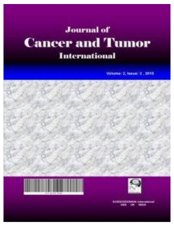

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Immunomodulatory Fungi: An Alternative for the Treatment of Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Author DLNM designed the study. Authors DLNM, HRSP and JSSC wrote the protocol and wrote the first draft of the manuscript. Authors DLNM, HRSP, JSSC, DMMF and ACVB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The present study aims to determine the role of immunomodulatory fungi for the treatment of cancer as an alternative way. Mushrooms have been part of human culture for thousands of years, many cultures especially from the East, recognized that the extracts of certain fungi could have great health benefits. Recent research has focused on identifying compounds that can modulate, positively or negatively, the biological responses of immune cells. These compounds stimulate immunity, and not only for the treatment of cancer, but also for immunodeficiency diseases; for drug-induced generalized immune suppression; for therapy combined with antibiotics and as adjuvant for vaccines. The medicinal mushrooms are considered as immunomodulators, they are able to regulate the immune system. A diverse collection of bioactive polysaccharides, glycoproteins, glycopeptides, and proteoglycans have an effect on the proliferation and differentiation of immune cells and cytokines. Different purified polysaccharides have had clinical

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use in Japan, China, and Korea for many years, without reports of negative effects in the short term or in the long term. Different studies have shown that the application of polysaccharide extracts can have a cancer prevention effect and a restriction of tumor metastasis; they have also been used to treat microbial and viral infections, cardiovascular diseases and diabetes.

Keywords: Fungi; cancer; immunomodulation; therapheutics.

1. INTRODUCTION

Mushrooms have been part of human culture for thousands of years, many cultures especially from the East, recognized that the extracts of certain fungi could have great health benefits, as a result, they became essential components in traditional Chinese medicine for the treatment of microbial, viral infections, cardiovascular diseases, diabetes, among others [1,2].

These fungi have been characterized for possessing bioactive molecules with anticancer and antitumor properties [3]. These molecules are found in the polysaccharides that make up the cell wall of fungi and for many years, polysaccharides have been successfully applied in the treatment of cancer [4], since they have been shown to enhance both the innate and acquired immune responses, activating host cells, such as macrophages, monocytes, neutrophils, natural killer cells, dendritic cells, also chemical messengers, such as cytokines: interleukins, interferons, and growth stimulating factors. The lymphocytes that govern the production of antibodies, B cells, and T cell-mediated cytotoxicity are also stimulated [5].

It has been shown that the polysaccharides present in the cell wall of fungi, have taken great importance for having an immunomodulatory effect (modifiers of the immune response) and possess powerful antiviral and antitumor agents, which do not directly destroy viruses or cancer cells, rather, they stimulate the innate ability of the organism to direct cellular defenses [6].

Technological advances have allowed the isolation and purification of some of the polysaccharide compounds that possess immunomodulation activities against cancer [7]. Bioactive polysaccharides isolated from the fruiting bodies of fungi have been characterized as water-soluble β-D-glucans, β-D-glucans with heterosaccharide chains composed of xylose, mannose, galactose or uronic acid, or β-D-glucans linked to proteins, that is, proteoglycans. These polymers interact with the immune system to regulate specific aspects of the immune response of the host, and in this way cause therapeutic effects [8].

2. MEDICINAL FUNGI IMMUNO-MODULATORS

2.1 Medicinal Fungi Immunomodulators

Fungi (members of the Basidiomycete class) have long been valued as nutritious and appetizing foods by many societies around the world, due to their pleasant taste and texture. For the ancient Romans they were "the food of the gods", for the Egyptians they were "a gift from the God Osiris", while the Chinese considered them "the elixir of life" [9]. Different cultures, especially the East, They determined that extracts of certain fungi could have great health benefits, becoming essential components in many traditional Chinese medicines for the treatment of various diseases [10].

The bioactivity of the fungi Basidiomycetes was confirmed for the first time in 1957 by the researcher Lucas. Lucas isolated a substance from *Boletus edulis*, determining that it had a significant inhibitory effect against tumor cells of S-180 sarcoma. Subsequently, in 1966 an extensive study was carried out by the researcher Gregory where he isolated the active principles of the fruiting bodies of more than 200 species of Basidiomycetes fungi and used 7000 culture media where he kept different fungi by submerged fermentation. The antitumor assays of these active substances were applied to three rodent models and revealed that polysaccharides isolated from 22 species of fungi and 50 culture media showed an inhibitory effect on tumor cells, including sarcoma S-180, adenocarcinoma 755, and leukemia L-1210 [1].

Currently, there are about 270 species of hogs known to have therapeutic properties, including edible species such as *Lentinula, Hericium, Agaricus, Grifola, Flammulina, Pleurotus*, and *Tremella*, while *Ganoderma lucidum* and *Trametes versicolor* are inedible mushrooms, due to its coarse texture and bitter taste, but which also possess medicinal or functional properties [9].

For example, *Lentinula edodes* is the second most popular edible fungus, its importance is attributed to both its nutritional value and its medical application [11,12]. It has a long history in Eastern culture in the treatment of tumors, flu, heart disease, high blood pressure, obesity, problems related to sexual dysfunction, aging, diabetes, liver diseases, respiratory diseases, fatigue and weakness [13].

L. edodes has antiviral properties and stimulators of the immune system that have been found in different compounds isolated from this fungus, the LEM (mycelium of *L. edodes*), lentinan, and KS-2. LEM is a protein-bound polysaccharide derived only from the mycelium, has an immunomodulatory effect, lowers lipid levels and is antiviral. It has been found to be capable of activating macrophages and lymphocytes to modulate the release of cytokines, which are antiviral [14]. Some studies report that LEM improves liver function in chronic hepatitis B patients and has the ability to inhibit the HIV virus in vitro. The lentinan, the most important polysaccharide isolated from *L. edodes*, due to its immunomodulatory and antitumor activity. Both compounds are enhancers of the immune system. Another active polysaccharide with antitumor power is KS-2, which has also been isolated from the mycelium of *L. edodes* [13].

