Review Paper

Immunomodulatory Fungi: an alternative for the treatment of cancer

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 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 IMMUNOMODULATORS

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 (the reference is missing). Lucas isolated a substance from Boletusedulis, 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 Ganodermalucidum and Trametesversicolor are inedible mushrooms, due to its coarse texture and bitter taste, but which also possess medicinal or functional properties [9].

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. It has been shown that these compounds potentiate the innate (non-specific) and acquired (specific) immune response and activate different types of immune cells [11]. More than 50 species of fungi contain organic immunomodulatory compounds of different molecular weight and structure [12]. The following table describes some of the main fungi with immunomodulatory activities:

Table 1. Main fungi with immunomodulatory activities. Source [12]

FUNGUS	IMMUNOMODULATOR ACTIVITY
Agaricus subrufescens (*A. BlazeióA. brasiliensis*)	This edible mushroom has different common names: almond mushroom, sun mushroom, real life mushroom, sun agaricus, princess matsutake. Characterized by the fragrance of almonds and a sweet taste. Contains immunostimulatory compounds such as β-1,3-D-glucans, glucomannan, and proteoglycans.
Ganoderma lucidum	Common names: Reishi, Ligzhi, plant of the spirit. It has a long history in traditional Chinese and Japanese medicine. This fungus contains more than 50 types of polysaccharides and peptide-polysaccharide complexes in addition to about 120 bioactive compounds (mainly triterpenes). Most of these compounds can act as strong immunostimulants.
Grifola frondosa	Common name: Maitake. This fungus is rich in β-glucans, which activates macrophages, NK cells and lymphokines. It also includes compounds such as ergosterol peroxide (EPO) and lipopolysaccharide (LPS) with significant immunomodulatory activities.
Lentinula edodes	Common name: Shiitake. This is an edible Japanese mushroom, famous for its immunomodulatory properties. It is rich in a special type of polysaccharide called lentinan (1-3-β-D-glucan with 1-6-β-D-glucopyranoside branching).
Pleurotus ostreatus	Common name: Mushroom oyster. It is widely cultivated in different parts of the world. This mushroom includes different types of polysaccharides such as β-glucan, heteroglycan, and the families of proteoglycans. The Pleuranoβ- (1-3 / 1-6) -D-glucan is the most effective and well studied polysaccharide of this fungus.

Trametes versicolor	Common name: Turkey Tail. It has strong immunomodulatory effects due to a polysaccharide called Krestin (PSK), and also contains the so-called FIPTVC.

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 [12]

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 [12]

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[13].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 Volvariellavolacea possess a strong immunomodulatory activity, lectins extracted from Tricholomamongolicum, 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 Clitocybenebularis, 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-□ [12]

Immunomodulatory Terpenes: Terpenes are a large and diversified group of organic compounds consisting of five carbon isoprene units of molecular formula (C5H6) 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 Ganodermasp., Such as Ganodermalucidum and Ganodermaapplanatum, are known for their high content of triterpenoids, for example, lanostane, which shows immunomodulatory and anti-infectious activities [12]

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 [12]

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 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 helix structure was isolated from the fruiting body of Lentinusedodes in the late 1960s in Japan. Since then there have been many efforts to discover new polysaccharide compounds with immunomodulatory activities of the extracts of the fruiting bodies of fungi. Until the late 1980s, only two more polysaccharides of the γ-glucan type, Schizophyllum's schizophyllum commune and the protein-bound polysaccharide, Krestin of Trametesversicolor, were fully characterized [12]

Table 2 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.

