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Bioactive Compounds from Edible Mushrooms and their Medicinal/Immunological Applications: Focus on *Pleurotus ostreatus* Species

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Abstract: *Pleurotus ostreatus* (oyster mushroom) has gained significant attention due to its nutritional value and the presence of bioactive compounds with therapeutic and immunomodulation potentials. This review comprehensively analyzes the bioactive compounds derived from *Pleurotus ostreatus* and their immunological applications. Bioactive compounds and extracts from *Pleurotus ostreatus* have been examined and found clinically important for both malignant and non-malignant diseases. They have displayed pronounced efficacy as anticancer, antitumor and antimicrobial agents in various pharmacological studies. They have been reported to possess anti-inflammatory, antioxidant, antibacterial, and antifungal activities. Polysaccharides, phenolic compounds, proteins, and secondary metabolites from *Pleurotus ostreatus* exhibit immunomodulatory, anti-inflammatory, antioxidant, and anticancer properties. This systematic review consolidates recent findings, highlighting medicinal/immunological uses and its application in vaccine development.

Keywords: *Pleurotus ostreatus*, bioactive compounds, polysaccharides, immunomodulation, medical applications.

Introduction

Edible mushrooms, otherwise known as macrofungi have been known as a source of human healthy food since ancient times and served also as traditional medicine in the curing of various types of diseases [1]. They are also white rot fungi, considered as one of the well- known foods with nutritional values and possessing various kinds of biopharmaceutical compounds. They are nutritious delicacies which can as well serve as a suitable substitute for meat and eggs, especially for vegetarians. The majority of mushrooms are not naturally photosynthetic, but rather are meaty, spore-bearing, and have a characteristic visible fruiting body that can be either hypogeous or epigeous. Mushrooms in addition to their nutritious benefits, are known to contain natural antibiotics with antioxidant capacity which have been used to overcome and combat some bacterial infections as well served as food supplements [2,3]. Mushrooms also contain abundant bioactive compounds with health-promoting properties. Studies on edible mushrooms showed the rich proteinous content of mushrooms, and these proteins have indicated varying biological activities such as antiproliferative, immunomodulatory, antiviral, antifungal and antibacterial effects [4, 5, 3, 6]. Numerous individuals have a preference for macrofungi belonging to the genus Pleurotus, commonly referred to as oyster mushrooms. The preference is due mainly to its unique taste, soft yet stringy texture and unique smell. This mushroom is in high demand globally and creates future opportunities for its international traders [7]. They are significantly important in human diet given the fact that they are very rich in dietary fiber, protein, non-starchy carbohydrates, minerals, and vitamin-B and contain no cholesterol, but an insignificant amount of fat. Mushrooms are rich in essential amino acids and have high-quality proteins [8]. According to study, *Pleurotus ostreatus* helps to lower cholesterol levels [9]. In their investigation, Fountoulakis et al. [10], found that the mushroom's spore-bearing section may also include lignin and phenol-degrading enzymes. The oyster mushroom contains a number of secondary metabolites, including phenolic compounds, flavonoids, terpenoids, sterols, saponins, ascorbic acid, ergothioneine, and carotenoids [11, 12]. The bioactive compounds derived from *P. ostreatus* include polysaccharides, phenolic compounds, sterols, proteins, and other metabolites. These compounds have been extensively studied for their immunomodulatory effects, which include the activation or suppression of immune responses to restore homeostasis or combat disease. They have shown promise in stimulating both innate and adaptive immune responses. According to reports, investigations have been carried out into several natural products that can be used as adjuvants [13, 14]. This review aims to explore the potential of *P. ostreatus* to enhance public health through its medicinal and immunological properties.

Pleurotus ostreatus

Methods

Search strategy

A systematic search of peer-reviewed literature was conducted using databases such as PubMed, SciFinder, Google Scholar Scopus, and Web of Science. Articles published from 1988 to 2024 were included, focusing on studies investigating the bioactive compounds of *P. ostreatus* and their immunological activities. Keywords included "*Pleurotus ostreatus*," "bioactive compounds," "polysaccharides," "immunomodulation," and "immunological applications." Major references from some of the articles were also further searched for additional information.

Inclusion and exclusion criteria

Based on the number of articles accessed, some inclusion and exclusion criteria were applied so as to include the most relevant articles in this review. Only articles published in English were considered. Publications that extensively examined the efficacy of the bioactive compounds and extracts of *Pleurotus ostreatus* were included. Moreover, those reporting in vitro and in vivo experiments using animal models were all included.

