Health Benefits of Edible Mushrooms Focused on Coriolus versicolor: A Review

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Abstract

The biological properties present in mushrooms have been extensively studied. Besides nutritional properties, mushrooms have attracted market attention because they are a potential source of bioactive compounds able to perform several functions in organisms with benefits for consumer health. In recent years Coriolus versicolor aroused interest among researchers because of the bioactive properties demonstrated. Polysaccharopeptide (PSP) and polysaccharopeptide Krestin (PSK) have shown to be useful adjuncts to the therapy of cancer; these polysaccharides from C. versicolor have also shown prebiotic activity, stimulating the growth of probiotic bacteria. Furthermore, enzymes such as laccases produced by Pleurotus eryngii and Ganoderma lucidum can confer activity against HIV; lectins produced by Pleurotus ostreatus and Ganoderma carpense have shown anti-proliferative activity in tumour cells; superoxide dismutase present in some mushrooms has antioxidant activity. Secondary metabolites such as terpenes, steroids, anthraquinones and benzoic acid have also antitumour activity. This review article highlights the health-promoting potential of several mushroom species with special emphasis on C. versicolor.

Keywords: Polysaccharopeptide, Polysaccharopeptide Krestin, Health-promoting Potential, Bioactive Compounds, Prebiotic Activity

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At a glance: Figures

1. Introduction

Mushroom cultivation has a long tradition mainly in Asian countries where it started centuries ago. Edible mushrooms constitute an element of human diet in many countries all over the world. At least 12000 species of fungi can be considered as mushrooms, and at least 2000 species are identified as edible [1]. According to Sánchez et al. [2], among the 2000 edible mushroom species found in different regions of the world, only 35 are grown on a commercial scale and 20 are cultivated on an industrial scale. The most cultivated mushroom worldwide is Agaricus bisporus (button mushroom),
followed by Lentinus edodes (shiitake), Pleurotus spp (oyster mushrooms), Auricularia auricula (wood ear mushroom), Flammulina velutipes (winter mushroom) and Volvariella volvacea [3].

Data reported by the Food and Agriculture Organization [4] indicate that in 2013 the world production of mushrooms was around 9.9 million tons. In the western countries mushrooms have been underestimated in nutrition field, although research has been demonstrating that mushrooms have low calorie content and high nutritive value. Edible mushrooms have high water content, for this only 5-15% of dry matter, which is mainly composed by dietary fibre and protein. They also contain vitamins B1, B2, D2, C, macro and microelements i.e. K, Mg, P, Zn, Fe and Cu [5].

Mushrooms have been used not only as a source of food, but also as medicinal resource. A total of 126 medicinal functions are thought to be produced by medicinal mushrooms, among which antitumour, immunomodulating, antioxidant, radical scavenging, cardiovascular, antihypercholesterolemia, antiviral, antibacterial, antiparasitic, antifungal, detoxification, hepatoprotective, and anti-diabetic properties are the most recognized [6, 7, 8, 9]. These properties are conferred by bioactive compounds present in the mushroom and include polysaccharides, polysaccharide-peptide complexes, ribonucleases, lectins, proteas inhibitors, lignocellulolytic enzymes, hydroxyns and superoxide dismutase that are present in the mycelium and fruiting body of the fungus [5, 10, 11]. Due to the health benefits demonstrated, some species of mushrooms have become attractive for development of functional foods and as a source of bioactive compounds towards the development of new drugs. Therefore, we will restrict our review to one of the most important medicinal mushroom, Coriolus versicolor.

