaply, and with less environmental impact (sustainable production).

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It can also offer a promising option for those seeking plant-based or sustainable protein sources and bioactive compounds.

Table 1: Some chemical compositions of mushrooms and their potential pharmacological activities

Compounds	Type	Biological activities	References
Polysaccharides	β-glucans, chitin, mannose, mannoglucan, galactose, xylose, lentinan, hetero-galactomannan	Antioxidant, anti-inflammatory, anti-acetylcholinesterase, antitumor, antidiabetic,immune-enhancing, antimicrobial, hepatoprotective, and hypoglycemic effects	[4, 6]
	N/A	Anticancer, anti-inflammatory, antiviral, antioxidant, and hypercholesterolemic effects	[4, 6]
Phenols	Phenolic acids, flavonoids, tannins, lignans, hydroxycinnamic acid, polyphenols, and hydroxybenzoic acid	Antimicrobial, antioxidant, anti-inflammatory, and inhibitory activities against tumor effects	[6, 10]
Terpenoids	Ganoderic acids, ergosterol, fungal sterols	Anti-inflammatory, inhibitors of inflammatory mediators, and anticancer activities	[6, 16]
Flavonoids	Isorhamnetin, genkwanin, icariin, acacetin, kaempferol, eriocitrin, silymarin, silibinin, and apigenin	Anti-mutagenic, anti-inflammatory, anti-allergic, antiviral, and antitumor effects	[6, 10]
Alkaloids	Indoles (psilocybin), isoxazoles, tropanes, piperidines, quinolones	Anticancer activities	[17]
Steroids	N/A	Inhibit cancer cells, antiviral, antibacterial, immunomodulatory, and antidiabetic properties.	[6, 16]
Fatty acids	Linoleic acid, oleic acid, linolenic acid	Anti-inflammatory, pain-regulatory, antimicrobial, cardiovascular, and antioxidant activities	[18]
Tocopherol	N/A	Vitamin E activity, antioxidant, antimicrobial, and anti-quorum sensing effects	[6]
Vitamins	Vitamin D, B, C	Antioxidant, immunomodulatory, and anti-inflammatory effects	[10]
Minerals	Macro and micro elements	Antioxidant, anti-metabolic disorder, and wound-healing effects	[15-16]