Medicinal Properties of *Pleurotus ostreatus*

Mushrooms have long been recognized for their therapeutic benefits, in vitro and in vivo through the use of animal models in several parts of the world. Pleurotus mushrooms are thought to be the best food for diabetics and obese people since they are low in calories and sugar without starch. Numerous pharmacological activities, including anti-tumor, immunomodulatory, antigenotoxic, antioxidant, anti-inflammatory, hypocholesterolaemic, antihypertensive, antiplatelet-aggregating, antihyperglycaemic, antimicrobial, and antiviral properties, have been found in numerous studies on different Pleurotus species [15-18]. Morris et al. [16] have also shown that Pleurotus species are effective immunomodulatory agents. Based on their immunostimulating qualities, these chemicals are referred to as "host defence potentiators" (HDPs). Pleurotus species have produced a number of molecules that have been isolated and shown to be able to enhance or complement a desired immune response. These include: proteoglycans, polysaccharides, and polysaccharopeptides from *P. ostreatus* mycelia [19, 20, 16]; a ubiquitin-like peptide from P. sajorcaju [21]; a glycoprotein from P. citrinopileatus [22]; and DNA from *P. ostreatus* fruiting bodies. Most of the compounds found in ostreatus species stimulate several immune system cell populations, such as macrophages, natural killer (NK) cells, T-cells, and also alter the cytokine system [15]. According to El and Hatti-Kaul [23], the cytokines in turn trigger adaptive immunity by encouraging the generation of antibodies by B cells and stimulating the development of T cells into T helper (Th1 and Th2) cells, which mediates humoral and cell immunities, respectively.

Bioactive Compounds

Pleurotus ostreatus is rich in bioactive compounds, including polysaccharides, lectins, proteins, and phenolic compounds. These components are known to exhibit various medicinal properties, such as antioxidant, anti-inflammatory, and antimicrobial effects [24]. Among these, polysaccharides like β-glucans and heteroglycans have been particularly highlighted for their immunostimulatory potential. These bioactive molecules can interact with immune cells such as macrophages, dendritic cells, and T lymphocytes, modulating immune responses [25]. β-glucans, for instance, are recognized for their ability to enhance phagocytic activity and promote the secretion of cytokines, leading to the activation of both innate and adaptive immune responses [26]. These mechanisms are of great interest in vaccine development, as they could help boost the immune response to antigens, potentially enhancing vaccine efficacy. The antimicrobial properties of *P. ostreatus* have been well documented, with extracts of the mushroom demonstrating activity against a range of pathogenic bacteria, including Streptococcus pneumoniae [27]. This antimicrobial effect is attributed to various bioactive compounds, such as phenolic acids and flavonoids, which exhibit bacteriostatic and bactericidal activities.

Active Compounds of *Pleurotus ostreatus* and its medicinal effects.

Pharmacological Effect	Substances	References
Anticancer	Water soluble protein or Polysaccharides	[28-30]
Antioxidant	β-D Glucan (Pleuran)	[31-33, 5]
	Lectin	
Antitumor	β-D Glucan (Pleuran)	[19, 31, 34-36]
	Glycopetides proteoglycans	
Antiviral	Ubiquitin-like proteins	[5, 37]
Antibacterial	β-D Glucan (Pleuran)	[38-40]
Antihypercholesterolic	Lovastatin	[41]
Eye health	Unspecified	[42]
Antiarthritic	B- (1,3/1,6) D Glucan	[43]
Immunostimulatory Effect	Unspecified	[44]

Roles of Bioactive Compounds in Immunomodulation

Natural compounds have gained significant attention for their potential to enhance immune responses, particularly in vaccine formulation. Numerous molecules have been isolated from mushrooms, including lectins, polysaccharides, polysaccharides-peptides, polysaccharide-protein complexes, phenolic compounds, and flavonoids, which have been demonstrated to enhance both innate and adaptive immune responses [5]. *P. ostreatus* is a rich source of bioactive molecules with immunomodulatory effects [44]. The most notable of these molecules are β-glucans, which have garnered attention for their ability to stimulate immune cells such as macrophages, dendritic cells, and natural killer (NK) cells. Among these, compounds from *Pleurotus ostreatus* such as saponins have emerged as promising candidates for improving vaccine efficacy. These compounds, including polysaccharides, β-glucans, and proteins, have shown the ability to activate various components of the immune system. The immunological effects of *P. ostreatus* are largely attributed to its polysaccharides, which can enhance the immune system's response to foreign pathogens. These compounds act through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) on immune cells. When these receptors bind to β-glucans, they trigger a cascade of immune responses, including the activation of macrophages, dendritic cells, and natural killer (NK) cells [45].