2. **Coriolus Versicolor**

Coriolus versicolor, also known in the literature by Trametes versicolor or *Polyporus versicolor*, belongs to the genus *Coriolus*, family *Polyporaceae*, order *Polyporales* and division *Basidiomycotina* [12]. This mushroom rise up from lignocellulosic wastes and has a fan-shaped wavy margin and may exist in nature in several different colours. Both extracellular and intracellular polysaccharides of *C. versicolor* are physiologically active as bioactive compounds. Two polysaccharides, polysaccharopeptide (PSP) and polysaccharopeptide Krestin (PSK) were isolated from *C. versicolor* and used as a supplement to support chemotherapy and radiotherapy of cancers due to its immunostimulatory properties [13, 14]. Furthermore, it seems that these polysaccharides may also act as prebiotics by stimulating the growth and/or activity of probiotic bacteria in the colon [15].

*C. versicolor* may be used in the extract or biomass forms. Extract forms (PSK and PSP) were extensively studied in past years. The biomass of *C. versicolor* is more resistant to proteolytic degradation and contains not only β-glucans but also other compounds with large clinical interest. The biomass form of *C. versicolor* contains a variety of relevant enzymes with different activities such as superoxide dismutase, peroxidase, glucoamylase, protease and laccase [16, 17, 18]. For example, this mushroom produces the enzyme laccase, which is a polyphenol oxidase belonging to the family of blue multicopper oxidases [19]. Laccase can oxidize a wide range of substrates, phenolic preferably. In the presence of mediators, the fungal laccases feature a wide range of substrates and then are able to oxidize compounds with a high redox potential. This enzyme has been used in biotechnology and industry, for the delignification of lignocellulose, bioremediation and sewage treatment [17].

Among the mushroom-derived compounds with therapeutic properties, the polysaccharides obtained from extracts of *C. versicolor* are the best known commercially. Both preparations (PSP and PSK) consist of β-glucans, polymers of D-glucose with β-1,3 and α-1,4 glycosidic linkages, but some of them can also contain arabinose, mannose, fucose, galactose, xylose and glucuronic acids. PSP and PSK extracted from *C. versicolor* typically contain 34-35% soluble carbohydrates, 28-35% protein, ~7% moisture, 6-7% ash and the remainder are free sugars and amino acids [20]. Among the 18 types of amino acids present, 70% consist of acidic and neutral amino acids such as aspartic acid, threonine, serine, glutamic acid, glycine, alanine, valine, and leucine [21]. Beneficial health properties reported over the years by Chinese and Japanese researchers have attracted the attention of the scientific community worldwide. Therefore, many clinical studies have been carried out in recent years with the aim to assess and identify the main bioactive properties of polysaccharides extracted from *C. versicolor*. These bioactive properties are detailed in Table 1.

The studies published so far have used extracts or polysaccharides isolated from the mushroom. However, the extract of the fruiting bodies is more susceptible to the action of proteolytic enzymes. The non-digestible property of the polysaccharides from *C. versicolor* make them potential prebiotic agents, but more studies are needed on this subject to efficiently validate its potential. Yu et al. [15] found that the presence of PSP from *C. versicolor* increased the levels of *Bifidobacterium* and *Lactobacillus* when in vitro studies were performed using the isolated polysaccharide form. They also identified an indirect effect in inhibiting pathogenic bacteria, including clostridial species, by lowering the pH. A study reported by Pallav et al. [22] demonstrated that the microbiome of volunteers randomly treated with PSP extracted from *C. versicolor* showed clear and consistent changes derived from a possible prebiotic activity.
Polysaccharides isolated from *C. versicolor* have demonstrated antitumour activity in the past [23, 24, 25]. *In vitro* studies showed that PSP acts selectively against certain tumour cells. Thus, it has been reported that *C. versicolor* extract, at the concentration of 1 mg/mL applied directly in human cancer lines, inhibited their growth namely gastric cancer, lung cancer, leukemia and lymphoma [26]. Moreover, PSP is active against Ehrlich ascites carcinoma, sarcoma 180 and leukemia P388. However, not all tumour cells appeared to respond to *C. versicolor* polysaccharopeptides [20].

