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Review

Occurrence and possible roles of polysaccharides in fungi and their influence on the development of new technologies

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ABSTRACT

The article summarizes the roles of polysaccharides in the biology of fungi and their relationship in the development of new technologies. The comparative approach between the evolution of fungi and the chemistry of glycobiology elucidated relevant aspects about the role of polysaccharides in fungi. Also, based on the knowledge of fungal glycobiology, it was possible to address the development of new technologies, such as the production of new anti-tumor drugs, vaccines, biomaterials, and applications in the field of robotics. We conclude that polysaccharides activate pathways of apoptosis, secretion of pro-inflammatory substances, and macrophage, inducing anticancer activity. Also, the activation of the immune system, which opens the way for the production of vaccines. The development of biomaterials and parts for robotics is a promising and little-explored field. Finally, the article is multidisciplinary, with a different and integrated approach to the role of nature in the sustainable development of new technologies.

1. Introduction

Understanding the fungal glycobiology will contribute to the development of numerous technologies. Glycobiology is the science that studies the structure, biosynthesis, and biology of saccharides that are widely distributed in nature (Varki, 2017). It has been found that saccharides come together to form numerous network connections, known as glycosidic bonds. The combination of numerous saccharide residues form increasingly complex structures, the polysaccharides (Varki, 2017). Several types of polysaccharides are found in nature, and glycoconjugates such as glycoproteins, proteoglycans, and glycolipids are common. Polysaccharides are part of the cell wall of fungi they are predominant. Polysaccharides and glycoconjugates have been shown to play prominent roles in the cellular environment. These biopolymers act on cell-cell interactions, due to the presence on the cell surface of several glycan-binding receptors, and other carbohydrate biopolymers (Hong et al., 2020).

Biologically active polysaccharides from fungi have been extracted, purified, and characterized. In recent years, numerous studies (Deshpande, Wilkins, Packer, & Nevalainen, 2008; Eerde, Grahn, Winter, Goldstein, & Krengel, 2015; Tateno et al., 2012), contributed to the understanding of fungal glycobiology. It is clear; to the scientific community that polysaccharides and glycoconjugates obtained from fungi have relevant physicochemical and structural properties, useful for pharmacological, food applications, among others (Penk, Baumann, Huster, & Samsonov, 2019; Perduca et al., 2020). Although many studies have explored the potential of polysaccharides, few have committed to understanding what roles these polymers play on the biology of fungi. Also, how evolution has influenced the development of more specialized fungi in the production of polysaccharides. We believe that understanding the evolution of fungi may be the point that was missing between glycobiology and the development of new bioinspired technologies.

The evolutionary development of fungi is a little understood mystery; however, recent discoveries help us to elucidate a fascinating scenario for this mystery. Probably fungi evolved in the primitive seas, becoming a living evolutionary link, between animals and plants (Torruella et al., 2015). Modern studies (Fisher & Lang, 2016; Lewis, 2016; Veselská & Kolařík, 2015), indicate that fungi have evolved to be sexually promiscuous. That is, these microorganisms evolved with several different types of mating. The evolution of fungi and their relationship with fungal glycobiology will be intensively discussed in the next topics. However, it is now worth noting that sexual evolution was crucial for the development of complex fungi, specialized in producing polysaccharides sophisticated. Polysaccharides throughout the evolutionary process played prominent roles; we can even clarify that without the presence of these polymers the kingdom of fungi could not exist (Janouškovec et al., 2017).

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The modern world, with its technologies and scientific advances, increasingly seeks in nature inspiration for the construction of new bioinspired materials. You see, the understanding of fungal glycobiology has aroused intense interest from the scientific community. Recent studies (Chen, Wang, Nie, & Marcone, 2013; Rathore, Prasad, Kapri, Tiwari, & Sharma, 2019; Khan, Huang et al., 2018), with polysaccharides and glycoconjugates show incredible results in the development of antitumor drugs, in the development of vaccines and in the production of biomaterials such as hydrogels, airgel, nanoparticles and materials for cell regeneration. It is clear that new technologies based on polysaccharides will lead civilization to a new technological leap in the coming years.

Finally, based on the fungi glycobiology, it is possible to investigate the possibility of developing new materials for robotics. In fact, robotics-based on bioinspired materials have grown a lot in recent years (Hwang et al., 2019). Although the development of robotics-based on biological materials just be in the beginning, we believe that in a few years sophisticated robots will be possible. The development of new robots, with complex systems of artificial neural networks and bioinspired flying robots must necessarily require complex polymers (Ji et al., 2019; Murphy, 2019). Thus, polysaccharides such as chitin and others, obtained from fungi have attractive and versatile structures that can be applied in the development of new robots (Dolan, Varela, Mendez, Whyte, & ST, 2017).

Therefore, the objective of the article is to address in a contextualized way which the roles that polysaccharides play in the biology of fungi and how, based on the nature of glycobiology, new technologies can be developed. Thus, the article addresses relevant aspects of the evolution of fungi, bringing untouched a fascinating scenario about adaptation and survival. Then, the main roles of polysaccharides in the biology of fungi are addressed. Also, new technologies inspired by fungal glycobiology are explored and analyzed. Finally, the development of bioinspired robotic science is studied and fungal polysaccharides are placed as potential polymeric materials for applications in robotics.

2. Evolution and aspects related to fungal glycobiology

The evolution of fungi and their relationship to glycobiology helps to find answers to persistent questions. Some of these issues underlie our quest to understand the real role of evolution. Moreover, how genetic evolution was decisive for the formation of complex chemical structures of polysaccharides. Although the real answers to deep questions like these not fully elucidated, it is clear that after years of intense academic efforts, some hypotheses can be raised and evaluated within scientific limits.

The evolution of fungi begins in the remote past, probably between 760–1060 million years ago, in the Proterozoic eon. In this period of terrestrial history two important events occur together, that is, the evolution of heterotrophic beings like animals and autotrophs like plants (Heitman, 2015). In this context, fungi evolve as independent beings, but with characteristics very similar to plants and animals. At some point, the common ancestor probably started producing polysaccharides using new genetic information. While plants and animals have on the cell wall (cellulose and glycogen) consecutively, fungi have evolved to produce chitin and glucans on the cell wall as a new strategy for survival and adaptation (Heitman, 2015). A truly interesting strategy, which after millions of years of evolution has helped in the diversity of species, reproduction cycles, adaptation, and defense.

The exact nature of the common ancestor remains unknown, but studies conducted by several experts such as Umen and Heitman (2013) and Levin and King (2013), bring to light clues about their biology and the place of origin. We think that this common ancestor evolved in the primitive seas, unicellular, aquatic and probably mobile creature, driven by scourges or other mechanisms of locomotion. Although this common ancestor is simple, its cell biology is complex, as it already has supramolecular organelles such as cell nucleus, mitochondria, secretory devices, ribonucleic acid (RNA), and probably a sophisticated reproduction system (sexual and asexual reproduction). Thus, when we think about the evolution of fungi, it is recurrent to think about the evolution of reproductive systems, both correlated by evolutionary biology. Therefore, the sexual evolution of fungi and their relationship with glycobiology takes us to a cell in the primitive seas, that is, sex evolved in the water, involving specialized swimming cells (Umen & Heitman, 2013).

Sex first evolved in the oceans, this involved gradual changes in the number of pairs of homologous chromosomes (chromosomes that have information for the same genes and are the same size). That is relevant changes in ploidy and the cell division system, more specifically in meiosis, the process in which a cell has its number of chromosomes reduced by half, given that the nature involved in these types of cellular processes is preserved in modern eukaryotes. Although cell maturation processes (cell-cell and nuclear-nuclear fusion) are essential and play important roles in the sexual reproduction of modern organisms, we believe that in the past, in primitive oceans, replication processes were followed by meiosis, with gradual changes in ploidy (Morran, Schmidt, Gelarden, Parrish, & Lively, 2011; Vergara, Lively, King, & Jokela, 2013).

