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Characterization and biological activities of polysaccharides extracted from the filamentous fungal cell wall: an updated literature review

Caracterização e atividades biológicas de polissacarídeos extraídos da parede celular de fungos filamentosos: uma revisão da literatura atualizada

Caracterización y actividades biológicas de polisacáridos extraídos de la pared celular de hongos filamentosos: revisión de la literatura actualizada

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Abstract

Filamentous fungi are eukaryotic organisms with several industrial and pharmaceutical applications. Polysaccharides are the principal components of cell walls from Fungi and other organisms like diatoms, and have been reported in the industrial and medical fields as products with a huge number of different biological activities and applications. The objectives of this narrative review were to assess the characterization methods and and biological activities of polysaccharides extracted from the filamentous fungal cell wall. Glucans, chitin and galactomannans are the most common polysaccharide often found in the cell walls of fungi. These polysaccharides can contain different glycosidic linkage either an α or β-configuration and at various positions, such as (1-3,1-4, 1-6), as well as several molecular sizes. This leads to an almost limitless diversity in their structure and biological activity. There are many methods for polysaccharides characterization, among them; the methods commonly used involve Infrared Spectrometry (FT-IR), Nuclear Magnetic Resonance Spectroscopy (MRS), and gas chromatography-mass spectrometry (CG-MS). Typically, cell wall polysaccharides from filamentous fungi have been shown to possess complex, important and multifaceted biological activities including mainly antioxidant, anti-inflammatory, immunomodulatory, antinociceptive, antitumor and hypoglycemic activities. Due to the large number of filamentous fungi genus and species capable of producing useful polysaccharides, perform scientific researches, and produce novel scientific knowledge and information are particularly interesting in order to identify polysaccharides with potential biological activity and that can be used for medicinal purposes.

Keywords: Polysaccharides; Filamentous fungi; Catacterization methods.

Resumo

Fungos filamentosos são organismos eucariontes com diversas aplicações industriais e farmacêuticas. Polissacarídeos são componentes da parede celular de fungos, e outros organismos, e têm sido reportados como produtos com inúmeras atividades biológicas e de aplicações na área industrial e médica. Este estudo trata-se de uma revisão narrativa acerca dos métodos de caracterização e atividade biológica de polissacarídeos isolados de da parede celular de fungos filamentosos. Os polissacarídeos mais frequentemente encontrados nas paredes celulares fúngicas são a quitina, glucanas e galactomananas. Esses polissacarídeos podem conter diferentes tipos de ligação (1-3,1-4, 1-6) dos tipos α ou β, como também, diversos tamanhos moleculares, e essas variações podem ser responsáveis pela variedade de atividade biológica que esses polímeros possuem. Os métodos mais comuns aplicados para caracterização dos polissacarídeos, incluem Espectrometria de Infravermelho, Ressonância Magnética Nuclear e Cromatografia Gasosa Acoplada à Espectrometria de Massas. As atividades biológicas mais frequentemente atribuídas à polissacarídeos de fungos filamentosos incluem, antioxidante, anti-inflamatória, imunomoduladora, antinociceptiva, antitumoral e hipoglicemiante. Devido a variedade de gênero e espécies de fungos filamentosos existentes, estudos de caracterização e atividade biológica são necessários, a fim de identificar polissacarídeos com potencial atividade biológica e que possam ser utilizados para fins medicinais.

Palavras-chave: Polissacarídeos; Fungos filamentosos; Métodos de catacterização.

Resumen

Los hongos filamentosos son organismos eucariotas con diversas aplicaciones industriales y farmacéuticas. Los polisacáridos son componentes de la pared celular de los hongos y otros organismos, y se han informado como productos con numerosas actividades biológicas y aplicaciones en los campos industrial y médico. Este estudio es una revisión narrativa sobre los métodos de caracterización y actividad biológica de polisacáridos aislados de la pared celular de hongos filamentosos. Los polisacáridos que se encuentran con mayor frecuencia en las paredes de las células de los hongos son la quitina, los glucanos y los galactomananos. Estos polisacáridos pueden contener diferentes tipos de enlaces (1-3,1-4, 1-6) de tipos α o β, así como varios tamaños moleculares, y estas variaciones pueden ser responsables de la variedad de actividad biológica que tienen estos polímeros. Los métodos más comunes

aplicados para la caracterización de polisacáridos incluyen espectrometría infrarroja, resonancia magnética nuclear y cromatografía de gases acoplada a espectrometría de masas. Las actividades biológicas atribuidas con mayor frecuencia a los polisacáridos de hongos filamentosos incluyen antioxidantes, antiinflamatorios, inmunomoduladores, antinociceptivos, antitumorales e hipoglucémicos. Debido a la variedad de géneros y especies de hongos filamentosos existentes, los estudios de caracterización y la actividad biológica son necesarios para identificar polisacáridos con potencial actividad biológica y que puedan utilizarse con fines medicinales.

