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Review

Anticancer and other therapeutic relevance of mushroom polysaccharides: A holistic appraisal

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ABSTRACT

The discovery of nutritious dietary supplements and side effect-free therapeutics are a priority in the current scenario of increasing instances of metabolic syndromes. In this direction, mushroom polysaccharides have shown immense promise. Scores of studies have characterized and evaluated their biological relevance, which range from antioxidant, anti-inflammatory, anticancer, antidiabetic, antimicrobial, and antilipemic to immunomodulatory. Hence, it is important to accumulate the key findings of these investigations, and to apply the insights to develop functional foods, and immunomodulators. This review attempts to meet this goal by gleaning the key discoveries on mushroom polysaccharides in the recent years, and to present them in a comprehensive manner. With this objective, the physiological relevance of the polysaccharides, the underlying mechanism, and hurdles in the path of their therapeutics transition, have been discussed. Finally, critical comments have been made to expedite research in this area.

1. Introduction

As metabolic syndromes are afflicting people from all age groups and cultures, and chemical compounds are being perceived as non-harmonious to the human body, natural resources are attracting attention. In this context, one of the most mysterious kingdom, fungi, holds immense prospects, particularly, mushrooms, the macrofungi. These epigeous, basidiomycetes groups formed of fruiting bodies and myceliua, comprising more than 20,000 known species, have been the subject of numerous studies [1]. Interestingly, those evaluated goes beyond the edible genera like *Agaricus* sp., *Lentinus* sp., *Pleurotus* sp., *Inonotus* sp., *Morchella* sp., *Calocybe* sp., *Auricularia* sp., *Flammulina* sp., *Tremella* sp., *Russula* sp., *Grifola* sp., *Hericium* sp. *etc.* Some non-edible mushrooms with high medicinal relevance include *Ganoderma* sp., *Trametes* sp., and *Cordyceps* sp. *etc.* Even hallucinogenic or lethal mushrooms such as *Amanita*, *Clitocybe*, *Psilocybe, Cortinarius*, and *Gyromitra* are being evaluated for their pharmaceutical scopes [2]. The well-characterized mushroom toxins are amatoxin, gyromitrin, psilocybin, orellanus, muscarine, ibotenic acid, psilocybin, and coprine, though the list can be exhaustive [3]. Most of these toxins affect human gastrointestinal, nephrological, and neurological machineries [4]. Despite the toxicities of some species, mushrooms continue to be regarded as gourmet foods and medicines across many pharmacopeias. The therapeutic spectrum of mushrooms is exhaustive, yet most common uses are against tumor, hypertension, stroke, Parkinson's disease, Alzheimer's disease, microbial infections, poor immunity *etc* [5]. A number of reviews have recounted the ameliorative scope of mushrooms, attributing the physiological benefits to the unique mycochemistry, which include polysaccharides, antioxidants, alkaloids, minerals, vitamins, amines, among other components [6,7]. Mushrooms have been verified to be good sources of dietary fibers, vitamins (B_1, B_2, niacin, biotin, C, D), and minerals (such as selenium, potassium) [8]. Fat profile in them consists of lipids such as mono-, di-, and tri-glycerides, sterols, and phospholipids [1]. The presence of sesquiterpenes, triterpenes, steroids, and essential amino acids (lysine, histidine) has been confirmed from scores of chemical profiling studies [9]. Apart from the ubiquitous fungal cell wall component chitin, the β-glucans are predominant components of mushroom cell walls. Versatile biological roles of β-glucans have been well-validated [10,11]. Modern medicine has observed ample nutraceutical and pharmaceutical prospects of mushroom polysaccharides (MPs). Antitumor, immunomodulating, antioxidant, radical scavenging, cardiovascular, anti-hypercholesterolaemic, antiviral, antibacterial, antiparasitic, antifungal, detoxification, hepatoprotective, and antidiabetic effects of MPs have been reported so far [12]. In the last three decades, numerous polysaccharides and polysaccharide-protein complexes have been isolated

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from mushrooms, of which several have been validated as therapeutic agents. To keep track of the emergent facts and advances on salutogenic MPs, this review has been compiled. Here, the scopes of the MPs in functional food and therapeutic sector has been explored and the pitfalls in the path to their optimal exploitation has been discused. Critical thoughts have been presented that might be instrumental in bridging many nagging issues and potentiating food and medical sector.

2. Types of polysaccharides

Depending on the species and strains, a myriad of MPs has been identified so far. The β-glucan, an essential component of fungal cell wall, is therapeutically the most important polysaccharide in mushrooms [13]. These glucans have a chain of glucose residues linked by β-(1→3)-glycosidic bonds with branches of β-(1→6) bonds [14]. Many variants of β-glucans have been identified in mushrooms such as pleuran from *Pleurotus* [15], lentinan from *Lentinus* [16], schizophyllan from *Schizophyllum*, grifolan from *Grifola etc* [17]. Some β-glucans are bound to proteins, as proteoglycan, such as PSK or krestin from *Trametes versicolor* [18]. A convincing number of immunological studies have unraveled the role of membrane receptors in the transduction of β-glucan-generated signals. Multiple research findings have reported that β-glucans exert their biological effect *via* the interaction with receptors of macrophages, and dendritic cells [19]. Collaborative signaling of Toll-like receptor (TLRs) and dectin-1 has been verified by many [20]. The stimulation of human innate immunity occurs on binding of the glucans to the membrane pattern recognition receptors, TLRs and dectin-1 (a non-TLR lectin receptor) [21]. On attachment to the β-glucan ligand, dectin-1 becomes phosphorylated by tyrosine kinases, and induces an intracellular signaling cascade. Stimulation of macrophages and dendritic cells contributes to internalization of the glucan [22]. Recognition of the glucan by the macrophage triggers proinflammatory cytokine production such as tumor necrosis factor (TNF-α) and various interleukins (ILs) [23]. It is beyond the scope of this topic, but further information on the crucial role of dectin-1 in signal propagation (*via* the Syk/CARD9 pathway) can be obtained from other studies [24,25]. The knowledge of the precise molecular mechanisms is important for finetuning of the β-glucan activity. The molecular mechanism of immune intervention of mushroom β-glucans has been illustrated in Fig. 1. β-glucans have been identified in yeast, seaweed, cereals as oat and barley as well [26].

