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IMMUNOMODULATORY EFFECTS OF EDIBLE MUSHROOMS AS A SOURCE OF NOVEL BIOMARKERS FOR EARLY CANCER DETECTION: A CLINICAL APPROACH

Abeeha Shahzad Khan[1], Fiza Shahbaz Ahmad[2], Ayesha Jabeen[3], Hafiz Ayaz Ahmad[*4], Hifsa Mobeen[5]

[1,2]*Department of Medical Laboratory Technology, Superior University, Lahore, Pakistan*
[3, *4,5]*Faculty of Allied Health Sciences, Superior University, Lahore, Pakistan*

[1]abeehakhan308@gmail.com, [2]fizzashahbazahmed5@gmail.com, [3]ayesha.jabeen@superior.edu.pk, [*4]hafizayaz.ahmad@superior.edu.pk, [5]hifsa.mobeen@superior.edu.pk

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Corresponding Author: *
Hafiz Ayaz Ahmad

Abstract

Cancer remains a major global health challenge, with early detection being crucial for improving survival and treatment outcomes. Edible mushrooms have gained attention as a source of immunomodulatory compounds—including β-glucans, polysaccharopeptides, lectins, triterpenoids, and phenolic compounds—that enhance innate and adaptive immunity, increase natural killer (NK) cell activity, and modulate cytokine production, thereby improving tumor surveillance and anti-cancer responses. Both preclinical and clinical studies suggest that these immune effects can be measured as biomarkers, offering a novel approach for early cancer detection and monitoring therapeutic responses. Human trials using extracts such as lentinan, PSK, Maitake D-fraction, and Ganoderma formulations demonstrate enhanced immune function, improved quality-of-life outcomes, and potential adjunctive benefits in cancer care. However, variability in mushroom species, extract composition, dosing, and study design underscores the need for standardized protocols. Further research, including large-scale, multicenter clinical trials and multi-omics biomarker profiling, is essential to validate efficacy, optimize dosing, and integrate mushroom-derived immunomodulators into precision oncology strategies for early detection and improved patient outcomes.

INTRODUCTION

Cancer is a leading cause of illness and death worldwide, with millions of new cases diagnosed each year. According to the World Health Organization, it caused nearly 10 million deaths in 2020, making it a critical public health challenge. Advances in molecular biology and genomics have enabled the detection of early genetic and cellular changes, allowing for earlier diagnosis and treatment, which significantly improves survival. Public health interventions—such as lifestyle modification, vaccination against HPV and hepatitis B, and routine cancer screening—have proven effective in preventing certain cancers, but access to early detection and advanced treatment remains limited in low- and middle-income countries, contributing to late diagnoses and poorer outcomes.1

Cancer arises when normal regulatory mechanisms controlling cell growth, division, and death are disrupted. Abnormal cells proliferate uncontrollably, form tumors, invade surrounding tissues, and can spread to distant organs through metastasis, making the disease particularly dangerous. Early detection is crucial because tumors identified at an initial stage are easier to treat, often require less aggressive therapies, reduce treatment costs, and improve recovery and quality of life. Screening methods for asymptomatic individuals (e.g., mammography, Pap smears) and early diagnosis in symptomatic patients are key strategies for reducing cancer mortality.2

Early-stage cancers, such as localized breast or colorectal tumors, show significantly higher five-year survival rates than advanced disease, highlighting the importance of timely detection. Cancer develops gradually through genetic and epigenetic mutations that promote uncontrolled growth, immune evasion, angiogenesis, and metastasis. 3 Despite improvements in surgery, chemotherapy, radiotherapy, and targeted therapies, challenges like limited sensitivity of diagnostics, drug resistance, and treatment toxicity remain. Emerging research on novel biomarkers, including immunomodulatory and anticancer compounds from edible mushrooms, offers promise for earlier, safer, and more precise detection and treatment, integrating food science, immunology, and oncology to improve global cancer management. 4

Rationale for Using Edible Mushrooms in Cancer Immunomodulation:

Edible mushrooms such as Lentinula edodes, Ganoderma lucidum, Grifola frondosa, and Agaricus blazei have attracted attention for their cancer-preventive and immunomodulatory properties. They contain bioactive compounds—including β-glucans, polysaccharopeptides, lectins, terpenoids, and phenolics—that stimulate macrophages, natural killer cells, dendritic cells, and T lymphocytes, enhancing cytokine production (IL-2, IL-6, TNF-α, IFN-γ), phagocytosis, and tumor immune surveillance. Acting as biological response modifiers, these compounds restore or enhance immune competence compromised by cancer or chemotherapy, while antioxidant and anti-inflammatory effects reduce oxidative stress and chronic inflammation. Additionally, mushrooms exhibit direct antitumor activity through inhibition of proliferation, induction of apoptosis, and cell-cycle arrest via triterpenoids, ergosterol, and polyphenols. Their favorable nutritional profile and long-standing dietary safety make them suitable for supportive cancer care, though further research is needed to standardize species, active compounds, dosing, and integration with conventional therapies for clinical use. 5

EDIBLE MUSHROOMS AS BIOACTIVE SOURCES

Major Edible Mushroom Species Used in Medicine (e.g., Ganoderma, Lentinula, Pleurotus): Early-stage cancers such as localized breast or colorectal tumors have significantly higher five-year survival rates compared to advanced-stage disease, underscoring the importance of early detection through screening and timely diagnosis. Cancer develops gradually through genetic and epigenetic mutations that disrupt normal cell regulation, enabling uncontrolled growth, immune evasion, angiogenesis, and metastasis. 6 Globally, cancer remains a major public health burden, particularly in low- and middle-income countries where late diagnosis and limited healthcare access worsen outcomes. Although current diagnostic tools and treatments—including surgery, chemotherapy, radiotherapy, and targeted therapy—have improved survival, limitations in sensitivity, specificity, drug resistance, and toxicity persist. Emerging research highlights the potential of novel biomarkers for earlier and more precise detection, with edible mushrooms gaining attention due to their immunomodulatory and anticancer properties. Integrating food science, immunology, and oncology may therefore support the development of safer, more accurate, and non-invasive diagnostic and therapeutic strategies for improved cancer management. 7

Biochemical Constituents Present in Edible Mushrooms

Edible mushrooms contain chemically diverse and biologically active compounds—including β-glucan polysaccharides, glycoproteins/lectins, proteoglycans, antioxidants such as ergothioneine and glutathione, phenolics, triterpenoids, sterols, B-vitamins, and trace minerals—that collectively support immune modulation and antioxidative protection. β-(1→3)/(1→6) glucans interact with innate immune receptors (e.g., dectin-1, CR3) to enhance phagocytosis, cytokine production, and antigen presentation, while mushroom proteins, lectins, and proteoglycan complexes may exert synergistic immunoregulatory and antiproliferative effects. Small-molecule antioxidants and triterpenoids further influence redox balance and inflammatory signaling pathways such as NF-κB and MAPK, contributing to potential antitumor activity. These bioactives can induce measurable immune changes—altered cytokine profiles, NK-cell activation, and T-cell modulation—supporting their investigation as candidate biomarkers for early cancer detection. However, clinical translation requires standardized extracts, robust biochemical characterization, well-designed trials, and rigorous validation before diagnostic application. 8

Extraction and Standardization of Mushroom Bioactive Compounds

Effective extraction and standardization are crucial for isolating immunomodulatory compounds—such as β-glucans, lectins, and secondary metabolites—from edible mushrooms. Modern techniques (enzyme-, ultrasonic-, microwave-assisted, or supercritical fluid extraction) improve yield and bioactivity preservation, while fractionation and structural characterization ensure potency. Analytical validation (HPLC, GC-MS, carbohydrate assays) and strict quality control guarantee reproducibility. Linking standardized extracts to immune endpoints like cytokine profiles, NK-cell activity, and proteomic/metabolomic markers provides a framework for developing mushroom-derived compounds as reliable biomarkers and adjuncts for early cancer detection. 9

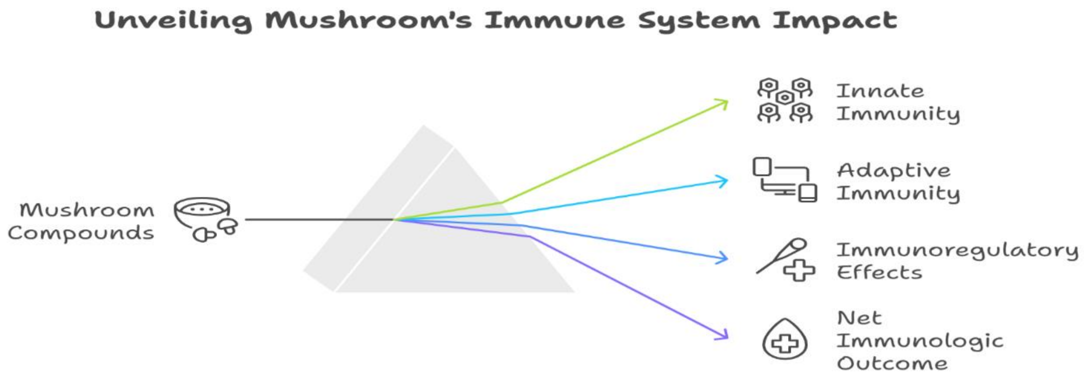
IMMUNOMODULATORY COMPOUNDS IN EDIBLE MUSHROOMS

