Macrofungi as a Promising Source of Nutraceuticals

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Abstract:

Bioactive compounds known as nutraceuticals have a significant impact in human well-being. Recently, there has been a significant understanding of the numerous health-promoting properties and exceptional nutritional value of mushrooms. Macrofungi have been considered functional in treating several health issues such as tumor, hypertension, owing to their rich composition of primary and secondary metabolites.

This review explores the nutraceutical capabilities of Macrofungi, particularly focusing on their polysaccharides, which showcase a variety of properties such as anticancer, antibacterial, antidiabetic, and immunostimulatory effects. The potential of medicinal mushrooms is discussed, with an acknowledgment of the significant drawback of their taste. It is emphasized that claims about their benefits need robust support from scientific studies to uphold trust and confidence. Further scientific investigation is crucial to assess the efficacy of nutraceuticals sourced from macrofungi, while also tackling prevailing apprehensions regarding the inadequacy of quality assurance protocols within this domain

Keywords: Nutraceuticals; antibiotics; Macrofungi

الفطريات الكبيرة(المشروم) كمصدر واعد للمكملات الغذائية

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خلاصة

المركبات الحيوية الفعالة من الفطريات (المشروم) باسم المكملات الغذائية لها تأثير كبير على الصحة العامة. في الآونة الأخيرة، زاد الفهم الكبير للخصائص الصحية المتعددة والقيمة الغذائية الاستثنائية للفطريات الكبيرة (المشروم). وقد اعتبرت الفطريات الكبيرة (المشروم) فعالة في علاج العديد من المشاكل الصحية مثل الورم وارتفاع ضغط الدم، نظرًا لتركيبها الغني من مركبات الايض الأولية والثانوية. تستعرض هذه المراجعة قدرات المكملات الغذائية للفطريات، مع التركيز بشكل خاص على السكريات المتعددة التي تظهر مجموعة متنوعة من الخصائص مثل التأثير المضاد للسرطان، والمضاد للبكتيريا، والمضاد لمرض السكري، والمحفز للمناعة. يتم مناقشة إمكانيات الفطريات الطبية، مع الاخذ بنظر الاعتبار الطعم الغير مستساغ

يتم التأكيد على ان فوائدها تحتاج إلى دعم قوي من الدراسات العلمية ومزيد من البحث العلمي الإضافي لتقييم فعالية المكملات الغذائية المستمدة من الفطريات الكبرى، بينما يتعامل أيضًا مع التخوفات السائدة بشأن عدم كفاية بروتوكولات ضمان الجودة ضمن هذا المجال.

الكلمات المفتاحية: المكملات الغذائية، الفطريات الكبيرة (المشروم) المضادات الحيوية

1. Introduction

Nutraceuticals, recognized for their potential health advantages, have garnered considerable attention. Macrofungi, which include both edible and medicinal mushrooms, have been identified as prolific sources of notable bioactive compounds, particularly polysaccharides [17,4].

The objective of this review is to provide a comprehensive summary of the potential of macrofungi as a source of nutraceuticals, including their bioactive polysaccharides and other compounds, as well as the challenges and opportunities in the mushroom nutraceutical market. Macrofungi, which are also known as mushrooms, belong to the phylum Basidiomycota, and a few Ascomycota species that produce conspicuous sporocarps or fruiting bodies, visible without microscopic aid, either above or below the soil surface [24,6]. There are approximately 14,000 macrofungal species found globally, with 350 of them being consumed in various cultures around the world.

Agaricus bisporus, *Pleurotus spp* and *Oyster sp* are among the most cultivated edible macrogungi [1,5].

Significant strains have recently been achieved in the cultivation of edible macrofungi, leading to a considerable surge in their production. Internationally, The escalating market demand for medicinal mushrooms, owing to their health-beneficial properties, has spurred their widespread consumption [23,8]. Hundreds of macrofungal species were listed as sources of secondary metabolites, and to be used as dietary supplements for health purposes [28]. The production and economic value of macrofungi have grown worldwide. It is expected that the Mushroom market will experience an annual increasing in value in the future dueto the increasing demand for mushrooms. The increasing market of macrofungi among health seekers is attributed to their unique flavors, as well as their health benefits [31,36].

Macrofungi can be characterized as a nutritious functional food, given their abundant nutritional composition.They are known for their high nutritional value due to the presence of Proteins, Minerals, vitamins, and fibers, with the added advantage of being low in calories and free of cholesterol. Out of the 14,000 identified species of macrofungi, more than 1500 are considered edible, and about 600 of these have medicinal activity [.30,32]. Macrofungi that are suitable for human consumption hold promise as a viable source of diverse nutraceuticals, including but not limited to lectins, unsaturated fatty acids, β-glucans, phenolic compounds, and antioxidants [29,33].

