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Therapeutic perspectives on medicinal mushrooms in oncology: A systematic review of bio-active metabolites and anti-tumor mechanisms

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Abstract

Medicinal mushrooms represent a robust reservoir of natural pharmacological agents, increasingly recognized as valuable integrative supplements to traditional oncology protocols like radiotherapy and chemotherapy. This review evaluates the clinical and molecular potential of prominent species, including *Ganoderma lucidum*, *Lentinula edodes*, *Grifola frondosa*, and *Coriolus versicolor*. These fungi synthesize high concentrations of bio-active metabolites-most notably -glucans, triterpenoids, and complex proteoglycans-that drive specialized anticancer activities. The underlying mechanisms are dual-action: they function as immunomodulators by stimulating T-lymphocytes, macrophages, and natural killer (NK) cells to trigger a host-mediated immune response, while simultaneously exerting direct cytotoxic pressure on malignant cells. These direct pathways include the induction of programmed cell death (apoptosis), suppression of migratory signaling (metastasis), and the arrest of the cellular division cycle at critical checkpoints. Additionally, evidence suggests that mushroom-derived extracts mitigate the systemic toxicity of conventional treatments, reducing patient fatigue and marrow suppression. While current laboratory data is compelling, this review emphasizes the necessity for standardized clinical validation to establish precise therapeutic dosages. Ultimately, integrating fungal biotechnology into modern medicine offers a strategic pathway for enhancing long-term patient outcomes and cancer prevention strategies.

Keywords: Mycology, immunotherapy, cytotoxicity, polysaccharides, integrative oncology

Introduction

Despite significant diagnostic and therapeutic breakthroughs, cancer remains a primary driver of global mortality, defined by its hallmark traits of erratic cellular growth and metastatic spread. While established protocols-surgery, ionizing radiation, and cytotoxic chemotherapy-are the cornerstones of modern oncology, their utility is frequently compromised by debilitating systemic side effects and the emergence of chemoresistance. This therapeutic gap has catalyzed a shift toward pharmacognosy, specifically the exploration of medicinal mushrooms as a reservoir for biocompatible, low-toxicity antineoplastic agents.

The ethnomycological application of fungi spans millennia, deeply rooted in the foundations of Ayurvedic and Traditional Chinese Medicine (TCM). Taxa such as *Ganoderma lucidum* (historically celebrated as the "Mushroom of Immortality") and *Lentinula edodes* have long been utilized to bolster host resilience and longevity. Today, rigorous pharmacological scrutiny is substantiating these traditional roles. Notably, in nations like Japan and China, purified fungal derivatives have been integrated into clinical oncology for over three decades to augment the efficacy of standard care.

The medicinal potency of these fungi is attributed to a sophisticated profile of secondary metabolites. Key among these are polysaccharides and β -glucans, which function as biological response modifiers by recalibrating the host's immune surveillance to identify and eliminate malignant cells. Furthermore, triterpenoids-highly concentrated in Reishi-demonstrate potent direct cytotoxicity and possess the ability to bypass the efflux pumps associated with multidrug-resistant phenotypes. Additionally, proteoglycans such as Polysaccharide-K (PSK) from *Coriolus versicolor* have demonstrated statistically significant

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improvements in survival rates for patients battling gastrointestinal and colorectal malignancies. The therapeutic impact of medicinal mushrooms is realized through a multifaceted, synergistic framework. Their primary modes of action include

- **Immunological Potentiation:** Systematic activation of macrophages, T-lymphocytes, and Natural Killer (NK) cells, alongside the up-regulation of tumor-suppressive cytokines.
- **Direct Oncostatic Activity:** The execution of programmed cell death (apoptosis) and the imposition of cell cycle checkpoints to effectively terminate tumor expansion.

Literature Review

For millennia, mushrooms have served as a dietary staple across diverse global cultures. Beyond their culinary utility, they are increasingly recognized as a vast, underutilized reservoir of high-value nutrients and bioactive metabolites (Kumar *at al.* 2021) [13]. While their nutritional profile is well-documented, contemporary research is shifting focus toward their profound therapeutic potential (Chopra *at al.* 2021) [4]. This has led to the emergence of "mycotherapy," where fungal derivatives are utilized as specialized nutraceuticals and health supplements. While the Western world has only recently begun to integrate these practices, Asian medical traditions have long leveraged fungi to maintain physiological homeostasis and treat chronic pathologies. The medicinal efficacy of mushrooms is intrinsically linked to their chemical composition. Edible varieties are prized for their sensory attributes-aroma, texture, and flavor-whereas wild medicinal species have historically been harvested to address a spectrum of conditions ranging from minor ailments to life-threatening diseases (Yasin *at al.* 2019) [22]. Distinguishing between "edible" and "medicinal" categories is often difficult, as many commonly consumed species exhibit potent pharmacological activities (Valverde *at al.* 2015) [20] of the approximately 2,000 documented mushroom species, only a fraction are cultivated for human consumption, with *Agaricus bisporus*, *Lentinus edodes*, and *Flammulina velutipes* dominating global production.