Immunomodulatory Compounds in Edible Mushrooms

Edible mushrooms contain several immunomodulatory compounds that enhance both innate and adaptive immunity. β-Glucans (β-1,3/1,6) bind receptors like Dectin-1, CR3, and TLRs, activating NF-κB, cytokine release (IL-6, TNF-α, IL-12), phagocytosis, and NK-cell activity, supporting antitumor and anti-infective effects. Fungal immunomodulatory proteins (FIPs) skew cytokines toward Th1 responses, activate macrophages, and exhibit antitumor and antiallergic properties, with potential for recombinant production. Additional compounds—lectins, terpenoids, non-β polysaccharides, and phenolics—modulate lymphocyte activity, inflammation, angiogenesis, and oxidative stress. Together, these molecules act synergistically, enhancing immune surveillance and regulating adaptive responses, particularly in whole mushroom extracts. 10

Mechanisms of Action: Innate vs Adaptive Immunity Regulation

Mushroom compounds act at multiple levels of the immune system. Innate immunity is principally affected by pattern recognition receptor engagement (eg, Dectin-1, TLRs), leading to immediate effector responses: macrophage activation, neutrophil recruitment, NK cell cytotoxicity, and maturation of antigen presenting cells. Adaptive immunity modulation follows, with enhanced antigen presentation and cytokine milieus that bias T-cell differentiation (Th1/Th17 vs Th2/Treg) and support B-cell responses and antibody production. Some mushroom constituents exert immunoregulatory/tolerogenic effects — for example, reducing excessive inflammation via suppression of proinflammatory cytokines or inducing regulatory T cells (Tregs) in specific contexts — which is important for preventing immunopathology. The net immunologic outcome depends on compound structure, dose, host immune status, and formulation (purified vs whole extract). 11



Evidence from In-vitro and In-vivo Studies

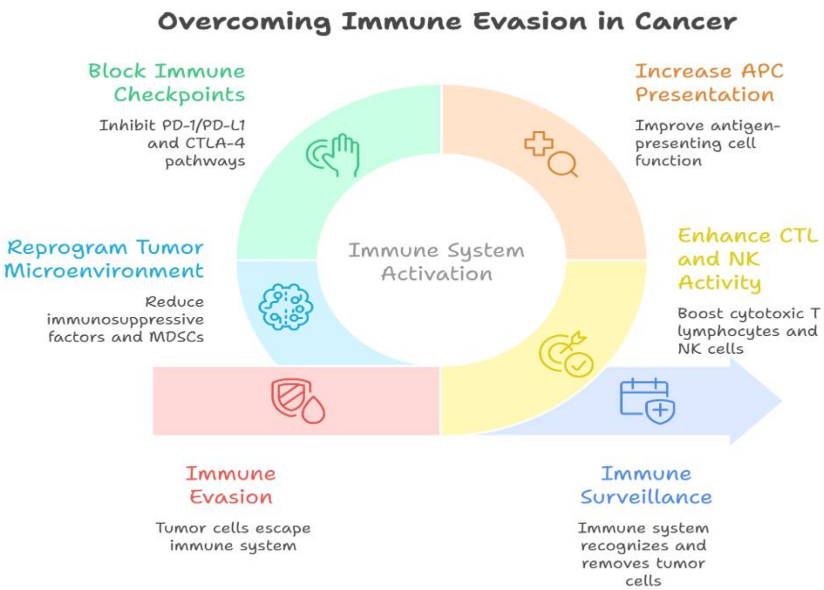
An extensive body of in-vitro studies documents macrophage and dendritic cell activation, NK cell enhancement, and modulation of cytokine expression by mushroom extracts and isolated constituents. In vivo, animal models show reduced tumor growth, improved survival when used as adjuvants with chemotherapy, attenuation of experimentally induced inflammation, improved metabolic markers, and modulation of gut microbiota with downstream immunologic benefits. Several human trials and clinical reports particularly with lentinan (from Lentinula edodes) and certain Ganoderma preparations report improved quality of life, immune biomarkers, and adjunctive benefits in oncology settings, although trial sizes and standardization vary. Limitations across studies include variability in extract composition, dosing regimens, lack of standardized outcome measures, and insufficient large randomized controlled trials. Translational gaps remain, but the concordant in-vitro, in-vivo, and early clinical data support continued development of mushroom-derived immunomodulators.12