Palabras clave: Polisacáridos; Hongos filamentosos; Métodos de catacterización.

1. Introduction

Fungi are eukaryotic organisms with broad spectrum distribution in the biosphere and great biotechnological potential. Due to their important biological activities, fungal polysaccharides are used in various biomedical applications, functional foods and pharmaceutical industries. Furthermore, increasing demand for environmentally acceptable alternatives instead of traditional use of chemical fungicides, herbicides and insecticides are attracting scientist' attention to the discovery of new economics, sustainability and natural occurring fungal polysaccharides. (Kanchiswamy, Malnoy & Maffei, 2015).

Although rigid, the fungal cell wall structures are dynamic, fundamental to cell viability, morphogenesis and pathogenesis. Furthermore, its composition is critical to the biology and ecology of each fungal species (Gow, Latge & Munro, 2017). Fungal cell walls are composed predominantly of Polysaccharides. For example, in Aspergillus species Polysaccharides account for > 90% of the cell wall. Thus, knowledge the functional design of this structure is an important step to assess of the biotechnological applications (Latge; Beauvais & Chamilos, 2017).

The fungal cell wall polysaccharide mainly consists of chitin, glucans and galactomannans. In general, fungi need to produce a variety of enzymes to degrade these polysaccharides into monomeric structures. In addition to polysaccharides, the extracellular secreted Exopolysaccharides are a major component of the fungal extracellular biofilm matrix, that characterized by the production of a medium of viscous high-molecular-mass when they diffuse in the liquid phase during fermentation (Wang et al., 2014; Du et al., 2017).

In recent decades, there has been growing interest in studying and application of polymers in several sectors (Bordenave, Janaswamy & Yao, 2014). Polysaccharides are

essentially complex carbohydrate polymers composed of long chains of monosaccharide units together by glycosidic bonds (Mahapatra & Banerjee, 2013), widely found in microorganisms, animal and plant cells (Wang et al., 2017). The Microbiological polysaccharides obtained into different groups according to their location in the cell (intracellular cytosolic polysaccharides, cell wall polysaccharides and extracellular polysaccharides) exhibit high potential biotechnological application, which has driven intense research (Mahapatra & Banerjee, 2013; Valasques Junior et al., 2014).

In the medical-pharmaceutical sector, because of its essential biological role, unique biochemistry and the absence in mammalian cells of most of its constitutive components, the cell wall polysaccharides are an attractive targets for the development of new antifungal agents. Furthermore, depending on their structure, polysaccharides can have a wide variety of bioactivities, including antitumor activity (Sharma, Khanna & Kapoor, 2016; Yu et al., 2017), immunomodulatory effects (Kaori Fukuda et al., 2009; Sharma, Khanna & Kapoor, 2016), anti-inflammatory (Cheng et al., 2016; Du et al., 2015), antioxidant (Wang et al., 2017; Tian et al., 2017) and strong ability to reduce free radicals. Thus, many polysaccharides are being evaluated in effective and safe drug screening researches (Wang et al., 2017).

Taking into consideration the importance and biotechnological perspectives of polysaccharides extracted from the filamentous fungal cell wall, in the present review we discuss the search for new bioactivity substances to pharmaceutical products development.

2. Materials and Methods

This work is a narrative review of the literature for the purpose of discussing the characterization methods and and biological activities of polysaccharides extracted from the filamentous fungal cell wall. Studies were identified by conducting Scientific Electronic Library Online (SCIELO), Science Direct and Google scholar electronic searches. Only articles published in English were included in this review (Pereira, A. S. et al. 2018).

Studies were selected that included Characterization of Polysaccharides by spectrometric methods, such as, Infrared Spectrometry (FT-IR), Nuclear Magnetic Resonance Spectroscopy (MRS), and gas chromatography-mass spectrometry (CG-MS).