β-glucans from *P. ostreatus* are known for their ability to stimulate innate immune responses. They interact with pattern recognition receptors (PRRs) such as dectin-1 and Toll-like receptors (TLRs) on immune cells, activate macrophages, dendritic cells, and natural killer cells in the process [46]. These interactions enhance the secretion of pro-inflammatory cytokines e.g., IL-6 and TNF-α and promote antigen presentation.

Polysaccharides (β-glucans)

The β-glucans found in *Pleurotus ostreatus* are among the most studied bioactive compounds. These complex carbohydrates are known for their ability to activate the immune system through pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) on the surface of immune cells. Upon binding, β-glucans stimulate the production of pro-inflammatory cytokines, enhance phagocytosis, and promote the recruitment of immune cells to the site of infection [26]. B-glucans are responsible for the primary therapeutic actions of mushrooms, which include immune potentiation and anticancer activity. When taken orally, β-glucans from different fungi are absorbed in the small intestine rather than being broken down by human enzymes, which promotes mucosal and systemic immunity [47]. The β-glucans from *P. ostreatus* can activate macrophages and dendritic cells, which are crucial for the initiation of adaptive immune responses. Through the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, these cells promote inflammation and recruit other immune cells to the site of infection.

In both humans and animals, the uptake of β-glucans promotes anticancer activity and protective effects against bacterial and fungal infections. Additionally, studies have shown that β-glucans activate adaptive immunity by stimulating macrophages to produce cytokines and local immunomodulators [48-50]. This can then stimulate the activity of cytokines like interleukin (IL)-2, IL-10, and IL-12. Additionally, dendritic cells act as antigen-presenting cells (APCs), which process pneumococcal antigens and present them to T lymphocytes, initiating a robust adaptive immune response [51]. By boosting the activity of antigen-presenting cells (APCs) such as dendritic cells and macrophages, β-glucans improve the efficiency of antigen uptake, processing, and presentation, thereby enhancing the activation of T lymphocytes and the generation of memory immune cells.

Phenolic Compounds

Phenolic compounds are renowned for their antioxidant activity, which helps neutralize reactive oxygen species (ROS) and reduce oxidative stress. This activity is essential in preventing cellular damage associated with chronic diseases like cardiovascular diseases and cancer. For instance, quercetin, a flavonoid, has been shown to reduce lipid peroxidation and protect DNA from oxidative damage [52]. Reports have demonstrated that Phenolic compounds, including flavonoids and phenolic acids, inhibit pro-inflammatory mediators like cytokines, prostaglandins, and nuclear factor-kappa B (NF-κB) [53]. These compounds also exhibit antimicrobial properties against a variety of pathogens. Their mechanisms include disrupting microbial cell membranes, inhibiting enzyme activity, and interfering with nucleic acid synthesis [54]. Phenolic compounds contribute to cardiovascular health by reducing LDL cholesterol oxidation, improving endothelial function, and inhibiting platelet aggregation. Resveratrol, a polyphenol, is particularly effective in mitigating atherosclerosis and hypertension [55]. According to Sharma et al., [56], Phenolic compounds demonstrate anticancer properties by modulating various cellular pathways involved in cell proliferation, apoptosis, and angiogenesis. These compounds also reduce oxidative damage, which can lead to DNA mutations and cancer development. In addition, phenolic compounds offer protection against neurodegenerative diseases such as Alzheimer's and Parkinson's. They reduce oxidative stress, inflammation, and amyloid-beta plaque formation. Polyphenols like resveratrol and EGCG have shown the potential to improve cognitive function and delay disease progression [57]. They also help regulate blood sugar levels by enhancing insulin sensitivity, inhibiting alpha-glucosidase and alpha-amylase enzymes, and reducing glucose absorption. Phenolic-rich foods are associated with improved glycemic control and reduced risk of type 2 diabetes [58]. Lastly, Phenolic compounds protect the skin from ultraviolet (UV) radiation-induced damage, promote collagen synthesis, and reduce signs of aging. Flavonoids like catechins and phenolic acids like ferulic acid are commonly used in cosmetic formulations for their photoprotective and anti-aging properties [59].

