

ORIGINAL ARTICLE

Microscopic Warriors - Immunomodulatory and Anticancer Properties of Fungi

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INTRODUCTION

Fungi, once classified as plants, have been assigned their own domain due to their distinctly different morphology. According to data from 2020, the kingdom Fungi includes approximately 148,000 known species, the vast majority of which belong to two main types: *Ascomycota* (sac fungi) and *Basidiomycota* (club fungi). It is estimated that over 90% of fungal species remain undiscovered, which means their total number may range from 2.2 million to even 3.8 million. They are present in every climatic zone, both on land and in aquatic environments. Despite being the least studied biological kingdom, fungi play a crucial role in ecosystems, including in nutrient cycling, in symbiotic relationships with plants, and in biotechnology and medicine¹.

The emergence of immunology as a branch of medical science found direct application in the diagnosis and treatment of mycoses. Additionally, many secondary metabolites with chemotherapeutic properties have been identified. The first

ABSTRACT

Background: Fungi, comprising a vast and diverse kingdom, are increasingly recognized for their bioactive compounds with potential health benefits, including anticancer properties. Mushrooms, rich in polysaccharides, proteins, vitamins, and trace elements, have traditionally been used for disease prevention and treatment, notably cancer.

Materials and Methods: A thorough review of the literature was carried out using the PubMed and Google Scholar databases, with search terms focusing on mushrooms and different types of cancer. The analysis included observational studies, meta-analyses, and experimental research that examined the relationship between mushroom consumption and cancer risk or progression.

Aim of the Study: to systematically review existing literature on the relationship between mushroom intake and cancer risk, focusing on breast, prostate, gastric, colorectal, and lung cancers, and to discuss the immunomodulatory and therapeutic effects of fungal bioactive compounds.

Results: Evidence indicates a notable negative correlation was observed between mushroom intake and the risk of specific types of cancer particularly breast and prostate cancer, with some studies highlighting immunomodulatory effects of β -glucans and other fungal compounds. Mushroom consumption is linked to lower overall mortality and reduced risk of breast cancer, especially in populations of Asian origin and postmenopausal females. While results are more consistent in Asian cohorts, data from Western countries are inconclusive, suggesting the need for further research. Mushroom extracts such as PSK have shown promise as adjunctive therapies in gastric and colorectal cancers.

Conclusion: Overall, mushrooms represent a valuable dietary component with potential cancer-preventive and supportive therapeutic roles, warranting further clinical investigation.

Keywords: mushrooms; fungus; prevention; risk; neoplasms; cancer.

successful antibiotic after penicillin was streptomycin, obtained using *Streptomyces griseus*. As early as 70 years ago, 96 antibiotics produced by fungi were known, of which 57 were well-characterized². Fungi represent a promising alternative source of novel antimicrobial agents, particularly due to their production of secondary metabolites like terpenes, steroids, anthraquinones, quinolones, and benzoic acid derivatives. Additionally, certain primary metabolites, including oxalic acid, proteins, and peptides, also contribute to their antimicrobial potential. Among various species, *Lentinus edodes* has been the most thoroughly investigated, exhibiting effectiveness against both Gram-negative and Gram-positive bacterial strains^{3,4}.

Furthermore, Fungi possess considerable nutritional value, offering a rich source of protein along with essential amino acids and dietary fiber. Although low in fat, they are notable for their content of beneficial fatty acids. Edible mushroom species also supply substantial levels of B-complex vitamins (including B1, B2, B3, B9, and B12), in addition to vitamins C, D, and E^{4,5}. In terms of mineral content, zinc, copper, magnesium, and selenium were present in the highest amounts in some mushroom species⁵.

Table 1. Mineral Composition of the Dry Matter of Selected Mushrooms

	Agaricus bisporus/white	Agaricus bisporus/brown	Lentinus edodes	Pleurotus ostreatus
Zn [mg]	66	47	92	83
Mg [g]	1.30	1.41	1.55	0.16
Se [µg]	1400	3200	39	150
Cu [mg]	29	35	5.2	8.4

Based on Mattila et al. 2001⁵.

