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Review

Basidiomycete mushrooms represent a valuable source of biologically active compounds with anticancer properties. This feature is primarily attributed to polysaccharides and their derivatives. The anticancer potential of polysaccharides is linked to their origin, composition and chemical structure, solubility and method of isolation. Moreover, their activity can be significantly increased by chemical modifications. Anticancer effects of polysaccharides can be expressed indirectly (immunostimulation) or directly (cell proliferation inhibition and/or apoptosis induction). Among the wide range of polysaccharides with documented anticancer properties, lentinan, polysaccharide-K (PSK) and schizophyllan deserve special attention. These polysaccharides for many years have been successfully applied in cancer treatment and their mechanism of action is the best known.

Key words: Basidiomycetes, anticancer properties, polysaccharides, lentinan, PSK, Krestin, schizophyllan.

Anticancer properties of polysaccharides isolated from fungi of the Basidiomycetes class

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Introduction

Health benefits from consumption of mushrooms have been known for thousands of years. Mushrooms products have been used as dietary supplements or as medicines for over 2000 years in Far East countries (China, Japan, Korea, the Asian part of Russia) [1]. In contrast, in the Western world, mushrooms have been consumed primarily because of their taste and smell. In recent years, however, mushrooms have been in the center of attention for scientists worldwide as a source of biologically active compounds with a favorable impact on functioning of the human body. As a result of these studies the so-called "mycopharmaceuticals" or "fungal supplements" were introduced to the global markets. The scale and importance of this phenomenon emphasizes the fact that edible mushrooms have been included in the product group defined as "functional food", i.e. food whose health benefit was documented by scientific research and whose favorable impact could not to attributed solely to the presence of nutrients traditionally deemed necessary [2–5].

It has been known for centuries that some representatives of Basidiomycetes have anticancer properties. One of the first studies pertaining to the anticancer properties of this class of mushrooms was carried out by Lucas and coworkers, who successfully applied an extract obtained from *Boletus edulis* fruiting bodies in the treatment of Sarcoma 180 in mice (1957) [6]. Lucas's team also isolated calvacin from *Calvatia gigantea*. In the 1960s, it was the most popular natural product with anticancer properties isolated from mushrooms [7]. Its effect was confirmed against many experimental tumors, including Sarcoma 180, mammary adenocarcinoma 755, leukemia L-1210 and HeLa cell lines [4].

Numerous studies have shown that the anticancer properties of biologically active compounds isolated from mushrooms are mostly attributed to polysaccharides [4, 8–12]. Their main source appears to be fungal cell walls. However, as shown in the study, chitin and chitosan have no anticancer activity [13]. Considering their chemical nature most mushroom polysaccharides with anticancer properties can be included in derivatives of (1→3), (1→6) β-glucans or (1→3) α-glucans [14]. These compounds are composed of a linear or branched chain made up of glucose molecules, and a side chain containing a different combination of other simple sugars, mainly glucuronic acid, xylose, galactose, mannose, arabinose, or ribose. Protein complexes are also very common. Glycans represents an equally large group of anticancer polysaccharides. Their molecules are created by monosaccharides other than glucose. In mushrooms most often there occur glycans containing arabinose, mannose, fucose, galactose, xylose, glucuronic acid and also glucose [12].

Chemical structure and antitumor properties

Depending on the source (each species and even strain has a slightly different set of polysaccharides), polysaccharides differ in chemical structure, mol-

ecular weight, branching rate and form, which affect their biological activity [5–18].

Anticancer properties of polysaccharides depend on:

- sugar composition – anticancer properties of polysaccharides have been described in the case of hetero-β-glucans [19], heteroglycans [20], complexes of β-glucan-protein [21], α-manno-β-glucans, complexes of α-glucan-protein [19] and complexes of heteroglycan-protein [22, 23];
- molecular weight – high molecular weight glucans appear to be more effective than those of low molecular weight [8–10, 13];
- water solubility – water-soluble glucans are characterized by greater activity [24];
- glucose linkage – it is obvious that structural features such as β-(1→3) linkages in the main chain of the glucan and additional β-(1→6) branch points are needed for anticancer activity; β-glucans containing mainly β-(1→6) linkages have lesser activity [8–10];
- tertiary structure – it has been shown that the destruction of the tertiary structure of polysaccharides by denaturation substantially reduces or completely abolishes their biological activity [25–27];
- branching rate and form – it was shown that the highest activity characterized glucans where the value of branching degree in relation to the molecular weight is 0.20–0.33 [16, 17, 28, 29];
- presence of other ligands – e.g. galactose, mannose, fructose, xylose and arabinose, profitably affected anticancer properties of polysaccharides; in addition, protein ligands increase the anticancer potential [13];
- chemical modification – it is often carried out to improve the anticancer activity of polysaccharides and their clinical qualities by increasing their water solubility and ability to penetrate the intestinal wall after oral administration; the main procedures used for chemical improvement are Smith degradation (oxydo-reducto-hydrolysis), activation by formolysis, and carboxymethylation [8, 9, 23, 30–33].

