Mushrooms – a human health booster, a skin health promoter and even a cancer therapeutic adjuvant

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Abstract
Science technology has confirmed *in vitro* and *in vivo* the ancient Asian beliefs on mushrooms being a rich source of bioactive compounds with therapeutic properties in diverse diseases, besides its value as an edible resource. So far, innumerous health valuable agents were isolated, which constitutes an incentive to keep researching for new bioactive metabolites and new applications. The most isolated and studied compounds have been polysaccharides, especially β-glucans. These compounds, extracted from the mushroom fruit body, cultured mycelium or culture filtrates, have been revealing beneficial applications such as enhancement of the immune system, allowing the prevention and recovering from various infections and diseases; antioxidant activity, helping to prevent the action of free radicals on cells; anti-tumor properties, influencing positively cancer progression and also showing activity as adjuvants in the recovery from the cancer drug therapies side effects. Accordingly, mushrooms can constitute a tasteful and healthy food source, a health promoting agent (nutriceuticals), and a source of extracts applicable in pharmacological and cosmeceutical formulations, improving health quality and nourishing and improving skin appearance. However, since there is a lack of regulatory affairs, quality control, and establishment of appropriate dosages, mushroom nutriceuticals should be used with precaution and further studies would be of most importance to fully understand the functional compounds of mushrooms and its mechanisms of action.

Keywords: Mushrooms; β-glucan; polysaccharides; antioxidant; immunomodulation, cancer therapies; nutriceuticals; cosmeceuticals.

Introduction
Mushrooms, classified separately from plants and animals, belong to the fungi kingdom. Mushrooms have long been appreciated for their organoleptic characteristics such as flavor and texture and, at the same time, for their prophylactic and therapeutic attributes. Moreover, mushrooms are an excellent source of B vitamins (riboflavin, niacin, pantothenic acid) which have an important function in nervous system; ergosterol, a precursor of vitamin D when in the presence of sunlight, preventing rickets and osteomalacia and minerals (selenium, copper, potassium), with antioxidant properties (1). These fungi are also low in calories, lipids, sodium and are cholesterol-free. Mushrooms contain high levels of water, are rich in proteins, polyunsaturated fatty acids, linoleic acid and are a source of fibers (Table 1) (2,3). Mushrooms contain a good amount of all the essential amino acids, carbohydrates (mainly glucose, mannitol and trehalose), and are a source of polysaccharides like β-glucans which biological activity has been proven in several studies as, for example, immunity-stimulating effects (2). Mushrooms are the only non-animal-based food containing vitamin D (3), although these values are superior in some species as *Chantharellus tubaeformis*, *Chantharellus cibarius* and *Lentinus edodes* whereas in some of the popular cultivated mushrooms as *Agaricus bisporus* there are only trace amounts of vitamin D (1). A detailed chemical composition and nutritional value of the dry matter of some European wild mushrooms species can be found in Kalač, 2009 (2), while in both articles of Barros et al. 2007 (4,5) it is described the nutritional value of some wild edible mushrooms from Northeast Portugal (*Agaricus arvensis*, *Lactarius deliciosus*, *Leucopaxillus giganteus*, *Sarcodon imbricatus* and *Tricholoma portentosum*). Some of the species with more interest to the industry due to its high cultivation are *Agaricus bisporus* (portobello), *Lenti-
nus edodes (shiitake), Pleurotus ostreatus (oyster) and Agaricus subrufescens (blazei). For medicinal uses, other popular species are Ganoderma lucidum (lingzhi or reishi), Grifola frondosa (maitake) and Flammulina velutipes (Enokitake) (6).

For a long time, aside from its use for its nutritional value, mushrooms have been used in Traditional Chinese Medicine taking into account their noticed medicinal properties and health benefits (7). Currently, several studies confirm that various fungal polysaccharides like β-glucans are potential active ingredients with medicinal functions applicable in pharmaceutical formulations. The bioactive polysaccharides reveal active functions in immune stimulation, antioxidant activity, antimutagenic capacities, cardiovascular health, antihypercholesterolemia and antiadhesive effects and appear to have a beneficial impact on cancer prevention and progression (reducing the capacity of invasion and metastasis) and also in viral, bacterial, parasitic and fungal infections (8).