Table 2. Immunomodulatory activities of polysaccharides. Source: [12]

Arrow	Active compound	Immuno-modulating activity
Agaricusblazei (*Agaricus subrufescens*)	Glycoprotein (ATOM), β-1,3-D-glucan, with β-1,6-D-glucan branches.	Induction of TNF, IFN-□, and IL-8 production.
Ganodermalucidum	Ganoderano, Heteroglicano, manoglucano, glycopeptid.	Stimulates TNF-□, IL-1, IFN-producción production, activation of NF-KB.
Lentinusedodes	Lentinano, glucano, manoglucano, proteoglicano.	Induces non-specific cytotoxicity in macrophages and increases cytokine production.
Pleurotusostreatus	Pleurano, heterogalactano, proteoglicano.	Induces IL-4 and IFN-producción production
Polystrictusversicolor	Krestin, heteroglycan-no, glycopeptide	It stimulates the activation of T cells, induces IFN-□ and the

	, polysaccharide K (PSK), peptide polysaccharide (PSP).	production of IL-2, induces the expression of cytokine genes (TNF-, IL-1, IL-6, IL-8)

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 [14]. 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 γ-glucans [14].

A large number of polysaccharides, including several α and βglucans, 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 (, 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].

B-glucans are glucose polymers, which can contain up to 250,000 units of this molecule [15, 16]. 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 [17] (Figure 1).

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 (Ganodermalucidum), Shiitake (Lentinusedodes), Maitake (Grifola frondosa), Trametesversicolor, 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 [18], 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].

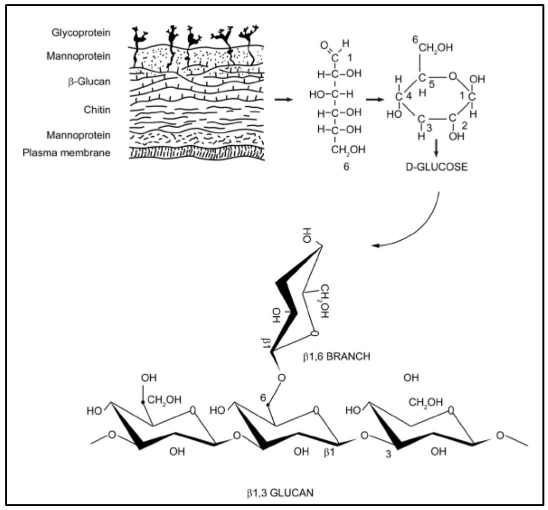

Figure 1. β-glucan is one of the key components of the fungal cell wall. Β-glucan is the basic subunit of fungi, they are β-D-glucose linked to each other by 1 → 3 glycosidic chains with 1 → 6 glycosidic branches. The length and ramifications of the β-glucans of various fungi are very different. Source: [8].

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 [11], 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 [19].

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 Lentinusedodesa 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 γ-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 [12].

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 [21]. 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, □-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.
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 [21].

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) [21, 22].

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 [21].

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 [23]. CR3 is able to recognize opsonin iC3b, which often occurs on the surface of cancer cells [24]. 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 [21].

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 [25]. 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 [26]. 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 Trametesversicolor 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].

Agaricus Bisporus

Also called champiñón de Paris or simply mushroom belongs to the group of basidiomycetes. The name bisporus corresponds to the fact that each basid forms only two spores when the normal number among the basidiomycetes is four [27]. With respect to the cell wall of A. bisporus it is constituted mainly by neutral polysaccharides (formed mainly by glucose and in a lower percentage by galactose, mannose and xylose) and amino acids (N-acetylglucosamine in the form of chitin), with a lower proportion of proteins and lipids, in amounts that differ significantly depending on whether the vegetative or aggregated mycelium is involved. The polysaccharides formed are mainly glucans together with galactans, mannans and xylans and often mixed polysaccharides (heteropolysaccharides) such as mannoxylans, glucoxylans etc., with different types of bonds, relatively branched and with both α or β configurations [28].