The Lentinan is a polysaccharide β- (1-3) -β- (1-6) -D Glucan with a structure of triple helix of high molecular weight (27.5kDa) [15], containing glucose molecules with β- bonds (1-3) in the central part and β- (1-6) -Glucose bonds in the side chains [16]. The configuration of glucose molecules in the helical structure is considered important for biological activity [11]. It is soluble in water, produced in the cell wall of the fungus, can be extracted from the mycelium and or the carpophore [17].

The lentinan does not directly attack cancer cells but produces its antitumor effect by activating different immune responses in the body, such as the increase in the response of cells to lymphocytokines, hormones and other biological substances, as well as stimulation, maturation, differentiation and proliferation of defending cells, stimulate phagocytosis by binding of β -glucans of polysaccharides to CR3, CD11b / CD18 receptors of phagocytes, also stimulates lymphocytes and NK activity, also inhibits activity Suppressor of T cells and increase the relationship between T cells and cytotoxic T cells [16]. Lentinan can restore the suppressed activity of helper T cells in the tumor-bearing host to its normal state, leading to the complete restoration of humoral immune responses. The introduction of eosinophils, neutrophils and granulocytes around the target tissues is also accelerated by lentinan. Activates the secretion of active oxygen and the production of cytokines in peritoneal macrophages (Fig. 1) [18].

On the other hand, *Agaricus bisporus* is one of the most common and widely consumed mushrooms in Europe and America. It has been revealed that *A. bisporus* contains abundant and diverse nutritional substances, such as proteins (23.9% - dry weight), polysaccharides, fatty acids, vitamins (vitamin A, thiamine (B1), riboflavin (B2), ascorbic acid (vitamin C) that is lost if they are not fresh, ergosterine (pro-vitamin D2) and biotin (vitamin H), phenols, essential amino acids such as cysteine, phenylalanine, isoleucine, leucine, lysine, methionine, tyrosine, threonine and valine, and minerals such as phosphorus, magnesium, potassium and selenium that gives it an antioxidant effect [20].

In recent years, many studies have shown that *Agaricus bisporus* has various biological effects, such as antioxidant, anticancer, aromatase inhibitor and hepatic anti-steatosis. It is well known that polysaccharides are the main bioactive component of *Agaricus bisporus*, for example, (1 → 6) -β-D-glucans presents an immunostimulating activity that contributes to the antitumor effects [21]. Other studies have shown that the active components of A. bisporus present medicinal qualities associated with potentially therapeutic immunomodulatory effects that stimulate the production of pro-inflammatory cytokines and enzymes, or adjuvant effects such as apoptosis [22].

These bioactive polysaccharides are recognized as having membrane receptors in leukocytes and macrophages, leading to the proliferation and differentiation of immune cells. By binding to their receptors, bioactive polysaccharides activate various immune pathways such as phagocytosis, complement activity and the production of cytokines such as tumor necrosis factor-α (TNF-α), different types of interleukins (IL'S) and enzymes All these effects collaborate to modulate cellular differentiation and proliferation, which allows the host to defend against pathogens and tumors [23,24,25].

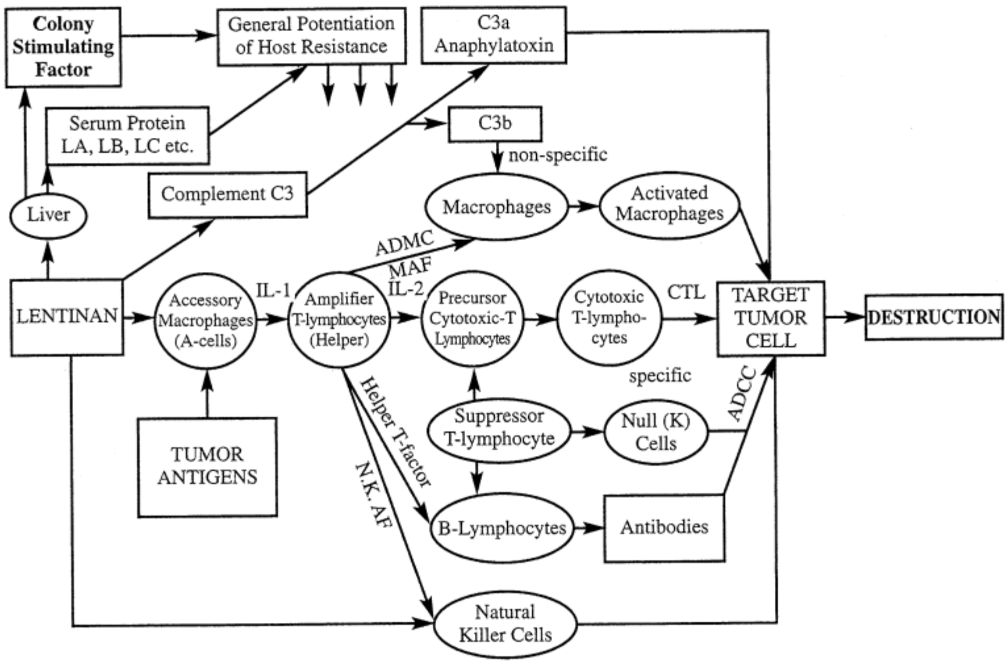

Fig. 1. Mechanisms of antitumor activity of lentinan as a β-glucan. Taken from Wasser, 2002 [19]

Also, *Pleurotus ostreatus* is classified within the so-called functional foods due to their medicinal effects. It has been shown that compounds such as lectins, polysaccharides, peptides, polysaccharide-protein complexes, all derivatives of oyster mushroom, decrease the level of fatty acids in the blood and cholesterol in the liver, also exhibit anti-inflammatory, antioxidant, antiviral effect, antibiotic, antimutagenic and immunomodulatory action [12,26,27,28], which gives them a potential therapeutic impact in the treatment of several diseases. Several studies have indicated that polysaccharide and protein extracts (β-glucans and lectins) isolated from fruiting bodies, from the mycelium and even from the medium where *Pleurotus* is grown, have been shown to have antitumor activity *in vitro* and *in vivo* [13].

