Biomedicine & Pharmacotherapy 105 (2018) 377–394

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

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

Damini Kothari[a], Seema Patel[b,*], Soo-Ki Kim[a,**]

[a] Department of Animal Science and Technology, Konkuk University, 120 Neungdong-ro, Gwangjin-gu, Seoul, 05029, Republic of Korea
[b] Bioinformatics and Medical Informatics Research Center, San Diego State University, San Diego, 92182, USA

ARTICLE INFO

Keywords:
Mushroom
Polysaccharides
β-glucan, Antioxidant
Anticancer
Immunomodulator

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

* Corresponding author at: Bioinformatics and Medical Informatics Research Center, San Diego State University, 5500 Campanile Dr, San Diego, CA, 92182, USA.
** Corresponding author at: Department of Animal Science and Technology, Konkuk University, 120 Neungdong-ro, Gwangjin-gu, Seoul, 05029, Republic of Korea.
E-mail addresses: Patel3@rohan.sdsu.edu, seemabiotech83@gmail.com (S. Patel), sookikim@konkuk.ac.kr (S.-K. Kim).

https://doi.org/10.1016/j.biopha.2018.05.138
Received 13 April 2018; Received in revised form 27 May 2018; Accepted 28 May 2018

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

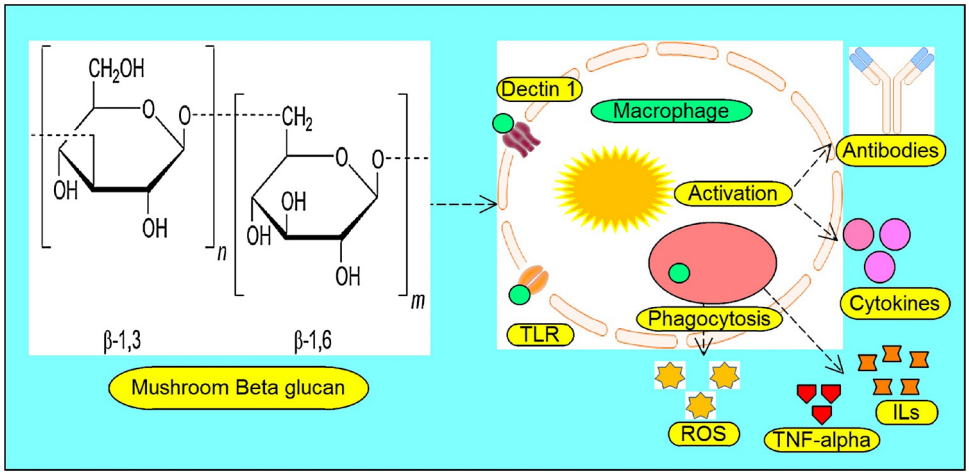

Fig. 1. β-Glucan molecular mechanism. This glucan binds to TLRs and dectin 1. Phosphorylation of dectin-1, activates tyrosine kinase, which sets off a signaling cascade. Also, the recognition of beta-glucan by macrophage triggers the elaboration of proinflammatory cytokines such as TNF-α and ILs.

Table 1
The mushroom species, their polysaccharides and biological effects.