### Polysaccharides - biological active compounds

Since the awareness of the presence of biological active compounds with medicinal applications, a large number of mushroom-extracted compounds with antitumor activity have been described (9). These natural compounds lead us to new hypotheses for prevention and therapeutic control of cancer, without the toxicity associated with the common, although effective, cancer therapies. Most of those beneficial properties have been attributed to natural bioactive polysaccharides extracted from fruit bodies, cultured mycelium, and cultured broth mainly from Filo Basidiomycota (7). Bioactive mushroom polysaccharides vary in the backbone sugar components, and sometimes are bound with proteins or peptides - showing higher antitumor activity (10). The first indication of polysaccharides inducing remission in cancer patients was by Nauts et al in 1946 (11). Since then, researchers have isolated diverse polysaccharides with multiple biological activities (10). β-glucans can be isolated from different sources: fungi, bacteria, seaweed and cereals. Zhang et al., 2007 (10), compiles a list of extracted polysaccharides, their fungi origin and the main demonstrated bioactivity, from species that have been widely studied. Most of the bioactive polysaccharides are β-glucans, polysaccharides that consist of a backbone of glucose monomers that require combination of β-(1-3) linkages in the main chain with β-(1-6) branching for anti-tumor activity (8,10,12,13). They also can be presented as polysaccharide – peptide complexes (krestin) or polysaccharide – protein complex (PSK) (10). The triple helical conformation of the (1-3)-β-D-glucan backbone chain as in lentenan from Lentinus edodes is essential to the anti-tumor and immune modulation activity (10,12). The efficiency also appears to be related do the high molecular weight.
glucans (14), although other polysaccharides activity is not dependent on molecular weights. Glucans with α-(1-3)-glucosidic links haven’t yet shown any biological activity (8).

**Health promoting applications**

**Anti-cancer and immune stimulating properties**

Some of the tumors where the inhibitory effects of polysaccharides were verified were sarcoma 180 solid cancers, Ehrlich solid cancer, sarcoma 37, Yoshida sarcoma and Lewis lung carcinoma (10), and growth inhibition was verified in various human carcinoma cell lines *in vitro* (15). Some entire mushrooms species (*Agaricus bisporus*, *Auricularia auricula*, *Collybia confluens*, *Coriolus versicolor*, *Flammulina velutipes*, *Ganoderma applanatum*, *Ganoderma lucidum*, *Lentinula edodes*, *Pholiota nameko*, *Pleutorus ostreatus*, *Schizophyllum commune*, *Tremella fuciformis*, *Tricholoma matsutake*, and *Volvariella volvacea*) or compounds extracted from them, have scientific studies reporting anti-tumor activity (1). Zong, Cao, & Wang, 2012 (16) compiled a list of mushrooms and the effects on different tumor models. Direct human studies of mushrooms or their extracts consumption are reduced compared to studies *in vitro* and with animals, in part due to extracts and mushrooms being well-tolerated, and thus results extrapolation may occur. Roupas et al. 2012 (17), summarizes in a table the active health components of edible mushrooms, with an emphasis on the mechanism of action and results obtained from human trials. Mushroom isolated components revealed stronger health benefits than the whole mushrooms in the few humans trials realized do date. However, both demonstrated various beneficial properties *in vitro* and in animal tests. Those effects are indirect, mostly due to immunomodulation or stimulation derived from the action of the content in polysaccharides (β-glucan or complexes) (17). These fungi polysaccharide seem to inhibit cancer progression through potentiation of innate and cell-mediated immune responses towards malignant cells (7) since these compounds are recognized by our immune systems as non-self-molecules (8), or having a direct action on tumor cells by inducing apoptosis. Another important antitumor effect is through the prevention of cancer development by including compounds isolated from medicinal mushrooms in daily diet (10). However, it is discussable whereas consumption of the entire mushrooms as part of the food intake can have preventive effects on cancer as well as other diseases (1). Mushrooms polysaccharides can also be beneficial when in combination with chemotherapy and radiotherapy, through relief and recovery of side effects, considering also that mushrooms metabolites are mostly innocuous in the correct doses (7,8).

