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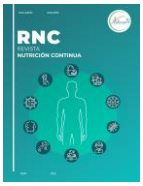

Clinical evidence on the immunomodulatory effects of mushroom-derived bioactive compounds in humans: a scoping review.

Evidencia clínica sobre los efectos inmunomoduladores de compuestos bioactivos derivados de hongos en humanos: una revisión de alcance.

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Keywords

Immunomodulation; Mushrooms; Clinical Trials; Immune System; Functional Foods.

ABSTRACT

Introduction: Edible and medicinal mushrooms have traditionally been consumed for their health-promoting properties, particularly their capacity to influence immune function. In recent decades, their incorporation into nutraceutical products and dietary supplements has expanded alongside growing scientific interest in mushroom-derived bioactive compounds. However, human clinical evidence remains heterogeneous regarding species studied, extract characterization, populations, and immunological endpoints assessed. A structured synthesis focused on quantitative immune outcomes was therefore needed to clarify the scope and methodological patterns of existing studies. **Methods:** A scoping review was conducted in accordance with PRISMA-ScR guidelines. PubMed, Scopus, SciELO, and LILACS were searched from inception through March 10, 2025. Eligible studies were primary human clinical investigations evaluating immunomodulatory effects of single-species mushroom interventions administered orally and assessed using predefined quantitative techniques. Studies involving mixed formulations, unidentified species, animal or *in vitro* designs, or lacking quantitative immunological methods were excluded. Data were charted independently by two reviewers and synthesized narratively using descriptive frequency analysis. **Results:** Thirty-three studies met inclusion criteria. Although nineteen genera were predefined, only eight were represented in eligible trials. *Ganoderma* and *Pleurotus* were most frequently investigated. Polysaccharides and glycoconjugates were the predominant bioactive category. Cancer patients comprised the largest subgroup. Cellular immunity was most commonly assessed. Immunostimulatory effects predominated, alongside anti-inflammatory and bidirectional responses. **Conclusions:** Mushroom-derived dietary interventions are associated with measurable immune modulation in humans, especially within cellular immunity and inflammatory pathways. Greater extract standardization and harmonized immune biomarkers are required to strengthen translational relevance in clinical nutrition.

Palabras clave

Inmunomodulación; Hongos; Ensayos clínicos; Sistema inmune; Alimentos funcionales.

RESUMEN

Introducción: Los hongos comestibles y medicinales han sido tradicionalmente consumidos por sus propiedades promotoras de la salud, especialmente por su capacidad de influir en la función inmunitaria. En las últimas décadas, su uso en suplementos dietarios y productos nutracéuticos ha aumentado, junto con el interés científico en sus compuestos bioactivos. Sin embargo, la evidencia clínica en humanos es heterogénea en cuanto a especies estudiadas, caracterización de extractos, poblaciones y desenlaces inmunológicos evaluados. Se realizó una síntesis estructurada enfocada en resultados inmunológicos cuantitativos para clarificar el alcance de la evidencia disponible. **Métodos:** Se llevó a cabo una revisión de alcance conforme a las directrices PRISMA-ScR. Se consultaron PubMed, Scopus, SciELO y LILACS desde su inicio hasta el 10 de marzo de 2025. Se incluyeron estudios clínicos primarios en humanos que evaluaran efectos inmunomoduladores de intervenciones con hongos de una sola especie administrados por vía oral y analizados mediante técnicas cuantitativas predefinidas. Los datos fueron extraídos por dos revisores y sintetizados mediante análisis descriptivo de frecuencias. **Resultados:** Treinta y tres estudios cumplieron los criterios de inclusión. Aunque se consideraron diecinueve géneros, solo ocho estuvieron representados. *Ganoderma* y *Pleurotus* fueron los más investigados. Los polisacáridos y glicoconjugados fueron la categoría predominante. La inmunidad celular fue el dominio más evaluado, predominando efectos inmunoestimulantes, así como respuestas antiinflamatorias y bidireccionales. **Conclusiones:** Las intervenciones dietarias derivadas de hongos se asocian con modulación inmunitaria medible en humanos. Se requiere mayor estandarización de extractos y armonización de biomarcadores para fortalecer su aplicabilidad en nutrición clínica.

INTRODUCTION.

In recent decades, growing interest in functional nutrition and food-derived bioactive compounds has intensified in response to the increasing global burden of inflammatory, infectious, metabolic, and oncological diseases. At the same time, conventional immunomodulatory therapies—including immunosuppressive agents, biologics, and cytokine-based immunostimulatory approaches—have substantially improved clinical management, but their use remains constrained by important limitations. In immunosuppressive and biologic regimens, these limitations include serious and opportunistic infections, and, in some settings, malignancy (Holmer & Singh, 2019). Cytokine-based immunostimulatory strategies may also be accompanied by substantial systemic toxicities that can limit their broader clinical use. In addition, several immunomodulatory regimens require

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routine laboratory monitoring, which adds complexity to long-term management (Rigby *et al*., 2017). Economic barriers further constrain access, particularly for biologic therapies, whose high cost has contributed to inequities in treatment availability. Moreover, clinical response to immunomodulatory therapies is often heterogeneous across patients, reflecting broader translational and implementation challenges in this therapeutic field (Baumgart *et al.,* 2019). Within this context, edible and medicinal mushrooms used as dietary or supplemental interventions have gained attention as sources of bioactive compounds with potential immunomodulatory effects in humans. Multiple reviews have highlighted the immunological relevance of fungal polysaccharides—particularly β-glucans—in regulating innate and adaptive immunity (Ayeka, 2018; Chugh *et al*., 2022; Loaiza-Ceballos *et al*., 2025). Advances in chemical and structural characterization have further strengthened the rationale for exploring mushroom-derived bioactives as functional nutritional ingredients and potential clinical adjuvants (Venturella *et al*., 2021; Wasser, 2011).

Medicinal mushrooms have been used for centuries in traditional Asian medical systems and are incorporated into dietary and ethnopharmacological practices in countries such as China, Japan, and India. Several genera—including *Ganoderma lucidum*, *Cordyceps sinensis*, *Grifola frondosa*, and *Lentinus edodes*—have traditionally been attributed immunomodulatory, antioxidant, antitumoral, and adaptogenic properties (Lull *et al*., 2005; Venturella *et al*., 2021). In contemporary contexts, many of these species are consumed not only as foods but also as orally administered extracts, powders, or capsules within the nutraceutical market. The global mushroom market has experienced sustained expansion, reflecting increasing scientific and industrial interest in mushroom-derived bioactives for nutraceutical, pharmaceutical, and food biotechnology applications (https://www.polarismarketresearch.com, 2025). Despite their historical dietary use and commercial growth, clinical validation of their immunological effects following oral supplementation remains incomplete and methodologically heterogeneous.