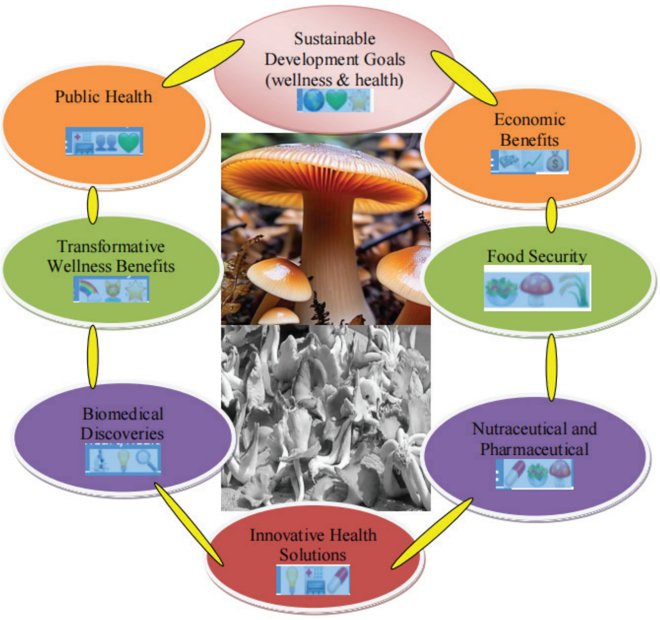

Fig. 2 Transformative potential of medicinal mushrooms: a summary framework

Isolation and identification of bioactive secondary metabolites from mushrooms

Conventionally, the main solvents used for the extraction of bioactive compounds from mushrooms are water and organic solvents. Water extraction offers moderate efficiency but stands the risk of degrading heat-sensitive components. A mixture of water-alcoholic extraction provides better extraction but involves a higher cost due to the solvent used. Maceration as a traditional technique is simple, reliable, but potentially time-consuming. The hydro-distillation method is a commonly employed technique, but it may require optimization for quality results. Enzyme-assisted extraction offers enhanced yield, reduced temperature, and extraction time, but is technically challenging. Furthermore, since it leverages the enzymatic degradation of cell walls, it offers quick release of bioactive substances. It has been employed for the effective extraction of certain compounds from mushrooms, like polysaccharides and enzymes. Nevertheless, the maintenance of enzyme stability and activity is a critical challenge for this method [6]. To mitigate the shortcomings associated with the conventional methods of extracting mushroom bioactive compounds, modern techniques have been developed; these include: (a) Ultrasound-assisted extraction (UAE), offering enhanced efficiency with reduced solvent use (b) Microwave-assisted extraction (MAE) extraction ensures efficiency and reduces thermal degradation (c) Supercritical fluid extraction (SFE) employs CO_2, yields higher extraction rates, especially for non-polar compounds (d) Pressurized liquid extraction (PLE) works based on optimized conditions, offering high extraction efficiencies (e) Subcritical water extraction boosts extraction yields without requiring high solvent volumes [6, 19]. In summary, modern extraction approaches generally offer higher efficiency and reduced solvent use, help prevent thermal degradation of bioactive compounds; however, some modern techniques like SFE require specialized equipment.

Factors affecting the bioactive disposition of mushrooms

Mushrooms contain many bioactive compounds, including polysaccharides, polyketides, phenolic compounds, and so on. The disparity in bioactive chemical composition of mushrooms is determined by certain factors, including species, cultivation conditions, and method of extraction [20-21]. According to Kumari et al [22], mushrooms' genetic disposition and their developmental history influence the chemical composition. Different mushroom species display distinctive genetic content, expressing unique bioactive compounds; of the many species of mushroom studied, *Ganoderma lucidum*, *Hericium erinaceus*, *Cordyceps militaris*, *Lentinus edodes*, and *Trametes versicolor* are thought to possess more pharmaceutical values. According to Parise *et al* [9], mushroom species suspected to possess activities against an array of COVID-19 infections include: *Agaricus blazei Murill, Ganoderma lucidum, Hericium erinaceus, Grifola frondosa, Inonotus obliquus, Lentinus edodes,* etc. The relationship between mushroom species and bioactive compound production is validated by *Inonotus obliquus* (Chaga), possessing a high proportion of polyketides, contrary to *Ganoderma lucidum* (Reishi), which contains a high profile of polysaccharides [15]. Furthermore, according to studies by Kumari et al [22] and Li et al [23], conditions including humidity, soil quality, temperature, and light, constituting environmental factors or cultivation conditions, have a tremendous impact on the chemical composition of mushrooms. For example, it has been observed that an increase in temperature enhances the synthesis of some bioactive substances in mushrooms, e.g., polysaccharides. Also, the yield of bioactive compounds like phenolic compounds has been improved by drought stress. Additionally, different extraction techniques, including supercritical fluid extraction, solvent extraction, and steam distillation, have been demonstrated to affect both the production and chemical constituents of mushrooms' bioactive compounds. Typically, more polysaccharides were obtained using

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ethanol than by distillation. Regarding phenolic compounds, a higher yield can be recorded by supercritical fluid extraction compared to extraction by the solvent method [24].

Pharmacological and therapeutic properties of mushrooms

Many studies have reported that the pharmacological potentials of mushrooms hold great promise. Interestingly, research has indicated immune improvement, lipid depletion, anticancer, anti-inflammatory, antioxidant, hepatoprotective, antitumor, antiviral, and several other biological activities as the pharmacological effects of mushroom extracts and their derived compounds (Table 2) [4, 6]. These pharmacological dispositions and the determinants of therapeutic potentials are thought to be due to the bioactive contents of the mushroom [15]. Edible mushroom proteins exhibit various therapeutic benefits, including: improved digestion, boosting nutrient absorption and immune function modification; anticancer properties, inhibiting cancer cell growth, inducing apoptosis, and arresting cell cycle progression; antimicrobial activity against bacteria, fungi, and other pathogens. Additionally, the bioactive protein portions of edible mushrooms like protein concentrates, hydrolysates, and peptides, Lectins, fungal immunomodulatory proteins, ribosome-inactivating proteins, and laccases boosted digestibility and potential health benefits, linked to ACE inhibitory, antioxidant, and anticancer immunomodulatory, antimicrobial, and antifungal activities [4,6].