Many fungi have traditionally been used across various cultures not only to maintain a healthy body but also in the management and mitigation of diverse diseases, including oncological diseases. As our knowledge of the molecular foundations of cancer has expanded, it has opened the door to the discovery of new therapeutic substances (e.g., from fungi) that can inhibit irregular molecular and biochemical signaling pathways associated with carcinogenesis.^{4,6,7}

Immunomodulatory and Anticancer Properties of Fungi

Fungi contain various bioactive compounds such as polysaccharides (such as β -glucans), triterpenoids, alkaloids, proteins that can influence the immune system. Polysaccharides, especially β -glucans, are particularly well known for their immunomodulatory effects.

Here are several examples of health-promoting compounds found in fungi:

1. **Polysaccharides** – These molecules are essential to various biological functions, acting as energy reserves such as glycogen and starch also forming structural elements of cell walls, like cellulose and chitin. They also participate in cellular signaling and communication between cells^{8,10}. Numerous studies indicate that polysaccharides are the main bioactive compounds in fungi with anticancer properties. They work by activating the host's immune response in other words, they indirectly lead to the death of cancer cells. These compounds have antioxidant properties, help prevent oxidative stress in the body, can reduce tumor size by up to 50%, and extend mortality timeline in tumor-implanted mice^{4,11}.

Among the polysaccharides found in fungi, **β -glucans** are the most prominent it is estimated they can make up to half the mass of the fungal cell wall. These substances exhibit strong immunostimulatory effects, activating macrophages and boosting the organism's ability to defend against infections caused by bacteria, viruses, fungi, and parasites. Additionally, they delay aging processes, support wound healing by strengthening the proliferative phase, inhibit tumor development, and improve the efficacy of standard cancer treatments while minimizing associated adverse effects. β -glucans also show the ability to prevent metastasis, lower cholesterol levels, support cardiovascular health, and influence glucose metabolism, contributing to their antiglycemic effects^{4,12,13}. β -glucans with branched chain structures, specifically β -1,3 and β -1,6 linkages, are particularly effective in modulating the immune response^{10,13}.

2. **Proteins** – These are essential functional components of fungi with significant therapeutic value. Fungi produce a wide variety of proteins and peptides with valuable Bioactive compounds including lectins, fungal immunomodulators, ribosome-inactivating agents, antimicrobial peptides, and ribonucleases, and lactases.

Lectins are carbohydrate-binding proteins or glycoproteins that recognize specific sugar moieties on the surfaces of cells. Numerous lectins of fungal origin have been discovered in recent years, possessing important pharmaceutical properties, including immunomodulatory, anticancer, antiviral, antimicrobial, and antifungal effects. Some have shown strong antiproliferative activity against certain tumor cell lines, including those from T-cell leukemia, Hep G2 liver cancer, and MCF7 mammary carcinoma lines^{4,14,15}.

To date, over 38 types of immunomodulatory proteins have been identified from fungi¹⁶. For example, protein YZP has been studied as a potential therapy in a mouse model of acute colitis, where its effect was primarily based on modulating B cells of the immune system¹⁷. Similarly, protein HEP3 not only showed beneficial effects in treating intestinal inflammation but also demonstrated potential in anticancer therapy. It can stimulate the proliferation and differentiation of T cells by influencing the gut microbiota, activate antigen-presenting cells (APCs) in the intestines during inflammatory conditions, and exert anticancer effects through immunological mechanisms in mouse models with transplanted tumor cells^{16,18}.

3. **Lipids** – Tocopherols (vitamin E), naturally found in the lipid fraction, function as potent antioxidants due to their ability to neutralize free radicals. These compounds demonstrate significant biological activity, contributing to the prevention of degenerative conditions, cancer, and cardiovascular disorders. Additionally, linoleic acid an essential fatty acid for humans—plays a crucial role in numerous physiological processes. Its presence has been linked to lowering the risk of heart disease, decreasing triglyceride levels and blood pressure, as well as alleviating arthritis-related symptoms^{4,19,20}.

Vitamin D is another crucial component supporting the immune system. In mushrooms, it occurs in an inactive form as ergosterol, a fat-soluble compound that

integrates into cell walls. Studies have shown that under ultraviolet (UV) radiation, both before and after harvest, mushrooms can rapidly convert ergosterol into active vitamin D2. Cases have been described in which the vitamin D content increased up to a hundredfold when mushrooms were sun-dried, compared to those dried in darkness^{13,20}. Vitamin D plays a significant role in cancer prevention, partly by enhancing phagocytic activity the ability of immune cells to engulf and destroy cancer cells as well as by supporting other immunomodulatory mechanisms. It is also responsible for the proper absorption of calcium and phosphorus, which contributes to healthy bone development and reduces the risk of osteoporosis. Angiogenesis is a critical process contributing to tumor growth and progression. Research indicates that vitamin D may inhibit the activity of proangiogenic factors, potentially limiting tumor progression¹³.