In relation to its structure, A. bisporus is made up of three parts: the hat or pileus, foot or stipe, and hymenium. The pileus is the most fleshy part of the fungus, has a rounded, globose shape, smooth texture and white color, its size can reach from 16 mm to 15 cm in diameter. The hymenium is located in the lower part of the pileus and is formed by numerous lamellae, arranged in the manner of spokes, which go from the foot to the outer edge of the pileus; said lamellae are pink at the beginning and then turn brown and even black. When the fungus is small the hymenium is protected by a thin membrane called veil, which is attached to the hat and foot. The veil is formed by a special set of flexible cells that protect the spores and the hymenium during the development period of the fungus until they reach the optimum degree of maturity. When it reaches maturity, the veil tears, thus allowing the release of the spores and only a small piece remains attached to the stem, called a ring. The stipe is the part of the fungus that serves as a support for the hat; It has a cylindrical shape and its lower part is joined to the mycelium that grows on the substrate [29] (Figure 2).

Figure 2. Morphology of Agaricusbisporus. Source: [30]

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 [31].

In recent years, many studies have shown that Agaricusbisporus 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 Agaricusbisporus, for example, (1 → 6) -β-D-glucans presents an immunostimulating activity that contributes to the antitumor effects [32]. 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 [33].,

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-□ (TNF-□), 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 [34].

Pleurotus Ostreatus

Its name derives from the Greek pleura or pleuron (side or side), and from the Latin otus, ear. It is a group of wide distribution in nature, they grow in living or dead parts of plants, which are generally poor in vitamins and nutrients, thanks to their ease of forming fruiting bodies of great organoleptic quality, they have been widely cultivated and are of great importance at the economic level. They have several common names that identify them in different regions of the world, Orellana, Gírgola, Mushroom Oyster or Pleuroto in the shape of an oyster. This type of fungus does not have a ring or vulva, is called oyster by its shape and color of the fruiting bodies (Hat or Carpóforo). Its diameter oscillates between 5 and 15 cm according to its age, it has several tonalities of color, from white, to gray or blue, but with the passage of time it starts to have a yellowish color, its flesh is white and it has a slight smell of anise [35].

Figure 3. Pleurotusostreatus morphology. Source: [36]

His hat is a rounded and smooth surface, convex and convex when young, but gradually flattening with the arrival of maturity. At the bottom of the hat are the lamellae arranged radially, ranging from the foot or stem that holds it, to the edge. They are wide, spaced from each other, white or cream, sometimes bifurcated, and in them, spores are produced for the reproduction of the species. These spores are small, oblong, almost cylindrical, which in large numbers form masses of dust or spore, white with a certain lilac-grayish tone. It has a short lateral foot, which can sometimes be eccentric; the meat or context is white, with pleasant taste and smell. Fruiting bodies grow in a gregarious and usually imbricate form, on fallen or standing trunks, or in various plant remains [35] (Figure 3).

The nutritional properties of Pleurotus are known for their high content of proteins that constitute 19 to 35% of their dry weight, they contain all the essential amino acids for human nutrition [37]. In addition to its value as a protein-rich food, Pleurotus contains other essential components in the diet, such as minerals (calcium, phosphorus, iron) and a wide variety of vitamins, particularly thiamine (B1), riboflavin (B2), pantothenic acid, Ascorbic acid (C) and biotin [38].

The fungi of this genus are 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 [39], 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 [40].

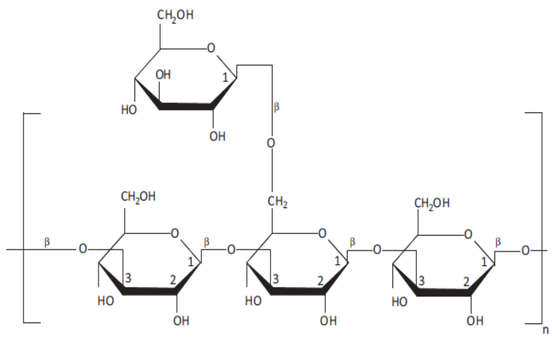

Figure 4. Structure of the Pleurane. [β- (1,3 / 1,6) -D-Glucan]. Source: [12]

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 [41].