The possible mechanism of action of these substances occurs through the activation of T cells, the induction of apoptosis in tumor cells, the stimulation of immune function, the increase in NK and the T helper cells. The β-glucans constitute the predominant form in the fungi of the genus Pleurotus and can bind to proteins, lipids or other polysaccharides, the therapeutic applications of these polysaccharides depend on the chemical structure and spatial conformation of each macromolecule, which provides them with the characteristics of each polymer for new applications [29].

Pleutorus ostreatus contains a polysaccharide called pleurane, which acts as a modifier of the biological response [12]. Pleurane is an insoluble alkaline biopolymer that has been isolated from the fruiting bodies of this edible mushroom. The primary structure of the pleurane is similar to that of the β-D-glucan that is commonly found in other Basidiomycetes and Ascomycetes [30], has an antitumor and immunomodulatory effect that includes the stimulation of phagocytic activity [31,32].

Immunomodulatory fungi, as mentioned above, activate components of the innate immune system such as NK cells, neutrophils and macrophages, and stimulate the expression and secretion of cytokines. These cytokines, in turn, activate adaptive immunity through the promotion of B cells for the production of antibodies and the stimulation of T cells for differentiation to Th1 and Th2 helper T cells, which mediate cellular and humoral immunity, respectively [33].

With respect to high molecular weight, fungal polysaccharides are not able to penetrate cells to directly activate the immune response. Therefore, the stimulation of the mechanisms of the polysaccharides involves different cellular receptors such as dectin-1, complement receptor 3 (CR3), lactosylceramide (LacCer), and the receptor of type "Toll-Like" (TLR-2). In such cases, the efficacy of the polysaccharides is governed by their binding affinity to the receptors of the immune cells. In general, immunomodulatory fungi are classified into four main groups: (i) lectins immunomodulatory; (ii) terpenes and terpenoides immunomodulators; (iii) immunomodulatory fungal proteins (FIPs); and (iv) immunomodulatory polysaccharides [33].

Lectins Immunomodulators: Lectins are proteins that recognize carbohydrates and are widely distributed in nature. They exhibit a diversity of chemical characteristics; some are monomeric, while others are dimers, trimers or tetramers. Their molecular weights are from 12 to 190 kDa. The sugar content goes from 0 to 18%. The specificity for carbohydrates is mainly for galactose, lactose, and N-acetylgalactosamine [34]. They have been isolated from different organisms, however, those derived from fungi are characterized by immunomodulatory, antiproliferative and antitumor activities, for example, lectins isolated from *Volvariella volacea* possess a strong immunomodulatory activity, lectins extracted from *Tricholoma mongolicum*, TML- 1 and TML-2, showed immunomodulatory and antitumor activity, mediating its action through the activation of the immune system instead of generating direct cytotoxic effects. Recently, a new 15.9 kDa homodimer, with lactose bonds, was purified from the basidiomycete *Clitocy benebularis*, showing antiproliferative activity against human leukemia cells. This lectin induces the maturation and activation of dendritic cells (DCs) and stimulates several proinflammatory cytokines such as IL-6, IL-8, and TNF-α [33].

Immunomodulatory Terpenes: Terpenes are a large and diversified group of organic compounds consisting of five carbon isoprene units of molecular formula (C_5H_6) n. These compounds exist widely in plants as main elements of resin and essential oils. In macrofungi, terpenes are present in the form of terpenoids or isoprenoids and show biological activities with potential medical applications. The fungi belonging to *Ganoderma sp.*, Such as *Ganoderma lucidum* and *Ganoderma applanatum*, are known for their high content of triterpenoids, for example, lanostane, which shows immunomodulatory and anti-infectious activities [33].

Fungal immunomodulatory proteins (FIPs): In recent years, some fungi have been reported to produce a new family of immunomodulatory proteins, called FIPs. So far 11 different classes of FIPs have been isolated. These proteins are grouped in a family based on very similar amino acid sequences and appear as dimers in a dumbbell structure similar to that of the variable region of the heavy chains of an immunoglobulin, presenting diverse activities. The best known is the protein FIP-LZ-8, it is composed of 110 amino acids and acts as an immunosuppressive agent [33].

Immunomodulatory polysaccharides: Fungi are an important source of different classes of polysaccharides with immunomodulatory activities. Most of these polysaccharides are homoglycans (polysaccharides containing residues of only one type of monosaccharide) or heteroglycans (polysaccharides containing residues of two or more types of monosaccharides), and are capable of combining with other proteins to form peptidoglycans or polysaccharide complexes proteins [33].

Table 1 provides information on immunomodulatory polysaccharides and polysaccharide-protein complexes of some fungi. These polysaccharides are highly diversified in their sugar composition, the main chain of the polymer structure, degree of branching, conformation, molecular weight, and other physical properties, which together have significant effects on the bioactivity and mode of action of the polysaccharide.

Different clinical studies have been carried out to evaluate the antitumor or immunostimulatory properties of the metabolites extracted from different fungi [10]. Tsang KW and colleagues, conducted a randomized, double-blind, placebo-controlled study of polysaccharide (PSP) peptides isolated from *Coriolus versicolor*, administered orally, in a total of 68 patients with stage non-small cell lung cancer advanced (III or IV). Patients received three capsules of 340 mg each (or placebo) three times a day for 4 weeks. The leukocyte and neutrophil counts increased significantly after treatment with PSP, while they decreased in the control group, as well as the total IgG and IgM levels increased significantly in the PSP group but not in the placebo group, and the difference between the groups was statistically significant [35].