4. **Trace Elements** Selenium is one of the key trace elements essential for the proper functioning of many enzymatic systems. Its most important function is its role in the synthesis of one of the strongest antioxidants – glutathione peroxidase is a key antioxidant enzyme that plays a protective role by neutralizing free radicals, thereby preventing oxidative damage to erythrocytes and cellular membranes. Moreover, this enzyme is essential for the optimal functioning of the immune system and contributes to the regulation of thyroid hormone metabolism. Numerous scientific studies suggest that selenium may help reduce the risk of developing various cancers, particularly prostate, lung, and stomach cancer²¹. The goat's foot (*Albatrellus pes-caprae*), which contains an average of approximately 200 µg of selenium per gram of dry matter, is considered the richest source of this element among the analyzed fungal species. One of the most commonly consumed wild culinary fungi, the penny bun (*Boletus edulis*) also stands out due to its high selenium content²².

The Role of Mushroom Intake in Lowering Cancer Risk

A systematic search of the literature was conducted in the PubMed and Google Scholar databases to identify observational studies evaluating the association between mushroom consumption and cancer risk, as well as their potential effects on tumor development in specific organs. Search terms included: *mushroom, mushrooms, fungus, prevention, risk, risks, neoplasms, breast cancer, prostate cancer, gastric cancer, colon cancer, and lung cancer*.

Mushroom intake may be associated with a lower risk of cancer development. A notable negative correlation has been observed between mushroom intake and cancer incidence Increased intake of mushrooms has been linked to a reduced risk. The strongest association was observed in the case of breast cancer²³⁻²⁵. In Eastern countries (Asia), mushroom consumption is significantly higher and more diverse compared to Western countries (Europe, America). As a result, a larger number of publications originate from China, Korea, and Japan. The following mushrooms were specifically considered: *Agaricus bisporus*, *Antrodia cinnamomea*, *Cordyceps sinensis*, *Cordyceps militaris*, *Ganoderma lucidum*, *Coriolus versicolor*, *Grifola frondosa*, *Lentinula edodes*, and *Pleurotus ostreatus*²⁴.

Breast Cancer

Long-term population studies suggest that regular mushroom consumption may positively influence longevity. An analysis of NHANES III data (USA) revealed that individuals who included mushrooms in their diet had a lower overall risk of mortality (HR = 0.84). Furthermore, replacing one serving of red meat with mushrooms further reduced this risk (HR = 0.65). However, no significant impact was observed on mortality due to cancer, cardiovascular diseases, or diabetes^{23,24}.

A 2014 meta-analysis encompassing 6,890 cases found that each additional gram of mushrooms consumed daily corresponded to a 3% decrease in the risk of developing breast cancer (RR = 0.97), particularly among postmenopausal women. A more recent meta-analysis involving 19,732 cases confirmed an overall reduction in cancer risk (RR = 0.66), with the most significant protective effect observed for breast cancer (RR = 0.65)^{24,25}.

In East Asian countries, mushrooms are a staple in daily diets, unlike in Western nations. A Chinese study demonstrated that consuming at least 10 g of fresh or 4 g of dried mushrooms daily significantly decreased breast cancer risk in both pre- and postmenopausal females²³.

Another Korean study involving 362 breast cancer patients and 362 healthy controls found a statistically significant inverse association has been identified between dietary mushroom intake and the risk of breast cancer, suggesting that

higher consumption may contribute to a reduced likelihood of disease development in the highest quintile (OR = 0.55; 95% CI: 0.33–0.94), with a notable dose-dependent effect in postmenopausal women ($p < 0.05$). In premenopausal women, a protective effect was also observed using one of the statistical analysis methods (OR = 0.38; 95% CI: 0.19–0.77 for the highest quintile of intake)²⁶.