From a mechanistic perspective, fungal β-glucans represent the most extensively studied immunologically active constituents. Structurally characterized by β-(1→3)-linked glucose backbones with β-(1→6) branching, these polysaccharides are recognized by pattern-recognition receptors (PRRs) such as Dectin-1, complement receptor 3 (CR3), and Toll-like receptors (TLR2 and TLR4) expressed on macrophages, dendritic cells, and neutrophils (Brown & Gordon, 2005; Chan *et al*., 2009; Goodridge *et al*., 2009). Engagement of these receptors activates intracellular signaling cascades—including Syk, NF-κB, MAPK, and PI3K/Akt pathways—leading to cytokine production (e.g., IL-1β, IL-6, TNF-α), enhanced phagocytosis, antigen presentation, and modulation of T lymphocyte and natural killer (NK) cell activity (Brown & Gordon, 2005; Chan *et al*., 2009; Goodridge *et al*., 2009). Through these pathways, mushroom-derived polysaccharides can influence both innate and adaptive immune responses and contribute to the maintenance of immune homeostasis depending on host immune status (Chugh *et al*., 2022; Goodridge *et al*., 2009).

In addition to immediate activation of innate immune signaling, β-glucans have been implicated in the induction of trained immunity, a process characterized by epigenetic and metabolic reprogramming of innate immune cells that enhances responsiveness upon secondary stimulation (Netea *et al*., 2016). This concept provides a framework for understanding sustained immunological effects observed after dietary supplementation in certain clinical contexts. However, β-glucans are not the only mushroom-derived compounds with putative immunomodulatory relevance. Review literature indicates that other polysaccharide classes, including heteroglycans, peptidoglycans, and polysaccharide–protein complexes, may also contribute to biological activity, and that their effects can vary according to structural features such as branching degree, linkage type, side-chain composition, and constituent monosaccharides (Venturella *et al.,* 2021). In parallel, medicinal mushrooms contain other bioactive metabolites and proteins of interest, including terpenes/terpenoids, lectins, fungal immunomodulatory proteins, and phenolic compounds (Venturella *et al.,* 2021; Chugh *et al.,* 2022). Preclinical evidence

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summarized in these reviews suggests that some of these constituents may participate in immune modulation through effects on immune-related gene expression or through activation of lymphocytes, macrophages, natural killer cells, and cytokine production, although these mechanistic data derive predominantly from *in vitro* and animal studies rather than controlled human trials (Lull *et al.,* 2005; Venturella *et al.,* 2021; Chugh *et al.,* 2022).

Clinical studies evaluating mushroom-derived products have reported immunological effects in diverse populations, although findings vary according to species, extract composition, dosage, duration, and baseline immune status. Randomized controlled trials have shown that β-glucans derived from *Ganoderma lucidum* can enhance NK cell cytotoxicity and modulate immunoglobulin levels in healthy adults without significant adverse effects (Chen *et al*., 2023). Supplementation with mushroom-derived polysaccharides has also been associated with increased T lymphocyte counts in pediatric populations (Henao *et al*., 2018). In oncology contexts, phase I/II clinical studies of *Grifola frondosa* extracts have demonstrated dose-dependent changes in cytokine production and NK cell activity, suggesting context-dependent or biphasic immunomodulation (G. Deng *et al*., 2009). However, other trials have reported limited or inconsistent changes in inflammatory markers, as observed in patients with rheumatoid arthritis treated with *Ganoderma lucidum* (Li *et al*., 2007).

Such variability may reflect differences in fungal species, extraction methods, molecular composition, dosage, duration of intervention, and baseline immune status of participants. In addition, the chemical profile and bioactive compound content of medicinal mushrooms may vary according to cultivation conditions, degree of maturity, environmental factors, and the world region from which they originate, while processing conditions can further affect the retention of nutritionally and nutraceutically relevant constituents (Łysakowska *et al.,* 2023; Yadav & Negi, 2021). Structural heterogeneity in β-glucans—including molecular weight and branching patterns—has been shown to influence receptor binding and downstream signaling intensity (Chan *et al*., 2009; Goodridge *et al*., 2009). Moreover, the frequent use of mixed or insufficiently characterized extracts limits mechanistic attribution and reproducibility, posing challenges for pharmaceutical development and regulatory standardization. The diversity of immunological biomarkers assessed across studies further complicates synthesis and comparison of findings.

Given the fragmented nature of the clinical literature and the absence of an integrative synthesis focused specifically on predefined quantitative immunological techniques in human supplementation studies, a scoping review following PRISMA-ScR guidelines was considered appropriate. This approach is particularly relevant in multidisciplinary and emerging fields such as medicinal mushroom immunomodulation, where clinical evidence is dispersed across diverse populations and study designs.
Therefore, the objective of the present review was to characterize and synthesize the available clinical evidence on the immunomodulatory effects of 19 genera of edible and medicinal mushrooms administered to humans as dietary or supplemental interventions, identifying the species most frequently studied, the categories of bioactive compounds evaluated, the immunological domains assessed, and the clinical contexts in which these effects have been investigated.

METHODS.

Protocol and Registration.

A protocol was developed *a priori* to define the objectives, eligibility criteria, search strategy, and data-charting framework of this scoping review, in accordance with the PRISMA Extension for Scoping Reviews (Tricco *et al*., 2018). The protocol was not formally registered and is not publicly available. This review does not represent an update of a previously published study.

Eligibility Criteria.

Eligibility criteria were established *a priori* and applied sequentially during title/abstract screening and full-text assessment. At the screening stage, studies were included if they were primary research articles involving human participants, reported immunomodulatory outcomes, and were published

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in English or Spanish. Reviews, editorials, letters, conference abstracts, animal studies, and *in vitro* investigations were excluded.

During full-text evaluation, studies were excluded if the fungal species was not taxonomically identified at the species level, or if it was reported only using generic, vernacular, commercial, or otherwise taxonomically imprecise denominations that did not allow adequate traceability of the fungal source. Studies were also excluded if the intervention consisted of mixed or multi-component formulations that precluded attribution of the immunological effects to a single mushroom species, if predefined quantitative immunological techniques (ELISA, quantitative polymerase chain reaction, Western blot, or flow cytometry) were not used, or if the full text was unavailable. No publication date restrictions were applied.

Information Sources and Search Strategy.

A comprehensive search was conducted between January and March 2025 in PubMed, Scopus, SciELO, and LILACS. The final search update was performed on March 10, 2025. Only peer-reviewed articles were considered.