Table 2: Therapeutic properties of bioactive proteins isolated from mushrooms

Bioactive protein	Biological activities	Mushroom sp	Nature	Reference
Protein hydrolysates	Neuroprotective, antioxidant, cytoprotective	*Pleurotus geesteranus*	hydrolysates	[4, 13]
Protein hydrolysates	Antioxidant, hepatoprotective, and antiproliferative, ACE inhibitory,	*Pleurotus ostreatus*	hydrolysates	[25-26]
Protein hydrolysates	Antioxidant, Lowers peroxidation (lipid)	*Ganoderma lucidum*	hydrolysates	[4]
Ribonuclease	Antiviral (HIV)	*Lepista personata*	ribonuclease (27.8 kDa)	[4, 27]
Ribotoxin	NA	*Cyclocybe aegerita*	ribotoxin-like enzymes (15 kDa)	[4]
Ostreatin	Novel biotechnological tool	*Pleurotus ostreatus*	ribotoxin-like proteins (131 amino acids and 14,263.51 Da)	[4]
Extract	Antitumor	*Pleurotus tuber-regium* *Pholiota nameko* *Boletus edulis*	Protein extract Protein extract Protein extract (16.7KD)	[28] [29] [30]
Extract	Antimicrobial	*Auricularia auricula-judae* *Mushroom (Oyster and button)* *Inonotus hispidus*	Aqueous protein extracts Protein extracts Proteins, peptides, and other compounds	[4] [4] [4]
Peptides	Antioxidant	*Agaricus bisporus*	Peptides, 1–3 kDa portion	[4]
Peptides	Antioxidant, ACE inhibitory	*Boletus mushroom*	KBMPHF1 (> 10 kDa), KBMPHF2 (3–10kDa) KBMPHF3 (1–3 kDa), and KBMPHF4(1 kDa)	[4]

The angiotensin-converting enzyme inhibitory activities

The bioactive peptides from mushrooms have been found to demonstrate angiotensin-converting enzyme (ACE) inhibitory effects, potentially treating hypertension. Peptides showing ACE inhibitory activities have been isolated from *Lentinula edodes* as 1265.43 Da and N-terminal (KIGSRSRFDVT [31], *S. rugosoannulata, Agaricus bisporus, Ganoderma sinense,* and *Grifola frondosa* in the form of peptide mixtures [4, 15, 23]. The ability of mushrooms to reduce blood pressure and cholesterol volume, prevent platelet accumulation and thrombosis, and shield from cardiovascular disease demonstrates their potential in ensuring cardiovascular health [10, 15]. Studies have highlighted that several mushroom species, like *Lentinula edodes, Stropharia rugosoannulata, and Grifola frondosa,* have produced peptides possessing ACE inhibitory effects. Additionally, *novel* peptides obtained from the hydrolysis of *Agaricus bisporus* scraps produced three ACE inhibitory peptides (LVYP, VYPW, and YPWT) displaying temperature, pH, and tolerance to digestive enzymes. These peptides work by binding to ACE active sites, zinc ions, or critical amino acids, inhibiting ACE activity [4]. Mushroom peptides may offer a promising alternative to synthetic ACE inhibitors, with potential benefits including fewer side effects and blood pressure reduction. Notwithstanding, clinical studies are crucial to confirm the efficacy and safety of mushroom peptides as ACE inhibitors.