Furthermore, biological activities studies of polysaccharides, such as antioxidant, anti-inflammatory, immunomodulatory, hypoglycemic, antitumor and antinociceptive, also were selected for the review. Characterization and biological activities studies from other polysaccharides sources, such as plant and bacterial were excluded.

3. Results and Discussion

The Biology of Fungi

In taxonomic terms, the fungi are classified as an independent kingdom, which is separate from the other eukaryotic life kingdoms of plants and animals, the Mycetae Kingdom, better known as the Fungi Kingdom (Raghukumar, 2017). They are extremely abundant and diverse worldwide, ubiquitous in air, water, and organic matter. Typically exhibit multiple morphological forms and generally accepted numbers of fungi species on earth is over 1,500,000 (Wang et al., 2017).

Fungi are important agents in the soil mineralization and contribute to the carbon cycle through redistribution of recently fixed carbon by the soil and release nutrients bound in organic matter. They decompose nonliving organic matter and their ecology and diversity-environment relationships contribute to sustain life on earth (Tedersoo et al., 2014). However, these microorganisms can also have negative effects where a limited number of fungi species are commonly associated with immunocompromised host as colonizers and opportunistic pathogens (Paulussen et al., 2017).

Despite the high genomic diversity and wide ecological distribution, fungal cells does not differ greatly from other eukaryotic cells and can be found in the wall conserved structures considered to be classical PAMPs (Pathogen-associated molecular pattern) (Wang et al., 2017).

The development of fungi covers a wide variety of complexities, having a vegetative structure that can be unicellular or filamentous, formed by hyphae, which together form the mycelium. The fungal cell wall consists mainly of chitin, glucans, mannans and glycoproteins (Bowman & Free, 2006). In addition, they have osmoheterotrophic nutrition, where obtain their food by dissolved organic matter absorption in the cell surface (Raghukumar, 2017).

Fungi play a pivotal role in primary and advanced biotechnology processes. The basic characteristics of these microorganisms have provided a well-validated model for genetic investigations. The rapid progresses in fungal biotechnology have resulted in a revolution in terms of what is known about several areas: food, medicine, environment, and agriculture.

Yeast and filamentous eukaryotic fungi are much attractive microorganisms to useful model valuable human cell model than prokaryotic bacteria cells (Moretti & Sarrocco, 2015; Brandl & Andersen, 2017). Furthermore, fungal cells have rapid growth, easy morphological

identification, and cultivation on simple defined media with short generation times and easy accessibility towards molecular and classical genetics (Wang, Zhi-Jun et al., 2017).

The yeast *Saccharomyces cerevisiae* (bread and wine yeast) has been used as a experimental fungal model to study cell cycle, signal transductions, regulation of gene expression, metabolism, apoptosis, neurodegenerative disorders and many other biological and molecular processes (Costanzo et al., 2016). Qi et al. (2018) used *S. cerevisiae* co-cultures to improve the solvents production from cassava without adding amylolytic enzymes, increasing the fermentation processes productivity.

Nuanpeng et al. (2018) used a thermotolerant *S. cerevisiae* strain immobilized in an alginate matrix for ethanol production from sweet sorghum juice, providing with a potential industrial application. Plant-derived oleanolic acid production has been effectively boosted via engineered *S. cerevisiae* to optimize the fermentation, transcriptional level of key genes, oxidation-reduction system, and increase over 7.5-fold compared to the maximum production reported (Zhao et al., 2018).

Molecular biology studies led to the development of genetically modified highly efficient filamentous fungi. Unfortunately, filamentous fungi have been less explored than yeast and bacteria. Recent developments in filamentous fungi model led to tools for enhanced and well-regulated heterologous protein production, such the ascomycetous species *Aspergillus nidulanse* and *Neurospora crassa*: Genetic control of melanin formation expression levels in *Aspergillus nidulanse* during trickle bed reactor fermentation reduce melanin formation in fungal mycelia and liquid medium in order to increase the enzyme production yield (Wang Zheng et al., 2017; Pardo-Lanas et al., 2017); Genetic induction of higher mRNA levels of the structural genes in *Neurospora crassa* mycelium increase the efficiency in carotenoid production at low temperature (Castrillo et al., 2017).