Scientific names	Common names	Polysaccharides	Biological functions	References
Agaricus bisporus	Button mushroom	ABP-1, ABP-2, ABMP-F, ABMP-V,	Anticancer, antioxidant	[13]
Agaricus blazei	Almond mushroom	ABMP-A		
Agaricus brasiliensis				
Antrodia camphorata	Stout camphor fungus	–	Immunomodulation	[9]
Auricularia auricula	Jew's ear	–	Antiviral, Antibacterial	[121]
Auricularia auricula-judae				
Boletus edulis	King bolete or porcini	BEPF60, BE3, BSF-A	Antioxidant, anticancer	[33]
Boletus speciosus				
Calocybe indica	Milky mushroom	–	Immunomodulation	[96]
Calocybe gambosa	St. George's mushroom	PS-Cg fC, PS-Cg fH, PS-Cg fB		
Caripia montagnei	Pod parachute	β-glucan	Anti-inflammatory	[64]
Coprinus comatus	Shaggy ink cap	–	Interference with androgen receptor function	[164]
Cordyceps militaris	Scarlet Catterpillar club	CP2-S	Anticancer, antioxidant	[34]
Cordyceps sinensis	Caterpillar Mushroom			
Cordyceps taii	–			
Coriolus versicolor or *Trametes versicolor*	Turkey tail	CVP	Immunomodulation	[106]
Catathelasma ventricosum	–	CVP-1S	Antioxidant, antilipemic, antidiabetic	[111]
Entoloma lividoalbum	–	PS-I	Antioxidant	[37]
Flammulina velutipes	Golden needle mushroom	FVP2	Anti-inflammatory	[42]
Ganoderma lucidum	Bracket fungi	GLP	Immune adjuvant for viral vaccine	[38]
Gomphidius rutilus	Brown slimecap	GRMP1, GRMP2	Antioxidant	[36]
Grifola frondosa	Hen of the woods	α-glucan, GFP1, GUMP-1-1,	Antidiabetic, Antiviral, Anticancer	[92]
Grifola umbellate	Umbrella polypore	GUMP-1-2		
Hericium erinaceus	Lion's mane mushroom	HEP3	Anticancer, immunomodulating, hypolipidemic,	[177]
	Hedgehog mushroom		antioxidant, neuro-protective	
Hohenbuehelia serotina	Late oyster	HSP	Antioxidant, immunomodulation	[46]
Hypsizigus marmoreus	White beech mushroom	–	Immunomodulation, angiotensin-converting enzyme	[94]
	Haesongi mushroom		inhibitory effect	
Inonotus obliquus	Chaga mushroom	β-glucan	Antioxidant, anticancer, immunomodulation	[57]
Lactarius lividatus	Milk-caps	β-glucan	Anti-inflammatory, antinociceptive	[62]
Lactarius rufus				
Laetiporus sulphurous	Crab of the woods	–	Antioxidant	[179]
Lentinus edodes	Shiitake	LT2	Antioxidant, immunomodulation	[98]
Lentinus squarrosulus	–			
Lepista sordid	–	LSPb1, LSPb2, LSPc1	Anticancer	[36]
Morchella esculenta	Morel mushroom	–	Antioxidant	[44]
Phellinus linteus	Black hoof mushroom	Sulfated β-glucan	Anticancer, antioxidant	[155]
Phellinus mori	Cracked-cap Polypore			
Phellinus rimosus				
Pleurotus abalones	King oyster mushroom	PAP-1, PAP-2, PAP-3	Anticancer, antilipemic, anti-inflammatory, antidiabetic,	[110]
Pleurotus eryngii	Florida oyster mushroom	PSPO-1a, PSPO-4a	antioxidant, immunomodulation	
Pleurotus florida	Oyster mushroom			
Pleurotus ostreatus	King tuber mushroom			
Pleurotus sajor-caju				
Pleurotus tuber-regium				
Poria cocos	China root	–	Anticancer, prebiotic	[83]
Russula albonigra	Blackening brittlegill	–	Antioxidant, immunomodulation	[103]
Schizophyllum commune	Split gill	Schizophyllan	Immunomodulation	[180]
Sparassis crispa	Cauliflower mushroom	β-glucan	Immunomodulation	[101]
Termitomyces robustus		PS-I, PS-II	Immunomodulation	[89]
Tremella fuciformis	White jelly mushroom	–	Antioxidant	[35]
Tricholoma matsutake	Pine mushroom	TMIP-1-4	Anticancer	[82]
Tricholoma mongolicum				
Volvariella volvacea	Paddy straw mushroom	–		[142]

NIH 3T3 cell line [35]. *Gomphidius rutilus* fruiting body-derived crude polysaccharides also showed strong reducing power [36]. The intracellular polysaccharides extracted from *Lepista sordida* mycelium showed significant antioxidative effect, as determined by DPPH assay [36]. In induced aging mice model, the polysaccharide significantly inhibited the formation of MDA and raised the activities of SOD, and GSH-Px in brain and serum in a dose-dependent manner [36]. A water soluble branched β-D-glucan (PS-I) from alkaline extract of the fruiting bodies of *Entoloma lividoalbum* (201 kDa) was found to possess hydroxyl and superoxide radical-scavenging activities [37]. The hot alkali extracted-polysaccharides from *Laetiporus sulphurous* had β-glucans antioxidant activity [179].

Ionizing radiations generate ROS in irradiated tissue. The ROS have damaging effect on the body. The *in vivo* radioprotective effect of a β-glucan from *Ganoderma lucidum* on radiation-induced damage was investigated in mice model [38]. The glucan when orally given to 4Gy-irradiated mice at a dose of 500 μg/kg body weight for 30 days, post irradiation survival rate increased by 66%. It was a remarkable effect as the same dose of radiation without any intervention causes 100% mortality, by generation of aberrant cells [38]. Also, radioprotective activity of polysaccharide protein complex from *Phellinus rimosus* has been found effective [39]. Intraperitoneal administration of the complex (5 and 10 mg/kg) to mice significantly increased leukocyte count, bone marrow cellularity, activities of antioxidant enzymes CAT, SOD, and GSH-Px in blood as well as intestinal mucosa. Tissue injury was attenuated as observed in intestinal jejunal mucosa [39].

