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Minireview

Antitumor polysaccharides from mushrooms: a review on the structural characteristics, antitumor mechanisms and immunomodulating activities

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ABSTRACT

Mushrooms are popular folk medicines that have attracted considerable attention because of their efficient antitumor activities. This review covers existing research achievements on the mechanisms of isolated mushroom polysaccharides, particularly (1→3)-β-D-glucans. Our review also describes the function in modulating the immune system and potential tumor-inhibitory effects of polysaccharides. The antitumor mechanisms of mushroom polysaccharides are mediated by stimulated T cells or other immune cells. These polysaccharides are able to trigger various cellular responses, such as the expression of cytokines and nitric oxide. Most polysaccharides could bind other conjugate molecules, such as polypeptides and proteins, whose conjugation always possess strong antitumor activities. The purpose of this review is to summarize available information, and to reflect the present situation of polysaccharide research filed with a view for future direction.

1. Introduction

In Asian countries such as China and Japan, polysaccharides extracted from mushrooms have played an important function as food and medicinal agent in the treatment of cancer. Numerous studies have reported that, through the ability of medicinal mushrooms to cure diseases, dietary intake of these mushrooms could be beneficial to humans.[1,2] Consumption of fresh mushrooms or dried mushroom powder could prevent breast cancer in pre- and postmenopausal women.[3] Mushroom with distinctive fruiting bodies, which exerts an effect in curing cancer, belongs to the class of Basidiomycetes, and sometimes in Ascomycetes. The primary taxa traditionally used are *Ganoderma lucidum* (*G. lucidum*), *Lentinus edodes* (Shiitake, *L. edodes*), *Tremella fuciformis* (*T. fuciformis*), *Griflola frondosa* (common name: Maitake, *G. frondosa*), *Hericium erinaceus* (*H. erinaceus*), *Agaricus blazei* Murrill (*A. blazei* Murrill), *Flammulina velutiper* (Fr.) Sing (*F. velutiper*), *Coriolus versicolor* (*Trametes versicolor*, *C. versicolor*, *T. versicolor*), *Inonotus obliquus* (*I. obliquus*), *Pleurotus ostreatus* (*P. ostreatus*), *Sparassis crispa* (*S. crispa*) and *Poria cocos* Wolf (*P. cocos* Wolf) among others. All of these species belong to the class Basidiomycetes, whereas *Cordyceps militaris* (*C. militaris*) is in the class of Ascomycetes. In 1957, the antitumor activity of the Basidiomycetes has been first demonstrated by Lucas. A substance isolated from *Boletus edulist* has been found to exert a significant inhibitory effect against Sarcoma 180 tumor cells in mice.[4] In recent years, Basidiomycetes mushrooms have been widely studied and used for their antitumor potential.[5] These Basidiomycetes mushrooms along with several species of the Ascomycota were used in traditional medicine for treatment of cancer, AIDS or universal immunosuppression.[1]

G. lucidum is a well-known medicinal fungus for the treatment of a variety of cancers.[6] As mentioned above, the benefits of *G. lucidum* are mainly reflected in antitumor activities, including cell-cycle arrest, induction of apoptosis, inhibition of motility, anti-angiogenesis, and anti-mutagenesis.[7] Polysaccharides from *G. lucidum* possessed preventive effects against the development of chemical carcinogen-induced aberrant crypt foci (ACF), colon adenoma, colon adenocarcinoma, and pulmonary adenocarcinoma in rats.[8] These polysaccharides are also used as a radio-protective agent that significantly prolongs animal survival,[9] and as a potential preventive agent against the side effects of chemotherapy.[10] Another important antitumor mushroom polysaccharide named lentinan was isolated from *L. edodes*, which is widely consumed as a nutritional health food worldwide. Lentinan activated the human immune system to perform antitumor function.[11] Lentinan was applied for clinical use in Japan since 1985, functioning as an immune adjuvant in conjunction with chemotherapy for stomach cancer treatment.[12] The equally important grifolan, which is extracted from *G. frondosa*, exhibits antitumor activity in gastrointestinal, lung, liver and breast cancers.[13,14] This polysaccharide is a macrophage activator that augments cytokine production without dependence on endotoxins. In addition, grifolan increased the expression of IL-6,