The reader must be wondering what is the relationship between the evolution of sex and the glycobiology of fungi. In addition, how to understand primitive aspects helps to build solid information on how to apply polysaccharides. Well, it is worth clarifying to the reader that the evolution of sex was not only decisive for the genetic diversification of fungi but it was also crucial in expanding the use of polysaccharides by these microorganisms. Fungi initially evolved in the primitive seas, using chitin as the main polysaccharide of the cell wall, as well as arthropods. With millions of years of evolution, these organisms invaded the mainland, adapting to a new ecological reality. The need for adaptation led fungi to improve their polysaccharide base, so new polysaccharides were emerging, such as glucans (Umen & Heitman, 2013).

Fungi and reproduction mechanisms have evolved; however, it seems that these organisms are a living link between animals and plants, mainly because they have similarities with both. Although the phylogenetic aspects show the direct relationship between fungi, plants, and animals, the type of reproduction shows significant differences between these kingdoms. Animals and humans have a sexual reproduction system, where sex chromosomes determine gender. In these beings, the genes are drastically different concerning size, known as heteromorphic sex chromosomes. Although this is a widely diversified feature in many living organisms, exceptions do exist. In some species of plants like Papaya and fish like Medaka, the sex chromosomes that determine and specify the gender are the same size, known as homomorphic sex chromosomes (Myosho et al., 2012).

As for fungi, it is evident that they have evolved to be sexually promiscuous. It means that fungi have literally thousands of types of mating. Relatively few fungi have large sex chromosomes; some examples already studied include *Neurospora* and *Microbotryum* (Ellison et al., 2011; Whittle, Votintseva, Ridout, & Filatov, 2015). Most fungi have small regions of chromosomes related to sexual life, as observed for the yeast *S. cerevisiae*. Most fungi have an exotic sex life, with various types of mating. In fact, two locations known as loci A and B MAT, located on sex chromosomes, stimulate homeotic genes, that is, regulatory genes that direct the development of certain segments or structures in the body, while B MAT controls the production of pheromones. With the possibility of countless types of mating, most sexual encounters in nature must produce a fertile progeny (Kües, 2015).

After many attempts to understand the complexity associated with fungi sex life, it is clear that bipolar mating is an ancestral state. Studies with fungi of species such as *Ascomycota*, and *Zygomycota*, primitive fungi indicate the predominance of bipolar mating (James, 2015). Therefore, the tetrapolar configuration is a derived state and more

adapted to the higher fungi, more evolved from the Basidiomycota branch as species of genus *Cryptococcus spp* (James, 2015).

The fungi of the Basidiomycota branch include organisms that produce spores in a rod-shaped structure called basidium (basidiomycetes); the mycelium is septate, divided by cell walls, with perforated septa or transverse walls. Basidiomycota branch fungi include more than 2500 known species, among which are edible mushrooms and medicinal (Gabriel & Švec, 2017). The fungi of this branch are complex structures organized in hyphae, specialized cells, which contain chitin and glucans in the cell wall. Fungi from this branch have polysaccharides relevant to society, with biological properties widely studied. It is worth mentioning that the process of evolution from the type of bipolar to tetrapolar reproduction is linked to relevant changes in the production of polysaccharides by fungi. The evolution of the type of mating forced changes in the entire glycobiology of fungi, leading to considerable changes in the biology, biochemistry, and lifestyle of these organisms (Halbwachs & Simmel, 2018).

Studies such as Phadke, Feretzaki, and Heitman (2013), suggest that gradual changes in the type of mating contributed to changes in the morphology of primitive single-celled species for hypha-producing organisms. The evolutionary leap was accompanied by important changes in the production of polysaccharides. Now, fungi would have the biological tools to produce polysaccharides that meet their needs in the face of a constantly changing world. For example, the hyphae produced, now function as growth and multiplication networks, place of food capture, the base for the formation of fruiting bodies, and connections with other fungi. It is evident that the polysaccharides present in hyphae have adapted and evolved along with fungi, these organic compounds function as a polymeric network of multitasking (Raudaskoski, 2015). In the next topic, will discuss more clearly how fungi use polysaccharides, and how evolutionary advances can help in the development of new technologies to assist humanity.

3. What roles do polysaccharides play in the biology of fungi?

The polysaccharides present in fungi comprise complex structures of monosaccharide linked by glycosidic bonds. Recent studies (Gao et al., 2020; Sun, Shi, Zheng, Nie, & Xu, 2019; Wang & Guo, 2020), show that fungi, be them whether simple as yeast or complex like mushrooms have widely distributed polysaccharides. The biology of fungi is modeled by the presence of polysaccharides, in particular chitin and glucans. These polysaccharides, together with others, come together through intermolecular bonds forming a compact polymeric structure, which makes up the entire cell wall, responsible for interactions with the external environment. Therefore, polysaccharides play a central role in the discussion of fungi biology and biochemistry (Kieliszek et al., 2017). From now on, we will address the roles that polysaccharides play in the biology of fungi. The lessons learned will be used to build valid arguments that contribute to the development of new technologies.

3.1. Polysaccharides modify the rheological properties

Fungi produce several types of polysaccharides according to biological needs and in response to external and internal conditions. Among polymers, hyper-branched polysaccharides have received special attention in recent years, mainly due to their physical and chemical properties. Polysaccharides have varied properties, depending on the place of origin and the strain studied. When necessary, fungi produce and excrete extracellular polysaccharides (exopolysaccharides). These polysaccharides in general analysis, act as important modifiers of viscosity, both in wet and dry environments. Also, polymers have interesting chemical characteristics, such as hyper-branching, varied chemical groups, and different molecular weights. Branches assist polysaccharides during molecular interactions, promoting various types of chemical bonds, from simple bonds to the most complex cross-bonds (Chen et al., 2019).

The hyper-branched polysaccharides produced by fungi aim to modify the physical and chemical conditions of the environment in which they live. You see, fungi need to move and they do it through hyphae that grow and expand. The movement is driven by the production of hyper-branched polysaccharides, which help to reduce friction with the substrate (Finlay et al., 2009; Rosling et al., 2009). The advancement of studies with hyper-branched polysaccharides, conducted by specialists, shows that these polymers have interesting properties such as, high density, large spatial cavities, and several terminal functional groups, which differentiate them from other polymers. Also, they are biodegradable, biocompatible and modifiers of rheological properties (Sovrani, de Jesus, Simas-Tosin, Smiderle, & Iacomini, 2017).

The vast majority of polysaccharides produced by fungi have interesting rheological properties, and these properties are directly linked to the structural characteristics, monosaccharide composition, and molecular weight of these biopolymers. The viscosity of a biopolymer as polysaccharides is directly related to intrinsic aspects of the molecules, such as size, shape, and conformations that they adopt in the solvent. Polysaccharides can twist their chemical bonds around their axis; this flexibility provides a strong entropic impulse, capable of overcoming energy barriers, inducing the chain to approach the disordered or random states of the coil. Although polysaccharides in aqueous solution are found in coil states, usually with helical segments, in nature due to the entropic states of changes in temperature, pH, humidity, and movement, other molecular states can be found (Sovrani et al., 2017).

Khan, Gani, Masoodi, Mushtaq, and Naik (2017), demonstrated that β-glucan polysaccharides extracted from edible mushrooms *Agaricus bisporus*, *Pleurotus ostreatus* and *Coprinus attrimentarius* have interesting rheological properties. The authors demonstrate that β-glucans with different molecular weights have different rheological properties. Also, the length of the linear chain increased the viscosity of aqueous solutions with the polysaccharides. The presence of a β-D-glucan-(1 → 3)-linked, substituted at O-6 by β-D-Glcp or (1 → 6)-linked β-D-Glcp side chains in the edible mushroom, *Pholiota nameko* assigns relevant rheological properties. It has been shown that this biopolymer produces a type of gel in aqueous solution, highly stable over various temperature ranges. As reported, this polysaccharide has properties of a thickening agent or gelling agents, which contributes to modifying the rheological properties. Soluble dietary fibers from mushroom residues *Lentinula edodes* (Berk.) Pegler also have relevant rheological properties. The hyphae present in the residues after the cultivation of these mushrooms have fractions of polysaccharides with various molecular weights. Four fractions with the following molecular weights (6. 43×10^7 Da, 6. 25×10^6 Da, 1. 58×10^5 Da and 2. 50×10^4 Da, respectively), presented different rheological properties. It was demonstrated that the higher average molecular weight and the degree of branching, the better elasticity results were obtained (Xue et al., 2019).