Polysaccharopeptides are known as useful adjuncts to conventional therapy [27]. Some examples in animal models suggested an increase of chemo- or immunotherapy efficacy when they are associated to polysaccharides. The therapeutic use of *Coriolus versicolor* as an adjunct therapy in cancer treatment has been substantiated by numerous clinical trials [28, 29]. In human therapy, *C. versicolor* polysaccharopeptides are usually administered orally although, according to Yang et al. [29], PSK is effective orally, intravenously or intraperitoneally. A study carried out on mice [30] demonstrated that PSP has significant inhibitory effect on the tumour growth, inhibiting angiogenesis, which is an important process underlying tumour progression.

It was found that PSP significantly increased the number of monocytes (CD14+/CD16) in *in vitro* studies. Thus, stimulating monocytes/macrophage function with polysaccharopeptides could be an effective therapeutic intervention in targeting tumours [31]. A study by Harhaji et al. (2008) has showed that *C. versicolor* methanol extract exerts pronounced anti-melanoma activity in mouse, both directly through antiproliferative and cytotoxic effects on tumour cells and indirectly through promotion of macrophage anti-tumour activity. All these studies indicated a great potential of polysaccharides from *C. versicolor* as base to develop new therapies for cancer [14, 33].

Significant literature support the immune and anticancer functions of *C. versicolor* PSP [30, 31, 32, 34]. According to Lee et al. [34] the culture duration affects the immunomodulatory and anticancer effect of polysaccharopeptide derived from *C. versicolor*. In this study, the extracts of PSP obtained at different days from *C. versicolor* culture were tested *in vitro* for their immune function on human normal peripheral blood mononuclear cells (PBMC) and cytotoxicity on human leukemia Molt 4 cells. Lau et al. [35] has carried out a study of the cytotoxic activities of *C. versicolor* extract on a B-cell lymphoma (Raji) and two human promyelocytic leukemia (HL-60, NB-4) cell lines using a MTT cytotoxicity assay. Results showed that *C. versicolor* extract selectively and dose-dependently inhibits the proliferation of lymphoma and leukemic cells possibly via an apoptosis-dependent pathway.

Recently, Luo et al. [36] showed that *C. versicolor* exhibited antitumour, anti-metastasis and immunomodulation effects in metastatic breast cancer mouse model, and could protect the bone from breast cancer-induced bone destruction. Another recent study by Yang et al. [41] characterized the imunopotentiating effects, which are related to the antitumour ability of the *C. versicolor* polysaccharides to bind and induce B cell activation using membrane Ig and TLR-4 as potential immune receptors.

In order to evaluate the pre-clinical and clinical evidence concerning the safety and effectiveness of the PSK as an adjuvant in the treatment of lung cancer, a recent review article examined thirty-one reports of 28 studies [43]. These results showed that PSK may enhance immune function, reduce symptoms of tumour-associated and prolong survival in lung cancer patients. Moreover, according to Fujita et al. [44] PSK may have an effect on the drug metabolizing enzymes in sarcoma-180 bearing mice, but not in normal mice.

Some studies have indicated that extracts of *C. versicolor* have antimicrobial activity against common pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, *Klebsiella pneumoniae*, *Listeria monocytogenes* and *Streptococcus pneumoniae*. The mechanism seems to be related with the activation of polymorphonuclear cells and an increased secretion of antimicrobial cytokines [45, 46].

### Table 1. Bioactive properties in *Coriolus versicolor*

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Antimicrobial activity</td>
<td>Against various bacterial strains.</td>
</tr>
<tr>
<td>Immunomodulatory effects</td>
<td>Enhances immune function in breast cancer model.</td>
</tr>
<tr>
<td>Antitumour, anti-metastasis</td>
<td>Protects bone from cancer-induced bone destruction.</td>
</tr>
<tr>
<td>Safety and effectiveness</td>
<td>PSK enhances immune function and prolongs survival.</td>
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Studies carried out with mice have shown that PSK increase the levels of glutathione peroxidase in macrophages [37]. Glutathione peroxidase is part of the first line of defense against lipid peroxidation, and protects the cell membrane in an early stage against attack by free radicals.