3.2. Hepatoprotective

Oxidizing agents, mutagens, and ionizing radiations cause liver

damage by perturbing the pro-oxidant and antioxidant balance. In this regard, the protective effects of MPs against liver inflammations has been reviewed [40]. The effect of mushroom insoluble non-starch polysaccharides on the CCl_4-induced hepatic damage in rat model was evaluated [41]. The daily oral administration of the MP (100 and 200 mg/kg), led to significant decline in the serum activities of the liver enzymes, lipid peroxides, and nitric oxide (NO) in the liver. In addition, the reduced glutathione (GSH) and total proteins (TP) contents in liver homogenate also increased after treatment with the polysaccharide. Furthermore, histopathological examination of hepatic tissue revealed that the polysaccharide administration alone protected hepatocytes from the insults by oxidizing agents [41]. In another study, polysaccharides from *Flammulina velutipes* (FVP) showed hepatoprotective effect on CCl_4-induced acute liver injury rat model [42]. The effect was attributed to decreased alanine transaminase (ALT) and aspartate transferase (AST) levels, improved antioxidant effect. and attenuated pathological injury. GC–MS based metabonomic analysis identified sixteen different metabolites as biomarkers which belonged to glyoxylate and dicarboxylate metabolism, galactose metabolism, glycine, serine and threonine metabolism, glycerolipid metabolism, alanine, aspartate and glutamate metabolism, TCA cycle, pyruvate metabolism, arginine and proline metabolism [42].

Polysaccharide-protein complex from *Phellinus rimosus* (PPC-Pr) significantly protected against gamma radiation-induced suppression of antioxidant status in both liver and brain tissues [43]. The PPC-Pr complex was administered to Swiss albino mice (5 and 10 mg/kg body weight) intraperitoneally for 5 days consecutively, and then exposed to gamma irradiation (4 Gy). PPC-Pr treatment showed enhanced antioxidant enzymes such as GSH-Px, SOD, CAT, in a dose-dependent manner. Also, the treatment reduced the comet parameters (DNA damage) to a significant level, indicating its antioxidant as well as DNA protecting potential. Furthermore, improved survival rate of irradiated animals after PPC-Pr treatment as compared with the standard drug amifostine, suggesting potential therapeutic use of PPC-Pr in radiotherapy [43].

Morchella esculenta extracellular polysaccharides exhibited strong hydroxyl radical scavenging activity, moderate DPPH scavenging activity and reductive power. On oral administration over a period of 60 days in a D-galactose-induced aged mice model, it significantly inhibited the formation of MDA in liver and serum, and raised the activities of antioxidant enzymes in a dose-dependent manner [44]. Radiation-countering efficacy of *Hohenbuehelia serotina* polysaccharides (HSP) was investigated in irradiated mice. The HSP exerted an effective protection against radiation-induced injury by enhancing the antioxidant and immunomodulation activities [46]. The antioxidant and hepatoprotective effects of water-soluble polysaccharides and alkali-soluble polysaccharides from *Russula vinosa* on CCl_4-induced acute liver damage in mice was investigated [45]. The polysaccharide showed DPPH radical scavenging, hydrogen peroxide scavenging activity, lipid peroxidation inhibitory effect and moderate reducing power and chelating activity. For the *in vivo* hepatoprotective activity, the administration of extracts (200 mg/kg) significantly prevented the elevation in serum ALT and AST activities in acute liver damage and suppressed hepatic MDA formation. Better profile of antioxidants with augmented activities of SOD and GSH-Px in the liver was also observed [45].