Additionally, macrofungi such as *L. edodes A. bisporus, velutipes,* and others have been harvested from their natural habitats and employed as medicinal remedies for centuries across various Asian nations. These traditional uses have stimulated contemporary scientific investigations into the medicinal potential of fungi, particularly their anticancer properties [4,8]. *Ophiocordyceps sinensis*, were explored for their medicinal uses. These species have been found to contain numerous bioactive compounds [11,15]. Hundred species of macrofungi have been studied for their nutraceuticals, which have the potential to be developed into food supplements for medicinal purposes. Recently, some countries has achieved significant results in the cultivation of edible macrofungi,

resulting in increased production. The ability for the health-enhancing advantages of medicinal macrofungi has resulted in a rise in their market worth [9,18].

1. Macrofungi

Macrofungi are a group of diverse eukaryotic organisms with form large fruiting bodies include Basidiomycota and Ascomycota. About 2,000 macrofungi from Europe and North America were investigated prior to the 1950s, and more than 700 found to produce antibacterial substances. Following substantial surveys of basidiomycete macrofungi and plant endophytic fungi.

Fruiting bodies are primarily composed of carbohydrates, ranging from 50-60%. Mannitol is the predominant free sugar in mushrooms, accounting for approximately 80% of the overall free sugars present [18]. Mushrooms possess a higher protein content in contrast to the majority of vegetables and wild plants, with Pleurotus ostreatus having a reported carbohydrate content of 56% [9]. The United States Department of Agriculture (USDA) released pertinent information in 2019, indicating that a 100-gram serving of uncooked mushrooms contains approximately 22 kilocalories, with a nutritional composition encompassing. Per 100 grams of dry weight, macrofungi exhibit nutritional content comprising 3.26 grams of carbohydrates, 3.09 grams of protein, 1.0 gram of fiber, and 0.34 grams of fat. Notably, their low glycemic index suggests a minimal impact on blood glucose levels. The glycemic index, serving as an indicator of a food item's potential to influence postprandial glycemia, suggests that mushrooms may hold promise in glycemic management and deserve further investigation in this context. Macrofungi are considered a rich source of micronutrients, including the vitamin B complex, proteins, and fat. Also they are considered a rich source of essential mineral elements required for human health, including magnesium (Mg), sodium (Na), potassium (K), phosphorus (P), calcium (Ca), and some of trace elements, including zinc (Zn), copper (Cu), molybdenum (Mo), iron (Fe), and cadmium (Cd). The mineral composition of mushrooms is primarily influenced by several factors, including the cultivation media, species, fruiting bodie size and age In comparison to cultivated mushrooms, wild mushrooms generally possess a higher mineral content [25].

1.1. Polysaccharides

Polysaccharides are a group of potent compounds extracted from mushrooms that possess diverse physiological activities including antioxidant, anticancer, anticarcinogenic, anti-inflammatory, and neuroprotective effects [3]. Several studies have established that macrofungal polysaccharides showed bioactivity [4]. Bioactive polysaccharides, including derivatives such as glucans, exhibit a varied array of structures and properties. Glycans, exemplified by heteropolymers, demonstrate anticancer activities through the stimulation of the host organism's immune system, specifically targeting cancer cells. The bioactive compounds effectively mitigate stress within the body, leading to a decrease in cancer cells and enhanced survival rates observed in mice induced with cancer[37]. According to Li et al. (2018), macrofungal polysaccharides from *Agaricus bisporus* have been found to produce anti-aging effect and can improve kidney functions Through enhancing of serum enzyme activities, modulation of biochemical levels, and

alteration of lipid content. Additionally, polysaccharides have demonstrated anti-tumor effect through inhibition the growth of MCF-7 cells and murine sarcoma cells in mice [16]. Moreover, these polysaccharides exhibit anti-aging and antioxidant effects. AcAPS-2 has been shown to have scavenging activity on hydroxyl and DPPH radicals [21].

Polysaccharides derived from various species of *Ganoderma sp* have demonstrated potential as nutraceuticals with diverse physiological effects, including antioxidation, antiproliferation, and immunomodulation. Specifically, *Ganoderma lucidum* polysaccharide (GLP) has been found to increase serum interleukins, tumor necrosis factors and interferons concentrations. Additionally, GLP increases natural killer cells and T cells toxicity [46].

The polysaccharides derived from Ganoderma lingzhi have exhibited notable effects in enhancing cognitive function and promoting neural progenitor proliferation in a murine model of Alzheimer's disease. These polysaccharides exert neuroprotective actions by modulating the expression of apoptosis-associated proteins and inhibiting neuronal apoptosis induced by oxidative stress. Additionally, Ganoderma lingzhi polysaccharides (GLPs) have demonstrated hypoglycemic effects in animal models, influencing glucose levels and lipid metabolism. Notably, the degraded polysaccharide GLPUD manifests more potent antioxidant and hypolipidemic effects compared to GLP. polysaccharides derived from *Grifola frondosa* possess antitumor properties, leading to the development and approval of a *G. frondosa* polysaccharide-based drug in China. This drug is utilized as an adjunctive therapeutic agent in cancer treatment [48].