Antioxidant properties

Mushroom-derivative compounds have been found to possess antioxidant activities, employing various mechanisms of action, including neutralization of free radicals, binding to metal ions to prevent oxidative reactions, hampering lipid damage, influencing cellular signaling pathways, and natural antioxidant defense architecture of the body [6]. Studies have uncovered that these mechanisms of action utilized by mushroom bioactive metabolites may be direct or indirect; it is direct if protons or electrons are mobilized to eradicate the free radicals, but when chelating metal ions and endogenous oxidases (enzymes) are impeded, it is indirect [4]. These bioactive compounds exhibit antioxidant properties, potentially mitigating oxidative stress and the diseases associated with it, such as aging, cancer, and atherosclerosis. Research has identified polysaccharides, phenolic compounds, triterpenoids, erinacines (unique diterpenoids), and ergothioneine as bioactive compounds from mushrooms demonstrating antioxidant activities. The bioactive compounds, particularly peptides involved in antioxidant activities, have been found to possess distinct characteristics such as amino acid composition (5-16 amino acids), molecular weight (0.65-3 kDa), and hydrophobic moiety, which enhance their antioxidant capabilities [4]. The mushroom species harbouring antioxidant bioactive compounds include *Schizophyllum* commune, *Hericium erinaceus, Agrocybe aegerita, and Ganoderma lucidum. Inonotus obliquus, Pleurotus ostreatus, Lentinula edodes, and Agaricus bisporus* [6, 10]. This review predicts the integration of mushroom-derived antioxidant compounds into functional foods, as well as the development of nutraceuticals and therapeutic agents.

Antitumor / anticancer effects

Research has found that the bioactive peptides from mushrooms exhibit antitumor activities, with potential therapeutic potency. These peptides employ two mechanisms of action, including mitochondrial-dependent pathway (obstructing cell proliferation and inducing apoptosis), and antioxidant and ACE inhibitory activity (enhancing antitumor properties). The bioactive compounds from mushrooms have demonstrated various anticancer activities by triggering programmed cell death, stimulating immune cells, suppressing vascular endothelial growth factor (VEGF) expression, mitigating oxidative stress, and cell cycle arrest, as mechanisms of action [6]. The bioactive compounds associated with anticancer properties include β-glucans (activate apoptotic pathways and stimulate immune cells), triterpenoids (suppress VEGF expression, blocking angiogenesis), and polysaccharides (stimulate immune cells and induce cell cycle arrest). β-glucans have displayed potential in treating numerous cancers, including gall bladder, liver, and breast cancer. Clinical trials have been conducted on mushroom-derived compounds, showing therapeutic potential.

Mushrooms, such as *Grifola frondosa* (Maitake) and *Agaricus blazei* (AndosanTM, made from its mycelium), have demonstrated anticancer activities. Again, studies highlighted numerous mushroom *novel* peptides: *Morchella importuna* peptide (MIPP) showed antitumor activity against human cervical cancer HeLa cells; Boletus mushroom peptides demonstrated antioxidant, ACE inhibitory, and anticancer activities; King Boletus mushroom protein hydrolysate (eb-KBM) displayed significant antioxidant, ACE inhibitory and anticancer activities against

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lung carcinoma and hepatocarcinoma cells [26]. The biological activities of eb-KBM have been linked to its rich hydrophobic and amino acid constituents. Again, *Cyclocybe aegerita*–derived ageritin has displayed antiproliferative properties, exhibiting selective toxicity against cancer cells. Also, the bioactive protein/protein extracts from edible mushrooms exhibited anticancer activities against various cancer cells, such as human non-small-cell lung cancer cells (*Boletus edulis* antitumor protein, BEAP), breast cancer (*Pleurotus tuber-regium* protein extract, PS60), and human breast cancer cells (*Pholiota nameko* protein, PNAP) [4]. Peptides reveal promise as potential antitumor agents, with further research required to explore their therapeutic potential.