Lectins and Proteins

Lectins in *Pleurotus ostreatus* also play an important role in modulating immune responses. These proteins bind to specific carbohydrate structures on the surface of pathogens and immune cells, triggering immune activation. Proteins derived from *P. ostreatus* have demonstrated adjuvant-like properties by enhancing the activation and maturation of dendritic cells. This increases the production of immunoglobulins and T-helper cell responses [44]. The bioactive compounds also mitigate excessive inflammation by modulating oxidative stress, which is important for balancing immune activation and preventing tissue damage during vaccine responses. Studies have shown that lectins can enhance the proliferation of immune cells and increase the production of antibodies. Additionally, certain proteins isolated from *Pleurotus ostreatus* have been demonstrated to have anti-inflammatory effects, which could help in modulating excessive immune responses and improving vaccine-induced immunity [45].

Saponins

Saponins, naturally occurring glycosides found in plants like Quillaja saponaria, and macrofungi like *Pleurotus ostreatus* are among the most studied natural adjuvants due to their potent immunostimulatory properties [60]. Saponins stimulate both humoral and cellular immune responses by activating dendritic cells, promoting antigen uptake, and enhancing the production of cytokines. They form immunostimulatory complexes (ISCOMs), which facilitate antigen presentation and improve the induction of CD8+ T cell responses [61]. Saponin-based adjuvants, such as QS-21 from Q. saponaria, are already used in licensed vaccines, including the malaria vaccine and herpes zoster vaccine. They enhance antigen delivery to immune cells, stimulate long-lasting memory responses, and increase the immunogenicity of subunit vaccines, which often lack sufficient intrinsic immunostimulatory activity [62]. Other promising natural adjuvants include chitosan, plant-derived lectins, and lipopolysaccharides (LPS) derivatives. They are commonly found in plants and crustacean shells where they drive potent immune responses [63]. Additionally, it has been demonstrated to elicit humoral and cellular responses to co-administered antigens, resulting in the production of T helper 1 (Th1) and cytotoxic lymphocytes (CTLs) [64]. The application of saponins as adjuvants was advanced by creating immune-stimulating complexes (ISCOMs) as one of the vital components in the formulation of the immunostimulatory complex. These have served as antigen-delivery vehicles that demonstrated the use of potent immune-stimulating properties while continuing to exhibit minimal toxicity in a variety of animal models [64-66]. ISCOMs have proven to up-regulate both Th1-and Th2-like immune reactions as well as to accelerate strong body fluid reactions (IgG1, IgG2b, and IgG2a) with cytotoxic T cell induction [66, 67].

Secondary Metabolites

Secondary metabolites are classified into various groups, including alkaloids, phenolics, terpenoids, and steroids. These compounds often serve ecological roles, such as defense mechanisms or signaling molecules, but they also exhibit therapeutic properties. Among the most studied secondary metabolites are ergosterol derivatives and terpenoids.

Medical Importance of Ergosterol Derivatives

Ergosterol is a sterol component of fungal cell membranes, analogous to cholesterol in animal cells. Ergosterol is a target for many antifungal drugs, such as amphotericin B and azoles. These drugs disrupt fungal cell membrane integrity by binding to ergosterol or inhibiting its biosynthesis, leading to cell lysis and death [68]. Ergosterol is a precursor for the synthesis of vitamin D2 when exposed to ultraviolet (UV) radiation. Holick [69], reported that Vitamin D2 supplementation is crucial in preventing and treating conditions like rickets and osteoporosis. Some ergosterol derivatives exhibit anticancer properties by inducing apoptosis and inhibiting tumor cell proliferation. Studies on ergosterol peroxide demonstrate its potential as a chemotherapeutic agent against various cancers, including leukemia and breast cancer [70]. Ergosterol derivatives have shown immunomodulatory activities by enhancing the production of cytokines and stimulating immune cell activity. These properties may help in managing infectious diseases and immune-related disorders [71].

Medical Importance of Terpenoids

Terpenoids (isoprenoids) are the largest class of secondary metabolites, derived from isoprene units. They exhibit strong antimicrobial effects against bacteria, fungi, and viruses. For instance, monoterpenes like thymol and carvacrol, found in essential oils, show broad-spectrum antimicrobial activity [72]. Many terpenoids demonstrate anticancer effects by modulating signaling pathways, inducing apoptosis, and inhibiting angiogenesis. Taxol (paclitaxel), is a well-known chemotherapeutic agent used in treating breast, ovarian, and lung cancers [73]. Terpenoids like boswellic acids have potent anti-inflammatory properties. They inhibit 5-lipoxygenase, a key enzyme in the inflammatory pathway, making them useful in treating arthritis and inflammatory bowel disease [74]. They also contribute to cardiovascular health by reducing blood pressure, improving lipid profiles, and preventing atherosclerosis [75]. Moreover, Terpenoids act as antioxidants by neutralizing free radicals and reducing oxidative stress. This helps in preventing chronic diseases like diabetes, neurodegenerative disorders, and cardiovascular conditions [76].