Finally, in a recently published article, Wang, Yin, Huang, and Nie (2020), demonstrated that polysaccharides of the fruit body of the mushroom *Dictyophora rubrovolvata* have rheological properties. This mushroom is known to produce a greenish-brown sludge, rich in polysaccharides, proteins and volatile compounds, which attracts flies and other insects that eat the spores and disperse them. The authors isolated a new polysaccharide, which consisted of glucose, and contained main sugar residues including →4)-α-Glcp-(1→, →3,6)-β-Glcp-(1→, →3)-β-Glcp-(1→ and α/β-Glcp-(1 →. The polysaccharide showed intrinsic viscosity, semicrystalline characteristics, microspherical shapes, and fibrous filaments. The polysaccharide showed characteristics of a pseudoplastic fluid, with high viscosity, exhibiting excellent heat resistance, strong gel stability, and gelling properties.

Fungi use interesting strategies to get food, and in some of these strategies, polysaccharides function as true chemical traps. The polysaccharides are present during the degradation of lignocellulosic material, helping in the production, displacement, and activity of enzymes.

In cases that are more complex, they help to maintain humidity and pH. The production of exopolysaccharides contributes to the maintenance of a humid environment, conducive to obtaining nutrients, growth, and reproduction (Donot, Fontana, Baccou, & Schorr-Galindo, 2012). The viscosity observed in some pileus, or as they are popularly known (mushroom cap), plays a crucial role in the control and spread of spores and in the production of pigments. Mushrooms like Boletus have the top of the pileus quite slimy and moist. Polysaccharides excreted out of the pileus control the amount of water available, preventing the reproductive part from drying out (Zhang, Hu et al., 2018).

3.2. Cellular communication and transmission of chemical signals

The patterns of cell development and morphogenesis for the production of biological structures and tissues are closely linked to the polysaccharides of the fungal cell wall. Therefore, the way the cell wall is synthesized determines the rules for the morphology of fungi. As we know, polysaccharides such as chitin and glucans present in the fungal cell wall form extensive networks of compact and uniform fibers, which during cell division and growth of fungi are used as channels of communication and cell signaling (Phillips et al., 2019). As an example, we have the chitin microfibrils, complex polymeric structures arranged in the cell wall of the fungi. Chitin microfibrils play important roles in the growth of fungi and in the transmission of chemical signals to other cells (Riquelme & Bartnicki-García, 2008).

Polysaccharides play an important role in the transmission of information for various biological processes, such as spore germination, colony morphogenesis, sexual development, dimorphism, in defense, and adaptation systems. These biopolymers act mainly as molecular receptors and connectors of proteins and enzymes at the cellular level. According to the study by Fleißner and Herzog (2016), polysaccharides play a crucial role as receptors for chemical information during fusion in filamentous fungi. Filamentous fungi like *Neurospora crassa* and many other species of ascomycetes, during the formation of their colonies, the established hyphae initiate the fusion process for the development of the mycelium. During this process, two partners have some type of communication in common *via* the emission and reception of chemical signals. In recent years, numerous molecular factors have been identified, such as polysaccharides, proteins, enzymes, and metal ions, which act as mediators of this cellular behavior. Also, polysaccharides have been identified as conserved signal transmission pathways, that is, they have been present in fungi since the beginning of their evolution (Hickey, Jacobson, Read, & Glass, 2002; Roca, Arlt, Jeffree, & Read, 2005).

Analysis of the subcellular dynamics related to essential proteins for the fusion of hyphae demonstrated that the protein kinase MAK-2 activated by mitogen and the SO protein are present in the cell wall of the fungi, mainly in the tips of the growing cells. As already demonstrated, the cell wall of the fungi has a complex system of interwoven networks of various types of polysaccharides. These biopolymers function as connectors between signaling proteins and signal receiving proteins below the cell wall (in the cytosol) (Read, Lichius, Shoji, & Goryachev, 2009). The complex hyphae fusion system requires coordinated and alternate recruitment of proteins and polysaccharides in two partner cells, responsible for sending and receiving signals mediated mainly *via* the MAK-2 pathway. (Dettmann, Heilig, Valerius, Ludwig, & Seiler, 2014; Jonkers et al., 2014). This extraordinary cellular behavior is guided by a sophisticated system of signal processing machines, which involve adjustments and backups. Therefore, within the context, polysaccharides are essential, especially as receptors for water molecules, which assist in the movement and transport of ions such as Ca^{2+} during cellular communication (Palma-Guerrero et al., 2013).

Although the understanding of the role of polysaccharides during hypha fusion is not yet fully understood, we know that these biopolymers, together with other organic molecules such as peptide pheromones and associations of glycoproteins with other biomolecules, are responsible for part of the cellular communication between hyphae (Leeder, Palma-Guerrero, & Glass, 2011). Furthermore, the current understanding on the subject shows that although some molecules such as cAMP (second messenger), are directly related to the cellular communication pathways in fungi, this is not the only pathway (Simonin, Palma-Guerrero, Fricker, & Glass, 2012). Other fungi use other self-signaling molecules, which include sesquiterpene alcohol, farnesol, and phenylethanoid tyrosol, as identified for the pathogenic dimorphic yeast *Candida albicans* (Chen, Fujita, Feng, Clardy, & Fink, 2004; Hornby et al., 2001). These examples illustrated that the cell fusion signal in fungi involves several molecules, and its identification is hampered mainly by the unreliability of the tests, which, although they illuminate a part of the phenomena, does not explain its complexity.

Polysaccharides are essential for hyphae of mycorrhizal fungi, where they play an important role in cellular communication. Although they are in compact structures or a network system, these biopolymers are fundamentally dynamic. Hyphae rich in structural polysaccharides move towards the roots of plants, where they begin a complex process of exploiting resources to obtain energy (Whiteside et al., 2019). In this context, polysaccharides still participate in the regulation and targeted transport of phosphorus and other nutrients, using molecular network systems. The molecular network system consists of a complex of millions of different polysaccharides joined together in a network, as if they were a cable with millions of small wires. In this case, polysaccharides are the threads and act as bridges between molecules, making simple and highly dynamic chemical bonds. Cellular communication is coordinated by molecular factors such as enzymes, proteins, and metal ions, but polysaccharides function as important receptors and cooking networks between the signal and the target (Whiteside et al., 2019).

Pathogenic fungi have also developed similar cellular communication strategies. Typically, pathogenic fungi use infection structures, composed of morphologies, complex chemical systems and highly specialized cells produced from conidia on the host's surface to obtain entry into them. Although the attack systems are coordinated by a complex cellular system, we know that polysaccharides present in the cell wall act as receptors for molecules in the host, opening the way for the entrance of pathogenic hyphae. When hyphae enter the host, the processes of reproduction and replication of genetic material begin (Kou & Naqvi, 2016).

The chemical signals and stimuli transported between cells need several components interlinked in a chain. The proper functioning of a network for the transmission of chemical information requires components that bridge the signal and the target. Thus, polysaccharides organized in a complex polymeric network work as a basis for the transmission of chemical signals in fungi (Apetrei et al., 2019). Although it is not fully understood how a polymeric network of polysaccharides is used for the transmission of chemical signals, we can say that they play a crucial role (Pawar & Trivedi, 2019). The need for other complementary platforms for the transmission of chemical information is evident. Perhaps the presence of molecular conjugates such as glycoproteins and polysaccharides associated with metals act as important connectors in this great puzzle (Kües, Khonsuntia, & Subba, 2018).