No gray literature sources were searched. This decision was made because the review aimed to synthesize clinical human studies reporting predefined quantitative immunological outcomes, in a field where intervention traceability and methodological consistency were particularly relevant. Restricting inclusion to peer-reviewed literature was considered a strategy to improve comparability of the included evidence, although it may also have limited the identification of potentially relevant non-indexed or unpublished studies.

The search strategy was developed and executed by the research team without involvement of an information specialist and was not externally peer-reviewed. Database-specific queries combined the truncated terms *Immu* and I*nflamma* with the names of 19 predefined mushroom genera (*Agaricus, Auricularia, Coprinus, Cordyceps, Flammulina, Ganoderma, Grifola, Hericium, Hypsizygus, Inonotus, Laetiporus, Lentinus, Ophiocordyceps, Phellinus, Pleurotus, Schizophyllum, Sclerotinia, Trametes, and Tricholoma*). The 19 predefined mushroom genera were selected based on their recurrent mention in the literature on edible and medicinal mushrooms with reported or putative immunomodulatory relevance, as well as their historical and nutraceutical importance in prior review-based syntheses (Lull et al., 2005; Wasser, 2011; Venturella et al., 2021; Chugh et al., 2022). Searches were restricted to title and abstract fields (or database equivalents). No automated filters for date, study design, species, or publication type were applied; these criteria were assessed manually during screening. Complete reproducible search strategies are provided in Supplementary Appendix 1.

All retrieved records were exported to a .csv master file, and duplicates were removed manually in Microsoft Excel®, followed by manual verification.

Selection of Sources of Evidence.

After duplicate removal, records were screened independently and in duplicate by two reviewers using a standardized form developed in Microsoft Excel®. Screening was conducted in two stages: title/abstract review followed by full-text assessment. Discrepancies were resolved through discussion; a third reviewer adjudicated unresolved disagreements. No formal calibration exercise was performed before screening; in this context, calibration would have involved a structured pilot assessment between reviewers to evaluate agreement and refine the operational application of the eligibility criteria. The entire selection process was conducted within Microsoft Excel®.

Data Charting and Data Items.

A standardized data-charting form was developed in Microsoft Excel® by the two reviewers and refined iteratively during extraction. Data were charted independently and in duplicate, with discrepancies resolved by consensus or third-reviewer adjudication.

Extracted variables included author and year, country, study design, population characteristics, fungal genus and species, type of preparation, bioactive compound category, immunological domain assessed, type of immunological effect, and

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principal molecular immunological outcomes measured using ELISA, qPCR, Western blot, or flow cytometry. Only the direction of effect was recorded; statistical significance levels and numerical values were not extracted.

Immunological domains were classified according to the measured parameter: cellular immunity (e.g., NK cell activity, T-cell subsets, IFN-γ, IL-2), humoral immunity (immunoglobulins or specific antibodies), inflammation (pro- or anti-inflammatory cytokines and acute-phase proteins), and phagocytosis (functional cellular assays).

Immunological effects were categorized as immunostimulatory, immunosuppressive/anti-inflammatory, bidirectional (biphasic), immunomodulatory (regulatory), or no effect, based on the functional direction of reported outcomes. Immunostimulatory effects were defined as changes consistent with enhancement of immune activity, such as increases in immune cell counts, immune cell function, or pro-activation cytokine responses. Immunosuppressive/anti-inflammatory effects were defined as changes consistent with attenuation of inflammatory activity or reduction of immune activation markers. Bidirectional (biphasic) effects were defined as responses showing both increases and decreases in different immune parameters, or opposite effects depending on the clinical context or immune marker assessed. Immunomodulatory (regulatory) effects were defined as context-dependent immune changes interpreted as contributing to immune balance or homeostasis, including stabilization, normalization, or selective modulation of biomarkers rather than a purely stimulatory or suppressive direction. No effect was assigned when studies reported no relevant change in the evaluated immunological outcomes. Classification required interpretative judgment by the review team; in cases of ambiguity, consensus was reached through discussion. When multiple outcomes were reported, the primary immunological endpoint defined by the original study was prioritized.

The final data-charting form is available from the authors upon reasonable request.

Critical Appraisal of Individual Sources of Evidence.

A formal critical appraisal of methodological quality or risk of bias was not conducted. This decision was consistent with the objective of this scoping review, which was to map and characterize the scope and distribution of clinical evidence rather than to evaluate internal validity or methodological rigor.

Synthesis of Results.

Evidence was synthesized using a narrative descriptive approach supported by simple frequency counts. No quantitative pooling or meta-analysis was performed.

Studies were organized according to study design, geographic region, publication period, fungal genus, bioactive compound category, immunological domain, type of immunological effect, and population characteristics. Findings were presented through narrative summaries and graphical representations, including a PRISMA-ScR flow diagram and distribution figures. Variability in study characteristics and outcomes was described descriptively; no subgroup analyses or formal assessments of heterogeneity were conducted.

Ethical statements.

This is a review article based on published clinical studies, and no primary data were collected by the authors. As such, ethical approval or consent was not required for the content of this manuscript. The authors ensured that all studies referenced in this review adhere to ethical guidelines, and proper acknowledgment of the original sources was provided for all included works. No human or animal subjects were involved in this review article.

RESULTS.

Study Selection.

The database search identified 20,285 records. After removal of 8,995 duplicates, 11,290 records underwent title and abstract screening. Of these, 11,183 were excluded for not meeting inclusion criteria. A total of 107 full-text articles were

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assessed for eligibility, and 74 were excluded due to lack of taxonomic identification, use of mixed formulations, absence of predefined quantitative immunological techniques, or unavailability of full text. Thirty-three clinical studies met all eligibility criteria and were included in the scoping review (Figure 1).

Structural Characteristics of the Included Studies.

The included studies were conducted predominantly in Asia, with additional contributions from Europe and the Americas and limited representation from Oceania (Figure 2A).

The temporal distribution spanned from the 1990s to 2025, with the largest number of publications occurring between 2010 and 2019, followed by studies published from 2020 onward (Figure 2B).

Randomized controlled trials represented the most frequent study design, followed by open-label or pilot clinical studies and phase I/II trials. Observational studies and case series accounted for a smaller proportion of the included evidence (Figure 2C).

Study Populations.

The characteristics of the study populations are detailed in Table 1. The included studies involved patients with cancer (n = 11), metabolic diseases (n = 4), autoimmune disorders (n = 1), infectious diseases (n = 2), and hematologic conditions (n = 1). Studies conducted in healthy adults accounted for n = 9, while healthy adults under physical stress represented n = 3. Pediatric populations with infectious conditions were evaluated in n = 2 studies.