Biochemical Composition and Nutritional Value

Fungal metabolism produces an array of secondary metabolites, including steroids, phenolic acids, benzoic acid derivatives, anthraquinones, and terpenes. Their primary structural components consist of proteins, peptides, and organic acids such as oxalic acid (Alves *at al.* 2012) [2]. From a nutritional standpoint, mushrooms are characterized by high protein and amino acid content, low levels of saturated fatty acids, and a rich density of essential vitamins (B1, B2, B12, C, D, and E) and minerals including phosphorus, iron, zinc, copper, iodine, and selenium (Kumar

K. 2015) [12]. These constituents collectively support skeletal health, fluid balance, and immune regulation. The inclusion of mushrooms in a standard diet, particularly as a gluten-free alternative, offers significant protective benefits. Specifically, β -glucans-highly concentrated in oyster, shiitake, and split-gill mushrooms-are recognized for their potent immunomodulatory effects and their role in regulating lipid and carbohydrate metabolism (Duyff R. L. 2006; Rop *at al.* 2009) [5, 19]. Furthermore, the high concentration of B-complex vitamins plays a vital role in maintaining neurological health.

Advances in Extraction and Anticancer Research

Current scientific efforts are centered on the isolation and characterization of bioactive polysaccharides. To maximize yield and purity, traditional extraction is being replaced by sophisticated technologies, including enzyme-assisted, microwave-assisted, subcritical water, and pulsed electric field extraction (Leong *at al.* 2021) [15]. These methods are essential for harvesting the multifaceted compounds that interact with malignant tissues. The anticancer potential of mushrooms is realized through complex biological pathways that target the metabolism of tumor-prone cells (Gmoser *at al.* 2020) [9]. While fungi were historically categorized as plants, modern taxonomy recognizes them as a distinct kingdom due to their chitinous cell walls. Of the 14,000 known fungal species, roughly 700 are identified as possessing medicinal traits. In the emerging field of "cancer fungotherapy," metabolites such as β -glucans, terpenes, and phenolic compounds are being rigorously studied as some of the most effective natural agents for malignancy prevention and treatment.

Phytochemical Profile of Medicinal Mushrooms

Mushrooms synthesize a diverse array of bioactive metabolites, ranging from primary structural components to complex secondary molecules Table-1. These include polysaccharide-protein complexes, alkaloids, polyphenols, terpenoids, lectins, sterols, and specialized β -glucans (Gargano *at al.* 2017; Friedman, 2015) [7, 8]. *Agaricus bisporus*, commonly known as the button mushroom, is recognized for its high nutritional density and specific bioactive fractions that contribute to its health-promoting properties (Khan *at al.* 2015) [11]. Among medicinal fungi, *Ganoderma lucidum* is perhaps the most chemically prolific, with approximately 400 identified bioactive constituents. Its pharmacological repertoire-comprising triterpenoids, polysaccharides, and nucleotides-exhibits a broad therapeutic spectrum, including antioxidant, anti-inflammatory, hepatoprotective, and potent antineoplastic activities (Ahmad, 2018) [1]. Recent evidence suggests that these fungal compounds are particularly effective in managing degenerative diseases and enhancing the efficacy of modern cancer therapies (Zhou *at al.* 2023) [24].

Table 1: Summary of Clinical Evidence for Fungal Anticancer Activity

S. No.	Mushroom Species	Cancer Type	Clinical Phase	Key Bioactive Fractions	Key Clinical Outcomes
1	<i>Agaricus bisporus</i>	Breast & Prostate	Phase I/Ib	Polysaccharides, Lectins	Reduction in immunosuppressive markers; improved host defense.
2	<i>Agaricus blazei</i>	Multiple Myeloma	Phase II	Genistein	Mixed results; primarily improved chemotherapy tolerance and reduced side effects.
3	<i>Lentinula edodes</i>	Prostate Cancer	Phase II	GCP	Failed to achieve >50% reduction in PSA