Fungal exudates, excreted out of the cellular environment, interestingly, provide us with good indications about the role of polysaccharides in the transmission of chemical information. The excreted polysaccharides carry with them several organic compounds such as hormones, pheromones, and pigments (Francia et al., 2011; Sun, Bonfante, & Tang, 2015). When a fly or other insect, attracted by the scents of fungus such as *Mutinus caninus*, *Phalus indusiatus* and *Clathrus archeri*, rests on top of its pileus, polysaccharide secretions and fungus spores cover its paws. Polysaccharide secretion protects spores from possible dangers and still acts as a basis for sexual pheromones to stick together (Boniface, 2020).

3.3. Cell protection and resistance

Cell-wall polysaccharides provide protection and resistance to hyphae, so fungi are distributed in all ecological niches, even in the most hostile environments on earth (Trygg, Beltrame, & Yang, 2019). Hyphae act in fixing nutrients, as well as in reproduction and extracellular digestion. All of these activities require solid, resistant, and modelable support, capable of adapting to the conditions imposed. The presence of polysaccharides in hyphae helps to improve mechanical strength and thus protect cells from external weathering (Halbwachs & Simmel, 2018).

When fungi grow, as in the case of mushrooms that produce fruiting bodies above ground, the polymeric network of hyphae acts as a barrier against mechanical damage. During their development, fungi must deal with physical weathering, attacks by predators, and contaminants (Bleackley et al., 2019). The presence of a resistant polymeric network helps, minimizing the side effects of weathering. Also, fungi use the polymeric network to release chemical substances that act as antibiotics and antifungals, reducing the risk of the progeny loss, contributing to the development and reproduction of fungi (Venkatesagowda, 2019).

In the cellular environment, the polysaccharides present in the inner and outer wall act on several fronts. First, polysaccharides act to protect cells from damage, such as those caused by water loss, changes in pH, and osmotic changes. Also, polysaccharides act as a barrier against attacks by contaminating agents and the entry of toxic substances (Ruytinx et al., 2020). Polysaccharides, such as glucans, have glucose monomers in their structure joined by glycosidic bonds and several free vicinal hydroxyl groups. Mushrooms such as *Pleurotus ostreatus*, produce several glucans, especially pleuran, a type of β-1,3- and β-1,6-glucan (Synytsya et al., 2009). The free hydroxyl groups can bind to water molecules through a hydrogen bridge, thus reducing the loss of water to the environment. The chemical bond between polysaccharides and water molecules is thermodynamically favored, contributing to the maintenance of osmotic balance in the cellular environment. Also, fungi produce extracellular polysaccharides, as in the example of the fungus *Lignosus rhinocerus* which produces the polysaccharide (1,3) -β-D-glucan responding to external stimuli (Usuldin et al., 2020). For example, when pH changes occur in the extracellular medium, as shown in the study with the fungus *Ganoderma lucidum* in submerged fermentation, the fungus increases the production of polysaccharides, which immediately retain water molecules, reducing free protons, and therefore controlling the pH (Hassan et al., 2019). Thus, the first defense barrier of fungal cells is linked to the presence of receptor polysaccharides. Second, cell wall polysaccharides can bind to metals and other chemical substances, which confer new properties. Among these properties, strength, structural flexibility, porosity and chemical-thermal stability (Nadar, Vaidya, Maurya, & Rathod, 2019; Ruytinx et al., 2020).

4. Development of new technologies with polysaccharides

The development of new technologies will no doubt drive considerable advances in the planning of new antitumor and antiviral drugs. Natural products play an important role in the current scenario of research and advances in drug development. In fact, since the beginning of humankind, we have explored nature to find cure for diseases. In this context, popular knowledge helped to transform the modern world, as it contributed relevant information that helped in the search for new drugs.

The development of a relevant product, be it a drug, vaccine, or even a biomaterial, is a complex process, which requires financial and human resources. From the beginning of the idea to the final stage, these products demand considerable time, high cost and strict control of the processes. Although the development of new technologies can be expensive, the final product will undoubtedly contribute to the scientific and social advancement of humanity. Therefore, the use of financial resources and the implementation of educational policies focused on graduate programs, with the objective of training researchers engaged in the rational development of new technologies, undoubtedly needs to move forward. In this context, the next subtopics addressed the development of technologies used for the production of drugs, vaccines, and biomaterials with polysaccharides obtained from fungi.

4.1. Production of antitumor drugs

Cancer covers several stages of medical complications, in a short time, and exposes patients to considerable limitations of the immune system. Cancer is universal; it does not choose patients, race or creed (Bode & Dong, 2000). In the world, more than 8.2 million deaths in recent years, and it has increased considerably, mainly associated with several risk factors such as sedentary lifestyle, autoimmune diseases, smoking, exposure to toxic substances and consumption of fatty foods (Saner et al., 2019; Steck & Murphy, 2019).

The cells function like true living machines, highly organized, and structured. The cells have complex systems, including small organelles responsible for various physiological functions. Inside the cells, an industrial line for the production of genetic material operates 24 h a day, without interruption, intending to produce information for the synthesis of proteins, as well as the transmission of genetic information to the next generation. In certain situations, not yet fully understood, some cells are defective (mutations) in the genetic information transmission system. These changes initiate a cycle of production of genetic material in an uncontrolled way, producing cells defective or neoplasms (Fane & Weeraratna, 2019).

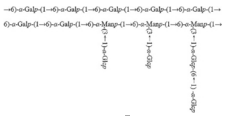
Neoplasms are able to reproduce, transmitting the wrong genetic information for the next generation, so cancer cells spread throughout the body, attacking organs and the lymphatic system. Initially, the innate immune system initiates an attack against defective cells, using chemical weapons such as cytokines, interleukins, and others (Shaked, 2019). Although the natural defense system is efficient, over time, and associated with the risk factors already mentioned, the system is less active. Therefore, due to the organism's low capacity to deal with minimal changes in cell production, cancer develops in the “shadows”, multiplies actively, and when the organism perceives the contamination, sometimes it is not able to reverse the situation (Goldberg, 2019; Harjes, 2019).

Polysaccharides from various fungi, especially mushrooms, show the potential to be used as antitumor drugs, as shown in the Table 1. Initially, three recently published bibliographic review articles will be addressed, to address, in general, the main mushroom polysaccharides and their bioactivities. Then, individual articles will be addressed, with an emphasis on the structure-bioactivity relationship and its mechanisms. In the review article proposed by Ruthes, Smiderle, and Iacomini (2015)), demonstrate that edible mushroom D-glucans are complex chemical structures. Currently, numerous types of glucans have been found, especially α-, β- and mixed D-glucans. The authors show that although glucans are simple in terms of monosaccharide composition (they contain only glucose), these polysaccharides are among the most complex in nature, mainly related to the diversity of chemical bonds, ramifications, and molecular weight. After evaluating numerous studies, it was clear that glucans have antitumor activity, mainly by activating the adaptive immune system, inhibiting the development of tumors, and reducing side effects.

In the review article proposed by Ruthes, Smiderle, and Iacomini (2016)), demonstrate that heteropolysaccharides obtained from mushrooms, especially from Basidiomycetes have relevant physicochemical properties such as varied monosaccharide composition, various types of bonds, anomeric configurations, ramifications, methylated groups, and acid monosaccharides. The authors demonstrated that in the last 12 years, a series of researches with these polymers revealed that they have important biological activities, especially anti-tumor.

In our recent work, we covered in a review article the

Table 1
Polysaccharides with antitumor potential, the main route of action, and considerations on the mechanisms of activity.