Comparisons of *G. frondosa* polysaccharides with those derived from other sources, including *G. sichuanense*, lentinan, and *Trametes versicolor*, have demonstrated their superior efficacy in fighting cancer [41].

Beta-glucans are a type of polysaccharide that are primarily located in the cell wall of various fungi and have been extensively studied for their broad range of biological activities [40]. Beta-glucans have been found to exhibit various physiological effects, including antidiabetic, and neuroprotective activities. Additionally, beta-glucans improve lipid balance and overall consumer well-being by stimulating biological responses in cell membrane that trigger immune responses [41]. Due to their biological response modifier properties, beta-glucans can be developed into drugs for various applications [47]. Lentinan, which is present in *Lentinula edodes*, has been demonstrated to be efficacious in enhancing the health condition of cancer patients undergoing chemotherapy. Moreover, lentinan exhibits immunomodulatory effects against viral infections and malaria [26]. Pleuran, produced by *Pleurotus ostreatus*, has been reported to treat upper respiratory tract infections caused by viruses[45]. Schizophyllan, produced by *Schizophyllum commune*, has properties similar to lentinan and can have synergistic effects of vaccines and antitumor therapies. Tramesan, of *Trametes versicolor*, has shown antioxidant properties, and antifungal effects against *Candida albicans*. It has also shown potential agricultural applications as a natural crop protection [22].

1.2. Lectins

macrofungi-derived proteins have been found to have diverse pharmaceutical

properties. These include antibacterial, antitumor, antiviral, and antifungal activities. Lectins are a class of proteins that exhibit diverse bioactivities, including antitumor, and anti-insect activities. Additionally, they participate in carbohydrate transport and storage within cells. Lectins are found in the reproductive form of mushrooms. It is also play a crucial role in their life cycle. *Ganoderma applanatum* lectin demonstrated growth inhibition activity against HT-29 cells, while lectin isolated from *Agaricus bisporus* exhibited in vivo immunomodulatory effects {10,50}.

Ergothioneine

an amino acid derivative of histidine Figure 1, is present in mushrooms such as *Agaricus bisporus* and *Pleurotus citrinopileatus*. Ergothioneine has been demonstrated to have antioxidant and cytoprotective properties in vitro, underscoring its potential therapeutic benefits against various human conditions. Since humans are incapable of synthesizing this compound, its presence in the bloodstream primarily relies on dietary intake. Certain proteins have been identified to possess potent anti-metastasis activities against specific tumor cells, including leukemic T cells, hepatoma Hep G2 cells, and MCF7 cells {30}.

A lectin-like protein, identified as the light subunit of mushroom *A. bisporus* tyrosinase (LSMT), has been found to exhibit such properties. Moreover, LSMT can traverse the monolayer of intestinal epithelial cells, rendering it a viable option for oral delivery. Studies have demonstrated that LSMT can inhibit breast cancer cell growth and stimulate cell proliferation of macrophage cells, indicating its potential therapeutic value. Macrofungi proteins have been demonstrated to possess diverse pharmaceutical activities, making them promising candidates for potential therapeutic agents. Lectins and ergothioneine have been found to exhibit cell bioactivities, including immunomodulatory, antitumor, antifungal, and anti-insect activities. Additionally, certain proteins have demonstrated potent antiproliferative and anti-metastasis activities against specific tumor cell lines, suggesting their potential use as drug carriers and anticancer treatments {7}. Specifically, ergothioneine has been proposed as a promisingl therapeutic agent for reducing the severity of various human conditions.

Fruiting bodies are a rich source of low-fat compounds, predominantly composed of carbohydrates and proteins with unsaturated fatty acids, such as the essential linolenic acid {34,49}. Tocopherols are lipid constituents with potent antioxidant activities that offer protection against degenerative, cardiovascular diseases, and cancer. Ergosterol, which present in cell membranes of protozoa, is also found in macrofungi, and showed antioxidant properties that assist in the prevention of cardiovascular diseases {13}. It is also a vitamin D2 precursor. *Pleurotus sp*, have high concentrations of ergosterol. Agarol, derived from ergosterol in *Agaricus blazei*, has been found to have anticancer properties {8}. Some macrofungal lipid extracts have antifungal activity against Candida species. Additionally, hemagglutinin isolated from *F. velutipes* fruiting bodies have the ability to stimulate immune reactions and inhibit the proliferation of cancer cells {2}.