Kozarski et al. [38] showed that polysaccharide extracts of C. versicolor have antioxidant activity. The extracts contained a mixture/complex of polysaccharides, proteins and polyphenols and the antioxidant effect measured was resistant to high temperatures. Another study developed by Santos Arteiro et al. [47] evaluated the antioxidant effect of the polysaccharides isolated from submerged cultures of C. versicolor. The radical scavenging for E-PPS (extracellular protein-polysaccharides) and 1-PPS (intracellular protein-polysaccharides) produced per litre of culture was equivalent of 2.115 ± 0.327 and 1.374 ± 0.364 g of ascorbic acid, respectively. These complexes have revealed a positive effect protecting erythrocyte membranes from oxidation. They also demonstrated the ability to inhibit the synthesis of methemoglobin in stressed cells.

Submerged fermentation culture of C. versicolor showed potential antidiabetic activity [16, 48]. One of the drugs that have been used in the treatment of type II diabetes consists of α-glucosidase inhibitors. According to Hsu et al. [16] C. versicolor LH1 mycelia can inhibit the enzyme α-glucosidase. The α-glucosidase inhibitory properties were related to the presence of α-1,4 glycosidic linkages in the polysaccharide structure and the total relative percentage of D-glucose and D-galactose in the structure of polysaccharides, other than tetrasaccharide.

The effect of PSF on the potential interaction of HIV-1 and its target cell was investigated by Collins and Ng [39]. They demonstrated inhibition of the interaction between HIV-1 gp120 and immobilized CD4 receptor by inhibiting the recombinant HIV-1 reverse transcriptase and a glycohydrolase enzyme associated with viral glycosylation.

The combination of Ginkgo Flavonoid (GF) and C. versicolor polysaccharide (CVP) in the prevention and treatment of a mouse model of Alzheimer’s disease was studied by Fang et al. [42]. A synergetic beneficial effect of GF and CVP has improved the memory in the mouse model providing new insights into the efficient utilization of traditional medicine for preventing dementia.

Recently, researchers have studied a protein expressed by C. versicolor biomass (lipoxin A4), which is able to modulate the inflammatory process involved in the Alzheimer’s disease pathogenesis. This
A recent study developed by Barros et al. [19] tested the safety profile of biomass of C. versicolor in rats. Of the results obtained, it was possible to infer about the degree of safety for human consumption.

### 3. Health-promoting Potential of Edible Mushrooms

Recently, mushrooms have attracted much research interest because among other benefits they are a good source of β-glucans. Some properties such as molecular weight, chemical composition and the number of branches of side chains can determine the physical and therapeutic properties of β-glucans, providing specific biological properties to mushrooms. It was shown that they are a rich source of bioactive compounds such as polysaccharides, polysaccharide-peptide complex, proteases and lectins, exhibiting antitumour, antioxidant, antimicrobial, prebiotic and anti-inflammatory properties [5, 50, 52]. Furthermore, mushrooms also accumulate enzymes and secondary metabolites that may play important metabolic functions in the body. Studies carried out in recent years in order to discover and study bioactive compounds from mushrooms are summarized in Table 2, except those related with C. versicolor, previously detailed.

#### 3.1. Antitumour Activity

Polysaccharides of mushrooms may have antitumour activity, which is associated with the immunostimulatory effect that they can exert, since they are foreign bodies to our immune system [53, 54, 55]. The immunostimulatory potential of glucans was recently summarized by Vannucci et al. [55]. This antitumour activity is not caused by a direct cytotoxic effect but via activation of the innate immune system of the host (Figure 1). The mechanism of action is related to the presence of pattern recognition receptors (PRRs) that can recognize the polysaccharides as pathogen-associated molecular patterns (PAMPs), due to its high molecular weight. Consequently, pro-inflammatory cytokines are secreted including tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) which regulate the mechanisms against infections, recognition of foreign cells and tumour cells [5]. Some structures of the β-glucans seem to be better adapted to the PRR receptors, which suggests a relationship between the structure and antitumour activity of polysaccharides. Chang et al. [11] found that glucans with β-1,3 and β-1,6 linkages have higher antitumour activity.