Source / name of the polysaccharide	Mechanism	Activity / cell line / animal model	Structure/ molecular weight (*Wb*)	Concluding remarks	References
Lentinus giganteus (LGPS)	Depolarization of the mitochondrial membrane	Cell viability. Cell line: HepG2.	 *Wb*: 1.547 × 10^5 Da	The polysaccharide increased the proportion of Ba / Bcl-2, promoted the release of cytochrome c in the cytoplasm, in addition to inhibiting Akt phosphorylation in HepG2 cells, inducing intrinsic mitochondrial apoptosis and PI3K / Akt signaling pathways.	(Tian, Zhao, Zeng, Zhang, & Zheng, 2016)
Armillaria mellea (AMP)	Depolarization of the mitochondrial membrane	Caspase 3 (c3) and caspase 9 (c9) activity after 2 h. Cell line: A549.	Glucan *Wb*: 4.6 × 10^5 Da	The polysaccharide induced an interruption of the cell cycle in the G0 / G1 phase, accompanied by an increase in apoptotic cells. It induced interruption of the mitochondrial membrane potential, leading to the release of cytochrome c by mitochondria and activation of caspase-3 and -9.	(Wu et al., 2012)
Trametes robiniophila (TRP)	Depolarization of the mitochondrial membrane	-Cell line: Human osteosarcoma cell (U-2 OS).	1,3,6- and 1,4-linked glucpyranosyl moieties, with 1-linked arabinofuranosyl and galactopyranosyl terminal at the O-3 position of 1,3,6-linked glucpyranosyl residues-	The polysaccharide increased the levels of the pro-apoptotic Bax protein and decreased the level of the anti-apoptotic Bcl-2 protein, increasing the Bax / Bcl-2 ratio and protein expression of caspase-9, caspase-3, and PARP.	(Zhao, Ma, Liu, Liu, & Wang, 2015)
Hirsutella sinensis (HSP-III)	Depolarization of the mitochondrial membrane	Cellular apoptosis. Cell line: lung cancer.	skeleton linked to β-glucan containing (1 → 3) and occasionally branched *Wb*: 513.89 kDa	The polysaccharide has a high molecular weight and significantly inhibited lung cancer growth. The apoptotic effects of HSP-III are triggered by the generation of reactive oxygen species (ROS).	(Liu, Xie, Sun, Meng, & Zhu, 2017)
Trametes robiniophil (W-NTRP)	Nitric oxide pathway	-Cell line: QBC939, Sk-ChA-1 and MZ-ChA-1.	Heteropolysaccharide.Galactose, arabinose, glucose. Relative molar ratio of 4.2: 2.5: 0.7 *Wb*: 2.5 × 10^4 Da	The polysaccharide activates macrophages and induces the production of nitric oxide (NO) through the positive regulation of the inducible activity of NO synthase (iNOS). In the three models evaluated, the polysaccharide showed a remarkable inhibitory effect against human cholangiocarcinoma cell lines.	(Sun et al., 2013)
Pleurotus ostreatus (WPOP-N1)	Nitric oxide pathway	–	–	The polysaccharide significantly inhibited tumor growth in mice bearing Sarcoma 180 tumor and markedly increased the level of TNF-α secretion in the serum, and increased NO secretion.	(Kong et al., 2014)
Trametes orientalis (TOP-2)	Immunomodulation	Serum levels of cytokine. Animal model: mice. Cell line: lung carcinoma.	Heteropolysaccharide. Galactose, glucose, mannose, and arabinose. Molar ratios of 5.79: 5.77: 3.45: 1 *Wb*: 63 kDa	The polysaccharide considerably increased the proliferation of splenocytes, significantly stimulated the phagocytotic function of macrophages, and markedly promoted the expression of serum cytokines.	(Zheng, Wang, & Li, 2015)
Boletus edulis (BEP)	Immunomodulation	TNF-α levels Animal model: mice. Cell line: kidney cancer.	Consisting of (1→6)-linked-α-D-glucopyranosyl, (1→2,6)-linked-α-D-galactopyranosyl, (1→6)-linked-α-D-galactopyranosyl, and (1→3)-linked-α-D-rhamnopyranosyl residues, which were branched at O-2 position of (1→2,6)-linked-α-D-galactopyranosyl residue with a single terminal (1→)-linked-α-L-arabinofuranosyl residue. *Wb*: 113.432 Da	The polysaccharide significantly increased the spleen and thymus indices, increased the proliferation of splenocytes, the activities of NK and CTL cells in the spleen, and promoted the secretion of cytokines IL-2 and TNF-α in mice with Renca tumor.	(Wang, Sun, Wu, Yang, & Tan, 2014)

polysaccharides of mushrooms of the genus *Pleurotus spp*. In the article, we demonstrate that mushrooms of this genus have numerous types of polysaccharides, especially glucans, and heteropolysaccharides. In addition to the physical-chemical and structural properties of these polymers, we address biological activities and their mechanisms. It evident that polysaccharides have antitumor activity by at least three different pathways. Therefore, the caspase and mitochondrial membrane depolarization pathways were addressed, *via* apoptosis and activation of the nitric oxide pathway. Finally, the article demonstrated that new technologies are being developed with these polysaccharides such as the production of selenized polysaccharides and vaccines (Barbosa, dos Santos Freitas, da Silva Martins, & de Carvalho Junior, 2019).

Studies, published since 1957, with the pioneering work of Byerrum and collaborators, showed that polysaccharides obtained from mushrooms have antitumor activity (Byerrum et al., 1957). After these pioneering studies, several studies reported that the polysaccharides obtained from the most varied fungi have antitumor activity. Also, the main avenues of activity and the relationship between structure and activity have been explored and major strides have been made. Today, we know that polysaccharides exert antimoral activity indirectly, that is, by activating defense cells and not by cytotoxic effects (Ruthes et al., 2016).

Polysaccharides obtained from fungi have several chemical structures that modify the immune response in different models of cell tests, *in vitro* and *in vivo*, against tumor cells. The main route of action is related to factors of the immune system, mainly those related to the modification of the innate immune response. Therefore, polysaccharides exert antitumor activity by accelerating the natural defense pathways, with the activation of effector cells, such as macrophages, T lymphocytes, B lymphocytes, cytotoxic T lymphocytes, and natural killer cells. These cells immediately initiate an active immune response, with the release of cytokines, such as TNFα, IFN-c, and IL-1β. The complex of released immunological reactions has antiproliferative properties, leading to a punctual cellular response, thus initiating processes of apoptosis and differentiation in tumor cells, by means of nitrogen secretion reactive, oxygen intermediates, and interleukins (Barbosa et al., 2019).

A homogeneous polysaccharide fraction, characterized as non-starch glucan (consisted of a backbone structure of (1→4)-linked α-D-glucopyranosyl residues substituted at the O-6 position with α-D-glucopyranosyl branches), with molecular weight of 1.617×10^7 g / mol, inhibits tumor growth in an *in vivo* model. The polysaccharide stimulates the production of nitric oxide and tumor necrosis factor-α by triggering phosphorylation of nitrogen-activated protein kinases and nuclear translocation of nuclear factor kappa B p65 in RAW 264.7 macrophage cells. Also, when the polysaccharide was used in conjunction with Fluorouracil, better results were obtained, with positive effects in reducing the cancerous tumor (Wei et al., 2018).

Meanwhile, the treatment of mice with cancer cells (CT26 cells), with a new polysaccharide isolated from the fungus *Trichoderma kanganensis*, reduced the size of tumors and oxidative processes induced by hydrogen peroxide. After the purification process, the polysaccharide was characterized as being a →6-α-D-Galp-1→5-β-D-Manf-1→5,6-β-D-Manf-1→5,6-β-D-Manf-1→, and the side chains are α-D-Glcp-1→4-α-D-Glcp-1→, β-D-Galf-1→, and α-D-Glcp-1→ (Lu et al., 2019). Another exopolysaccharide, now obtained from the fungus *Lachnum sp* (LEP-2a), was characterized as being a galactomannan. With a backbone structure composed of α-(1 → 3,4)-D-Manp, α-(1 → 2)-D-Manp, α-(1 → 2,6)-D-Manp and β-(1 → 3)-D-Galp residues, which was substituted at O-3, O-4, O-2, O-6 by branches, with molecular weight of 2.3×10^4 Da (Jing, Zong, Li, Surhio, & Ye, 2016). This exopolysaccharide has an anti-tumor effect on H22 cells *in vitro*. Also, the combination with cyclophosphamide, a potent chemotherapy, improved antimoral activity, through a synergistic effect. The synergistic effect is reported to be mediated *via* the death receptor and mitochondrial apoptosis pathway, and antiangiogenic activity is mediated by the activation of an immune response, reducing the side effects of cyclophosphamide therapy (Zong et al., 2018).