A subsequent Korean study with a similar design (358 cases, 360 controls) yielded partly different results. An inverse, dose-dependent relationship between mushroom consumption and breast cancer was found in premenopausal women ($p < 0.05$), but no significant association was observed in postmenopausal women. Additionally, the protective effect was primarily noted in patients with hormone-dependent breast cancer (ER+/PR+), especially among premenopausal women. No significant effects were observed for receptor-independent cancers (ER-/PR-). This suggests that the potential protective action of mushrooms may stem from their ability to inhibit aromatase activity²⁷.

The UK Women's Cohort Study, comprising 35,372 women, found no significant association between mushroom consumption and breast cancer risk (HR = 0.98), both in pre- and postmenopausal women. Similar results were obtained in a large American cohort study involving over 112,000 participants, which reported no significant impact of mushroom intake on overall cancer risk or specific types, including breast cancer (HR = 0.89)^{25,30}.

Researchers note significant differences between Asian and Western study outcomes, potentially due to genetic, ethnic factors, and variations in the type, quantity, and preparation methods of consumed mushrooms. They emphasize the need for further research focusing on specific mushroom species and their bioactive properties.

Prostate Cancer

A study conducted in Japan involved 36,499 men aged 40 to 79 over an average follow-up period of 13.2 years. Mushroom consumption data (1–2 times and ≥ 3 times per week) were collected via questionnaire. Throughout a total of 574,397 person-years of follow-up, 1,204 incident cases of prostate cancer were documented. It was shown that more frequent mushroom intake (1–2 times/week: HR = 0.92; ≥ 3 times/week: HR = 0.83) was associated with a lower likelihood of prostate cancer onset, particularly in males above the age of 50. This association was independent of cancer stage or consumption of other foods. The results suggest that regular mushroom consumption may contribute to reducing prostate cancer risk in Japanese men²⁹.

Moreover, laboratory and animal model studies indicate that extracts from mushrooms like *Agaricus bisporus* and *Agaricus blazei* Murill may suppress the proliferation of prostate cancer cells in immunocompromised mice and hinder disease progression. Based on these observations, researchers proposed that such mushrooms could have potential preventive and therapeutic effects against prostate cancer in humans³⁰.

Gastric Cancer

A literature review showed the inhibitory effect of the Turkey Tail mushroom on the progression of gastric cancer^{31–33}. Studies conducted by Hsu et al. involving 918 individuals diagnosed with stage II and III gastric cancer indicates that therapy with PSK (Polysaccharide K), derived from the Turkey Tail mushroom, may enhance the immune system's capacity to combat cancer through immune response modulation³². Furthermore, research by Ito et al. on 349 patients with stage II and III gastric cancer demonstrated that adding Turkey Tail extract (PSK) to therapy improves survival outcomes in patients after tumor resection, especially in those at risk of recurrence due to lymph node metastases and lack of class I MHC expression. This substance may help prevent lymph node metastases that might involve cancer cells evading the immune system's antitumor function³³. Tanaka et al. conducted a retrospective study on 254 gastric cancer patients to assess the effect of Turkey Tail mushroom-derived PSK on patient survival outcomes. They compared a group treated with PSK + fluoropyrimidine to a control group receiving only fluoropyrimidine. The study involved postoperative patients with stage II or III cancer who underwent adjuvant therapy. While no notable variation was observed in recurrence-free or total survival rates across the general cohort, patients with multiple lymph node metastases who received PSK demonstrated enhanced survival outcomes³⁴.

Colorectal Cancer

In a phase III clinical trial, Miyake et al. evaluated the efficacy of adjuvant chemotherapy using uracil and tegafur combined with leucovorin (UFT/LV) versus an immunochemotherapy regimen of UFT with PSK in a cohort of 351 patients following surgical resection of colorectal cancer. At the three-year mark, the disease-free survival (DFS) rate was 82.3% for patients receiving UFT/LV, compared to 72.1% for those treated with UFT combined with PSK. Results suggest that UFT/LV + PSK therapy may be considered an effective adjuvant treatment option for patients diagnosed with stage IIB or III colorectal cancer³⁵.

Lung Cancer

There are published reports on mushroom and mushroom extract consumption indicating a association between mushroom consumption and a lower incidence of cancer, along with improved survival outcomes in oncology patients. Although evidence linking mushroom consumption to lung cancer risk remains limited, studies point to their potential in risk reduction, preventive actions, and symptom relief in patients undergoing chemotherapy and radiotherapy^{36–38}. An example is lentinan, a polysaccharide found in shiitake mushrooms, which supports lung cancer treatment and may reduce the nephrotoxicity of drugs. Given the numerous side effects of traditional anticancer drugs and growing interest in natural therapies, medicinal mushrooms appear as a promising supportive option for cancer treatment. However, further in-depth studies are required to validate their effectiveness and safety, especially in the context of lung cancer³⁹.