Table 1. Immunomodulatory activities of fungi polysaccharides-protein complex

Arrow	Active compound	Immuno-modulating activity
Agaricus blazei (*Agaricus subrufescens*)	Glycoprotein (ATOM), β-1,3-D-glucan, with β-1,6-D-glucan branches.	Induction of TNFα, IFN-γ, and IL-8 production.
Ganoderma lucidum	Ganoderan B, Heteroglican, Manoglucan	Stimulates TNFα, IL-1, IFN-producción production, activation of NF-kB.
Lentinus edodes	Lentinan, Glucan, Manoglucan, Proteoglycan.	Induces non-specific cytotoxicity in macrophages and increases cytokine production.
Pleurotus ostreatus	Pleuran, Heterogalactane, Proteoglycan.	Induces IL-4 and IFN-producción production
Polystrictus versicolor	Krestin, heteroglycan-no, glycopeptide, polysaccharide K (PSK), peptide polysaccharide (PSP).	Stimulates the activation of T cells, induces IFN-γ and the production of IL-2, induces the expression of cytokine genes (TNF-α, IL-1, IL-6, IL-8)

Source: [33]

In another clinical study conducted by Gao and colleagues, they used the crude polysaccharide fraction of *Ganoderma lucidum* (Ganopoly) to evaluate the efficacy and safety of Ganopoly in patients with advanced cancer. They administered 600 mg orally three times a day for a total dose of 1800 mg / day. Immune parameters were evaluated in 75 of 143 patients originally recruited and found to be unaffected by the fungal fraction [36]. However, in a subgroup of 32 patients with stable disease for 12 weeks, the mitogenic response of the lymphocytes to PHA (phytohaemagglutinin) and Con A (concanavalin A) increased significantly, as did the activity of the NK cells [37].

An open, non-randomized study conducted by DeVere et al. In patients with prostate cancer who were orally administered capsules containing a polysaccharide / oligosaccharide complex obtained from a shiitake mushroom extract (*Lentinula edodes*) (SME), three times a day for 6 months. Of the 62 men enrolled in the study, 61 were evaluable of whom 38 patients had stable prostate-specific antigen (PSA) levels after 6 months. The study concluded that fungus extract was not an effective treatment for prostate cancer. However, the authors noted that several of the patients in the treatment group had stable PSA levels [38].

On the other hand fraction D, extracted from the fruiting body of the fungus Maitake (*Grifola frondosa*), which has been marketed as a health material, whose safety has been confirmed by "Consumer Product Testing Co." (New Jersey, USA). Kodoma et al. conducted a nonrandomized clinical trial with D fractions for patients with lung and breast cancer in stages II to IV. We administered 100 mg of fraction D, daily for 34 months, where there was increased activity of the NK. To determine the mechanism of activation of NK cells, they conducted a study with C3H / HeN mice to which fraction D was administered for 19 days and the levels of IFN-γ and TNF-α were evaluated [39].

Fraction D markedly suppressed tumor growth, corresponding to increases in TNF-α and IFN-g released from spleen cells and a significant increase in TNF-α expressed in NK cells. This suggests that D-Fraction activates NK cells even on the twentieth day after treatment. In addition, the D-Fraction increased the interleukin (IL) -12 derived from macrophages, which serves to activate the NK cells. These results suggest that NK cells are not only responsible for the early effects of Fraction D on tumor growth, but also for the long-term tumor suppressive effects of Fraction D through the increase in IL-12 released from the macrophages [39].

2.2 Composition of Polysaccharides

The polysaccharides belong to a particular class of macromolecules, they are polymers containing monosaccharides linked by glycosidic linkages. It is important to note that, compared to other biopolymers such as proteins and nucleic acids, polysaccharides have a greater capacity to carry biological information since they have a greater potential for structural variability [40]. Indeed, the nucleotides in the nucleic acids and the amino acids in the proteins can be bound in one way only while the monosaccharide units in the polysaccharides can be interconnected at several points to form a wide variety of linear or branched structures; this provides the necessary flexibility for the precision of the regulatory mechanisms of cell-cell interactions in higher organisms [6]. Polysaccharides are present in fungi mainly as glucans, that is to say where the constituent monosaccharide is the glucose that is bound by different types of glycosidic bonds, such as (1-3), (1-6) in the β-glucans and (1-3) in the α-glucans [40].

A large number of polysaccharides, including several α and β glucans, have been isolated and chemically characterized from a wide variety of fungi. Different bioactive polysaccharides have been isolated from mycelium, fruiting bodies, and sclerotium, representing three different stages in the life cycle of the fungus. The polysaccharides are differentiated by their primary structure (type of basic sugar), type of bond (α, β), the degree of branching and molecular weight, among other parameters. Various therapeutic capacities have been attributed to fungal polysaccharides and in particular to β-glucans [7]. β-glucans are glucose polymers, which can contain up to 250,000 units of this molecule [41]. They constitute the main structural component of the cell wall of fungi and yeast. The β-glucans have different structures, sizes, branching frequencies, structural modification, conformation, and solubility. In the β-glucans the glucose molecules are linked together by a β- (1 - 3) bond, which make up a linear β-glucosidic bond chain [42,43] (Fig. 2).

They are found in cereals, seaweed, yeast, and fungi. Regarding insoluble β-glucans (1-3 / 1-6) such as those found in beer yeast (*Saccharomyces cerevisiae*), fungi Reishi (*Ganoderma lucidum*), Shiitake (*Lentinula edodes*), Maitake (*Grifola frondosa*), *Trametes versicolor*, some algae and bacteria, have higher biological activity than the soluble β-glucans (1-3 / 1-4), whose most important source are oat and barley [44], which help reduce heart disease by lowering the level of cholesterol and reducing the glycemic reaction of carbohydrates. They are used commercially to replace fats and to modify the texture of food products [6].

It is demonstrated that β-glucans enhance and modulate the immune response activating the production of macrophages, neutrophils, monocytes, natural killer cells, and dendritic cells. These cells that are part of the first line of defense of the immune system, are able to destroy bacteria, viruses and other pathogens by phagocytosis, being incorporated and fragmented in cells and transported by macrophages to the bone marrow and the reticular endothelial system [8].