				(Polysaccharide)	levels in early-stage patients.
4	<i>Grifola frondosa</i>	Hepatocellular; Breast; Lung	Phase I/II	Arabinoxylan; Polysaccharides	Modulated immune signaling in postmenopausal patients.
5	<i>Omphalotus illudens</i>	Thyroid; Gastric; Ovarian	Phase II	Illudin S derivative	Investigated for cytotoxic activity in recurrent or persistent cases.
6	<i>Trametes versicolor</i>	Gastric Cancer	Controlled Trial	PSK, PSP, Krestin	Significant alleviation of "Qi and Yin" deficiency symptoms during chemo.
7	<i>Agaricus sylvaticus</i>	Breast Cancer	RCT	Not specified	Enhanced nutritional status and reduced nausea/anorexia in Stages II-III.

Mechanisms of Action: Immunomodulation and Ribotoxicity: The antitumor efficacy of mushroom derivatives is often non-toxic to healthy cells. For instance, polysaccharides from *Phellinus linteus* suppress metastasis and tumor expansion by fortifying the host's immune response rather than through direct cellular poisoning. In *G. lucidum*, β -D-glucans provide a dual benefit: they inhibit malignant proliferation while simultaneously neutralizing free radicals to protect healthy tissues (Joseph *et al.* 2018) [10].

A more specialized defensive mechanism involves the production of ribotoxic proteins, such as ribonucleases and N-glycosylases. These enzymes function as protein synthesis inhibitors by targeting the sarcin-ricin loop (SRL) of the ribosome (Landi *et al.* 2022) [14]. By disrupting mRNA-tRNA translocation at the ribosomal level, these toxins trigger a cascade that results in apoptotic cell death (Endo *et al.* 1983). Specifically, ribotoxins from ascomycetes and ribotoxin-like proteins (RL-PS) from edible fungi catalyze the hydrolysis of phosphodiester bonds within the SRL, releasing a diagnostic " β -fragment" of rRNA that signals the termination of cellular translation (Ragucci *et al.* 2021) [18]. These low-molecular-weight proteins utilize a precise catalytic triad (His50, His137, and Glu96) to deactivate the protein-making machinery of the cell (Landi *et al.* 2021) [14].

Pharmacological Significance of Anticancer Metabolites

The therapeutic versatility of mushrooms stems from an expansive chemical library that includes polysaccharides, specialized proteins, lipids, polyphenols, alkaloids, and trace elements like selenium and folate. Within this matrix, specific molecular moieties-such as lanosterol, ergosterol peroxide, inotodiol, cordycepin, and hispolon have been identified as potent antineoplastic agents (Ayeka, 2018; Naim, 2024) [3, 17]. These compounds, illustrated in Figure 1, represent the structural diversity that allows fungal extracts to interact with multiple oncogenic pathways.

Polysaccharides and Immunological Surveillance

Mushroom-derived polysaccharides, particularly β -glucans, are among the most rigorously studied "biological response modifiers." These molecules typically feature a D-glucose backbone with β -(1,3)-glycosidic linkages and β -(1,6) branching. Their primary function is to fortify the host's immune surveillance by stimulating the production of pro-inflammatory cytokines. This signaling cascade activates a suite of defensive cells, including

- **Phagocytes and Leukocytes:** Enhanced pathogen and tumor cell engulfment.
- **Natural Killer (NK) and T-cells:** Improved recognition and destruction of malignant cells (Israilides *et al.*, 2008; Mizuno, 1999) [16]. Clinical validation of these effects is evident in Japan, where purified fungal derivatives like Lentinan (from *L.*

edodes), Schizophyllan, and Krestin have been formally approved as adjunct cancer therapies for decades.

Targeted Molecular Mechanisms

Beyond general immune stimulation, specific fungal metabolites exert direct pressure on cancer cell survival:

- **Cordycepin (3-deoxyadenosine):** Isolated from *Cordyceps* species, this adenosine analogue acts as a deceptive building block. During the synthesis of genetic material, it binds to nucleic acid sites and disrupts polyadenylation, effectively terminating the elongation of DNA or RNA chains and triggering apoptosis (Wasser, 2017) [21].
- **Hispolon:** This phenolic compound is gaining attention for its dual role; it possesses intrinsic anticancer properties and acts as a chemosensitizer, potentially amplifying the efficacy of traditional cytotoxic drugs (Yoon *et al.*, 2018) [23].
- **Lectins and Lentinan:** Research indicates these proteins and polysaccharides from *Lentinula edodes* exhibit direct cytotoxic effects specifically against breast cancer cell lines (Chen & Seviour, 2007).