Patients with cancer constituted the largest clinical subgroup within the included evidence base.

Mushroom Genera and Bioactive Compounds.

The distribution of mushroom genera and bioactive compound categories evaluated across studies is summarized in Table 1. Nineteen genera were predefined in the search strategy. However, only eight genera met the eligibility criteria and were represented in the final synthesis: The most frequently investigated genus was *Ganoderma* (n = 10), followed by *Pleurotus* (n = 6) and *Agaricus* (n = 4). Fewer studies evaluated *Grifola* (n = 4), *Cordyceps* (n = 3), *Phellinus* (n = 3), and *Lentinus* (n = 2), while *Schizophyllum* was examined in a single study (n = 1).

With respect to bioactive material, polysaccharides and glycoconjugates constituted the predominant category (n = 20), whereas mixed or non-characterized extracts were evaluated in n = 12 studies. In this classification, the category “mixed/non-characterized extracts” referred to single-species interventions in which the bioactive preparation was reported as a crude, composite, or insufficiently characterized extract, rather than to formulations combining multiple mushroom species. A single investigation assessed a defined nucleoside compound derived from *Cordyceps* (n = 1).

Table 1 provides study-level detail on the corresponding compound type, direction of effect, and evaluated population.

Molecular and Cellular Immunological Outcomes.

Table 1 details the specific molecular and cellular immunological endpoints reported in each study, including mushroom genus, bioactive compound type, direction of effect, and study population.

Across studies, increases were reported in immune cell subsets, including $CD3^+$, $CD4^+$, $CD8^+$ T lymphocytes, B lymphocytes, and NK cells, as well as in functional parameters such as NK cell activity, lymphocyte proliferation indices, respiratory burst, and phagocytic capacity. Elevations in cytokines associated with cellular activation, including IL-2, IL-6, IFN-γ, IL-12, and TNF-α, were also documented.

Decreases were reported in pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, as well as in C-reactive protein, eosinophil counts, B lymphocytes, helper T cells, and selected activation markers. In certain studies, reductions in inflammatory mediators occurred alongside increases in cellular immune parameters.

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Some investigations described preservation or stabilization of immune markers, particularly NK cell activity and immunoglobulin levels. Isolated studies reported no significant changes in measured inflammatory or antioxidant parameters.

The evaluated endpoints encompassed cellular immunity (NK cells, T-cell subsets, regulatory T cells), humoral immunity (immunoglobulin concentrations and B-cell counts), inflammatory mediators (pro- and anti-inflammatory cytokines and acute-phase proteins), and functional immune assays.

Classification of Immunological Effects.

Reported immunological responses were categorized as immunostimulatory, bidirectional (biphasic), immunosuppressive/anti-inflammatory, immunomodulatory (regulatory), or no effect (Figure 3A). Immunostimulatory effects were the most frequently reported category. Bidirectional responses and immunosuppressive/anti-inflammatory effects were also observed across multiple studies, whereas immunomodulatory (regulatory) effects and absence of detectable change were less frequently reported.

Immune Domains Evaluated.

The immunological parameters assessed were grouped into four domains: cell-mediated immunity, inflammation, humoral immunity, and phagocytosis (Figure 3B).

Cell-mediated immunity was the most frequently evaluated domain, followed by inflammatory markers. Humoral immunity and phagocytic function were assessed in a smaller subset of studies.

DISCUSSION.

This scoping review mapped human clinical evidence on the immunomodulatory effects of single-species edible and medicinal mushrooms administered as dietary or supplemental interventions and assessed using predefined quantitative immunological techniques. Across 33 studies, reported immune outcomes clustered primarily around modulation of cellular immunity and inflammatory mediators. Recurrent signals involved NK-cell activity, T-lymphocyte subsets, and cytokine patterns consistent with Th1-associated activation and/or attenuation of inflammatory pathways. These clinical patterns were most frequently described for polysaccharide- and glycoconjugate-rich preparations and, to a lesser extent, for mixed or insufficiently characterized extracts. Collectively, the findings suggest biological plausibility for mushroom-derived polysaccharides as functional nutritional bioactives, while simultaneously underscoring the interpretative challenges introduced by heterogeneous product characterization.

From a mechanistic perspective, fungal polysaccharides—particularly β-glucans—are recognized by innate immune receptors expressed on monocytes/macrophages, neutrophils, dendritic cells, and other effector populations, thereby shaping downstream cytokine and functional responses. Canonical recognition involves Dectin-1 and complement receptor 3 (CR3), with cooperative signaling capable of engaging Syk-dependent pathways and converging on NF-κB/MAPK activation. These cascades influence cytokine production, phagocytosis, and antigen presentation, providing a coherent biological framework for interpreting clinical changes in immune cell function and cytokine profiles reported in supplementation studies (Brown & Gordon, 2005; Goodridge *et al.*, 2009). Broader immunopharmacological syntheses further support the plausibility of these receptor-mediated effects across immune and cancer-related contexts (Ayeka, 2018; Chan *et al*., 2009). Importantly, however, the mapped evidence supports association rather than causality, particularly given the variability in formulations and clinical designs.

In oncology settings, the predominance of cell-mediated endpoints is clinically meaningful because these biomarkers are closely related to antitumor immune surveillance. In the trials by Gao *et al.* (2003, 2005), *Ganoderma lucidum* polysaccharides in advanced-stage cancer and advanced lung cancer were associated with increases in IL-2, IL-6, IFN-γ, CD56+ cells, and NK-cell activity; in the lung cancer study, increases in CD3+, CD4+, and CD8+ cells were also reported, together with decreases in IL-1 and TNF-α (Gao *et*

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al., 2003, 2005). Likewise, *Grifola frondosa* D-fraction was associated with sustained enhancement of NK cytotoxic activity in cancer patients (Kodama *et al.,* 2002), while postoperative biomarker studies with *Ganoderma* spore powder also pointed toward immunological benefit in breast and lung cancer settings (Deng *et al.,* 2021). Taken together, these findings suggest that, in cancer populations, mushroom-derived preparations have mainly been investigated as adjunctive nutritional interventions with potential relevance for immune surveillance, rather than as isolated anti-inflammatory agents.