The β-glucans also show anticancer activity, they allow preventing oncogenesis [45], since they protect the cells from potent genotoxic carcinogens. As immunostimulants act by activating macrophages and increasing the cytotoxicity of natural killer cells, inhibiting tumor growth, reducing proliferation and preventing metastasis. And as adjuvants of chemotherapy and radiotherapy in cancer play an important role in the restoration of hematopoiesis (process of formation, development, and maturation of erythrocytes, leukocytes and platelets) when bone marrow lesions occur [5].

In addition, they activate important cytokines, such as IL-1 (interleukin-1), IL-6 y and TNF-α (tumor necrosis factor), which form the basis of a chain reaction that can also activate the humoral immune system, as well like interferon α (gamma), which is important in the fight against viruses. In this sense, it is important for the stimulation of the immune system, that the chains of β-glucans contain a large amount of 1-3 / 1-6 bonds. Other links, such as 2-3 and 3-6, on the other hand, will be ineffective (they only contribute to the fiber content). The differences between enlaces-glucan bonds and their chemical structure, in relation to solubility, mode of action, biological activity, in general, are very important, with links 1-3 / 1-6 is the most important [5].

The first reported polysaccharide with immunomodulatory potential and anticancer activity was lentinan, an β-1-3-D-glucan with β-1-6 branches. This polysaccharide with a triple helical structure was isolated from the fruiting body of *Lentinus edodes* a late 1960 in Japan.

Since then, there have been many research efforts to discover new polysaccharide compounds with immunomodulatory activities of extracts from fungal bodies of fungi. Until the end of the 1980s, only two more polysaccharides of the β-glucan type, cyclopentane *of Schizophyllum commune* and the Krestin polysaccharide bound to *Coriolus versicolor* protein, were fully characterized and successfully introduced into the pharmaceutical and nutraceutical market as biological response modifiers [33].

Different nutraceutical products derived from edible fungi and administered to the organism orally have been of great help as a complement to the diet [46,47]. Obtaining is done through different biotechnological routes of fermentation and in the market they are found in various ways such as: tablets and capsules of dried and powdered wild fruit bodies, powders of artificially grown fruiting bodies and their extracts alone or mixed, grains of the substrate, mycelium and combined primordia, after inoculated in semi-solid medium and pharmaceutical preparations derived from biomass, mycelium extracts, or culture medium, obtained by submerged culture in bioreactors [48].

Some of the products that are marketed as a dietary supplement are the following (all labels specify that the purpose is not to treat, diagnose, cure or prevent any disease): Products of Pharmaceutical Mushrooms, a division of Northwest Botanicals, Inc. (Oregon, USA): Maitake, *Grifola frondosa*, contains *Grifola frondosa*, has immunoenhancing effect. It stimulates the production of T cells. It is used frequently and effectively in cases of immunodeficiencies without manifesting adverse effects. Presentation: bottle of 90 capsules (500 mg) and *Agaricus blazei* Murrill, contains *Agaricus blazei* Murrill, has antitumor and immunopotentiating effect. Presentation: bottle of 90 capsules (500 mg). Duration of treatment: 1 month [10].

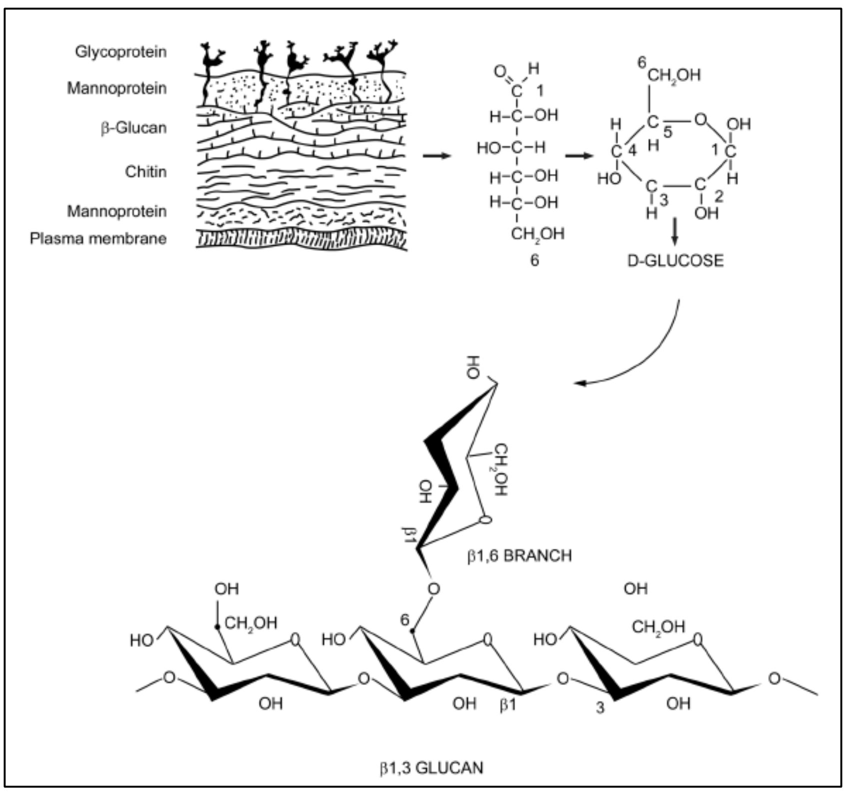

Fig. 2. β-glucan is one of the key components of the fungal cell wall. β-glucan is the basic subunit of fungi, they are β-D-glucose linked to each other by 1 → 3 glycosidic chains with 1 → 6 glycosidic branches. The length and ramifications of the β-glucans of various fungi are very different

Source: [8]

Products marketed by 4life products (USA): Transfer Factor Plus Tri-Factor Formula, contains *L. edodes, G. frondosa, Corrdyceps*, inositol hexaphosphate, β-sitosterol, and olive leaf extract, immunoprotective effect for the organism. Yeast betaglucans, contains β-glucans (1,3 and 1,6) of: *S. cerevisiae, L. edodes* (combination of concentrated β-glucans and purified), is a natural stimulant of the immune system and Shiitake and Maitake, contains Lentinano and *G. frondosa*, Presentation: jars of 60 capsules (300 mg). Each contains 174 mg of β-glucans [10].