The most popular anticancer agents derived from Basidiomycetes

Major and still largely untapped source of potent new anticancer polysaccharides are higher Basidiomycetes. This was confirmed by extensive research done by Chinese and Japanese scientists, who have shown that most if not all Basidiomycetes contain biologically active polysaccharides. Studies were performed on animals with Sarcoma 180 and Ehrlich cancer [11]. So far, the best characterized were three polysaccharides, which for nearly 50 years have been commercially available: lentinan, PSK (Krestin) and schizophyllan [8, 34].

Lentinan is a highly purified polysaccharide fraction isolated from *Lentinus edodes* (Shiitake). Considering its chemical nature it is classified as a β-glucan. Its main chain is formed of glucose units linked by β-(1→3) glycosidic bonds, while side chains are connected with the main chain by β-(1→6) glycosidic bonds [9]. It is an approved, commonly used, anticancer drug in Japan. It is generally administered in conjunction with other conventional pharmaceutical drugs in cancer therapy, e.g. against bowel, liver, stomach, ovarian and lung cancer. It increases the effectiveness of therapy and thus patients' survival [35]. Experimental studies have shown that administration of lentinan prevents oncogenesis induced chemically or by viruses, as well as preventing metastasis [25, 36–38].

Krestin (PSK) is a polysaccharide isolated from *Trametes versicolor*. Apart from the sugar which is β-glucan, PSK also consists of peptide. The sugar part is composed of the main chain created by glucose units linked by β-(1→3) glycosidic bonds, while in the side branches occur β-(1→6) glycosidic bonds [9]. Like lentinan it is a very popular drug in Japan. Numerous clinical studies have shown that its administration increases the effectiveness of chemotherapy in patients suffering from breast, liver, prostate, stomach, lung, and colon cancer. Alone, as an anticancer drug, it is used in veterinary medicine against adenosarcoma, fibrosarcoma, mastocytoma, plasmacytoma, melanoma, sarcoma, carcinoma, mammary cancer, colon cancer, and lung cancer [35].

Schizophyllan is obtained from *Schizophyllum commune*. In terms of chemical structure, i.e. the composition of sugars and their manner of linking, it is similar to lentinan. The commercial name of this β-glucan is Sonifilan [9]. This product is used in the treatment of stomach and neck cancer [2]. Additionally, it is administered during radiotherapy due to its radioprotective properties. Schizophyllan restores mitosis of bone marrow cells previously suppressed by gamma radiation [39–41].

Polysaccharides derived from other Basidiomycetes also exhibit pro-healthy properties. Lot of scientific reports have confirmed their ability to prevent carcinogenesis and metastasis, and inhibit the development of existing tumor lesions [25, 36–38].

Mechanisms of action

The diversity of the polysaccharides and their derivatives is reflected in the diversity of their mechanisms of action. Generally there are two basic mechanisms of polysaccharide action against tumor cells: indirect action (immunostimulation) and direct action (inhibition of tumor cell growth and apoptosis induction).

Indirect action

Indirect action is based on stimulation of host defense mechanisms, primarily on activation of T and B lymphocytes, macrophages and natural killer (NK) cells [15, 16, 18, 28]. Many mushroom β-glucans have been shown to stimulate production of interferons (IFNs), interleukins (ILs), and others cytokines. These are regarded as the first line in the host defense system, and may themselves successfully transform cells prior to the establishment of fully fledged humoral and cell-mediated immune responses [42].

Studies have shown that β-glucans induce the body's response by binding to membrane receptors on immunologically competent cells [43]. One of the most important β-glucan receptors is CR3 receptor (syn. Mac-1, CD11b/CD18) [44, 45]. This receptor occurs commonly on the surface of immune effector cells, such as macrophages, neutrophils, NK cells and K cells. CR3 is able to recognize opsonin iC3b, which often presents on the cancer cells' surface. Simultaneous connection to the CR3 complement component iC3b and β-glu-

can induces stimulation of phagocyte activity, while the lack of any of these components prevents cytotoxicity induction [44, 46, 47]. Numerous reports have suggested that polysaccharides enhance the ability of immune cells to recognize tumor cells as foreign and thereby enhance the effectiveness of host defense mechanisms [48]. The best documented immune stimulating properties have been described in the case of lentinan, PSK and schizophyllan.