Generally, fungal microorganisms such as genera species of *Aspergillus, Trichoderma, Fusarium, Penicillium,* and *Neurospora* produces beneficial primary and secondary metabolites and compounds, ranging from economically important proteins and enzymes to antibiotics, organic acids, alcohols, immunosuppressants, pigments, vitamins and immunomodulatory agents and, thus having the industrial importance that to revolutionize biotechnology (Moretti & Sarrocco, 2015; Kulkarni, Nene & Joshi, 2017).

Fungal secondary metabolic pathways, used for development of microbial structures, provide high molecular weight compounds (proteins, coenzymes, nucleic acids, polysaccharides and lipids) from the small molecules (amino acids, nucleotides, vitamins, carbohydrates and fatty acids) (Sanches & Demain, 2002). The cell wall is one the most

important structures of fungi that promotes growth, biological morphogenesis, protection against Adverse environmental conditions and survival (Free, 2013).

Fungal cell walls

Fungal cells are surrounded by a polysaccharide-rich envelope; these structures plays a multifunctional role in the maintenance of intracellular fungi homeostasis, including providing cell rigidity and shape, metabolism, ion exchange, interactions with host defense mechanisms. Furthermore, presents antigenic and adhesive characteristics, osmotic stress, dimorphism, and transmembrane transport signaling control (Magnelli, Cipollo & Robbins, 2005).

The fungal cell wall is uniquely composed glucans, chitin and chitosan, mannans and / or galactomannans and glycoproteins. The cell wall composition varies between species of fungi but a major component of many fungal cell walls is β1,3-glucan, but other glucans, such as β-1,6 bonds, mixed with β-1,3 or β-1,4, α-1,3 or α-1,4-glucan can also be found in fungal cell walls. Glucans include diverse glucose polymers that differ in the glycosidic bonds position, which can be short or long, branched or unbranched (Bowman & Free, 2006).

Chitin (poli-N-acetil-D-glucosamine) is an essential part of the carbohydrate skeleton of the fungal and is a molecule that is not represented in humans and other vertebrates. Glucan and chitin are joined together in perfect harmony where chitin is a component of the fungal cell wall located closest to the plasma membrane and is strengthened by its covalent attachment to glucan (Fesel & Zuccaro, 2016; Bowman & Free, 2006).

The cell wall is much more than covalently linked polysaccharides and a fungal outer layer, it is also a dynamic structure in order to allow growth, budding and adaptation and whose composition is highly regulated in response to growth conditions, stage of development, environmental conditions, and imposed stresses (Bowman & Free, 2006; De Groot, Ram & Klis, 2005). The cell wall makes up between 20% and 30% of the cell mass from filamentous fungi (Bowman & Free, 2006).

In this way, the fungal cell wall composition interferes with host defense mechanisms and has functions in dormancy establishment or in resistance to external aggressions like radiation, chemical reagents, lytic enzymes, etc. Chitin is the main component responsible for the cell-mechanical protection (Sokolov et al., 2002). However, in some yeasts, such as ascomycites (*Hansenulapolymorpha*), chitin does not promote this protection, the special cell

wall proteins perform more important role in environmental resistance functions and the structure formation of the wall than the polysaccharides (Feofilova, 2010).

Polysaccharides: Classification and Properties

Polysaccharides are long chains of monosaccharides that are synthesized at different stages in the life cycle of all living organism to different purposes (Mahapatra & Banerjee, 2013). They are generally composed of more than ten monomeric units (such as, glucose, mannose, galactose, xylose, and arabinose) linked by glycosidic bonds, showing different anomeric configurations (α and β), molecular weights (number of monosaccharide's per molecule), conformations (linear, branched, helical), connection positions, among others (Zhang et al., 2018; Wang, Liu & Qin, 2017; Guo et al., 2013; Li & Wang, 2016; Chen et al., 2013). All these polysaccharide features together give as a result a great diversity of structure, properties and functions, requiring chemical characterization to drive the polysaccharides applications as well as the bioactivity studies (Ding, Hou & Hou, 2012).

Photosynthetic plants, fungi, algae, bacteria are by far the commonest sources of polysaccharides. Comparing and contrasting among all these live sources, microorganisms shows a major ability of synthesize polymers with different structural complexities (Mahapatra & Banerjee, 2013). In this organisms, intracell polysaccharides are responsible for delivery carbon as an energy source, peptidoglycans and lipopolyssacharides form the cell wall and exopolysaccharides (EPS) provides extracellular environment capsule and biofilm (Donot et al., 2012).