Recently, Liu et al. hypothesized that MPs might protect the liver from CCl_4-induced hepatic damage *via* antioxidant mechanisms in mice [46]. The *in vivo* hepatoprotective activities of water-soluble polysaccharides (ORWP) and alkali-soluble polysaccharides (ORAP) from *Oudemansiella radicata* reduced serum ALT and AST activities, suppressed hepatic MDA formation, and stimulated the activities of hepatic SOD and GSH-Px [46]. Xu et al. reported antioxidant and hepatoprotective effects of enzymatic-extractable mycelia zinc polysaccharides from *Pleurotus eryngii* var. *tuoliensis* in hyperlipidemic mice [47]. The MP reduced hepatic lipid levels by moderating the serum enzyme activities (alkaline phosphatase (ALP), ALT and AST)) and serum lipid levels (total cholesterol (TC), total glycerides (TG), high density lipoprotein-cholesterol (HDL-C), high density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C)), enhancing the antioxidant enzymes (SOD, GSH-Px, CAT), and reducing lipid peroxidation (MDA and LPO). Furthermore, the *in vitro* scavenging results indicated that the inhibition effects of the MP on hydroxyl radicals and DPPH radicals reached 59.98 ± 6.29% and 37.01 ± 2.15%, respectively. These results suggested that the MP might be developed to treat hyperlipidemia and non-alcoholic fatty liver [47]. The findings reported above imply that MPs can be exploited to alleviate oxidant-caused maladies.

3.3. Anti-inflammatory

Inflammation, characterized by *calor* (heat), *dolor* (pain), *rubor* (redness), and tumor, can arise from perturbed metabolic or immunologic pathways [48,49]. If not restrained they lead to chronic disease like colitis, diabetes, cancer, nerve damage, among many others. MPs have shown anti-inflammatory roles in several *in vitro* and *in vivo* studies. However, a very limited number of clinical studies in humans have been conducted. Recently, the anti-inflammatory role of edible mushroom is extensively reviewed by Muszynska et al. [50]. The β-glucans from mushrooms have been found to influence the production of both pro-inflammatory (IL-1β, IL-6, and TNF-α) as well as anti-inflammatory (IL-10) cytokines [51]. Beta-Glucans also exhibit high-affinity binding to the immune cell surface receptors with pattern recognition receptors (PRRs) as pathogen-associated molecular patterns, *viz.* dectins-1, complementary receptor 3 (CR3, CD11b/CD18), or TLRs. Thus, β-glucans activate proliferation and maturation of immune cells, stimulate activation of macrophages and natural killer (NK) cells [50,52].

Lentinan from *L. edodes* is the best known β-glucan for the treatment of inflammation. The anti-inflammation effect of this β-glucan and its molecular mechanism was evaluated by monitoring body weight, disease activity index (DAI), inflammatory symptoms, levels of myeloperoxidase (MPO), NO, MDA and the expression of pro-inflammatory factors [53]. The oral administrations of β-glucan in mice decreased the contents of MDA and MPO of colonic tissues, and downregulated the expression of inducible nitric oxide synthase (iNOS), tumor necrosis factor (TNF-α), and interleukins (IL-1β and IL-6) in the colonic tissues of mice [54]. Schwartz and Hadar described that mushroom glucans may be used as inhibitors of inflammation in the prevention or adjuvant therapy of inflammatory bowel disease (IBD) [55].

Linear β-(1→3)-D-glucan of *Cordyceps militaris* showed *in vitro* and *in vivo* anti-inflammatory activities [56]. Glucan from *C. militaris* inhibited inflammation of THP-1 (human monocytic leukemia macrophages) cells *in vitro* by the inhibition of IL-1β, TNF-α, and COX-2 expression. *In vivo*, β-(1→3)-D-glucan also inhibited significantly the inflammatory phase of formalin-induced nociceptive response in LPS-induced inflammation mice model [56]. The glucans from *Inonotus obliquus* (Chaga mushroom) demonstrated anti-inflammatory property in RAW 264.7 cells by inhibiting the signaling pathway of nuclear factor-κB (NF-κB), COX-2, and iNOS [57]. The linear structured (1→6)-β-D-glucan from *A. bisporus* downregulated the expression of pro-inflammatory genes as well as inhibition of inflammatory reaction caused by lipopolysaccharides (LPS) in THP-1 cell line [58]. It was recently reported that α- and β-D-glucans from *Pleurotus albidus* differentially regulate lipid-induced inflammation and pro-inflammatory lipid-laden macrophage (foam cell) formation in THP-1 cells [59]. *Amanita muscaria* fruiting body-derived fuco-mannogalactan exerted anti-inflammatory and antinociceptive potential, and they produced potent inhibition of inflammatory pain in mice models [60]. *Pleurotus florida* extract exerted anti-inflammatory potential activity in rats as validated by hot plate method, tail flick method, acetic acid-induced writhing and formalin induced pain. The ameliorate activities are linked to MPs, along with flavonoids, and phenolics [61]. *Lactarius rufus* fruiting body yielded two

β-glucans with structural variations. The soluble MP possessed anti-inflammatory and antinociceptive potential, as evaluated by formalin model. The insoluble was devoid of the biological properties, suggesting that the solubility and/or branching degree can alter the activity of β-glucans [62]. *F. velutipes* polysaccharide composed of glucose, mannose and xylose, significantly decreased CD4+ CD8+, ICAM-1, and myeloperoxidase (expressed in neutrophil granulocytes) in serum and colon of normal and burned rats, indicating that the MP possessed strong anti-inflammatory activity [63].