Mushroom polysaccharides like lentinan, schizophyllan and krstine have clinical evidences and are already commercialized as immunocuticals in Japan, Korea and China (13,18). Krestin (polysaccharide-K (PSK)) derives from cultured mycelial biomass of *Trametes versicolor*, lentinan from fruiting bodies of *Lentinus edodes* and schizophyllan from the liquid culture broth of *Schizophyllum commune* (12). Other polysaccharides that revealed antitumor efficacy in several human cancers are the D-fraction isolated from both mycelia and fruit body of *Grifola frondosa*, and the polysaccharide-peptide (PSP) from *Trametes versicolor* (12,16). D- and MD-fractions were proposed for phase II/III clinical trials in the United States and Japan due to the high anti-tumor activity (by inducing cell apoptosis). Lentinan is nowadays used for gastric cancer, although for great effect it is required injection route (19). As mentioned previously, β-glucans like lentinan can be also beneficial as an adjuvant in advanced cancer such as gastric, pancreatic, colorectal and hepatocellular carcinoma, attenuating the adverse effects of chemotherapy, giving quality and longer life (16). PSK stimulates the host immunity (by preventing T-cells destruction and other suppressions caused by chemotherapy) and enhances cytotoxicity of conventional chemotherapy drugs. PSK and PSP polysaccharides induce also tumor cells apoptosis. PSK and PSP have been used in the treatment of gastric and colorectal cancers with other chemotherapeutic agents, influencing positively the disease prognosis (16). Secondary metabolites such lectins, lactones, terpenoids, alkaloids, antibiotics and metal chelating agents are other compounds with medicinal applications, especially in the immune function, based on their low molecular weight, which facilitates penetration on cell membrane (7). Although, more studies are required to recognize which compounds are best for which disorders.

**Antioxidant activity**

Enzymes such as laccase, superoxide dismutase, glucose oxidase and peroxidase, isolated from mycelium and fruiting bodies of edible mushrooms have shown antioxidant activity *in vitro*, preventing oxidative stress and inhibiting cell growth in cancer treatment (7,20), which potentiates its application *in vivo*, to assist in reducing oxidative damage and preventing a variety of diseases in which free radicals contribute to their pathogenesis. Some diseases like cancer, diabetes, cardiovascular diseases, and neurologic disorders have already been associated to free radicals (6). Extracts with antioxidant properties were isolated from various edibles specie: *Agaricus bisporus*, *Boletus badius*, *Hericium erinaceus*, *Hypsizygus marmoreus*, *Lentinula edodes*, *Lepista nuda*, *Pleuotus sp.*, *Polyporus squamosus*, *Russula delica*, *Termitomyces sp.*, *Volvariella volvacea*, *Verpa conica*, *Ganoderma applanatum*, *Ganoderma lucidum*, and *Trametes versicolor* (21). β-glucans extracts from *Geastrum saccatum* studied by Guerra Dore et al., 2007 (22) also demonstrated anti-inflammatory and antioxidant activity in superoxide radical, hydroxyl radical and lipid peroxidation. Besides their polysaccharide content, mushrooms also contain a source of phenolic compounds, flavonoids, tocopherols, ascorbic acid and carotenoids that are responsible for the antioxidant properties (23). The antioxidant action
may happen through direct action by prevention of reactive oxygen species (ROS) production, induction of antioxidant enzymes defense, and radical scavenging which reduces the level of free radicals already produced (6). We may benefit from mushroom extracts antioxidant properties. One way is through ingesting dietary supplements that will act as health promotion and preventive agents. Antioxidant properties may also have an important role in prevention of skin aging, by incorporation in skin care products lines.