Antimicrobial and antiviral activities

The bioactive compounds from mushrooms have demonstrated antibacterial, antifungal, and antiviral properties by disrupting microbial colony formation and causing the leakage of nuclear materials (DNA and protein). The antiviral activities displayed by bioactive compounds isolated from mushrooms involved diverse mechanisms of action, such as inhibiting viral replication, inducing overexpression of antiviral genes, enhancing immune cell activity and production, and preventing viral attachment to host cells [6]. Numerous studies have confirmed the antibacterial, antifungal, and antiviral effects of mushrooms [6, 15]. Several bioactive compounds isolated from different species of mushrooms, such as *Agaricus bisporus, Pleurotus ostreatus, Sanghuangporus sanghuang, Thelephora palmata, Hygrophorus crispus, Gyroporus castaneus, Neoboletus luridiformis, Gyromitra esculenta, and Lentinula edodes,* exhibited inhibitory activities against pathogens: *Staphylococcus aureus, Clavibacter michiganensis*, *Burkholderia aglumae, and Peptobacterium carotovorum*. Furthermore, research has found that bioactive compounds like triterpenoids (isolated from *S. sanghuang*), panisaldehyde (found in *P. ostreatus*), polyacetylenes and sulphur compounds (present in *L. edodes*), and terpenes (extracted from *F. velutipes* mycelium culture filtrate) exhibited antimicrobial properties [6]. The beta-glucans, flavonoids, ergosterol, and ganoderic acid contents play vital roles in the antimicrobial and antitumor properties of mushrooms [4]. Additionally, Liu et al [1] indicated the antiviral and antifungal effects of mushrooms. It is worth noting that peptides (mixtures of peptides) isolated from *Pseudoplectania nigrella*, *Russula paludosa*, and *Clitocybe sinopica* displayed significant effects against COVID-19 [32]. This property is possible due to its ability to bind and compromise the integrity of certain coronavirus proteins, such as the ACE-associated carboxypeptidase, the SARS-CoV HR2 Domain, and the COVID-19 major protease enzyme. Furthermore, a ribonuclease (ageritin) obtained from *Cyclocybe aegerita*, an edible fungus, displays antifungal, antibacterial, entomotoxic, antiviral, and nematotoxic activities. Its inhibitory effects against HIV-1 reverse transcriptase have also been indicated by research [4, 6]. Interestingly, it demonstrates these biological functions by exhibiting ribonucleolytic (cleaving phosphodiester linkages in 23-28S rRNAs, hampering protein synthesis, and causing apoptosis) and endonuclease activities (acting on plasmids and genomic DNAs) [4]. Rijia et al [6] indicated that the mushroom-derived compounds found to possess antiviral properties are: (a) Polysaccharide peptide (PSP), which shows antiviral effects by hindering viral replication and triggering antiviral genes; (b) Lentinan (LTN1) that boosts immune cell activity and production, enhancing defenses against infections; (c) Heliantriol F, semicohlidinol A, and semicohilidinol B, thought to possess antiviral activity against chikungunya virus; and (d) Polysaccharide Krestin (PSK), which exhibits antiviral effects on HIV and cytomegalovirus. In summary, the mushroom bioactive compounds exhibit antibacterial activities, adopting several mechanisms of action, including inhibition of metabolic pathways, disruption of polymerases, obstruction of protein synthesis, destruction of cell membranes, destruction of cell walls, and nucleic acid damage.