The water-soluble exopolysaccharide, activated by the fungus *Rhodotorula mucilaginosa* CICC 33,013, has an anti-carcinoma and antioxidant effect. The authors identified to be a highly branched polysaccharide with a backbone of (1 → 3)-linked Gal with Man, Gal, and Ara terminals. The branches were identified as (1 → 2)-linked Glc, (1 → 4)-linked Man, (1 → 3)-linked Glc, (1 → 4,6)-linked Man, and (1 → 2,3,4)-linked Ara, with molecular weight of 7.125×10^6 Da. Exopolysaccharide reduces the development of tumor cells by inducing dose and time-dependent cell cycle arrest in the G1 / S phase (Ma et al., 2018). Macromolecular structures such as α-glucan from fruiting bodies of *Volvariella volvacea* activating RAW264. 7 macrophages through MAPKs pathway. The polysaccharide stimulated the release and expression of mRNA, NO, TNF-α, IL-6, and IL-1β, modulating the immune response through the MAPK signaling pathway. The modular potential of this polysaccharide in macrophage cells may be useful in the treatment of cancer patients (Cui et al., 2020).

The structural characteristics, molecular weight, branching size, and conformation affect the physical-chemical and biological characteristics of the polysaccharides. Understanding the relationship between chemical structure and anticancer activity is critical to the development of more efficient drugs. Also, synergism between different polysaccharides may be an option for anti-cancer cocktails. As demonstrated by Fan et al. (2018), Combined fungal polysaccharides of *Cordyceps sinensis* and *Ganoderma atrum* improve the immune response by T cell-specific regulatory T cell (Treg) Foxp3 secretion, as well as the significant CP-induced elevation of CP, interleukin (IL) -17 and IL-21.

Recent studies (Guo, Meng, Duan, Feng, & Wang, 2019; Meng, Liang, & Luo, 2016; Zhang, Nie et al., 2018), have shown that triple-stranded and helical-chain polysaccharides, although not a general rule, have a stronger anticancer capacity than those in coils or random lines. he water-soluble polysaccharide, obtained from the mushroom *Agaricus blazei*, after the purification process, consisting of (1 → 6)-linked-α-D-galactopyranosyl and (1 → 2,6)-linked-α-D-glucopyranosyl, which was branched with one single terminal (1→)-α-D-glucopyranosyl at the O-2 position of (1 → 2,6)-linked-α-D-glucopyranosyl, with molecular weight of 3.9×10^2 kDa. It was demonstrated that the polysaccharide chain was a triple helix when in aqueous solution, this type of conformation improves the solubility and the interaction between the polysaccharide and cellular receptors, improving the anticancer capacity (Liu et al., 2011).

Another work explored the modulating activity of polysaccharide fractions of the fungus *Cordyceps militaris* (CPM), obtained by hot water. It was shown that one of the fractions was a high molecular weight polysaccharide with random coil conformation. This fraction showed better modulation activities, activating macrophages, and regulating the production of antitumor substances. (Lee et al., 2010). Two polysaccharides obtained from the mushroom *Hericium erinaceuspor*, after purification and characterization, it was reported that one of the fractions has low molecular weight with a triple-helix conformation of the β-1,3-branched-β-1,2-mannan type. The same fraction characterized showed modulating activity of immune response by the activation of pathways such as nitric oxide (NO) and expression of cytokines (IL-1β and TNF-α), important to modulate responses against cancer cells (Lee, Cho, & Hong, 2009). Although the results indicate that helical chain conformation has a direct relationship with anticancer activity, the exact mechanisms and the effect of interactions remain unknown.

Another relevant parameter for understanding the interaction of polysaccharides with cellular receptors and antitumor potential is the molecular weight. Some works (He et al., 2020; Maity et al., 2019), evaluated the influence of the molecular weight of some polysaccharides, especially glucans. These studies showed that high molecular weight glucans triggered more efficient antitumor effects when compared to low molecular weight glucans. Based on these studies, it

was believed that the higher the molecular weight of glucans, the greater the chances of these biopolymers to interact with cell membrane receptors and proteins. While it is true that some high molecular weight glucans have better antitumor activity, this principle is not true for all polysaccharides. For example, the antitumor activity of mushroom polysaccharides such as (1 → 3) -α-glucuronoxylomannans is not dependent on molecular weight. It has been shown that lower molecular weight fractions may have higher rates of antitumor activity when compared to higher molecular weight fractions (Zhang, Kong, Fang, Nishinari, & Phillips, 2013). Other polysaccharides, however, have bounded tracks to exercise anticancer activity. For example, certain schizophyllan of 450 KDa, exhibit antitumor activity. However, others of low molecular weight, in the range between 100–104 kDa, also have antitumor activity. These biopolymers have a triple helix structure, as previously reported; improve anticancer activity (Zhang et al., 2013). Therefore, regardless of the molecular weight, these biopolymers have variable antitumor activity and can be used in the development of potential anticancer drugs.

In general, but not a consensus, it is believed based on the results of several works (Khan, Gani, Khanday, & Masoodi, 2018; Li & Cheung, 2019; Zhu et al., 2012), that high molecular polysaccharides have more efficient anticancer mechanisms than low molecular weight ones. However, as previously listed, low molecular weight polysaccharides and others in well-defined ranges have anticancer activity. At the moment, the research community in carbohydrate chemistry and pharmacology there is no consensus on aspects of the influence of molecular weight. More research is needed to be focused on randomized studies, which seek to understand the relationship between molecular weight and the mechanisms of structural conformations, and how this can affect the binding of these biopolymers to receptors and proteins present in the cell wall, thereby inducing activity anticancer.

4.2. Platforms for vaccine production

The development of vaccines has undoubtedly contributed to the survival of modern society. Vaccines have helped humanity to prevent diseases such as flu, smallpox, cholera, bubonic plague, polio, hepatitis A, rabies, among many others (Schrager, Vekemens, Drager, Lewinsohn, & Olesen, 2020). At present, with outbreaks of new diseases like COVID-19, the role of vaccines and their importance are again on the agenda of numerous researches. Research groups distributed around the world focus their efforts on developing vaccines against various diseases, especially viral ones. There are several methods of producing vaccines such as use dead or inactive microorganisms, or purified substances derived from them. Although vaccine production technology is quite advanced, the need for new production platforms is a reality (Mazur et al., 2018).

Currently, there are several types of vaccines on the market, mainly those that use attenuated and inactive microorganisms, however, these bases are in doubt, mainly due to the risk of contamination. Other more interesting bases for vaccine development include peptides, carbohydrates, and antigens (Lindsey, Armitage, Kampmann, & de Silva, 2019). In this context, polysaccharides obtained from fungi, especially those that have immunomodulatory and antioxidant activities, are platforms with potential for vaccine production. The use of fungi for the production of polysaccharides consists of a low-cost source, ideal for large-scale production. Polysaccharides would be produced in various ways, but the technology of submerged cultivation is undoubtedly the most suitable for large-scale production. Polysaccharides, after purification, would be used as platforms for formulating oral vaccines, as they are more economical and efficient (Moreno-Mendieta, Guillén, Hernández-Pando, Sanchez, & Rodriguez-Sanoja, 2017).