Polysaccharides are found in large quantities and usually show safety low toxicity (Yu et al., 2017). As a result, there is an increased interest in their complex biological activity as well in their characterization, application, and modification in these relevant new structure-activity and mechanisms of action studies (Shi, 2016). Hence, polysaccharides of microbial sources can be used as substrates for the development of new drugs with great potential prospects (Wang et al., 2013) and a wide variety of pharmacological activities, such as antitumor, immunomodulatory, hypoglycemic antioxidants, and anti- inflammatory (Yu et al., 2017; Chen et al, 2016). Such fruiting bodies polysaccharides from *Ganoderma lucidum* isolated by different drying methods (GLP-H, GLP-V and GLP-F) had different levels of scavenging effects on free radicals, showing their strong antioxidant activities (Fan et al., 2012). Polysaccharides from *Cordyceps sinensis* are shown to be one of the responsible for

regulating anti-tumori, anti-microbial, immune functions, and anti-aging activity (Nie et al., 2013).

Chemical characterization of polysaccharides

The physicochemical properties of a polysaccharides and its association with other macromolecules, such as proteins are key factors in evaluating their biological activity (Ding, Hou & Hou, 2012). Therefore, structural and chemical characteristics such as water solubility, molecular weight, monomeric composition, types of glycosidic linkages from the main chain and branches are necessary for the understanding and application of their pharmacological effects (Chen et al., 2016).

Fungi has a multilayered cell wall composed of an outer layer of carbohydrates and an inner skeletal layer of proteins. All cell wall components are covalently linked to each other to form a hardy network with covalent cross-links between glucans and either chitin or strongly glycosylated proteins. Commonly, study of components cell layers requires alkali and HF-pyridine treatment to cell wall polysaccharides and proteins liberation.

The chemical analysis of polysaccharides extracted from the filamentous fungal cell wall requires a variety of specialized techniques, which diverge significantly from those methods used for small molecules and other biopolymers: the total carbohydrates is often determined by phenol-sulfuric, carbazole-sulfuric or anthracenone-sulfuric colorimetric acid methods (Dubois et al., 1956; Chen et al., 2016; Xu et al., 2015); The total protein quantification can be run in Bradfor protein assay (Bradford, 1976); Various chromatographic analytical assays or the combination of them are often used for purification of cell wall constituent, these methods have been widely applied in compositional and structural polysaccharide analysis with a High Performance Liquid Chromatography-HPLC alone or together with other structural analytical techniques combinations, including FT-IR (Fourier Transform Infrared Spectroscopy), NMR (Resonance Nuclear Magnetic), CG-MS (Gas Chromatography coupled to Mass Spectrometry), and so on (Chen et al., 2016; Zhang et al., 2015; Ruthes et al., 2013).

Chromatography is one of the most ubiquitous and effective methods that enables the separation, identification, and purification of the compounds of a mixture with sensitivity, selectivity and separation resolution. Gel-permeation chromatography (GPC), and ion-exchange chromatography (IEC) are commonly used to separate polysaccharides (Chen et al., 2016).

GPC is a most popular method to polysaccharides chemical analysis. The preference for GPC is because of its relatively simplicity, low cost, and ability to provide accurate, reliable information about the molecular-weight distribution. GPC method is based on separation by shape and molecular size properties from polysaccharides. In these assays, gels commonly used are Sephadex, Sepharose, Sephacryl, Superdex and different concentrations of salt solutions and buffers are used as an eluent (Shi, 2016; Orlandelli et al., 2016).

IEC is an important analytical technique for the separation and determination of acidic and neutral compounds according to differences in their net surface charge. The chromatography ion exchange columns contain resins bearing either positively or negatively charged chemical groups. Resins attract negatively or positively the oppositely charged solutes in graduated elution under different concentration of salt solutions. Compounds with a positive surface charge will bind to negatively charged columns and compounds with a negative surface charge will bind to positively charged columns. Thus, provides unique separation selectivity and is well suited to separate and quantification a wide range of biomolecules (Chen et al., 2016). In addition, other techniques also can be used to purify polysaccharides, such as ultracentrifugation, ultrafiltration (Xu et al., 2016).