Anti-inflammatory properties

The bioactive compounds isolated from mushrooms have exhibited significant anti-inflammatory effects, engaging various mechanisms of action, including regulation of cytokine production, reducing inflammation, influencing immune cell activity, mitigating excessive inflammation, reducing oxidative stress, contributing to anti-inflammatory effects, influencing enzymatic activity, further reducing inflammation [6 Rijia et al. 2025]. Studies have identified mushrooms with anti-inflammatory activities: *Pleurotus florida*, *Sanghuangporous sanghuang*, *Trametes versicolor*, *Dictyophora indusiata*, *Grifola frondosa*, and *Pleurotus eryngii*. Bioactive compounds from mushrooms linked to anti-inflammatory activity are flavonoids, β-linked polysaccharides, ascorbic acid, beta-carotene, and lycopene [6, 33]. *Cordyceps militaris novel* selenium peptides (Se-Ps), VPRKL(Se)M (Se-P1) and RYNA(Se) MNDYT (Se-P2) exhibited anti-inflammatory activities against lipopolysaccharide-stimulated inflammatory and oxidative stress around the colon-brain axis [4]. This activity is demonstrated by impeding the generation of inflammatory cytokines. Additionally, studies indicated that Se-Ps enhanced the functions of the intestinal mucosa and gut microbiota dysbiosis. *Tricholoma matsutake* peptides, SDIKHFPF and SDLKHFPF, suppressed ethanol-dependent cytokine-mediated responses by NF-κB inhibition and programmed cell death [23]. *H. erinaceus* metabolites have been found to possess the ability to combat inflammation and oxidative stress, critical determinants in neurodegenerative disorders. This metabolite may present a natural source for therapeutic agents targeting neuroinflammation and oxidative damage, which is substantiated by the suggestion that the metabolites may be developed into therapeutic agents for the treatment of Alzheimer's and Parkinson's diseases [6]. Again, it is worth noting that the ethanol extract of *P. eryngii* shows potential for the enhancement of neurological health. Edible mushroom bioactive compounds, like proteins, demonstrate potential therapeutic applications in disease prevention and cure, necessitating further research and exploitation. Continued research into mushroom bioactive compounds may lead to new natural anti-inflammatory agents.

Hepatoprotective properties

Studies have uncovered the liver-shielding properties of mushroom bioactive constituents. The bioactive compounds, polysaccharide-peptides (PSI and PSII) from *Pleurotus citrinopileatus* demonstrated potency in the treatment of non-alcoholic fatty liver disease (NAFLD) [34]. It also regulates gut microbiota and improves liver function [4]. A paracetamol-induced hepatitis in a rat model treated with *Volvariella volvacea*, *Lentinula edodes*, *Flammulina velutipes*, *Auricularia auricular*, *Tremella fuciformis*, *Grifola frondosa*, and *Tricholoma lobayense* water extracts exhibited hepatoprotective activities after incubation [10].

Antidiabetic effects

The number of diabetic patients is projected to hit about 380 million, from the reported 190 million, in the next 5 years (2030), stimulating research for natural sources of antidiabetic bioactivity [6]. Mushrooms and their derivatives have been proven to adopt a multifaceted approach while displaying antidiabetic effects, including: enhancement of insulin sensitivity, blocking the activities of enzymes participating in glucose metabolic processes, affecting glucose production in the hepatic region, reducing oxidative stress linked to free radicals, and exhibiting anti-inflammatory activity [6, 35]. This compelling mechanistic fact positions mushrooms for therapeutic exploitation in antidiabetic therapy. Diverse mushroom species indicated to possess antidiabetic properties include: *Pleurotus abalonus, Pleurotus florida*, *Pleurotus pulmonarius, Agaricus blazei Murill, Pleurotus eryngii, Cordyceps sinensis, Agaricus* subrufescens, *Hericium erinaceus*, and *Cordyceps militaris* [6, 36]. Findings revealed that mushroom bioactive compounds demonstrate antidiabetic effects, like polysaccharide-protein complexes present in *P. abalonus*, displaying hypoglycemic effects, phenolic compounds found in *P. florida*, playing a crucial role in antidiabetic activity, β-glucans and oligosaccharides present in *A. subrufescens*, boosting insulin resistance, and fractions of polysaccharide (CSP-1 found in *C. sinensis* trigger insulin production. Potentially, mushrooms may offer a valuable dietary component for managing diabetes, insulin sensitizers, and anti-hyperlipidemic agents. For clinical applications of mushroom-derived compounds in diabetes management, further research is required for the specific identification of compounds involved in antidiabetic activities [6].

Safety, toxicity, and quality control of mushroom-based products: Current status, challenges, limitations, and prospects

The pharmacological effects exhibited by a wide range of mushroom species, including antimicrobial, antiviral, anti-inflammatory, antidiabetic, hepatoprotective, angiotensin-converting enzyme inhibitory, antioxidant, and anticancer activities, have earned them an enviable position in the pharmaceutical landscape [6]. These pharmaceutical properties of mushrooms have stimulated well-known research interest currently. The clinical setbacks elicited by mushroom-related safety and toxicity concerns require attention to strengthen their effective use as therapeutic agents. Various plans can be employed to mitigate these issues, which include identifying mushroom species accurately by experts, standardizing extraction and testing procedures, thorough examination for safety and efficacy profile, and adequate adherence to safety regulations. Additionally, with research confirming the presence of certain toxic compounds in mushrooms, evaluation of mushrooms and their derived products to

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ascertain their toxicity and side effects on public health becomes very imperative.