Immunomodulation and Cancer Biology

Immunomodulation is the process of altering immune activity—either enhancing or suppressing responses—and is central to cancer biology because tumors actively evade immune surveillance. Normally, cytotoxic T lymphocytes, natural killer (NK) cells, macrophages, and antigen-presenting cells eliminate abnormal cells; however, cancer cells disrupt this defense by expressing immune checkpoint molecules such as PD-L1, secreting immunosuppressive cytokines (e.g., IL-10, TGF-β), and expanding regulatory T cells, thereby creating a tumor-promoting microenvironment. Advances in immuno-oncology, including immune checkpoint inhibitors, cancer vaccines, and adoptive cell therapies like CAR-T cells, aim to restore effective anti-tumor immunity and have shown success in malignancies such as melanoma, lung cancer, and hematologic cancers. Understanding immunomodulation also supports the identification of clinically relevant biomarkers—circulating cytokines, immune-cell signatures, and tumor-associated antigens—that aid early detection, prognostication, and treatment selection. Thus, integrating immunological insights is critical for precision oncology and improved long-term cancer outcomes. 13

Tumor Immune Escape Mechanisms

Cancer expansion is carefully linked to the disappointment of immune surveillance mechanisms. Below normal circumstances, the immune classification recognizes and removes transformed cells concluded the corresponding activity of cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and antigen giving cells (APCs). But, tumor cells frequently escape immune demolition through a variety of escape approaches. 14 These contain downregulation of main histocompatibility compound class I (MHC-I) molecules, excretion of immunosuppressive cytokines such as interleukin-10 (IL-10) and converting development influence beta (TGF-β), and the instigation of regulatory T cells (Tregs) that suppress effecter purposes. Furthermore, tumors activity immune checkpoint paths such as PD-1/PD-L1 and CTLA-4 to deactivate T-cell responses, permitting malignant cells to flourish unrestricted. The aptitude of tumors to generate an immunosuppressive microenvironment over metabolic reprogramming, hypoxia, and myeloid resultant suppressor cell (MDSC) conscription more delays anti-tumor immunity, instead of major challenges for cancer immunotherapy. 15



NK Cells, T-Cells, Dendritic Cells, and Macrophage Involvement

Innate and adaptive immune cells cooperatively regulate the conclusion of tumor-immune connections. NK cells serve as a initial line of resistance by unswervingly lysing tumor cells deficient MHC-I and concealing interferon-gamma (IFN-γ) to stimulate further immune mechanisms. Dendritic cells (DCs) imprisonment and present tumor related antigens, introducing cytotoxic T-cell initiation. Effecter CD8+ T cells then facilitate tumor cell killing via perforin/granzyme pathways, whereas CD4+ helper T cells adjust cytokine networks to endure anti-tumor activity. Macrophages performance dual characters conditional on their opposition: characteristically stimulated M1 macrophages encourage tumor suppression via nitrous oxide and pro-inflammatory cytokine issue, while otherwise activated M2 macrophages support tumor development concluded angiogenesis and tissue restoration. Current cancer immunotherapy purposes to reprogram immune cells near a tumoricidal phenotype, enhancing M1 separation, NK cell cytotoxicity, and antigen-specific T-cell replies. 16

Mushroom-Induced Enhancement of Anti-Tumor Immune Responses

Edible and therapeutic mushrooms comprise a extensive range of bioactive complexes capable of retreating tumor-induced immunosuppression and inspiring host anti-tumor defenses. β-glucans, triterpenoids, and fungal immunomodulatory proteins (FIPs) from species such as Ganoderma lucidum, Lentinula edodes, and Pleurotus ostreatus have demonstrated potent immunostimulatory effects. These complexes improve macrophage initiation, upregulate cytokines like IFN-γ and IL-12, and rise NK and T-cell activity. Aimed at occurrence, lentinan, a β-glucan as of Lentinula edodes, stood used as an accessory in cancer therapy to supplement chemotherapeutic efficacy and progress patient survival by activation macrophages and cytotoxic lymphocytes. 17 Likewise, Ganoderma lucidum extracts have revealed the ability to downregulate immunosuppressive cytokines (IL-10, TGF-β) though promoting dendritic cell maturing and antigen exhibition. In vivo studies expose that mushroom polysaccharides can prevent tumor growth, induce apoptosis, and reestablish immune cell populations in tumor-bearing masses. This suggestion emphasizes the therapeutic possible of mushrooms as natural immunomodulators in oncological tenders. 18