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IL-1 and tumor necrosis factor-alpha (TNF-α) of macrophages.[15] Maitake D fraction functions as an apoptosis inducer and immune enhancer against cancer.[16] A study showed that 69% of breast cancer patients consuming whole Maitake powder significantly suppressed the development of cancer.[17] In addition, Maitake could decrease metastatic progression, reduce the expression of tumor markers and enhance natural killer cell activity in breast cancer patients.[18,19] Schizophyllan (sizofiran or SCH/SPG), which is isolated from the inedible Chinese mushroom *S. commune*, is a highly potent antitumor polysaccharide that works against solid S-180 tumors.[20] In humans, schizophyllan is not only effective in suppressing gastric cancer, but also could prolong survival in patients who suffered head and neck cancer.[21] At the same time, schizophyllan is supposed to increase immune responses and acts as biological response modifiers *in vivo*.[22] One dose of schizophyllan is used to reduce the probability of mammary tumor, and decrease the progression of mammary carcinoma.[23] *S. crispa* is an edible medicinal mushroom. β-glucan from *S. crispa* is regarded as a good source of antitumor polysaccharide.[24,25] Meanwhile, in China, Japan, Korea, and North America, *P. cocos* Wolf is a well-known traditional medicine that grows around the roots of pine trees. Polysaccharide from *P. cocos* Wolf possesses antitumor potential and pharmacological properties, and could relieve the gastritis, edema, nephrosis, among others.[26] In addition, heteropolysaccharides from *P. cocos* Wolf which are cultured in a corn steep liquor medium exhibited higher antitumor activities against S-180 *in vivo* compared with that cultured in bran extract media.[27] Pleuran (β-1, 3-D-glucan), which is isolated from the oyster mushroom *P. ostreatus*, has been proven to retard the development of precancerous ACF lesions in the colon of the male Wistar rats.[28] *P. ostreatus* is a traditional Chinese medicinal and edible fungus that is distributed in Heilongjiang Province of China. Another study showed that polysaccharide isolated from *P. ostreatus* could increase the proliferation of lymphocyte caused by concanavalin A (Con A, a T-lymphocyte mitogen) or lipopolysaccharide (LPS, a B-lymphocyte mitogen).[29]

The majority of these antitumor polysaccharides are homoglycans or heteroglycans, which can be converted to glycopeptides, proteoglucans or glycoproteins when connected with other proteins.[30,31] In addition to the basic structure of polysaccharides, a higher structure such as chain conformation performs a key function in antitumor activities.[32] Polysaccharides that act as adjuvant medicines are more commonly used in combination with chemotherapy/radiotherapy to treat various cancers.

This article reviews recent work in this field with focus on the mechanisms of polysaccharide antitumor activities, structural features, physical properties, and adjuvant therapy.

2. Structure of polysaccharides

2.1. Relationship between the structure and antitumor activities of polysaccharides

Antitumor polysaccharides differ greatly in their chemical structure and physical properties. Polysaccharides are composed of certain amounts of monosaccharide residues. The primary structure of polysaccharides is defined by placement of the monosaccharide residues, position of glycosidic linkages, and the sequence of monosaccharide residues. These three factors result in the highest potential structural variability. The greatest structural variability could induce the highest polysaccharide capacity for carrying biological information. In general, numerous polysaccharides extracted from mushrooms possess immunomodulating activities. Multiple kinds of polysaccharides include β-glucans,[33] hetero-β-glucans, glycans and heteroglycans.[34] Various β-glucans generally possess different structural characteristics, mainly involving the degree of branching (DB), molecular weight (MW), and conformation, like triple helix, single helix, and random coil structures (Table 1).[35] β-glucans strengthen phagocytosis and trigger the expression of a series of cytokines, such as TNF-α and various types of interleukins.[36] In addition, several natural antitumor mushroom polysaccharides are bound to protein or peptide residues, such as glycopeptides, proteoglucans or glycoproteins. Based on different structures, different polysaccharides possess different MW, and the MW is closely related to the antitumor activities of polysaccharide.