Furthermore, pharmacokinetic studies are essential for determining the bioavailability, absorption, distribution, and elimination of mushrooms and their derivative products in the human system. Clinical trials are also crucial to evaluate the safety and efficacy of these products [37]. These trials, encompassing Phase I, Phase II, and Phase III, help to establish the efficacy, safety, and optimal dosing regimens for various applications. Clinical trials of mushrooms and their based products have faced significant limitations, including variable mushroom constituents and quality, poor understanding of bioavailability and pharmacokinetics, and interaction with several other medications. Abundant evidence has confirmed that clinical trials conducted on the Reishi (*Ganoderma lucidum*) extract for anticancer effects, Shiitake (*Lentinula edodes*) extract for immunomodulatory activities, and Chaga (*Inonotus obliquus*) extract for antimicrobial and antioxidant properties have recorded huge success [15]. Processes, such as validation and standardization, policy adherence verification, and regulatory framework, must be thoroughly confirmed before any products of plant origin can be accepted by the global community [38]. To ameliorate the molecular weight-associated limitation polysaccharides face from production to extraction, particularly from fruit bodies, culture broth, and cultured mycelium, extraction and analytical technologies are standardized, which ensures sufficient uniformity and product quality [6]. The extraction procedures require various standardization strategies, including solvent-based extraction, enzyme-assisted extraction, and ultrasonic-assisted extraction, coupled with analysis techniques, such as HPLC, GC-MS, and NMR spectroscopy [15]. The involvement of high-throughput biotechnological techniques, such as X-ray crystallography, nuclear magnetic resonance spectroscopy, and mass spectrometry, to delineate the link between the structural conformation of mushroom active ingredients and their pharmacological properties is also very crucial, ensuring the standardization of mushroom-based products [36].

With the spike in the pharmaceutical prospects of mushrooms, numerous future directions ought to be sought for their full utilization as therapeutic agents. It becomes very essential to streamline the various regulatory frameworks. For robust development, production, and marketing of mushroom-derived medicinal products, international collaboration is pivotal in setting up strict regulations, leading to enhanced global recognition and use. Standardized extraction, authentication, and testing protocols are necessary for sufficient product quality and consistency of mushroom-based bioactive ingredients [36]. This standardization can offer a favorable environment for data assessment emanating from diverse research, thereby boosting high-quality product development. Furthermore, a partnership must exist between industry and academia for enhanced development of high-quality pharmaceutical products. As researchers from academia contribute expertise towards the development and examination of the mushroom-based products (Figure 3), industry collaborators play a vital role in commercializing and marketing the products. Also, evaluating the interaction between mushroom-based active ingredients and other therapeutics like conventional drugs and plant-based products may result in the development of *novel* therapeutic innovations. To arrest regulatory issues, robust strategies must be set up, including (1) Classification of mushroom-derived products as either dietary supplements or medicinal products, (2) Provision of sustainable cultivation practices, (3) Continuous supply of high-quality mushroom biomass for the production of medicinal products, and (4) Implementation of public education and awareness campaigns.