2.3 Antitumor Properties of Mushroom Polysaccharides

Polysaccharides are a diverse group of macromolecules that are divided into two classes: homopolysaccharides (starch, glycogen, dextrans, chitin) and heteropolysaccharides (hyaluronic acid, peptidoglycans, glycosaminoglycans). The polysaccharides that are mostly found in fungi are hetero-β-glucans, which have been shown to have immunomodulatory and antitumor properties, capable of restoring or improving the immune response both *in vivo* and *in vitro* [20], however, depending on the species of the fungus, the polysaccharides may differ in their chemical structure, molecular weight or degree and branching form, affecting their biological activity [49]. Several polysaccharides such as lentinan (β-glucan) and PSK (β-glucan-protein) have been shown to have effective antitumor action against a variety of animal tumors and have been used successfully in clinical treatments [20].

The anticancer properties of polysaccharides depend on: Sugar composition: Anticancer properties of polysaccharides have been described in the case of hetero-β-glucans, heteroglycans, β-glucan-protein complexes and heteroglycan-protein complexes. Molecular weight: High molecular weight glucans appear to be more effective than low molecular weight glucans. Solubility: Insoluble glucans are characterized by greater activity. Glucose bonds: Structural features such as β- (1 → 3) junctions in the glucan backbone and additional β- (1 → 6) branches are necessary for anti-carcinogenic activity; β-glucans containing only β- (1 → 6) junctions have lower activity. Tertiary structure: It has been shown that the destruction of the tertiary structure of polysaccharides by denaturation reduces or completely suppresses their biological activity and presence of other ligands: For example, galactose, mannose, fructose, xylose, and arabinose, participate in a positive way in the anticancer properties of the polysaccharides; In addition, protein ligands increase the anticancer potential [49].

2.4 Mechanism of Action of Polysaccharides

The diversity of polysaccharides and their derivatives is reflected in the variety of their mechanisms of action. There are two basic mechanisms of action of polysaccharides against tumor cells: indirect action (immunostimulation) and direct action (inhibition of tumor cell growth and induction of apoptosis) [49,30].

Indirect Action: It is based on the stimulation of host defense mechanisms, mainly in the activation of T and B lymphocytes, macrophages and natural killer cells (NK) [5]. It has been shown that the β-glucans of many fungi stimulate the production of interferons (IFNs), interleukins (IL), and other cytokines, considered as the first line of defense of the host's immune system [49].

Different studies have shown that β-glucans induce the body's response by binding to membrane receptors in immunologically competent cells. One of the most important β-glucan receptors is the CR3 receptor. This receptor is commonly produced on the surface of immune effector cells, such as macrophages, neutrophils, NK cells, and K cells [31]. CR3 is able to recognize opsonin iC3b, which often occurs on the surface of cancer cells [50]. The simultaneous connection of complement iC3b-CR3 and β-glucan induces the stimulation of phagocytic activity, while the lack of any of these components prevents the induction of cytotoxicity. Numerous reports have indicated that polysaccharides improve the ability of immune cells to recognize tumor cells as foreign and therefore improve the efficiency of reception of defense mechanisms [49].

Direct action: In addition to the indirect action, several polysaccharides have been shown to have direct effects on cancer cells. Many *in vitro* and *in vivo* studies have shown that polysaccharides inhibit tumor proliferation and/or induce death by apoptosis [1].

One of the best-described mechanisms of the direct action of polysaccharides extracted from Basidiomycetes is the modulation of the activity of NF-κβ (nuclear factor enhancer of the light chains kappa of activated B cells). Excessive activation of NF-κβ is seen in many types of cancer [51]. The activation of NF-κβ promotes tumor growth by increasing the transcription of genes that induce cell proliferation, inhibits apoptosis, or promotes angiogenesis and metastasis [52]. It was found that the polysaccharides inhibit the phosphorylation and/or degradation of NF-κβ (Iκβα), which prevents the activation of the transcription factor and consequently the expression of subordinate genes. In addition to the modulation of the NF-κβ pathway, polysaccharides can also affect cancer cells in other ways. An example of this is the protein complex - polysaccharide extracted from *Trametes versicolor* known as PSP. It was shown that PSP induces the cell cycle arrest in G1 / S and G2 / M restriction sites in leukemia cells and in breast cancer cells, also inhibited antiapoptotic proteins, resulting in the repression of cell division and the increase of apoptosis [1].

3. CONCLUSIONS

Fungi represent a valuable source of bioactive agents with medicinal properties. Many of them are not strictly pharmaceutical products, but represent a new class of dietary supplements or "mushroom nutritional products". Agents derived from fruiting bodies of medicinal mushrooms, cultivated mycelia or culture filtrates exert a wide range of beneficial biological effects when tested in vitro or animal models are used [48].

It has been shown that compounds derived from fungi are able to stimulate components of the innate or acquired immune response. Such compounds are called Biological Response Modifiers (BRMs) or immunomodulators and have evolved as a new method for the treatment of cancer. It is considered that the polysaccharides of some fungi function locally as BRMs where they influence the immune system by exerting a non-specific response in the organism since they do not directly attack the cancer cells, but produce their antitumor effects by activating different immune responses in the host [9].

The main immunomodulatory effects of these active principles derived from fungi include the mitogenicity and activation of immune cells, such as hematopoietic stem cells, lymphocytes, macrophages, dendritic cells and natural killer (NK) cells, which give result in the production of cytokines. The therapeutic effects of fungi, such as anticancer activity, the suppression of autoimmune diseases and allergies, have been associated in many cases with their immunomodulatory effects [47].