**Anti-microbial activity**

Some β-glucans are effective against different infections, by modulating cellular and humoral immune responses (24). Studies have been made in hepatitis virus, influenza virus, and some preliminary clinical trials have been conducted with lentian in the treatment of HIV patients (25) and in reducing the appearance of HIV symptomatology (1). PSK from *T. versicolor* and *G. frondosa* also exhibited anti-HIV effects (19,26). Some β-glucans, including lentian and others derived from other fungal, are also effective against bacterial infections like *Mycobacterium tuberculosis* (27), *Bacillus anthrax* (28) between others microorganisms. However, it is suggested that the best use of β-glucans should be to infection prevention, since β-glucans are considered potent immunological activators. Immunomodulation represents one of the properties with most interest and with more beneficial effects related to mushrooms, (12) with studies in vitro and in animals, showing the enhancement of the function of immune cells. Although, one curious polysaccharide extract from *Phellinus linteus* fruiting body showed, in vitro, an immunosuppressive effect which may be useful in treatment of autoimmune diseases (13). The development of new antimicrobials is critical due to the increasing number of isolated multi-drug resistant microorganisms on the environment, human and veterinary medicine. Based on these facts, some studies have been made to test the antibacterial and antifungal properties of mushrooms extracts. *Lentinula edodes* has shown antimicrobial activity, however further studies need to be done in order to identify active compounds on this and other mushroom species (29).

**Hypocholesterolemic and reducing hypertension effects**

The mechanisms or the active components by whether β-glucans interfere in reducing cholesterol levels and contribute to influence positively diabetes are still unclear (8). *Lentinula edodes* and *Agaricus bisporus* have reduced plasma cholesterol levels in animals fed with a diet supplemented with these mushrooms. (30). The *Lentinula edodes* isolated compound responsible for hypocholesterolemic effect is nowadays called eritadenine, which reduces the levels of all lipoproteins types (31). The capacity to reduce hypertension by β-glucans was observed in hypertension rat model when a diet with *Grifola frondosa* caused the systemic blood pressure to reduce (32).

**Mushrooms in skin and hair care cosmetics**

Taking into account the proven medicinal properties of some mushrooms, and considering the new growing consumer demand for natural products, the cosmetic industry explored the application of bioactive fungi metabolites in skin cosmetics lines such as creams, lotions, ointments and hair care products. The properties in skin and hair care aimed to obtain with formulations containing active ingredients extracted from mushrooms, especially β-glucans are: anti-aging, moisturizing, strengthen the skin, lifting and firming, antioxidant, skin revitalization, reduce skin pigmentation, and moisture and softness to the hair (33). Some species presently used in cosmeceuticals and nutricosmetics with skin beautifying properties include: *Agaricus subrufescens*, *Choiromyces maeandriformis*, *Cordyceps sinensis*, *Ganoderma lucidum*, *Grifola frondosa*, *Hypsizygus ulmarius*, *Inonotus obliquus*, *Lentinula edodes*, *Polyporus spp.*, *Trametes versicolor*, *Tremella fuciformis*, *Tuber spp.* and *Schizophyllum commune* (33). *Agaricus subrufescens* has been used to obtain dermatological functions such as hydration and revitalization of dry skin and chemical exfoliation. As for the hair, claims more hydration, shine, softness, and movement. Lentian and schizphyllan, whose properties were previously mentioned and are widely studied, are also used and sold in famous cosmetic brands, claiming ageless properties, reducing inflammation, and other damages due to the environment action. L-ergothioneine, present in brown and white *Agaricus bisporus* and *Ganoderma lucidum*, phenols and vestigial amounts of β-carotene and lycopene found in some wild mushrooms (5) protect against oxidative damages. Trehalose, is a disaccharide with capacity of water retention and thus is being used as a moisturizer and anti-oxidant. It can be isolated from *Lentinula edodes*, *Grifola frondosa*, and *Pholiota nameko*. A mushroom extract from *Tremella fuciformis*, for the same above mentioned reasons, can be a replacement for sodium hyaluronic acid (33). Skin pigmentation disorders are a cause for which many women seek solutions in cosmetics. Light skin is also considered a beauty standard by many oriental women (34). Common skin whiteners used are lactic and glycolic acids. These compounds can have a natural source as they can be produced from fungi species of *Rhizopus* (10). Also, Kojic dipalmitate (a stable version of kojic acid found in *Lentinula edodes*) has lightning skin properties and can be extracted from Japanese mushrooms. Important tyrosinase inhibitors, an enzyme that catalyzes the production of melanin, can be found in extracts of *Ganoderma lucidum*, with proven results in the inhibiting of enzyme activity, hence being an ingredient used in some depigmenting cosmetic lines. (34). Studies suggest effects of β-glucan in wound healing (35). Thus, new ointments with curative properties and to treat other dermatologic conditions can be developed based on natural polysaccharides.
Some oral supplements products with extracts from mushrooms fruit body as *Grifola frondosa* contain active ingredients that claim to have beneficial influences on skin quality and body exterior appearance (33), acting from the inside to the outside. Those dietary supplements are called nutriceuticals. Oral administration of *Sparassis crispa* improved the healing of diabetic wounds in rats, increasing macrophages and fibroblasts, synthesis of type I collagen and epithelization (36). β-glucans, extracted from mushrooms and even from other sources such as other fungi, microorganisms and cereals, undoubtedly have important and diverse health promoting applications. Application as an active ingredient in cosmetology and skin pathologies treatment reveals another benefit of the mushrooms polysaccharides application (35), and encourages the development of new cosmetics products and more research for better understanding the mechanisms of action.