Immunomodulation as a Basis for Biomarker Development

The immunomodulatory belongings of edible mushrooms not individual suggestion therapeutic value but similarly grip promise for biomarker detection in cancer immunology. Biomarkers resultant from immune modulation can assist as early indicators of behavior response, ailment development, or host immune status. Mushroom-derived bioactive molecules might affect measurable immune restrictions, such as cytokine profiles (IL-2, IL-6, IFN-γ), lymphocyte stimulation markers (CD69, CD25), and gene expression signs related with immune activation or suppression. Besides, participating proteomic and metabolomic investigates with mushroom-based clinical interferences can expose novel immune-related biomarkers analytical of therapeutic conclusions. Such biomarkers might facilitate early discovery of immune modifications throughout carcinogenesis and enable modified immunonutrition approaches in cancer inhibition and management. The capability of mushrooms to modify both innate and adaptive immunity so provides a exclusive platform for translational biomarker research involving nutrition, immunity, and oncology. 19

Emerging Novel Biomarkers for Early Cancer Detection

Emerging biomarkers for early cancer detection emphasis on classifying delicate molecular changes that happen throughout the early stages of tumor expansion. Current advances in genomics, proteomics, and metabolomics have allowed the detection of socializing tumor DNA (ctDNA), microRNAs (miRNAs), exosomes, and epigenetic symbols such as DNA methylation outlines. These biomarkers remain detectable in slightly invasive samples like blood, saliva, or urine, production them ideal for initial screening. Liquid biopsy technologies are particularly promising since they provide real-time data about tumor dynamics and can distinguish cancer earlier clinical symptoms seem. Additionally, advances in machine learning are improving the accuracy of biomarker-based prediction models. 20

Another growing area involves the integration of multi-omics biomarkers, where genomic, proteomic, and metabolic signatures are combined to improve diagnostic specificity and sensitivity. Multi-omics panels can distinguish between benign and malignant changes more effectively than single biomarkers. For example, panels combining ctDNA mutations, methylation signatures, and protein markers have shown increased accuracy in detecting cancers such as lung, breast, and colorectal cancer at early stages. These innovations are moving towards personalized screening strategies that could significantly reduce cancer morbidity and mortality through earlier intervention. 21

Immune-Based Biomarkers for Early Cancer Detection

Immune cell profiles and cytokine panels offer promising early indicators of malignancy. NK-cell frequency and activation reflect tumor surveillance, while T-cell metrics (CD8+ abundance, CD4:CD8 ratios, effector vs. regulatory balance) correlate with prognosis and treatment response, often preceding clinical changes. Multiplexed cytokine and chemokine panels—including pro-inflammatory (IL-6, TNF-α), immunosuppressive (IL-10, TGF-β), and chemotactic markers—capture the complex immune environment, helping distinguish early tumorigenesis from benign inflammation. These markers, measured via advanced platforms like multiplex immunoassays, provide minimally invasive, reproducible tools for early detection and risk stratification. 22

Exosome microRNAs and cell-free DNA (cfDNA) as cancer indicators

Two non-invasive liquid-biopsy approaches have advanced rapidly: exosome microRNAs (miRNAs) and cfDNA. Exosome miRNAs are packaged in extracellular vesicles that protect RNA from degradation, allowing detection of tumor-derived signatures in blood; panels of exosomes miRNAs have been reported to discriminate specific cancers with good sensitivity in early studies. Cell-free DNA approaches (mutation detection, methylation profiling, and fragment omics) can directly signal the presence of tumor DNA in plasma; combined analytic strategies (mutation + methylation + fragment size patterns) markedly improve early-detection performance in multi-cancer assays. Both modalities are complementary: exosomes provide RNA/protein context and cfDNA provides direct genomic evidence of tumor cells. 23

Soluble immune-checkpoint markers (sPD-L1, sPD-1)

Soluble forms of checkpoint molecules such as sPD-L1 and sPD-1 are measurable in plasma and have emerged as candidate biomarkers for disease status and therapeutic response. Elevated sPD-L1 levels have been associated with more advanced disease and, in some cohorts, with poorer prognosis or differential response to immune checkpoint inhibitors although results vary by cancer type and assay. The biology likely reflects alternative splicing/cleavage or vesicle-associated release of checkpoint proteins and underscores how immune-derived soluble markers can complement cellular and nucleic acid biomarkers. Standardization of assays and larger prospective validations are still required. 24

Table 1. Key edible mushrooms, their bioactive compounds, immunomodulatory effects, and potential biomarkers for early cancer detection.