While it is known that fungal extracts have immunomodulatory and / or antitumor activity, the approach has been to isolate, characterize and administer the pure active constituents. However, different components in a mushroom extract may have synergistic activities [18,53]. There are several reports of fungi that contain more than one polysaccharide with antitumor activity. It is likely that responses to different polysaccharides are mediated by different cell surface receptors, which may be present only in specific subsets of cells and may trigger different subsequent responses. A combination of responses of this type involving different subsets of cells could provide greater inhibition of the tumor than could be induced by a single polysaccharide [47].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zhang M, Cui SW, Cheung PCK, Wang Q. Antitumor polysaccharides from mushrooms: A review on their isolation process, structural characteristics and antitumor activity. Trends in Food Science & Technology. 2007;18:4-19.
2. Lemieszek M, Rzeski W. Anticancer properties of polysaccharides isolated from fungi of the Basidiomycetes class. Contemporary Oncology. 2012;16(4):285–289.
3. Chatterjee S, Biswas G, Kumar S, Acharya K. Antineoplastic effect of mushrooms: A review. Australian Journal of Crop Science. 2011;5(7):904-911.
4. Jiang J, Sliva D. Novel medicinal mushroom blend suppresses growth and invasiveness of human breast cancer cells. International Journal of Oncology. 2010;37: 1529-1536.

5. Akramienė D, Kondrotas A, Didžiapetrienė J, Kėvelaitis E. Effects of β-glucans on the immune system. Medicina (Kaunas). 2007;43(8):597-606.
6. Chi-Fung Chan G, Keung Chan W, Man-Yuen Sze D. The effects of β-glucan on human immune and cancer cells. Journal of Hematology & Oncology. 2009;2-25.
7. Smith J, Rowan N, Sullivan R. Medicinal mushrooms: A rapidly developing area of biotechnology for cancer therapy and other bioactivities. Biotechnology Letters. 2002; 24:1839–1845.
8. Smith J, Sullivan R, Rowan N. Mushrooms and cancer therapy. Biologist. 2005;52(6): 328-336.
9. Ferreira I, Vaz J, Vasconcelos H, Martins A. Compounds from wild mushrooms with antitumor potential. Anticancer Agents in Medicinal Chemistry. 2010;10(5):424-36.
10. Llauradó G, Morris H, Marcos J, Castán L, Bermúdez R. Plantas y hongos comestibles en la modulación del sistema inmune. Revista Cubana de Investigaciones Biomédicas. 2011;30(4): 511-527.
11. Zhang Y, Li S, Wang X, Zhang L, Cheung P. Advance in lentinan: Isolation, structure, chain conformation and bioactivities. Food Hydrocolloids. 2011;25:196-206.
12. Daba A, Ezeronye O. Anti-cancer effect of polysaccharides isolated from higher basidiomycetes mushrooms. African Journal of Biotechnology. 2003;2(12):672-678.
13. Chen Y, Hu D, Cheong K, Li J, Xie J, Zhao J, Li S. Quality evaluation of lentinan injection produced in China. Journal of Pharmaceutical and Biomedical Analysis. 2013;78(79):176–182.
14. Zheng R, Jie S, Hanchuan D, Moucheng W. Characterization and immuno-modulating activities of polysaccharide from *Lentinus edodes*. International Immunopharmacology. 2005;5:811-820.
15. Ooi V, Liu F. Immunomodulation and anti-cancer activity of polysaccharide-protein complexes. Current Medicinal Chemistry. 2000;7:715-729.
16. El Enshasy H, Hatti-Kaul R. Mushroom immunomodulators: Unique molecules with unlimited applications. Trends in Biotechnology. 2013;31(12):668-676.
17. Sonawane H, Bhosle S, Bapat G, Vikram G. Pharmaceutical metabolites with potent bioactivity from mushrooms. Journal of Pharmacy Research. 2014;8(7):969-972.
18. Gao Y, Zhou S. Cancer prevention and treatment by *Ganoderma*, a mushroom with medicinal properties. Food Rev Int. 2003;19:275–325.
19. Wasser S. Medicinal mushrooms as a source of antitumor and immuno-modulating polysaccharides. Applied Microbiology and Biotechnology. 2002; 60(3):258–274.
20. Zhang Y, Ma G, Fang L, Wang L, Xie J. The immunostimulatory and anti-tumor activities of polysaccharide from *Agaricus bisporus* (brown). Journal of Food and Nutrition Research. 2014;2(3):122-126.
21. Kozarski M, Klaus A, Jakovljevic D, Todorovic N, Niksic M, Vrvic M, Griensven L. Dietary polysaccharide extracts of *Agaricus brasiliensis* fruiting bodies: Chemical characterization and bioactivities at different levels of purification. Food Research International. 2014;64:53-64.
22. Kozarski M, Klaus A, Niksic M, Jakovljevic D, Helsper J, Griensven L. Antioxidative and immunomodulating activities of polysaccharide extracts of the medicinal mushrooms *Agaricus bisporus, Agaricus brasiliensis, Ganoderma lucidum* and *Phellinus linteus*. Food Chemistry. 2011;129:1667-1675.
23. Smiderle F, Sassaki G, Arkel J, Iacomini M, Wichers H, Griensven L. High molecular weight glucan of the culinary medicinal mushroom *Agaricus bisporus* is an α-glucan that forms complexes with low molecular weight galactan. Molecules. 2010;15:5818-5830.
24. Adams L, Phung S, Wu X, Ki L, Chen S. White button mushroom (*Agaricus bisporus*) exhibits antiproliferative and proapoptotic properties and inhibits prostate tumor growth in athymic mice. Nutricion and Cancer. 2008;60(6):744-756.
25. Volman J, Mensink R, Griensven L, Plat J. Effects of α-glucans from *Agaricus bisporus* on *ex vivo* cytokine production by LPS and PHA-stimulated PBMCs; a placebo-controlled study in slightly hypercholesterolemic subjects. European Journal of Clinical Nutrition. 2010;64:720-726.
26. Sun Y, Liu J. Purification, structure and immunobiological activity of a water-soluble polysaccharide from the fruiting body of *Pleurotus ostreatus*. Bioresource Technology. 2009;100:983-986.
27. Sarangi I, Ghosh D, Bhutia S, Mallick S, Maiti T. Anti-tumor and immunomodulating