3. Biological activities

The pharmacological spectrum of MPs span from antioxidant, anti-inflammation, anticancer, immunomodulation, antilipemic, antidiabetic and antimicrobial to prebiotics. The section below summarizes some recent relevant medicinal potential of the MPs and their underlying mechanisms. Major edible mushrooms with validated medicinal properties of MP have been presented in Table 1.

3.1. Antioxidant

It is universally agreed that antioxidants offer safeguard against diseases by scavenging the deleterious free radicals as reactive oxygen species (ROS) [27]. The antioxidant activity of MPs is mediated by the free radical scavenging, lipid peroxidation inhibition, and the enhancement of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) [28]. *P. ostreatus*-derived heteropolysaccharide fractions PSPO-1a (18 kDa) and PSPO-4a (11 kDa) were evaluated for prospective antioxidant applications, which exerted strong and dose-dependent 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and superoxide anion radical scavenging activities [29]. The intra- and extracellular-polysaccharides of various *P. ostreatus* strains showed variable antioxidant efficacy [30]. Polysaccharides of *P. tuber-regium* possessed antioxidant potency which depended on the extraction mode and the oxidant to be quenched. Water-extracted polysaccharide was better for superoxide scavenging, while alkali-extracted polysaccharide was stronger for hydroxyl and DPPH inhibition effects on liver lipid peroxidation, liver mitochondria swelling, and red blood cell (RBC) hemolysis [31]. Polysaccharide purified from *Lentinus edodes* conferred protection towards D-galactose-caused oxidative stress in mice model. Among the three fractions LT1, LT2, and LT3, with molecular weights 25.5, 306.2, and 605.4 kDa, respectively, LT2 was most promising in attenuating malondialdehyde (MDA), and enhancing SOD and GSH-Px content in liver [32]. *Boletus edulis* fruiting body extract gave rise to three polysaccharides (BEPF30, BEPF60 and BEPF80) fractions, of which BEPF60 showed the most remarkable reducing power and chelating activity; and highest inhibitory effects on superoxide as well as hydroxyl radicals [33]. Ameliorative effects of *Cordyceps sinensis* polysaccharides on exercise-induced oxidative stress in mice were investigated. The treated groups received the MP through intra-gastric route (100, 200 and 400 mg/kg) prior to exhaustive swimming [34]. The polysaccharide-administered mice sustained their swimming potential for longer duration. Serum, liver and muscle level of SOD, CAT, GSH-Px was higher while that of MDA and 8-Oxo-2′-deoxyguanosine (8-OHdG) was significantly lower [34]. *Tremella fuciformis* exopolysaccharide demonstrated *in vitro* chelating abilities of ferrous ion and reducing power. Also, the cytoprotective potential of the exopolysaccharide was verified by its benign effect on mouse skin fibroblasts

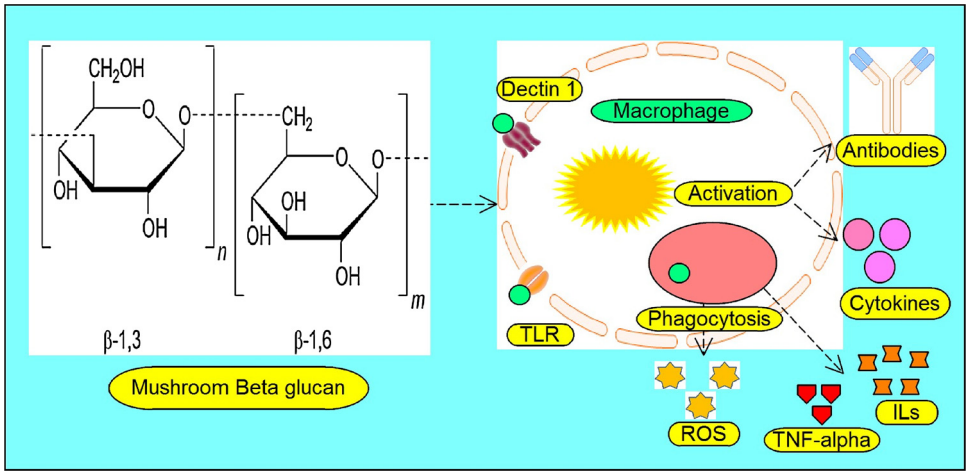

Fig. 1. β-Glucan molecular mechanism. This glucan binds to TLRs and dectin 1. Phosphorylation of dectin-1, activates tyrosine kinase, which sets off a signaling cascade. Also, the recognition of beta-glucan by macrophage triggers the elaboration of proinflammatory cytokines such as TNF-α and ILs.