Fourier-transform infrared (FT-IR) has been known to be a very promising method to characterize biological samples by their chemical composition and provides qualitative and quantitative estimates of polysaccharides. FT-IR is an important method to sugars analysis and identification, since it is possible to observe the vibrating spectra of polysaccharides with stronger absorption in the specific regions, called the fingerprint region. Therefore, depending on the intensity of the bands that are specific to every polysaccharide, information obtained by molecular structure can be gained from the spectrum (Cerna et al., 2003).

In FTIR polysaccharides analysis, the absorption bands within the range of 3200 to 3400 cm-1 are the characteristic absorption peaks of polysaccharides due to the stretching vibration of hydrogen bonded -OH group (Zhang et al., 2018). Also, absorption peak between 2930-2970 cm-1 corresponding to the vibration of C, including CH, CH2 and CH3 (Zhang et al., 2015), the stretch bands in the 950-1200 cm-1 of characteristic polysaccharide absorption range (Ahmad, 2010) and the range of 1040 to 1010 cm-1corresponding to the stretching of COC or COH (Yan et al., 2014; Valasques Junior et al, 2017) which can also explain polysaccharide ring conformation existence (Li & Wang, 2016).

Therefore, the first step in the characterization of a cell wall polysaccharide is their purity determination, which relates to sample chemical composition, including the total of sugar, reducing sugars, proteins, etc. The second step is the monosaccharide composition

determination, which informs the type, or different types, of monosaccharides present and predicts the core structure of the polysaccharide main and the relative percentage of each component in the macromolecule. High performance liquid chromatography (HPLC) is a typically analytical method used to monosaccharide composition determinations (Valasques Junior et al., 2017; Corradi da Silva et al., 2005).

Example of method's application to cell wall structures prediction has been demonstrated in the polysaccharide (TJ2) isolation and purification from *Agaricus brasiliensis* and determination its purity and structure character. In *A. brasiliensis* polysaccharide, glucose, mannose and galactose were found as monomer units (Zhang et al., 2018). These analysis also has been utilized in identification and determination of *Oidiodendron truncatum* exopolysaccharide (Os2-1), where the chain was mainly composed of glucose with minor amounts of glucosamine, and its average molecular weight was about 9.6 kDa (Guo et al., 2013).

Glycosyl linkage (methylation) of polysaccharides is used widely in the structural determination to identity linkage positions for each component sugar and ring size analysis (Ciucanu & Kerek, 1984). In summary, the method involves the complete methylation of a polysaccharide, hydrolysis to a mixture of monosaccharides partially methylated, reduction to alditols, and alditols acetates intensification from alditon acetates partially methylated by gas chromatography coupled to mass spectrometry (CG -MS). Features of alditon acetates partially methylated serves to deduce the types of the bonds (Pazur, 1994).

The anomeric configuration analyze from glycosidic linkages (α and β) is usually done using nuclear magnetic resonance (NMR) spectroscopy, selective oxidations or enzymatic hydrolysis. Because of its capacity to provide non-destructive analysis and intimate structural details of biomolecular interactions, NMR spectroscopy is one the most powerful physical-chemical tool to chemical polysaccharide determination (Cui, 2005). The principle of NMR spectroscopy involves the structural characterization of compounds by recording the interaction of radiofrequency (Rf) electromagnetic radiations with the nuclei of molecules placed in a strong magnetic field. Depending on the atomic number and mass number, there is an angular moment associated with the spin number. Most nuclei of biologic interest (e.g.. 1H, 13C, 15N, 19F and 31P) have two nuclear spin states +1/2 and -1/2. For carbohydrates the useful nuclei are 1H and 13C. NMR spectra generally contain all structural information from oligo and polysaccharides samples (Synytsya & Novak, 2013).

In a study carried out to characterize the *Oidiodendron truncatum* polysaccharides (GW), the spectroscopic chemical analysis, including NMR, showed polysaccharide chain

formed by (1 → 6) -α – D-glucopyranose bonds with a small amount of type branches (1 → 2) - α-D-glucopyranose (Guo et al., 2013).

Biological activities of polysaccharides from fungal origin

Previous studies have already shown that among the various sources of polysaccharides, compounds found in microorganisms are the most promising source of bioactive. In addition, microbial organisms including fungi, yeasts and algae have the advantage availability, easy cultivation and their metabolites can be synthesized on industrial large-scale level by bioreactors in fermentation processes under controlled conditions (Sánchez; Montoya; Vargas, 2014).