Macrofungi are known to contain wide range of secondary metabolites, such as phenols which can have either a simple or complex

polymer phenolic structure. Phenolic compounds have been reported to have various physiological effects, incuding anti-allergenic, cardioprotective, and vasodilator effects Extensive studies has been confirmed that the antioxidative properties of phenolic compounds, revealing their ability to function as scavengers of free radicals and quenchers of singlet oxygen {36}

1.3. Vitamins, essential micronutrients pivotal for various physiological processes including metabolism, digestion, and immunity, play a crucial role in the human body. Macrofungi are recognized for their abundance in vitamins, particularly those belonging to the B group. Boletus edulis stands out for its elevated content of group B vitamins, while *Pleurotus ostreatus* is notable for its high folacin (B9) levels. *Lentinula edodes* is also rich sources of vitamin D. Vitamin D4 (22-dihydroergocalciferol) has been detected in Agarics species. Although present in small amounts compared to vitamin D2, the presence of vitamin D4 in these species adds to their overall nutritional value.

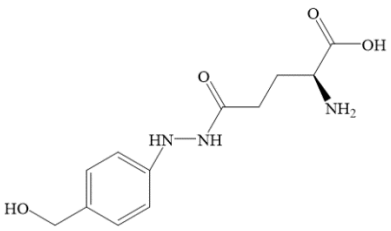
1.4. Agaritine, Figure 1, which is found in Agaricus species, is considered toxic in large doses and has been classified as an IARC Group 3 carcinogen {19}. However, currently, there is no available evidence indicating that the ingestion of cultivated *Agaricus bisporus* mushrooms carries any toxicological hazard for individuals for health. Agaritine has potential as an antiviral drug and and antitumor effects against leukemic cells. Cordycepin, which is the primary bioactive compound produced by Cordyceps species, exhibits a diverse range of nutraceutical and pharmaceutical uses such as anti-aging, anti-inflammatory, antiviral, and antidiabetic properties {29. Ganoderic acids are triterpenoids that are used as adjuvants in therapies and other medications and have been shown to have neuroprotective effects and potential for treating neuroblastomas {3}.

In the coming years, the nutraceutical industry is expected to experience a substantial increase in market value driven by increasing product development and innovation in response to the growing demand for dietary supplements and functional food.

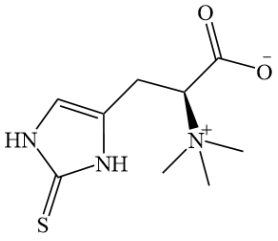
1.5. The potential of macrofungi, particularly polysaccharides, for nutraceutical applications is significant due to their diverse bioactivities, including anticancer, immunostimulatory, antibacterial, immunoregulatory,hepato- and kidney-protective effects, antidiabetic, antiviral, and anti-aging activity. Bioactive vitamins and proteins also offer potential opportunities for nutraceutical applications. The trend towards natural products among consumers has further increased the demand for macrofungi-based nutraceuticals. However, despite the rich diversity of macrofungi in Iraq, there is still limited of research on their potential as source of bioactive compounds and nutritional components. Therefore, more studies are required to explore the potential of Iraqi macrofungi as a source of bioactive compounds and a valuable source of nutrition. Such research may provide insights into the optimization of cultivation and harvesting practices of macrofungi for nutraceutical applications, which may contribute to the growth of the nutraceutical industry in Iraq.

1.6. Challenges and Opportunities in the Mushroom Nutraceutical Market:In the mushroom nutraceutical market, challenges arise predominantly from taste perceptions and limited research. While mushrooms offer diverse health benefits, their distinct taste often poses a barrier to widespread acceptance among consumers. Moreover, inadequate research, particularly in regions like Iraq, impedes the optimization of cultivation practices and hinders the exploration of mushroom nutraceutical applications. Additionally, concerns persist regarding the consistency of quality assurance protocols, undermining consumer trust and confidence in mushroom-derived products.

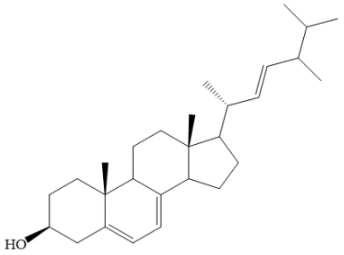
However, amidst these challenges, significant opportunities emerge for market growth. The escalating demand for medicinal mushrooms, driven by their recognized health benefits, presents a promising avenue for expansion. Technological advancements in cultivation techniques further enhance production efficiency, offering opportunities for increased supply. Moreover, the growing trend towards natural products among consumers aligns well with the inherent health-promoting properties of mushrooms, creating a conducive environment for market expansion. By addressing taste perceptions, investing in research, and improving quality assurance protocols, the mushroom nutraceutical market can capitalize on these opportunities to meet the rising demand and contribute to human well-being.



Agaritine



Ergothioneine



Ergosterol

Figure 1. Chemical structures of Agaritine, Ergothioneine, and Ergosterol.

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