A polysaccharide from *A. blazei* Murrill named ABP-W1, possess a triple helix in water solution. Most polysaccharides in triple strand helical chain conformation often possess stronger anticancer capacity than those in random coils or lines.[38] In addition, β-glucan (β-1, 3, β-1, 6 linked glucan) from *A. blazei* Murrill has been reported to act as an immunoaccelerator against cancer cells.[32] Polysaccharides of *Antrodia camphorate* (also called *Antrodia cinnamomea*, *Cinnamomum kanehirae* mushroom, camphor mushroom, camphor chamber mushroom and yin-yang mushroom) show antitumor activity, and their helical structure may be important in resisting tumors.[42] In addition, polysaccharide from *C. militaris* adopts a random coil conformation and exhibits considerable antitumor activity.[46,47] An alkaline-soluble antitumor polysaccharide from *Flammulina velutipes* exhibits strong antitumor activity against sarcoma S-180 *in vivo* but not *in vitro*. This polysaccharide is converted to random coils from single helices with increasing pH.[75] The majority of *G. lucidum* polysaccharides are glucans, and (1→3)- and (1→6)-β-D-glucans possess antitumor activity and superior absorption than others in *G. lucidum*.[52] However, several hetero-β-D-glycans, such as glucurono-β-D-glucan, arabinoxylo-β-D-glucan, xylo-β-D-glucan, manno-β-D-glucan and xylomanno-β-D-glucan, show strong antitumor properties as well.[51] These polysaccharides could enhance the antitumor, antibacterial, antiviral, anticoagulatory and wound healing activities.[52] HEB-AP Fr I was found to act as an immunostimulant through the activation of macrophages, which is isolated from *H. erinaceus* and show a β-mannan with a laminarin-like triple helix conformation.[55] FII-1 (from *H. erinaceus*) also shows good antitumor effect.[57] HE (from *H. erinaceus*) acted as an enhancer to increase the intracellular Dox accumulation.[58] The purified endo-polysaccharide isolated from *I. obliquus* mycelia is an α-fucoglucomannan, which is a specific activator of B cells and macrophages.[59] The water soluble polysaccharide from *I. obliquus* sclerotia is a heteropolysaccharide.[60] IOPS-F and IOPS-H are polysaccharides that are extracted from *I. obliquus*. The two polysaccharides possess a triple helix structure, and exhibit superior antioxidant capacity.[77] Lentinan is considered as bioactive immunomodulator agent and classified as a β-glucan, the conformation of which was important for immunostimulating activity.[52,60] The helical conformation is commonly believed to play an important function in enhancing immunopotentiating activity, but increasing data presently suggest that not only triple helical structures but also the distribution of the branch units along the backbone chain are the main mechanisms for activity as well.[52] In general, the most active polymers possess between 20% and 33% DB. The DB of lentinan is 40%.[78] More recently, a study on the correlation between branching and bioactivity showed that debranching of lentinan could enhance its biological proficiency. However, maximal immunomodulating and antitumor activities are achieved with a DB of 32%.[79] The main constituent of polysaccharide isolated from *P. cocos* Wolf is β-pachyman with DB of 1.5% to 2%.[64,65] Schizophyllan, an efficient polysaccharide isolated from *S. commune*, is another extensively studied mushroom-derived polysaccharide with immunopotentiating activity with a DB of 33%.[78] The highly water soluble SCG from *S. crispa* possesses a triple helix conformation and possibly exists in an irregular single helical conformation. This conformation promotes cytokine production and the synthesis of subsequently iNOS, NO and type I collagen.[73,80] Polysaccharopeptide krestin (PSK), an antitumor polysaccharide that is isolated from