![Figure 1. Possible immune mechanism for β-D-glucan biological response modifier [56]](image)

#### Table 2. Bioactive properties found in edible mushrooms
A recent study by Li et al. [50] showed that polysaccharide extracts from *Hericium erinaceus* are active against liver cancer cells *in vitro* and *in vivo*. According to Zhang et al. [57] the highest consumption of dietary mushrooms, including *Agaricus bisporus* and *Lentinula edodes*, is associated with a decreased risk of breast cancer in premenopausal women and postmenopausal women. *Grifola frondosa* is one of the most popular medicinal mushrooms. The levels of Natural Killer (NK) cell cytotoxic activity in cancer patients receiving D-fraction extracted from *G. frondosa* were monitored by Kodama et al. [58]. D-fraction markedly suppressed tumour growth, corresponding with increases in TNF-α and IFN-γ released from spleen cells and a significant increase in TNF-α expressed in NK cells. *Ganoderma tsugae* is the other medicinal mushroom in which polysaccharides have been well investigated in both the fruiting body and mycelia. Sixteen polysaccharides obtained from *G. tsugae* were examined for antitumour effects on Sarcoma 180 in mice.

The heteroglucan had a low tumour inhibition ratio, but caused a high survival ratio [70, 71, 72].

### 3.2. Antioxidant Activity

Polysaccharopeptides found in mushrooms can benefit general health by inducing enzymes that remove free radicals and reduce the oxidative damage. Many synthetic chemicals, such as synthetic phenolic compounds, are strong radical scavengers, but they usually have side effects. For this reason, natural antioxidants have been preferred for food applications [38] in particular due to the increasing demand of consumer by natural additives and ingredients. The antioxidant activities of ethanolic extract from edible mushroom *Agaricus bisporus* were evaluated by Liu et al. [52] and the results suggested that ethanolic extract of *A. bisporus* had potent antioxidant activity and could be explored as a novel natural antioxidant.

An analysis of the antioxidant capacity of *Phallus indusiatus* polysaccharides carried out by Ker et al. [62] demonstrated a potent scavenging effect against oxygen free radicals. A study by Chen et al. [69] showed that the water-extractable polysaccharide fraction from *Lentinula edodes* exhibited significantly antioxidant activity against hydroxyl radicals, superoxide radicals and Fe²⁺ chelating ability.

Besides the antioxidant effect that polysaccharides may have, there are phenolic compounds naturally occurring in mushrooms. Total phenolic and flavonoid contents occurring in eight types of edible mushrooms (*Agaricus bisporus*, *Boletus edulis*, *Calocybe gambosa*, *Cantharellus cibarius*, *Craterellus cornucopioides*, *Hygrophorus marzuolus*, *Lactarius deliciosus* and *Pleurotus ostreatus*)
have been evaluated by Palacios et al. [73] with C. cibarius being the most effective against lipid oxidation and A. bisporus the species with lowest antioxidant activity.

3.3. Prebiotic Activity
The interest in the gut microbiome and host interaction is increasing. Initially, prebiotics were defined as non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth of one or a limited number of bacteria in the colon [74]. In 2004, the concept has been updated as “selectively fermented ingredients that allow specific changes in the composition and/or activity in the gastrointestinal microbiota that confers benefits upon host well-being and health” [75].