Fungi, when subjected to ideal cultivation conditions, produce biomass and polysaccharides in large quantities, which contributes to the development of technologies for the production of oral vaccines. Fungi have characteristics that contribute to be used as platforms for the production of vaccines, such as low production costs, short growth periods, large-scale production, in addition to control over production parameters. See, oral vaccines produced in this way, require low biomass processing for polysaccharide recovery, also, the method reduces production and formulation costs (Moreno-Mendieta et al., 2017).

The use of fungi for vaccine production has already reported in recent studies such as Han et al. (2019) and Liu et al. (2016). Fungi, like yeasts, are simple and economical hosts for the expression of proteins and polysaccharides for the development of vaccines. However, some important aspects must be considered for the production and delivery of vaccines using fungi as production platforms. First, vaccine production depends on efficient platforms, so genetic engineering approaches such as cloning and CRISPR are applied to generate a sufficient number of high-expression clones. Second, the choice of suitable hosts should be considered, mainly because it is related to the post-tradutional modification pathways, such as the protein glycosylation pathway. For more information, the following articles can be consulted (Kang, Park, Lee, Yoo, & Hwang, 2018; Kay, Cuccui, & Wren, 2019; Wild et al., 2018). Finally, the polysaccharides produced must have potential immunomodulatory activity. In this regard, we believe that fungi produce excellent polysaccharides with immunomodulatory properties that have been extensively studied (Manna et al., 2017).

The idea of using polysaccharides as adjuvants in vaccines has grown in recent years, due to the latest scientific findings and understandings about the importance of new sources of potential immunomodulatory drugs. Although there are currently more than 70 licensed vaccines being used against pathogens such as bacteria and viruses, there are still important challenges in this area. Major challenges are related to the delivery of antigens and immune counterbalance systems, that is, systems to compensate for risk factors, such as an uncontrolled immune response and the development of severe hyperinflammatory conditions (Michael, Berti, Schneider & Vojtek, 2017). Thus, natural polysaccharides, especially those obtained from fungi, are a viable option to be used as immunological compensation platforms and potent adjuvants.

Currently, great international effort has been employed in the development of engineering projects for the production of nanoparticles for the delivery of antigens. Polysaccharide nanoparticles have played a crucial role in the development of safe and efficient vaccines. Studies with these biopolymers (Correia-Pinto, Csaba, & Alonso, 2013; Gonzalez-Aramundiz, Cordeiro, Csaba, de la Fuente, & Alonso, 2012; Rice-Ficht, Arenas-Gamboa, Kahl-McDonagh, & Ficht, 2010), show that the encapsulation of antigens with polysaccharides improves the immune response, reduces side effects, increases the rate of immunomodulatory activity, and maintains antigens in a controlled and prolonged manner. Although studies with polysaccharides, especially lactic-co-glycolic acid, have been prolonged, researchers concluded that new biomaterials should be applied in the development of vaccines, mainly due to the problems of biocompatibility and biodegradability.

Therefore, polysaccharides obtained from natural sources have now been studied in antigen engineering. The synthesis of glycoconjugates in the development of polysaccharide vaccines has been a promising strategy in this field. Thus, researchers have already proposed to explore the potential of dextran, mannan, fungal glucans and protein glycoconjugates in vaccine nanoengineering (Petrovsky & Cooper, 2011). Yeasts have been the main fungi used for the production of glucans, mainly due to the low cost, ease of cultivation and the possibility of expanding the production scale (Petrovsky & Cooper, 2011).

The mixture of polysaccharides from different sources has also been used as an innovative strategy in the development of vaccine formulations. According to the work of Zhu et al. (2020), the mixture of polysaccharides obtained from mushroom Shiitake, Poriacocos, Ginger, and bark Tangerine, improved immune responses in mice induced by the inactivated H1N1 vaccine. The results of the study showed that the mixture of polysaccharides increased the serum levels of IgG and IgG2a in mice. Also, polysaccharides influenced the prevention of pulmonary

inflammation, reducing the risks of airway collapse, eliminating viral load, and increasing serum IFN-γ levels.

In a study conducted by Engel et al. (2013), it is reported that the polysaccharide-protein complex obtained from the fungus *Trametes versicolor* activates the Toll-like receptor 2 in dendritic cells (DC). The researchers evaluated the potential of the polysaccharide-protein as a vaccine adjuvant. In *in vitro* tests, it was shown that the polymeric complex induces maturation of dendritic cells, in a dose-dependent manner, as demonstrated by the expression of CD80, CD86, MHCII, and CD40. Also, it induces the production of inflammatory cytokines, including IL-12, TNF-α, and IL-6, at the mRNA and protein levels. Then, in *in vivo* assays, as an adjuvant to the OVAp323 − 339 vaccine, it was observed that dendritic cells increase the activity of draining lymph nodes and the proliferation of specific T cells, and induce T cells that produce multiple cytokines, IFN-γ, IL-2, and TNF-α, thus improving the potential of the vaccine.

4.3. Production of new biomaterials

Mushroom polysaccharides were explored in recent work (Mingyi, Belwal, Devkota, Li, & Luo, 2019; Yang et al., 2019), these biopolymers vary from glucans to heteropolysaccharides, with varied properties. These polymers include complex structures organized in monosaccharide chains. The physical-chemical and structural characteristics help in choosing the most suitable polysaccharides for applications in biomaterials. Several biomaterials such as nanoparticles, hydrogels, airgel and biomaterials for cell regeneration are produced using polysaccharides. Polysaccharides are the polymeric basis for the manufacture of numerous products, including functioning as a wall material for the encapsulation of drugs and bioactive compounds. Also, most polysaccharides have important biological properties, such as antiviral, antioxidant and immunomodulatory activities (He et al., 2020; Liu, Choi, Li, & Cheung, 2018; Yan et al., 2019). These properties contribute to the choice of these polymers and their application in the development of biomaterials, as well as, these polymers are biodegradable and biocompatible.

The development of technologies applied to tissue repair engineering is in full development. Currently, countless works as (Kumar, Rao, & Han, 2018; Negi et al., 2020; Tchobanian, Van Oosterwyck, & Fardim, 2019), show that polysaccharides can be used in the production of tissue grafts and bone regeneration engineering. Polysaccharides such as chitin and chitosan have biocompatible biological properties and adjustable for applications in tissue engineering. Promoting tissue regeneration is an urgent challenge and of course, this technology has numerous applications. Chitin and chitosan nanofibers have interesting applications, such as in the development of molecular scaffolds, used mainly to assist cell growth (Tao et al., 2019).

Polysaccharides have also been applied in the development of hydrogels, aerogels, and nanoemulsions. These biomaterials are mainly applied to the loading of drugs and bioactive compounds. Although they are applied in the loading of other drugs, polysaccharides obtained from fungi, as previously explored, have relevant biological properties; therefore, they contribute with beneficial effects. (Luesakul, Puthong, Sansanaphongpricha, & Muangsin, 2020). Fungal chitosan and those from arthropods are used in the synthesis of hydrogels and in the development of polymeric airgel. These biomaterials have interesting and divergent properties. That is, hydrogels have high water activity, and a polymeric network dispersed in an aqueous medium. While aerogels have a polymeric network with low water content, they are porous, low density, and malleable. Each of these biomaterials, depending on their properties, can be used in different applications (Pellá et al., 2018).

Several technologies have used natural polysaccharides for the development of value-added products. Currently, almost a trend, several researchers have used polysaccharides to develop and synthesize micro/nanoparticles. These biomaterials are used mainly for drug delivery. Methods used to produce micro/nanoparticles include self-assembly, ionic gelation, complex coacervation method, emulsification, and desolvation (Pitombeira et al., 2015). Polysaccharide micro/nanoparticles have applications in addition to drug delivery. Thus, due to their properties, they are used as emulsifiers to stabilize the Pickering emulsion. These emulsifiers based on micro/nanoparticles polysaccharides have received special attention, due to the potential for applications in food, drugs, and cosmetics (Yang, Han, Zheng, Dong, & Liu, 2015).