DISCUSSION

The collected literature data indicate a potentially protective effect of mushroom consumption on the development of certain cancer types, particularly breast cancer^{23,24,26–27,31}. A notable observation is that many studies report an inverse relationship between the frequency of mushroom intake and cancer risk, which may suggest the existence of a biological mechanism responsible for this effect. For breast cancer, most data come from Asian studies, which consistently show a strong, significant connection between frequent mushroom intake and decreased cancer susceptibility. This relationship was more pronounced among postmenopausal women, possibly indicating the involvement of hormonal mechanisms, including the inhibition of aromatase activity by certain mushroom species such as *Agaricus bisporus*^{25,28}. However, studies conducted in countries such as the United Kingdom and United States, which represent Western populations, did not observe similar health benefits, which could be attributed to variations in mushroom species commonly consumed, their quantity, preparation methods, as well as genetic and environmental factors of the populations studied^{24,27}. Data regarding prostate cancer are also promising both epidemiological and experimental studies (in vitro and in vivo) confirm that regular mushroom consumption, especially of species like *Agaricus blazei* Murill, may exert a protective effect. The potential mechanism may involve the immunomodulatory and antiproliferative properties of bioactive compounds present in mushrooms, e.g., polysaccharides^{28–29}.

Interesting results were also reported for gastric and colorectal cancers, where mushroom extracts—particularly PSK (Polysaccharide K) from *Coriolus versicolor*—showed beneficial effects on survival outcomes and immune response in patients undergoing oncological treatment. Although not all studies established meaningful variations in overall survival rates. Positive therapeutic effects were documented in selected patient groups, especially those with lymph node metastases^{34–37}. Currently, evidence regarding the specific impact of dietary mushrooms on reducing lung cancer risk remains limited. However, certain substances derived from medicinal mushrooms indicate significant antitumor potential and may be used in the future as supportive therapy in lung cancer patients⁴⁰. Despite these promising results, several limitations of the available studies should be noted. Firstly, most data come from observational studies, which do not allow for definitive causal conclusions. Secondly, methodological differences (e.g., methods of dietary data collection, length of follow-up, definitions of exposure) may significantly affect outcomes. Treating mushrooms as a single, homogeneous group is also a potential oversimplification, as individual species differ considerably in their bioactive compound content. Randomized clinical trials confirming the effectiveness of mushrooms as a preventive or adjunctive cancer treatment strategy are lacking.

It is also worth emphasizing that mushroom consumption may benefit general health not only through potential anticancer properties but also due to their content of fiber, vitamins (e.g., E, D, C, B), antioxidants, and immunostimulatory compounds. Replacing highly processed foods or red meat with mushrooms may confer additional health benefits, as supported by cohort study data.

CONCLUSION

Edible and medicinal mushrooms exhibit multifaceted health-promoting effects as a result of containing various bioactive compounds, including β -glucans, lectins, antioxidants, and vitamins. The accumulated literature suggests their significant potential in cancer prevention and as adjunctive therapy, particularly for breast, prostate, and gastrointestinal cancers. Although the influence of mushrooms on lung cancer risk requires further study, current observations point to their possible protective effects and mitigation of side effects from oncological treatments. Including mushrooms in the diet can be a beneficial component of a healthy lifestyle strategy and a complement to conventional therapeutic methods.

Given the growing interest in mushrooms as a natural source of anticancer substances, continued research into their properties is warranted to better understand their mechanisms of action and establish optimal usage protocols.

Furthermore, incorporating mushrooms into the diet may provide an alternative for individuals seeking natural ways to support cancer treatment, offering additional protection against malignancies. The future of research in this field may yield new, innovative solutions for supportive oncology therapies.

DECLARATION

All authors involved in this manuscript have met the following authorship criteria:

1. Participation in the study's conception and design, data collection, or the analysis and interpretation of results.
2. Involvement in drafting the article or providing critical revisions that added significant intellectual value.
3. Approval of the final version to be submitted for publication.

Each author accepts full responsibility for the integrity and accuracy of the work presented.

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