Pleutorus ostreatus contains a polysaccharide called pleurane, which acts as a modifier of the biological response [39]. 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 (Figure 4) that is commonly found in other Basidiomycetes and Ascomycetes [30], has an antitumor and immunomodulatory effect that includes the stimulation of phagocytic activity [31].

Lentinula Edodes

Lentinula edodes is the scientific name of the fungus popularly called Shiitake. The word Shiitake comes from the Japanese: "shii" which is a tree (Pasania) where this species grows naturally, and "take" which means fungus [42]. In the United States, it is known as "black mushroom of the forest", in France as "lectin" and in Korea as "pyogo" which means "mushroom". In China, the different types of Shiitake mushrooms have names like "shiang-gu", which means "fragrant mushrooms"; "Dong-gu", which means "fungus of winter"; and "hua-gu", which means "flower mushroom" [32].

It is characterized by having a hat of 5 to 25 cm in diameter, hemispherical, with flat and white lamellae. Initially, it presents a dark brown color almost black, but with time its color becomes clear. The shape of the hat can sometimes be irregular, however, usually the fungus at the beginning is rolled and when it reaches maturity its hat becomes flatter. Another important indicator of the development of the fungus, are the spots that appear irregularly in the hat, whitish but that get to take darker colors when the fungus matures. The foot is generally in the central position, it is whitish on the upper part and light brownish on the middle part towards the base, its texture is fibrilous-scaly; sometimes when she is young she has remains of a curtain of fine fibrils that join it to the brim of the hat (pileus) (Figure 5) [32],, its spores are white in mass, tetrapolar, forming four spores in the basidium [43].

Figure 5. Morphology of Lentinula Edodes. Source: [35]

Nutritionally, Lentinulaedodes, has great value, because they are a good resource of vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin) and D (the highest vitamin D content of any vegetable food), also contains all the essential amino acids, dietary fiber, high calorific value and the amount of protein is comparable to that of chicken and pork, but with more fiber than these meats. It contains high levels of minerals such as iron, potassium, and phosphorus [36].
Lentinula edodes (Shiitake) is the second most popular edible fungus, its importance is attributed to both its nutritional value and its medical application [37]. 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 [38].

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. 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* [38]

The Lentinanes a polysaccharide β- (1-3) -β- (1-6) -D Glucan with a structure of triple helix of high molecular weight (27.5kDa) [41, 44], containing glucose molecules with β- bonds (1-3) in the central part and β- (1-6) -Glucose bonds in the side chains [46] (Figure 6). The configuration of glucose molecules in the helical structure is considered important for biological activity [36]. It is soluble in water, produced in the cell wall of the fungus, can be extracted from the mycelium and or the carpophore [43].

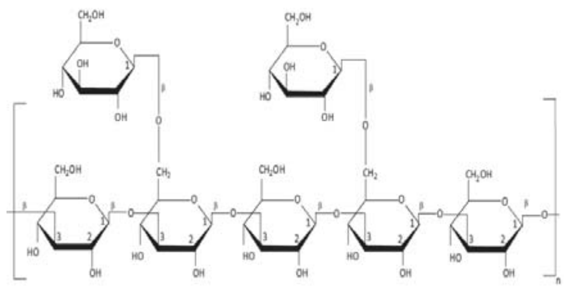

Figure 6. Structure of the Lentinan. [β-1,3-glucan with β-1,6 branches]. Source: [12]

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 γ-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. Preclinical studies in animal models with lentinan have produced considerable information on antitumor activity, prevention, and blocking of metastasis [10, 46].

4. CONCLUSION

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. 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 immunosuppression; for therapy combined with antibiotics and as adjuvants for vaccines.

Different purified polysaccharides have had clinical use in Japan, China, and Korea for many years, without reports of negative effects in the short term or in the long term. These compounds are not "miracle" drugs but can increase the quality of life of cancer patients and may offer a better survival for some types of cancer. 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

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