5. Perspectives and hypotheses of innovation applied to bioinspired materials and robotics

Based on fungal biology and on how fungi use polysaccharides for various purposes, such as cellular communication and chemical information transmission, we can evaluate in perspectives and hypotheses about the potential of polysaccharides for new applications. Also, we remember that polysaccharides function as a barrier film, defense and a system to reduce mechanical impacts on fungi. Therefore, based on the importance that polysaccharides have for the biology of fungi, we believe that we can use the knowledge of evolution to develop new materials. Many hypotheses about the use of polysaccharides can be raised, thinking of futuristic applications, however, we focus on the possibility of using polysaccharides from fungi to implement new technologies in robotics. See, although there are no consistent studies on the use of fungal polysaccharides for the production of robotics components, we will describe a hypothetical approach, based on modern articles, highlighting advances in the development of neural networks for artificial intelligence and the production of bioinspired materials such as robots.

Although the development of neural networks for artificial brains is a science, still little explored, several research groups distributed around the world are committed to the study of this technology. In living organisms, the brain performs several functions ranging from memory control to motor coordination. The neural networks of living organisms are groups of specialized cells, capable of transmitting chemical information with great excellence (McCain, 2019). Inspired by the neural networks of living organisms, researchers in advanced robotics try to imitate such networks using complex electronic component systems. Even though at present, we do not have artificial neural networks based on biological material, we believe it is only a matter of time (Thuruthel, Shih, Laschi, & Tolley, 2019). In this context, we believe that fungal polysaccharides could play a crucial role in the future development of artificial neural networks based on biological material.

It is not clear how neural networks based on biological material will be developed. However, polymers should be used; in this case, biologically active polymers played prominent roles. In this sense, fungal polysaccharides have potential, especially when we highlight that these same polysaccharides are already used by fungi as important routes and connections for the transmission of chemical information. The idea of producing organic materials for the development of neural networks is old, in the 90 s; researchers like Bains (1997), already showed that silicone cells could be used in neural network systems.

The reader may be thinking that the production of neural networks based on organic material is very futuristic. Well, we believe that although considerable advances in robotics science are still needed, this technology may be a reality in a few years. However, we present a new proposal for applications of fungal polysaccharides. A vision for future bioinspired and biohybrid based robots. Recent works like those of Trimmer (2020), showed that biology-inspired the development of new robots, and now, new advances have contributed to the production of robots from living cells. In this context, fungal polysaccharides could be applied as a biocompatible coating material with biological systems.

In the last decade, several projects with nano-bio-hybrid systems have contributed to the evolution of current knowledge about the use of biomolecules and their influence on the development of components for the field of robotics. Nano-bio-hybrids have a synthetic component and

a biological organic component. A notable effort in recent years has shown that biomolecules such as polysaccharides, proteins and nucleic acid molecules (DNA and RNA), are fundamentally interesting for applications in the field of robotics (Su et al., 2016). Meanwhile, synthetic materials include inorganic materials (carbon, $CaCO_3$, SiO_2, Au and iron oxide materials), organic materials (for example, polymers and lipids), hybrid materials and metal-phenolic networks (Lykourinou et al., 2011; Lynge, van der Westen, Postma, & Städler, 2011).

The interest in polymeric materials, especially those from biological sources has grown, mainly due to the ability of certain organisms to produce these biopolymers in a sustainable, inexpensive and efficient way. Natural polymers can be synthesized from fungi, mainly in submerged culture, with controlled culture parameters. Stimulated by external factors such as light, electricity, heat, pH, composition of the culture medium and carbon-nitrogen (C / N) ratio, several polysaccharides can be synthesized (Hwang et al., 2019). Applying polymer assembly techniques such as sequential polymer deposition (LbL), polymerization and grafting, several organic covalent structures are assembled, and can be applied in robotics (Zelikin, 2010).

Another class of biomaterial with potential for applications in robotics is the bio-MOF nanocomposites. MOFs, or porous coordination polymers, are a network of materials linked by chemical coordination systems to various structural topologies of metal ligands and organic ligands (Liang, Coghlan, Bell, Doonan, & Falcaro, 2016). Several synthesis technologies are proposed, however, it is not the focus of this topic to address them, for more details see the article of Guo, Richardson, Kong, and Liang (2020). However, it should be noted that a variety of biomolecules such as amino acids, proteins, enzymes, DNA and polysaccharides, are safe, ecological and in some cases potentially biologically active building blocks (Liang et al., 2016). MOFs are compact and porous structures, with the potential to be applied in the development of weights for the field of robotics, especially to simulate bio-inspired structures in nature (Liang et al., 2016).

These biomaterials can be applied in the development of cyborg-type exoskeleton, malleable, with thermostable, ultralight, low density and high resistance properties (Sankai & Sakurai, 2018). As demonstrated by Sato, Hiratsuka, Kawamata, Murata, and Nomura (2017), polymeric biological molecules are useful in the development of nanoscale bioengineering, with the production of biomolecular devices that act as sensors, actuators, and even logic circuits. Also, biological molecules are an interesting platform for building increasingly complex and functional molecular systems with controllable motility. Also, studies like the one by Justus et al. (2019), reveal that integrated organic and inorganic interfaces are useful for developing networks for transmitting chemical signals in a flexible biosensitivity robot.

Imagine bioinspired robots on insects like beetles, that's exactly what Baek, Yim, Chae, Lee, and Cho (2020), they did, when designing structures in the format of origami, compact, and light. The authors noted that the beetle-shaped wings can be folded quickly, which helps to sustain aerodynamic forces during flight. The author may question the relevance of producing robots in the shape of beetles, well, it is clear that the development of small flying robots paves the way for product designs with numerous applications, be they civilian or military. Fungal polysaccharides, such as chitin, could be applied in the development of wings, more compact, light, and cheap. Also, polysaccharides would assist in the development of artificial products more similar to those of nature.

6. Conclusions

The process of evolution of fungi, in particular, the mechanisms of sexual evolution directly influenced the adaptation processes for the production of polysaccharides. Each biological process has a group of active polysaccharides, so these biopolymers have a direct influence on lifestyle, reproduction cycles, food search mechanisms, and the defense system. Observing the roles that polysaccharides play in fungi helps in the development of new technologies. The properties of polysaccharides helped researchers in the development of antitumor drugs, biomaterials and vaccine production. The development of new antitumor drugs using polysaccharides also depends on a deep compression of the relationship between structure and bioactivity. The use of polysaccharides as adjuvants to chemotherapy is promising, reduces levels of oxidative stress and side effects of chemotherapy, but requires further studies. The main mechanisms of antitumor activity are already elucidated and can be used to outline therapy strategies. The use of polysaccharides for vaccine production delimits a new and exciting field of research. There is still a need to explore the efficacy of the polysaccharide conjugate vaccine to the antibody response to the carrier as a primary result. Polysaccharide mixtures prove to be an interesting option to be applied as vaccine adjuvants. Also, these biopolymers were effective in reducing inflammatory conditions and viral load, which is undoubtedly necessary for the development of safe vaccines. As for the development of biomaterials, polysaccharides can lead to a new paradigm of technologies; have unique properties and qualities, which helps in the development of new airgel, nanoparticles, and materials for cell regeneration. In addition to the structural qualities, these biopolymers are interesting because they are biodegradable and biocompatible. Finally, polysaccharides are promising molecules for applications in the field of robotics, from ultralight parts for flying robots to the development of organic neural networks. Although few studies are in advanced stages regarding the use of these natural polymers, recent findings indicate that polysaccharides should soon play a central role in discussions on bioinspired materials and artificial intelligence. The field of robotics is undoubtedly a frontier, if efforts are made; we believe that the field may have leaps in technology with profound impacts on the development of humanity. Lastly, an open and multidisciplinary dialogue was carried out on the role of polysaccharides in fungi and the impact on the development of new technologies. Therefore, we believe that this discussion is useful to form new opinions on broad topics, but in the background interconnected.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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