effects of *Pleurotus ostreatus* mycelia-derived proteoglycans. International Immunopharmacology. 2006;6:1287-1297.
28. Synytsya A, Míčková K, Synytsya A, Jablonský I, Spěváček J, Erban V, Čopíková J. Glucans from fruit bodies of cultivated mushrooms *Pleurotus ostreatus* and *Pleurotus eryngii*: Structure and potential prebiotic activity. Carbohydrate Polymers. 2009;76(4):548–556.
29. Facchini J, Alves E, Aguilera C, Miranda R, Lange M, Wisbeck E, Furlan S. Antitumor activity of *Pleurotus ostreatus* polysaccharide fractions on Ehrlich tumor and Sarcoma 180. International Journal of Biological Macromolecules. 2014;68:72-77.
30. Lavi I, Levinson D, Peri I, Tekoah Y, Hadar Y, Schwartz B. Chemical characterization, antiproliferative and antiadhesive properties of polysaccharides extracted from *Pleurotus pulmonarius* mycelium and fruiting bodies. Applied Microbiology and Biotechnology. 2010;85:1977-1990.
31. Ross G, Vêtviĉka V, Yan J, Xia Y, Vêtviĉková J. Therapeutic intervention with complement and β-glucan in cancer. Immunopharmacology. 1999;42:61-74.
32. Synytsya A, Míčková K, Jablonský I, Sluková M, Čopíková J. Mushrooms of genus *Pleurotus* as a source of dietary fibres and glucans for food supplements. Czech Journal of Food Sciences. 2008;26(6):441-446.
33. Cruz E. Especies novedosas de champiñones (*Agaricus*) con propiedades funcionales antioxidantes y antimicrobianas, aisladas de zonas rurales de Mexico. Tesis Maestría; 2012.
34. Xia F, Fan J, Zhu M, Tong H. Antioxidant effects of a water-soluble proteoglycan isolated from the fruiting bodies of *Pleurotus ostreatus*. Journal of the Taiwan Institute of Chemical Engineers. 2011;042: 402–407.
35. Tsang K, Lam C, Yan C, Mak J, Ooi G, Ho J, Lam B, Man R, Sham J, Lam W. *Coriolus versicolor* polysaccharide peptide slows progression of advanced non-small cell lung cancer. Respiratory Medicine. 2003;97(6):618–624.
36. Borchers A, Keen C, Gershwin E. Mushrooms, tumors, and immunity: An update. Experimental Biology and Medicine. 2004;229(5):393-406.
37. Gao Y, Zhou S, Chen G, Dai X, Ye J. A phase I/II study of a *Ganoderma lucidum* (Curt.: Fr.) P. Karst. Extract (Ganopofy) in patients with advanced cancer. International Journal of Medicinal Mushrooms. 2002;4(3).
38. DeVere R, Hackman R, Soares S, Beckett L, Sun B. Effects of a mushroom mycelium extract on the treatment of prostate cancer. Urology. 2002;60(4):640-4.
39. Kodama N, Komuta K, Sakai N, Nanba H. Effects of D-Fraction, a polysaccharide from *Grifola frondosa* on tumor growth involve activation of NK cells. Biological & Pharmaceutical Bulletin. 2002;25(12): 1647–1650.
40. Sandoval L. Estudio de las cualidades nutritivas de cuatro tipos de sustratos para el cultivo de champiñones (*Agaricus bisporus*). Tesis Pregrado. Pontificia Universidad Católica del Ecuador; 2012.
41. Caruffo M, López P, Navarrete N. Uso de β-glucanos como inmunoestimulantes en la agricultura. Acuaindustria. 2013;118-121.
42. Synytsya A, Novák M. Structural diversity of fungal glucans. Carbohydrate Polymers. 2013;92:792-809.
43. García C. Algunos aspectos estructurales y funcionales de la pared celular de *Agaricus bisporus* y sus aplicaciones más inmediatas. Anales de la Real Academia de Farmacia. 2000;66(1):2-19.
44. Ardón C. La producción de los hongos comestibles. Universidad de San Carlos de Guatemala; 2007.
45. Curvetto N. *Grifola frondosa* (Maitake): Su valor nutracéutico, nutricéutico, farmacéutico y cosmecéutico. Tecnología de Producción; 2009.
46. Camelini C, Maraschin M, De Mendonça M, Zucco C, Ferreira A, Tavares L. Structural characterization of β-glucans of *Agaricus brasiliensis* in different stages of fruiting body maturity and their use in nutraceutical products. Biotechnology Letters. 2005;27(17):1295–1299.
47. Lull C, Wichers H, Savelkoul H. Antiinflammatory and immunomodulating properties of fungal metabolites. Mediators of Inflammation. 2005;2:63–80.
48. Wasser S, Didukh M. Dietary supplements from culinary-medicinal mushrooms: A variety of regulations and safety concerns for the 21st Century. International Journal of Medicinal Mushrooms. 2004;6(3).
49. Ballesteros H. Determinación de las características productivas de cepas nativas mexicanas de champiñón *Agaricus*

bisporus (J.E. Lange) Imbach para su potencial uso comercial. Tesis Pregrado. Universidad Veracruzana; 2012.
50. Smiderle F, Ruthes A, Arkel J, Chanput W, Iacomini M, Wichers H, Griensven L. Polysaccharides from *Agaricus bisporus* and *Agaricus brasiliensis* show similarities in their structures and their immuno-modulatory effects on human monocytic THP-1 cells. BMC Complementary and Alternative Medicine. 2011;11-58.
51. Ravi R, Bedi A. NF-κB in cancer—a friend turned foe. Drug Resistance Updates. 2004;7:53–67.
52. Sánchez C. Evaluación de la productividad del hongo comestible *Pleurotus ostreatus* sobre un residuo agroindustrial del departamento del Valle del Cauca y residuos de poda de la Universidad Autónoma de Occidente. Tesis Pregrado. Universidad Autónoma de Occidente; 2013.
53. Vickers A. Botanical medicines for the treatment of cancer: Rationale, overview of current data, and methodological considerations for phase I and II trials. Cancer Investigation. 2002;20(7-8):1069–1079.

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