Microbial polysaccharides are also industrially important substances and there are many scientific papers, reports, and patents on them in various fields. The current research on the biological activity of polysaccharides reveal a broad spectrum of therapeutic indications, witches relates to the anti-inflammatory, antitumor, hypoglycemic, immunomodulatory, antimicrobial, and antioxidant actions.

Table 1 shows a series of producing fungi and their biological activities of polysaccharides described in the literature.

Table 1. Producing fungi and their biological activities of polysaccharides.

Fungus name	Biological activity	References
Grifola frondosa, *Pleurotus*sp. *Monascuspurpureus*,*Lentinulaedodes*e *Trametes versicolor*	Antioxidant.	(Smith; Doyle & Murphy, 2015).
Tylopilusballouii	Anti-inflammatory and antioxidants.	(Lima et al., 2016)
Ganodermalucidum; Inonotusobliquus	Antidiabetic	(Xiao et al., 2017; (Wang et al., 2017).
*Lachnum*sp.	Anti-fatigue, hypoglycemic and hypolecemic.	(Surhio et al., 2017; Wang et al., 2017).
*Cordycepssinensis*e	Hepatoprotective effects	(Fan et al., 2018a; Fan et

Ganodermaatrum	(hepatic antioxidant, anti-apoptotic and anti-inflammatory activities) and protective effect on colon immune dysfunction	al., 2018b)
Flammulinavelutipes	Immunomodulatory	(Wang et al., 2018).
Rhizopusstolonifer	Antimicrobian	(Darwesh et al., 2018).
Fusarium sp.; *Cordycepsmilitaris*	Antitumor	(Salehi et al., 2018; Liu et al., 2019).
Polyporusumbellatus	Renoprotective effect	(Li et al., 2019)
Trichodermakanganensis	Anticancer and antioxidante	(Lu et al., 2019)
Rhodotorula mucilaginosa	Antinociceptive	(Valasques Junior et al, 2014)
MushroomPholiotanameko	Antinociceptive	(Abreu et al., 2019)
Sarcodonaspratus	Immunomodulatory	(Dan-Dan Wang et al., 2018)

Source: Authors, (2019).

Microbial polysaccharides show favorable chemical, physical, rheological, and structural characteristics. They are biodegradable, non-toxic and withstand extreme conditions, remaining active when exposed to temperatures, pH and salinity variations. Furthermore, are highly available, and often of relatively low cost. Those advantages result in industrial predominant use of microbial polysaccharides rather than others (Jindal & Khattar, 2018).

Currently, a large number of natural polysaccharides have been reported having interesting properties that render them suitable for use as active drug, excipients, drug delivery agents or biomaterials in the pharmaceutical industry. Despite the multitude of fungi able to produce polysaccharides, very few have become a commodity or at least are produced at a scale that is economically relevant, mainly because of their production costs due to the difficulties in separating and purifying them. However, numerous studies have been performed to separate, isolate and make fungal polysaccharide production cost effective in order to achieve bigger markets (Yan et al. 2014; Yu et al, 2017). In this sense, numerous

chemical approaches have been pursued to improve the polysaccharide's pharmacological actions to leverage its commercialization.

Numerous studies have been carried out and the role of polysaccharides in antinociception and immunomodulation is increasingly consolidated. In a literature review presented in Tables 1, it can be seen that polysaccharides from different sources have great antinociceptive and immunomodulatory potential, which justifies the use of the animal model to study the antinociceptive and immunomodulator potential from filamentous fungi polysaccharides.

4. Conclusion

Polysaccharides extracted from the filamentous fungal cell wall have been produced and isolated in large microbial diversity together with the broad spectrum of compounds that show unlimited perspectives for the discovery of new applications with potential in nutraceuticals, as well as pharmaceuticals or functional foods.

These natural polymers present an almost infinite range of composition, structure and physicochemical properties, resulting them promising features and bioactivities such as antimicrobial, immunomodulating, hypoglycemic or anticancer activities among others.

Polysaccharide chemical characterization is important for structural detailing of the monosaccharide composition, type of bond, molecular size which has a great influence on biological activity. Therefore, the study of chemical characterization, extraction methods, and biological activity would result in an expansion in the commercialization and medical utilization of fungal polysaccharides extracted from the filamentous fungal cell wall.

Through this compilation, it is possible to infer that new studies using filamentous fungi are fundamental for the discovery of new treatments for diseases highlighted in the text.

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