Molecular Mechanisms of Fungal Antitumor Activity

While the ethnomycological use of fungi has a deep historical foundation in Asia, its integration into global oncology has accelerated only recently. The therapeutic efficacy of these organisms is attributed to a complex profile of bioactive metabolites that target specific oncogenic drivers. To optimize the success rates of integrative cancer therapies, it is critical to map the molecular interactions between fungal compounds and the signaling pathways involved in tumor initiation, proliferation, and the circumvention of multidrug resistance (MDR).

A primary mechanism involves the immunological processing of β -glucan polysaccharides, as illustrated in Figure 2. Unlike direct cytotoxic drugs, β -glucans function as high-affinity ligands for specific pattern recognition receptors (PRRs) on innate immune cells.

The Glucan Signaling Cascade

1. **Receptor Binding:** Fungal β -glucans are initially recognized and internalised by macrophages through specialized surface receptors, primarily Dectin-1 and the Toll-like receptor (TLR-2/6) complex.
2. **Intracellular Processing:** Once engulfed, these polysaccharides are enzymatically processed and fragmented into smaller, bioactive subunits within the macrophage.
3. **Systemic Priming:** These soluble fragments are subsequently released and captured by granulocytes (such as neutrophils) via the Complement Receptor 3 (CR3).

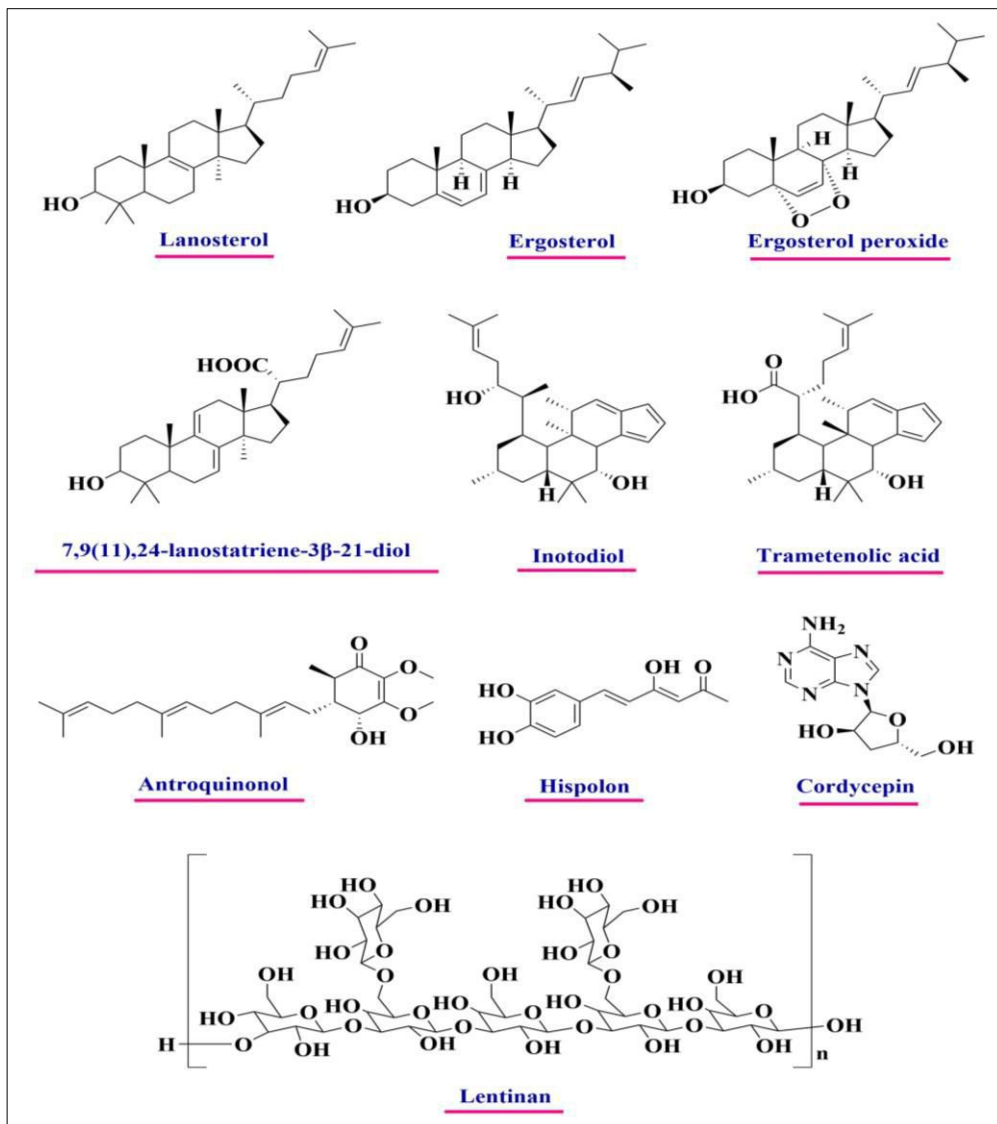


Fig 1: Chemical structures of some important bioactive constituents in mushrooms showing anticancer potential.