By contrast, in metabolic and autoimmune conditions, the most clinically relevant signal was not consistent immune stimulation but selective dampening of inflammatory or dysregulated immune responses. In slightly hypercholesterolemic subjects, *Agaricus bisporus* α-glucans reduced LPS-induced TNF-α production *ex vivo* without broad Th1/Th2 skewing (Volman *et al.,* 2010), which supports a more targeted anti-inflammatory interpretation than a generalized stimulatory one. In autoimmune thyroid disease, the Corbrin Capsule study reported dual-directional immunomodulatory effects, with restoration of helper/cytotoxic T-cell balance and reductions in autoantibody levels in both Graves' disease and Hashimoto's thyroiditis (He *et al.,* 2016). These patterns are important because, in such populations, the desirable nutritional effect is more plausibly immune rebalancing than indiscriminate activation.

In healthy adults, the immune domains evaluated were again predominantly cellular, but their interpretation differs from that in clinical disease. Here, increases in NK-cell activity, lymphocyte proliferation, and selected Th1-related cytokines after *Cordyceps militaris* supplementation are more appropriately interpreted as enhancement of functional immune responsiveness within physiological ranges, rather than correction of overt immune dysfunction (Kang *et al.,* 2015). Similar patterns were observed in trials of *Pleurotus*, *Phellinus*, and *Lentinus* preparations, where maintenance or enhancement of NK-cell parameters, selected lymphocyte subsets, or phagocytic function was reported, including in physically stressed individuals (Bergendiova *et al.,* 2011; Bobovčák *et al.,* 2010; Gaullier *et al.,* 2011; Ku *et al*., 2022; Ku & Kang, 2022; Tanaka *et al.*, 2016). However, the relevance of these changes for real-world health outcomes in otherwise healthy populations remains less direct than in oncology or recurrent infection settings, especially when immune markers were not predefined as primary clinical endpoints.

Pediatric studies in recurrent respiratory tract infections illustrate a different translational scenario, in which immunological readouts were assessed alongside clinically meaningful outcomes. In the randomized trial by Jesenak *et al*. (2013), pleuran-based supplementation was associated with reduced respiratory morbidity together with modulation of humoral and cellular immunity, while a subsequent trial reported decreased eosinophilia and stabilization of total IgE, particularly in atopic children (Jesenak *et al.,* 2014). In this context, the value of mushroom-derived interventions may lie less in maximizing immune activation *per se* and more in supporting host defense while modulating allergy-related inflammation. This applied pediatric setting is particularly relevant for clinical nutrition because it links biomarker changes with a more patient-centered pattern of benefit than that seen in many adult exploratory trials.

Interpretability across the evidence base is constrained by formulation heterogeneity and incomplete compositional reporting. Many trials relied on mixed or insufficiently characterized extracts, limiting attribution of observed immune effects to defined molecules and complicating reproducibility. For a readership interested in functional foods and clinical nutrition, this issue is particularly relevant: structural characteristics of polysaccharides—such as molecular weight distribution, branching patterns, solubility, and batch-to-batch variability—can plausibly influence receptor engagement and downstream bioactivity, yet these parameters are not consistently reported in human supplementation studies (Brown & Gordon, 2005; Chan *et al*., 2009; Goodridge *et al*., 2009). Additionally, immune outcome heterogeneity is substantial, with variation in cytokine panels, cell phenotyping strategies, and functional assays. Immune markers are not always predefined as primary endpoints, further limiting interpretability

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and comparability.

This scoping review has limitations. No formal risk-of-bias assessment was conducted, consistent with the objective of mapping rather than grading evidence strength. Inclusion was restricted to studies employing predefined quantitative immunological techniques (ELISA, qPCR, Western blot, flow cytometry), which may have excluded clinically relevant trials using alternative assays. Accordingly, the reported immunological effects should be interpreted with caution, as this review was designed to map and characterize the available evidence rather than to provide quantitative effect estimates or statistical synthesis. In addition, the search was restricted to peer-reviewed literature and did not include gray literature sources. Although this decision may have improved consistency and traceability across the included studies, it may also have resulted in omission of relevant non-indexed or unpublished evidence. Although nineteen genera were included in the search strategy, eligible clinical evidence was identified only for a subset, indicating that translational clinical research remains concentrated in relatively few mushroom taxa.

Future research in the field of mushroom-based nutritional supplementation would benefit from standardized extract characterization, transparent compositional reporting, and harmonized immune endpoint selection. Clearly defined primary immunological outcomes, adequate sample sizes, and consistent timing of sampling would improve cross-study comparability. Integrating mechanistically informed biomarkers with clinically meaningful endpoints may help clarify whether observed immune changes represent transient activation, sustained modulation, or context-dependent rebalancing. Such methodological refinement is essential for advancing mushroom-derived bioactives within evidence-based clinical nutrition frameworks.

CONCLUSION.

The mapped clinical literature indicates that single-species edible and medicinal mushrooms administered as dietary or supplemental interventions are associated with measurable modulation of immune parameters in humans. The most consistent signals involve cell-mediated immunity and inflammatory mediator profiles, with recurrent observations related to NK-cell activity and cytokine patterns across diverse populations and clinical contexts.

For the field of clinical nutrition and functional foods, the principal challenge is not merely to expand the number of trials, but to improve extract standardization, compositional transparency, and harmonization of immunological endpoints. Advancing mushroom-derived bioactives as credible components of nutritional strategies aimed at supporting immune health will require bridging immunomarker findings with well-characterized preparations and clinically anchored outcomes. Strengthening this translational pathway will enable more reliable integration of mushroom-based interventions into evidence-informed nutritional practice.

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CRediT authorship contribution statement.

VZC: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. MCLC: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. DMGG: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability.
As this manuscript is a scoping review, no new datasets were generated or analyzed during the current study. All data used in this review are publicly available in the referenced studies, which can be accessed through the appropriate academic journals and repositories.

Declaration of generative AI in scientific writing.
The authors declare that during the preparation of this manuscript, the language-editing tool Trinka was used to improve readability, grammar, and clarity. The tool was used solely for language refinement and did not contribute to the study design, data analysis, interpretation of results, or scientific content. All authors reviewed and edited the manuscript after its use and take full responsibility for the content of this publication.

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Figures.