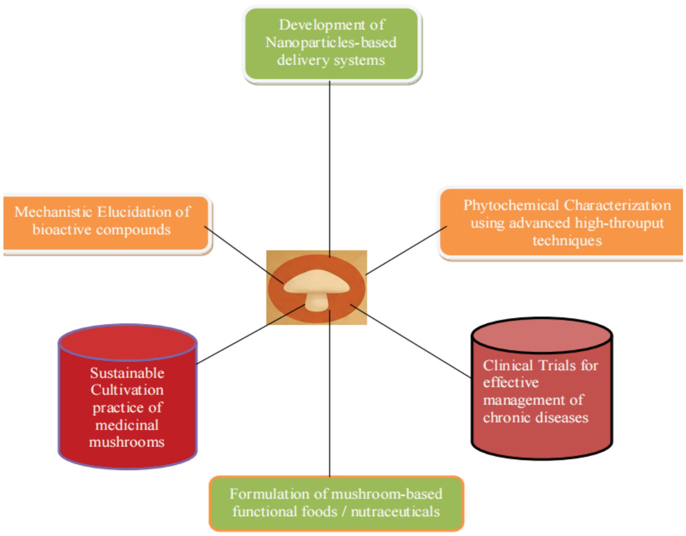

Fig. 3 Groundbreaking research opportunities in medicinal mushrooms

Regulatory framework of mushroom-based products

There is a need for standardization of mushroom-based pharmaceutical or neutraceutical products since the regulatory framework varies from country to country. For example, mushroom-based products classified as dietary supplements are regulated by the FDA under the jurisdiction of the Dietary Supplement Health and Education Act (DSHEA) in the United States. Additionally, in Europe, mushroom-based products are categorized under food supplements or traditional herbal medicinal formulations, regulated by the European Medicines Agency (EMA). Similarly, in China, mushroom-based products are grouped as traditional Chinese medicine, supervised by the China Food and Drug Administration (CFDA). Furthermore, in India, mushroom-based products classified as Ayurvedic, Siddha, or Unani medicines are regulated by the Ministry of AYUSH. In Nigeria, the agency regulating mushroom-based products is not well-known; the National Agency for Food and Drug Administration and Control (NAFDAC) or the Federal Ministry of Agriculture and Food Security might play a crucial role, since these bodies regulate similar products.

To standardize mushroom-based pharmaceutical products in Nigeria, this review suggests implementing integrated processes, including (1) Establishing National Standards for industry involved in the productions of plant-based products, encompassing setting up examination procedures and prerequisites for labeling, (2) Consolidating Regulatory Framework, aimed to bring strict compliance with national standards and guidelines, (3) Translating Quality Control and Assurance policy to practical assessment and certification plans, (4) Supporting robust Research and Development towards the potency, safety, and potential interactions of plant-based products, (5) Carrying out Public Education, acquainting the end users with advantages and disadvantages of consuming mushroom-based products for enhanced decision-making, and (6) Strengthening co-operation among industries, stakeholders, regulatory bodies, and research institutions to contribute towards achieving standardization of the mushroom-based products.

To ensure standardization is attained and sustained, it is important to collaborate with agencies like NAFDAC, Federal Ministry of Agriculture and Food Security, National Agricultural Seeds Council of Nigeria, CropLife Nigeria, Standards Organization of Nigeria (SON), and National Biosafety Management Agency (NBMA).

3. Conclusion

Mushrooms provide intriguing opportunities for researchers to develop *novel* drugs, given the wide range of pharmacological effects demonstrated by their bioactive ingredients. The prospective pharmaceutical applications of these mushroom-derived active molecules are enormous, encompassing the treatment of life-threatening diseases, including cancer, infections, diabetes, and several other chronic diseases. However, significant challenges, including poor bioavailability, variable bioactive composition, and dose-dependent adverse effects, must be addressed to advance the clinical exploration of mushroom-based products. Additionally, the isolation of each mushroom bioactive constituent for medication is cumbersome due to the complex nature of mushroom components, which are found to work synergistically. Furthermore, regulatory authorization calls for top-notch clinical research and standardized pharmaceutical formulations. Leveraging improved extraction methodologies, nanoparticle-based delivery systems, and rigorous clinical trials, the therapeutic usefulness of mushroom-based products can be harnessed fully. Research focused on bioavailability, pharmacokinetics, and clinical effectiveness can drive the findings into effective medications for enhanced public health.

Ethics approval and consent to participate

It is not applicable.

Availability of data and materials

Not applicable

Consent for publication

The authors have given their consent for this article to be published.

Competing interests

The authors declare that there is no competing interest.

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