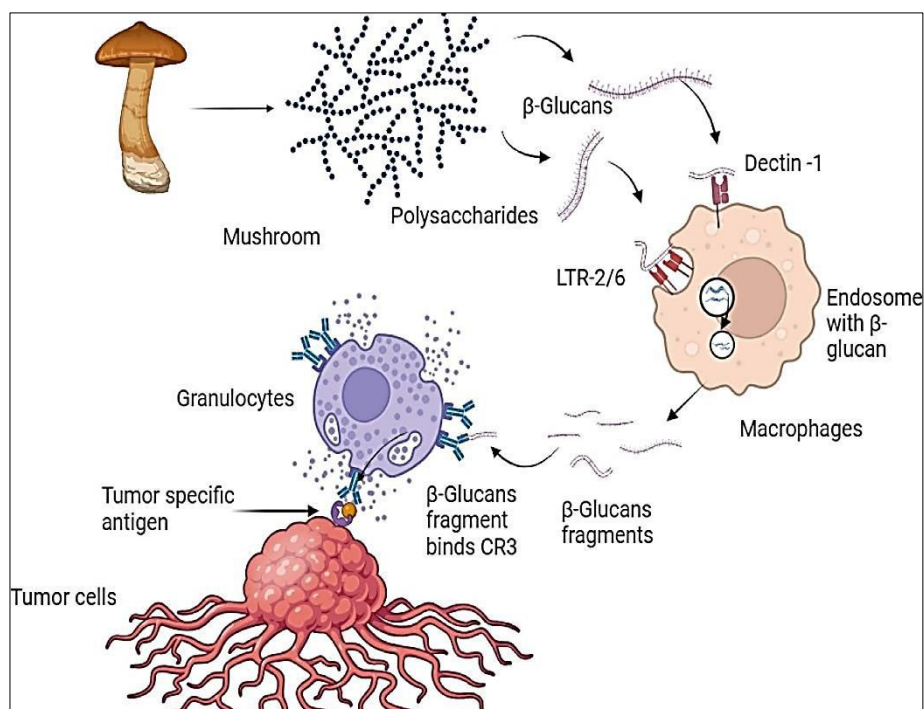


Fig 2: Mushroom-derived β -glucan polysaccharides and its mechanism of action on tumor cells.

Targeted Cytolysis

This binding primes the granulocytes, triggering a potent respiratory burst and directed phagocytosis. The activated immune cells then identify and eliminate tumor cells that have been opsonized by the host's natural antibodies.

Concluding Remarks and Clinical Outlook

The therapeutic potential of medicinal mushrooms as a pillar of integrative oncology is predicated on their unique ability to modulate the host's immune landscape. By governing the maturation and proliferative capacity of key immune effectors, fungal bioactives can effectively impede metastatic progression and the expansion of malignant cell populations. A profound understanding of these molecular mechanisms is not only essential for inhibiting tumorigenesis but is also critical for improving the systemic resilience and overall quality of life for patients undergoing traditional cytotoxic treatments.

However, a significant disparity exists between promising preclinical findings and large-scale clinical validation. To bridge this gap, future research must move beyond preliminary studies to incorporate expansive patient cohorts, standardized fungal formulations, and longitudinal follow-up protocols. Furthermore, the role of medicinal mushrooms as a preventive nutritional strategy remains a vital area for investigation; incorporating these bioactive-rich organisms into a balanced dietary framework may offer a sustainable method for long-term cancer prophylaxis.

As we transition into an era of precision medicine, medicinal mushrooms represent a sophisticated, biotechnology-driven asset. Future scientific efforts should prioritize bioassay-guided fractionation to identify highly specific antineoplastic candidates and explore the synergistic interactions within complex fungal extracts. Ultimately, the successful translation of mycotherapy from traditional practice to standardized clinical application offers a transformative pathway for the next generation of non-toxic cancer therapies.

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