Conclusions

Humans are nowadays more aware and seek for new natural products that promote a healthy and improved life. According to the previous discussed beneficial properties, there is a growing interest in medicinal mushrooms as a complement in food intake, acting as functional foods that naturally improve health and body functions, as medicines and as daily dietary supplements or nutriceuticals (comprising refined compounds extracted from mushrooms parts, for example, in the form of capsules) (6). Dietary supplements are based on mushrooms extracts to be ingested as a part of a healthy and preventive diet (37), modulating immune function and improving resistance against pathogens; as adjuvants or to treat diseases due to their therapeutic value. Nutriceuticals are mostly derived from edible mushroom species, which reduces the danger of toxicity (38). A lot of supplements brands are already commercialized based on extracted mushroom compounds. The claimed beneficial properties leads to the recognized “health sustaining effect” of mushrooms (6).

With the increasing consume of mushroom nutriceuticals, some problems considering the human safety may arise and need resolution. There is a lack of studies and information relatively to the effects of combining different extracts, interaction with other drugs, doses and duration of administration. Dangerous and toxic metabolites may also be found in some wild mushroom species, as well as species collected from polluted areas that may cause accumulation of pollutants. Those should be avoided because may cause severe allergic reactions (2). Dermatitis and toxic reactions can also appear from the ingestion of raw mushrooms. A few cases of dermatitis are described with Shiitake (39). There is also insufficient quality control and regulatory affairs for polysaccharides extraction and product safety, whether for its use in dietary supplements, cosmetics and pharmaceutical industries (7) which requires the use of medicinal mushrooms with precaution, restricting the use to the certified β-glucan products of known chemical composition (8). Adulteration in the product preparation with similar species, or adulterated β-glucans resulted in severe adverse effects (40). The investment in scientific knowledge of mushroom composition and properties is essential to promote its cultivation and consume since it is a healthy food and a promising bioactive compound source for the healthy industry. Furthermore, thousands of Basidiomycota species are still to explore and represent a source for novel applicable metabolites. New compounds may be used to reduce the use of toxic compounds, developing new antimicrobials, potentiate the treatment of new diseases, or prevent them with a prophylactic behavior. It might also allow the production of new molecules through molecular modifications of existing metabolites (6).

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References