Lentinan

Studies have shown that lentinan stimulates the proliferation of blood mononuclear cells such as lymphocytes, monocytes and macrophages [49, 50]. Furthermore, it also stimulates the maturation and differentiation of cells involved in host defense mechanisms. Lentinan is also able to increase the reactivity of immune cells and stimulate them to secrete cytokines, hormones and/or other biologically active substances. As a result of such properties, lentinan increases the body's resistance to malignant transformation [51, 52]. Lentinan has been described as an adjuvant focused on T cells [53]. It shifts the balance of Th1/2 towards Th1 by a significant increase of IL-12 production [54]. It intensifies macrophage phagocytosis and increases the secretion of cytokines, particularly tumor necrosis factor α (TNF-α) by the activation of NF-χ^2 [55, 56]. Its stimulating effect on the population of NK cells was also observed [57]. Plentiful evidence suggests that lentinan stimulates dendritic cells, which is essential for immunomodulation and antitumor activity of this agent. Dendritic cells in collaboration with K cells play a key role in the elimination of tumor cells [52]. Additionally, it was observed that lentinan treatment in patients suffering from stomach cancer inhibits prostaglandin synthesis, which compounds in many cases leading to a slowdown of T lymphocyte differentiation, as well as inhibition of Treg cell activity [49]. At the same time, increased levels of activated and cytotoxic T lymphocytes were observed in the spleen [50] as well as stimulation of peripheral blood mononuclear cells to produce interleukin 1α (IL-1α), IL-1β and TNF-α [52]. Lentinan ability to stimulate IL-1 release has been demonstrated in other tumor types [51]. Additionally, many other interesting biological activities of lentinan have been described, including increased non-specific inflammatory response evidenced by stimulated production of acute phase proteins [58] and inhibition of the complement system [54].

Krestin

It has been demonstrated that (krestin PSK) stimulates components of both cellular and humoral immunity [59]. After injection of PSK at the tumor site, its direct interaction with tumor cells and induction of an inflammatory response leading to elimination of transformed cells have been observed [60]. Increased numbers of immunologically competent cells and a rise in dendritic and Tc cells capacity of tumor infiltrate were noted in patients who received PSK. Krestin affects the phenotypic and functional maturation of dendritic cells from human CD14+ cells [61], and stimulates the phagocytic activity of macrophages [41]. In addition, it stimulates expression of TNF-α, IL-1, IL-6, and IL-8 [62–65]. These cytokines induce reactions leading to the stimulation of T cell cytotoxicity against tumor cells, intensification of antibody production by B cells, or induction of receptor expression for IL-2 on T cells [63]. The study indicated that antitumor activity of PSK relies on its ability to stimulate T cells and antigen-presenting cells, which allows efficient recognition and destruction of tumor cells [59, 66].

Schizophyllan

Schizophyllan's chemical structure and mechanism of action are very similar to lentinan. Its antitumor action is based on the modulation of the immune response [66]. Like lentinan, antitumor properties of schizophyllan appear only in the presence of T cells, which has been proven in studies performed on mice with sarcoma 180. Administration of cyclosporine A (T cell suppressor) to mice resulted in the abolition of anticancer properties of both agents [67, 68]. Schizophyllan stimulates production of acute phase proteins and CSF, resulting in incitement of macrophage, peripheral blood mononuclear cell and lymphocyte proliferation as well as stimulation of the complement system [69]. Moreover, this formulation increases the production of Th lymphocytes and macrophages [69]. It is characterized by strong activation of phagocytes, increases the production of reactive oxygen species, proinflammatory cytokines IL-6, IL-8 and TNF-α, and also increases the expression of CD11b and CD69L markers on leukocytes' surface [70, 71].

Direct action

Besides the indirect action, several polysaccharides have shown direct effects on cancer cells. Many *in vitro* and *in vivo* studies have suggested that polysaccharides inhibit tumor cell proliferation and/or induce their death by apoptosis [16, 17, 28, 29, 72].

One of the best described mechanisms of direct anticancer action of polysaccharides extracted from Basidiomycetes is modulation of NF-κβ activity. Excessive activation of NF-κβ is observed in many types of cancer. Active NF-κβ promotes tumor growth by increasing the transcription of genes that induce cell proliferation, inhibit apoptosis, or promote angiogenesis and metastasis [73]. It was proven that polysaccharides inhibit phosphorylation of and/or degradation of the inhibitor of NF-κβ (Iκβα) [4, 19, 28, 74–77], which prevents activation of the transcription factor and consequently the expression of its subordinate genes [78, 79]. In addition to NF-κβ pathway modulation, polysaccharides may also affect cancer cells in other ways. An excellent example of that is the protein complex of polysaccharide extracted from Trametes versicolor known as PSP. It was demonstrated that PSP induced cell cycle arrest at restrictive points G1/S and G2/M in leukemia cells U-937 and breast cancer cells MDA-MB-231, and also inhibited antiapoptotic proteins, resulting in repression of cell division and increase of apoptosis [80, 81]. However, in leukemia cells HL-60, PSP elicited a similar effect through decrease of NF-κβ level and expression of ERK kinase [81].

Summary

For centuries, mushrooms in the Western world have been treated only as a tasty supplement to the daily diet. Far East-

ern medicine has created a foundation for their therapeutic use. The last half-century is a period of a flourishing new field of medicine – mycopharmacology. The scientific approach to compounds contained in mushrooms allowed the isolation of many valuable active substances which are used in the prevention and treatment of lifestyle diseases, including cancer.

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