Applications of Bioactive Compounds of *Pleurotus Ostreatus* in Vaccine Development

Enhancement of Adaptive Immunity

The activation of T helper cells (Th1 and Th2) is another critical aspect of the immune response induced by *Pleurotus ostreatus*. Th1 cells help in the production of interferon-gamma (IFN-γ), which enhances the activity of cytotoxic T lymphocytes (CTLs) and macrophages, leading to improved antigen clearance. On the other hand, Th2 responses contribute to antibody production, which is essential for neutralizing extracellular pathogens [77]. The ability of *P. ostreatus* to boost both cellular and humoral immunity makes it a promising candidate for enhancing vaccine efficacy.

Adjuvant Development

Adjuvants are substances that enhance the body's immune response to an antigen. *Pleurotus ostreatus* and its bioactive compounds, particularly its polysaccharides, have shown considerable promise as natural adjuvants. These compounds when integrated into vaccine formulations help to amplify the immune response, thereby improving vaccine effectiveness, especially in vulnerable populations such as the elderly or immunocompromised individuals [78]. The immunomodulatory properties of *P. ostreatus* have been shown to improve the persistence of immune memory, ensuring long-term protection against pneumococcal infections. By enhancing antigen presentation and stimulating the production of neutralizing antibodies, these compounds may help in overcoming the limitations of current vaccines, which often offer incomplete protection.

Long-Term Immunity and Memory Response

One of the most important aspects of vaccine efficacy is the ability to generate long-lasting immunity. Memory B cells and T cells play a crucial role in the immune system's ability to respond to future exposures to pathogens [79, 80]. Pleurotus. ostreatus has been shown to enhance the persistence of immune memory through the activation of both T-helper (Th) cells and cytotoxic T lymphocytes (CTLs). This could result in improved long-term protection against some bacteria.

In addition to generating a robust primary immune response, *P. ostreatus* may help stimulate the production of memory B cells that can quickly produce antibodies upon re-exposure to some pathogen. This aspect of memory immunity is particularly important for vaccines, against pathogens such as S. pneumoniae known to exhibit antigenic variation across its many serotypes.

Enhancing immune memory could lead to broader protection against different pneumococcal strains [77].

synergy with nanoparticle delivery systems

To maximize the potential of *P. ostreatus* in vaccine development, its bioactive compounds could be incorporated into advanced delivery systems such as nanoparticles. Nanoparticle-based delivery systems allow for the targeted delivery of antigens and adjuvants to specific immune cells, increasing the effectiveness of vaccination and minimizing side effects. Studies have shown that nanoparticles, such as liposomes or polymeric nanoparticles, can encapsulate the bioactive compounds of *P. ostreatus* and improve their stability, bioavailability, and controlled release [25. Additionally, nanoparticles can facilitate the efficient delivery of *P. ostreatus* polysaccharides directly to antigen presenting cells (APCs), thereby enhancing immune activation and ensuring a stronger and more sustained immune response [25].

Challenges and Future Directions

Despite the promising potential of *P. ostreatus*, several challenges remain in its integration into vaccine production. The standardization of *P. ostreatus* extracts, the identification of the most effective immunomodulatory compounds, and the optimization of production methods are key areas requiring further investigation. Additionally, clinical trials assessing the safety, efficacy, and immunogenicity of *P. ostreatus*-based adjuvants in human populations are essential to validate their role in vaccine formulations.

Future Research

Future research should focus on elucidating the specific molecular pathways through which *Pleurotus ostreatus* enhances immune responses. Additionally, the development of advanced extraction techniques to isolate and purify the bioactive compounds of *Pleurotus ostreatus* could help maximize its potential as a vaccine adjuvant. The investigation of synergistic effects between *P. ostreatus* extracts and existing vaccine platforms, including the development of nanoparticle-based delivery systems, is another promising area for future study.

Conclusion

Pleurotus ostreatus offers significant promise as a natural source of immunomodulatory agents that can enhance the production and efficacy of vaccines. Its bioactive compounds have also demonstrated the potency of combating different infections of public threat. These bioactive compounds, particularly polysaccharides, can stimulate both innate and adaptive immune responses, potentially improving vaccine effectiveness and providing broader protection against numerous microorganisms. Future studies should explore the molecular mechanisms involved, clinical safety, and the integration of *Pleurotus ostreatus* in vaccine formulations to address the growing challenge of many human infections.

Conflict of Interest: The authors declare that there is no conflict of interest.

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