The prebiotics added to the foods are living microorganisms that must be kept alive and may be killed by heat, stomach acid or simply die with time. However, prebiotics are essentially dietary fibre and are not affected by heat, acid or time. Prebiotics act as food for probiotics. Furthermore, some health benefits of prebiotics (such as reducing glucose levels in the blood and improvement of the bowel function) have been medically proven and recognized by the European Food Safety Authority [76], [77].

Currently, inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), lactulose and polydextrose are recognized as the well-established prebiotics in the market but there is evidence that the beta-glucans can also be a source of long chain prebiotics [79], Synytsya et al. [7] indicated that mushroom extract of Pleurotus ostreatus and Pleurotus eryngii have a potential stimulator effect on the growth of probiotic bacteria. Later, a study carried out by Chou et al. [78] showed that a low concentration of polysaccharides from Lentinula edodes, P. eryngii and Flammulina velutipes may enhance the survival rate of Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium longum during cold storage.

According to Yamin et al. [80] polysaccharide mixtures from Ganoderma lucidum supported the growth of probiotics with population of Bifidobacterium and Lactobacillus genus with 0.3–0.7 and 0.7–1 log_{10} cells/mL increase, respectively. Giannenas et al. [81] investigated the consequences of consumption of Agaricus bisporus on turkey. The populations of total aerobes and anaerobes, Lactobacillus spp., Bifidobacterium spp., Escherichia coli, Bacteroides spp. and Enterococcus spp. were enumerated in ileum and caecum and the results showed that dietary mushroom inclusion beneficially affected performance and exerted changes in intestinal microbial communities.

3.4. Enzymes and Secondary Metabolites
Some species of mushrooms synthesize enzymes that may play important functions in the organism. Pleurotus eryngii and Ganoderma lucidum can produce laccases. In the human body this protein can confer activity against HIV by inhibiting the reverse transcriptase [82, 83]. The lectins produced by the species Pleurotus ostreatus and Ganoderma carpense have shown anti-proliferative activity on tumour cells [84].

Superoxide dismutase (SOD) is also present in some mushrooms. The recent interest in this enzyme is determined by its important physiological role in primary cellular antioxidant defense and its potential therapeutic use. Sabotic et al. [85] investigated the proteolytic potential of a large number of basidiomycetes. Proteolysis is an essential part of many physiological processes in all living organisms and basidiomycetes could prove to be a valuable source of proteases that could find use in biotechnological processes.

In addition to the presence of enzymes, mushroom low-molecular-weight secondary metabolites (such as terpenes, steroids, anthraquinones and benzoic acid) can regulate processes such as apoptosis, autophagy, angiogenesis, metastasis, cell cycle regulation, and signal transduction cascades that are associated with the development of cancer [86].

4. Conclusions

Nowadays mushrooms are used not only as a source of nutrients, but also as medicinal resources. Polysaccharides from mushrooms were reported to exhibit immunomodulation properties, antitumour, antioxidant, antimicrobial and prebiotic activity due to the greatest potential for structural variability in comparison with other biological active molecules.

An extremely large range of bioactive properties has been linked with the use of C. versicolor polysaccharides. Throughout the literature survey conducted to accomplish this review article, no studies were found using biomass from Coprinus cinereus mushroom to demonstrate bioactive effects. Two polysaccharides extracted from C. versicolor (PSP and PSK) have shown important biological properties during the past few years, and a special interest in researches in the area of cancer has aroused. It seems that C. versicolor polysaccharopeptide can be a useful adjunct to the therapy of cancer but, in certain cases, further work is necessary to prove some of the effects that have been observed in vitro and in experimental animal studies.

The role of prebiotics in improving human health has been extensively studied. It is hypothesized that prebiotic substances, like PSP and PSK found in C. versicolor, may be applied to modulate any microbial community to achieve advantageous effects. Furthermore, the antidiabetic, antimicrobial...
and antioxidant activity demonstrated by studies carried out in C. versicolor indicate that this is a potential source of bioactive compounds that can bring important benefits to health.

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