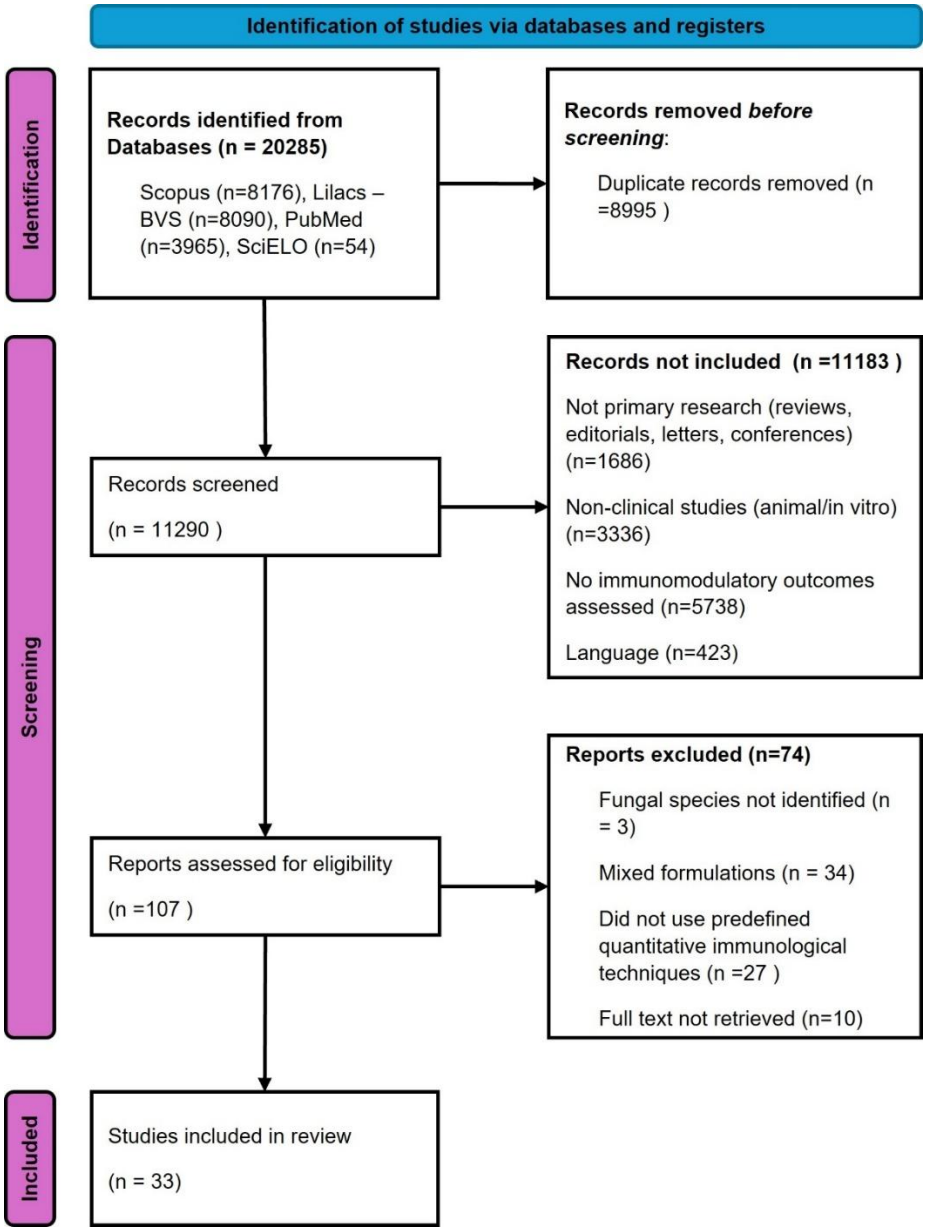

Figure 1. PRISMA-ScR Flow Diagram of Study Selection for the Scoping Review

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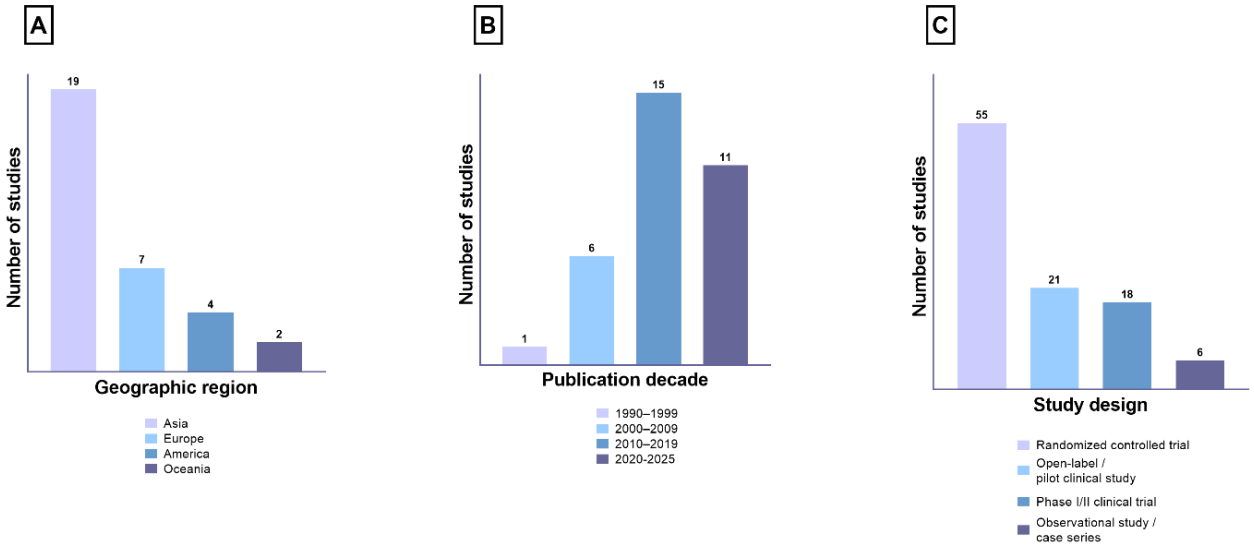

Figure 2. Study Characteristics of the Included Evidence Base. (A) Geographic distribution of included studies. (B) Distribution according to decade of publication. (C) Distribution by study design.