Mushroom	Bioactive Compounds	Immune/Antitumor Effects	Biomarker Potential
Lentinula edodes	β-Glucans, polysaccharopeptides	NK-cell activation, cytokine modulation	NK activity, cytokine panels
Ganoderma lucidum	Triterpenoids, FIPs, lectins	Anti-inflammatory, T-cell regulation	T-cell ratios, exosomal miRNAs
Grifola frondosa	D-fraction β-glucans	Enhanced phagocytosis, tumor surveillance	NK-cell activity, cytokines
Agaricus blazei	β-Glucans, phenolics	Immune stimulation, antioxidant	Cytokine & chemokine panels

Clinical evidence and trials

Human clinical trials evaluating edible mushroom extracts—such as lentinan from Lentinula edodes, PSK (Krestin), Maitake D-fraction from Grifola frondosa, and formulations derived from Ganoderma lucidum and Agaricus blazei—have primarily investigated their role as immunomodulatory adjuvants alongside surgery or chemotherapy rather than as standalone anticancer agents. Evidence is strongest for PSK in resected gastric and some colorectal cancers, where randomized trials in East Asia have shown improved survival and reduced recurrence when combined with standard therapy, although results vary across studies. 25 Lentinan has demonstrated potential benefits in advanced gastric and colorectal cancers, particularly in earlier trials, while Maitake and Ganoderma extracts have shown consistent immune-enhancing effects (e.g., increased NK-cell activity, cytokine modulation) in early-phase studies but lack robust large-scale survival data. Overall, findings suggest biological plausibility and possible quality-of-life improvements, yet heterogeneity in extract composition, dosing, and trial design limits definitive conclusions.

Safety profiles are generally favorable, with mostly mild gastrointestinal or allergic adverse effects reported; however, potential drug interactions and variability in preparation require careful monitoring. Major limitations across the literature include small sample sizes, inconsistent endpoints (immune biomarkers vs. survival), geographic concentration of studies, and insufficient standardization of extracts. Moving forward, a structured clinical framework is essential—incorporating appropriate patient selection, standardized sample collection (blood, serum, exosomal markers), validated laboratory methods (flow cytometry, ELISA, NGS, qPCR), and rigorous statistical modeling of immune-response patterns. Integration of mushroom-derived immunomodulatory biomarkers into established cancer screening programs will require multicenter randomized trials, regulatory validation, and cost-effectiveness evaluation to ensure reliable translation into clinical oncology practice. 26

Challenges and Future Directions

The clinical translation of edible mushroom–based immunotherapy faces several challenges, foremost among them the need for rigorous standardization of extracts with respect to species/strain selection, cultivation conditions, extraction methodology, dose, and purity to ensure reproducibility and consistent bioactive composition. Biological variability in immune responses—driven by genetics, age, comorbidities, and gut microbiome differences—further necessitates personalized approaches and predictive biomarkers to identify likely responders. Although promising preclinical and early-phase data exist for species such as Lentinula edodes, Ganoderma lucidum, and Grifola frondosa, there remains a shortage of large, multicenter randomized controlled trials with standardized protocols and clinically meaningful endpoints to confirm safety, efficacy, optimal dosing, and interaction profiles with conventional therapies. Advancing the field will require integration of personalized immunonutrition strategies, multi-omics biomarker discovery, long-term safety evaluation, and strong interdisciplinary collaboration to establish mushroom-derived immunomodulators as credible adjuncts in precision oncology.

Conclusion:

In conclusion, edible mushrooms offer promising immunomodulatory compounds that can enhance anti-tumor immunity and serve as novel biomarkers for early cancer detection. Bioactives like β-glucans, lectins, and triterpenoids modulate immune responses and may reflect early tumor changes. Translating this potential clinically requires standardized extracts, robust trials, and biomarker validation, positioning mushrooms as valuable adjuncts for early detection and improved cancer outcomes.

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