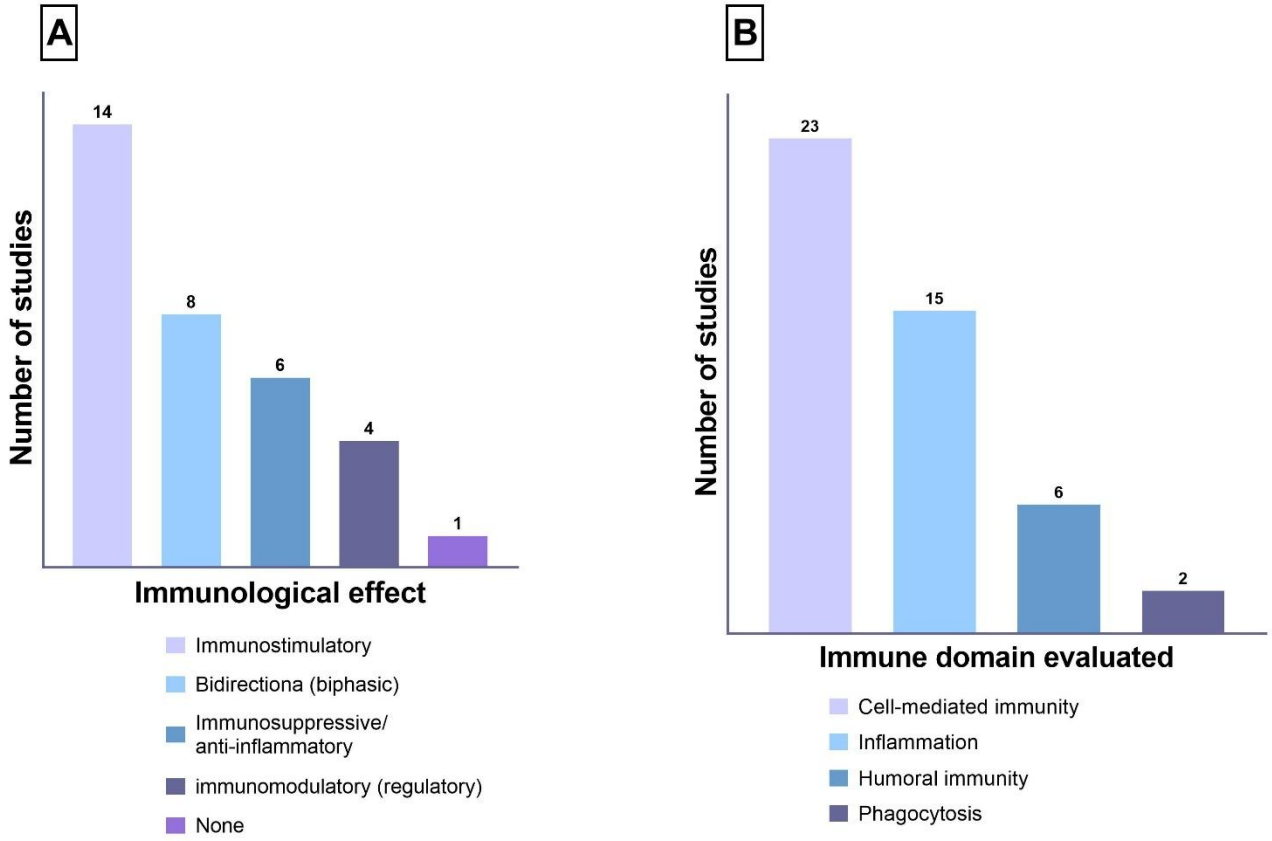

Figure 3. Classification of Immunological Effects and Immune Domains Evaluated in Included Clinical Studies. A) Distribution of studies according to the predominant type of immunological effect reported. (B) Frequency of immune domains evaluated across included studies.

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Tables

Table 1. Summary of Immunological Outcomes Reported in Included Clinical Studies

Article	Mushroom	Bioactive Compound Evaluated	Direction of Immunological Effect	Immunological Mechanism Details	Immunological Effect	Study population	Dose	Route	Period
(Volman et al., 2010)	Agaricus	Polysaccharides and glycoconjugates	Decrease	TNF-α	Immunosuppressive/anti-inflammatory	Patients with metabolic disease	5 g/day	Orally	5 weeks
(Fortes et al., 2009)	Agaricus	Mixed/non-characterized extract	Increase	Neutrophils	Immunostimulatory	Patients with cancer	30 mg/kg/day	Orally	6 weeks
(Costa Fortes & Carvalho Garbi Novaes, 2011)	Agaricus	Mixed/non-characterized extract	Decrease	IgA, IgM	Immunomodulatory (regulatory)	Patients with cancer	30 mg/kg/day	Orally	26 weeks
(Hashemi Yusefabad et al., 2022)	Agaricus	Mixed/non-characterized extract	No significant change	IL-6, CRP, TAC	None	Patients with metabolic disease	16 g/day	Orally	8 weeks
(Kang et al., 2015)	Cordyceps	Mixed/non-characterized extract	Increase	NK cell activity, lymphocyte proliferation index, IFN-γ, IL-12, IL-2, TNF-α	Immunostimulatory	Healthy adults	1,5 g/day	Orally	4 weeks
(He et al., 2016)	Cordyceps	Mixed/non-characterized extract	Increase	$CD8^+$ and $CD4^+$ T lymphocytes	Bidirectional (Biphasic)	Patients with autoimmune disease (Hashimoto's thyroiditis)	2,0 g tid	Orally	24 weeks
			Decrease	$CD4^+$ and $CD8^+$ T lymphocytes		Patients with autoimmune disease (Graves' disease)			
(Ontawong et al., 2024)	Cordyceps	Nucleoside	Increase	NK cell activity	Bidirectional (Biphasic)	Healthy adults	2,85 mg/day	Orally	8 weeks
			Decrease	TNF-α, IL-1β, IL-6					
(Y. Deng et al., 2021)	Ganoderma	Mixed/non-characterized extract	Increase	$CD3^+CD4^+$ cells, $CD3^+HLA\text{-}DR^-$ cells, IL-12, IL-2	Bidirectional (Biphasic)	Patients with cancer	2000 mg bid	Orally	6 weeks
			Decrease	$CD4^+CD25^+$ Treg cells, $CD3^+HLA\text{-}DR^+$ cells, IL-					

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				10, COX-2, TGF-β1					
(Gao et al., 2003)	Ganoderma	Polysaccharides and glycoconjugates	Increase	IL-2, IL-6, IFN-γ, $CD56^+$, $CD3^+$, $CD4^+$, $CD8^+$ cells, NK cell activity	Bidirectional (Biphasic)	Patients with cancer	1800 mg tid	Orally	12 weeks
			Decrease	IL-1, TNF-α			1800 mg tid	Orally	12 weeks
(Gao et al., 2005)	Ganoderma	Polysaccharides and glycoconjugates	Increase	IL-2, IL-6, IFN-γ, $CD3^+$, $CD4^+$, $CD8^+$, $CD56^+$ cells, NK cell activity	Bidirectional (Biphasic)	Patients with cancer	1800 mg tid	Orally	12 weeks
			Decrease	IL-1, TNF-α, CD4:CD8 ratio			1800 mg tid	Orally	12 weeks
(Chen et al., 2023)	Ganoderma	Polysaccharides and glycoconjugates	Increase	$CD3^+$, $CD4^+$, $CD8^+$ T cells, NK cell activity	Immunostimulatory	Healthy adults	200 mg/day	Orally	12 weeks
(Tangkhaphiphat et al., 2022)	Ganoderma	Mixed/non-characterized extract	Increase	Neutrophils, IgG, IgE	Bidirectional (Biphasic)	Patients with cancer	250 mg tid	Orally	8 weeks
			Decrease	IgM, IgA			250 mg tid	Orally	8 weeks
(Zhao et al., 2012)	Ganoderma	Mixed/non-characterized extract	Decrease	IL-6, TNF-α	Immunosuppressive/ anti-inflammatory	Patients with cancer	1000 mg tid	Orally	4 weeks
(Chu et al., 2012)	Ganoderma	Mixed/non-characterized extract	Decrease	B lymphocytes, helper T cells	Immunosuppressive/ anti-inflammatory	Patients with metabolic disease	1,44 g/day	Orally	12 weeks
(AL-jumaili et al., 2020)	Ganoderma	Mixed/non-characterized extract	Increase	IgG, lymphocytes	Immunostimulatory	Patients with infections	Healthy patients: 0.3 g/kg of body weight/day Patients with COVID-19: 0.3 g/kg of body weight/day	Healthy patients:Orally Patients with COVID-19: Orally	Healthy patients: Not specified Patients with COVID-19: 1 week and 3 days
(Poedjomartono et al., 2020)	Ganoderma	Polysaccharides and glycoconjugates	Increase	$CD4^+$ and $CD8^+$ T lymphocytes, IL-2	Immunostimulatory	Patients with cancer	Not specified	Not specified	Not specified
(Aryanugraha et al., 2024)	Ganoderma	Polysaccharides and glycoconjugates	Decrease	TNF-α, CRP	Immunosuppressive/ anti-inflammatory	Patients with metabolic disease	250 mg tid	Orally	13 weeks
(G. Deng et al., 2009)	Grifola	Polysaccharides and glycoconjugates	Increase	IL-10, IL-2, TNF-α, $CD3^+CD56^+$ NK T cells, $CD4^+CD25^+$ T cells	Bidirectional (Biphasic)	Patients with cancer	0.1, 0.5, 1.5, 3, or 5 mg/kg bid	Orally	3 weeks

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			Decrease	IFN-γ			0.1, 0.5, 1.5, 3, or 5 mg/kg bid	Orally	3 weeks
(Kodama et al., 2002)	Grifola	Polysaccharides and glycoconjugates	Increase	NK cell activity	Immunostimulatory	Patients with cancer	100 mg/day	Orally	147 weeks
(Nanba et al., 2000)	Grifola	Polysaccharides and glycoconjugates	Increase	$CD4^+$ cell count, IL-2	Bidirectional (Biphasic)	Patients with infections	Option A: 6 g of Maitake tablets per day. Option B: 20 mg of purified MD-Fraction + 4 g of Maitake tablets per day.	Orally	51 weeks
			Decrease	$CD4^+$ cell count, IL-2			Option A: 6 g of Maitake tablets per day. Option B: 20 mg of purified MD-Fraction + 4 g of Maitake tablets per day.	Orally	51 weeks
(Wesa et al., 2015)	Grifola	Polysaccharides and glycoconjugates	Increase	Respiratory burst / ROS production	Immunostimulatory	Patients with hematologic disease	3 mg/kg bid	Orally	12 weeks
(Zembron-Lacny et al., 2013)	Lentinus	Mixed/non-characterized extract	Increase	IL-10	Immunomodulatory (regulatory)	Healthy adults under physical stress	700 mg bid	Orally	3 weeks
(Gaullier et al., 2011)	Lentinus	Polysaccharides and glycoconjugates	Increase	$CD19^+$ B cells, preservation of $CD4^+$ T cells, NK cells	Immunostimulatory	Healthy adults	2,5 mg/day	Intravenously	6 weeks
(Ku et al., 2022)	Phellinus	Polysaccharides and glycoconjugates	Increase	NK cell activity	Immunostimulatory	Healthy adults	1000 mg/day	Orally	8 weeks
(Ku & Kang, 2022)	Phellinus	Polysaccharides and glycoconjugates	Increase	IL-6, IgG1, IgG2, IgM (preservation), NK cell activity	Immunostimulatory	Healthy adults	PL1000 group: 1000 mg/day PL2000 group: 2000 mg/day	Orally	8 weeks

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(Lee et al., 2010)	Phellinus	Mixed/non-characterized extract	Decrease	IL-1β	Immunosuppressive/anti-inflammatory	Healthy adults	1,5 L/day	Orally	4 weeks
(Jesenak et al., 2013)	Pleurotus	Polysaccharides and glycoconjugates	Increase	IgG, IgA, IgM, preservation of NK cells and $CD8^+$ T cells	Immunomodulatory (regulatory)	Children with infections	1 mL per 5 kg of Imunogluk an P4H® syrup	Orally	26 weeks
(Jesenak et al., 2014)	Pleurotus	Polysaccharides and glycoconjugates	Decrease	Eosinophil count	Immunomodulatory (regulatory)	Children with infections	1 mL per 5 kg of Imunogluk an P4H® syrup	Orally	26 weeks
			Stabilization	IgE			1 mL per 5 kg of Imunogluk an P4H® syrup	Orally	26 weeks
(Bobovčák et al., 2010)	Pleurotus	Polysaccharides and glycoconjugates	Relative functional increase / preservation	NK cell number and activity	Immunostimulatory	Healthy adults under physical stress	200 mg/day	Orally	8 weeks
(Tanaka et al., 2016)	Pleurotus	Polysaccharides and glycoconjugates	Increase	IFN-γ, IL-12, NK cell activity	Immunostimulatory	Healthy adults	80 mL/day	Orally	8 weeks
(Bergendiova et al., 2011)	Pleurotus	Polysaccharides and glycoconjugates	Increase	NK cell count, phagocytic capacity	Immunostimulatory	Healthy adults under physical stress	100 mg/day	Orally	13 weeks
(Dündar et al., 2024)	Pleurotus	Polysaccharides and glycoconjugates	Decrease	TNF-α, IFN-γ, IL-1β	Immunosuppressive/anti-inflammatory	Healthy adults	100 mL/day	Orally	4 weeks
(Miyazaki et al., 1995)	Schizophyllum	Polysaccharides and glycoconjugates	Increase	$CD4^+$ and $CD8^+$ T lymphocytes	Immunostimulatory	Patients with cancer	Sizofiran: 20-40 mg/semana 5-Fluorouracilo (5-FU): 200-300 mg al día	Sizofiran: Intramuscular route 5-Fluorouracilo (5-FU): Orally	Sizofiran: 104 weeks 5-Fluorouracilo (5-FU): 52 weeks

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