The effect of polysaccharides (α- and β-glucans) from *Caripia montagnei* on 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in rat model was evaluated by examining their effects on interleukin levels (IL-1, IL-6), CAT, MPO and NO production [64]. Its glucans significantly reduced the levels of inflammatory mediators (IL-6 and NO) and enzyme activities (ALP and MPO), as confirmed by the reduction of cellular infiltration observed microscopically. The protective effect of these glucans on colonic tissue was also verified by increased CAT activity, confirming their anti-inflammatory potential. Hence, these glucans might attenuate or prevent the development of experimental colitis in mice by the inhibition of inflammatory mediators [64].

Chronic inflammation begets cancer. In some types of cancer, inflammation precedes malignant changes in the cells and in other types, oncogenic change incites an inflammatory microenvironment that promotes tumor development [65]. Inflammation and carcinogenesis are connected by some common pathways such as the activation of transcription factors, mainly NF-κB, signal transducer and activator of transcription 3 (STAT3) and hypoxia-inducible factor 1α (HIF1α), in tumor cells [66]. Schwartz and Hadar reviewed the possible mechanism of action of mushroom-derived glucans on IBD and associated cancer [55]. They recapitulated that oral consumption of glucans from mushrooms can be an efficient treatment to prevent colitis-associated dysplasia through modulation of mucosal inflammation and cell proliferation [67].

3.4. Anticancer

Cancer is a leading cause of death worldwide, and its frequency is rising in sync with all sorts of pollutions. Natural anticancer therapeutics is being sought-after in the wake of vicious side-effects and resistance of chemicals. In this regard, MPs have been evaluated for antitumor potency and promising results have been obtained. Multiple assays (MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; BrdU, 5-bromo-2'-deoxyuridine; LDH, lactate dehydrogenase)) and techniques (Western blotting, PCR, flow cytometry) have served to measure the efficacy of the polysaccharides by *in vitro*, *in vivo* and clinical trials. A number of insightful reviews on MPs have presented the success achieved and scopes ahead [5]. Nutritional, chemical and biological aspects of the MPs have been discussed [14]. *Antrodia camphorata* and *Ganoderma lucidium* extracts are well-studied anticancer agents [9]. Modern approaches of cancer treatment with implication of mushroom products, including DNA vaccinotherapy with mushroom immunomodulatory adjuvants, creation of pro-drugs with mushroom lectins that can recognize glycoconjugates on the cancer cell surface, development of nano-vectors *etc.* are being studied [68].

A. bisporus polysaccharide fractions, ABP-1 (2000 kDa) and ABP-2 (40–70 kDa), containing glucose, mannose, xylose, and fructose triggered the production of NO, IL-6, and TNF-α in murine macrophages [69]. The manipulation of macrophage function by the polysaccharides was partially mediated through activation of NF-κB, with the production p50/105 heterodimers. Both fractions had the ability to inhibit the growth of human breast cancer MCF-7 cells. The polysaccharide-treated murine Sarcoma 180 cells on subcutaneous implantation into mice has slow growth [69]. *A. brasiliensis* polysaccharides isolated from the fruiting body and mycelium showed different degree of biological efficacy. Further, sulfation lowered their molecular weight and improved functionality. Cytotoxicity on human lung adenocarcinoma tumor (A549) cells after 48 h incubation was investigated. The EC_{50} values of native polysaccharides (from fruiting body and mycelium), sulfated fruiting body and sulfated mycelium were $EC_{50} > 1500$ μg/mL, 605.6 μg/mL, and 342.1 μg/mL, respectively [70]. *Cordyceps militaris* derived polysaccharide exerted anti-angiogenesis activities [71]. Its structure and function could be modified with the addition of salt. *Pholiota adiposa* mycelia-derived polysaccharide demonstrated significant antitumor activity in mice, with high efficacy of a particular compound PAP80-2a [72]. A L-fucose-enriched fraction of *G. lucidum* polysaccharides was used to immunize mice [73]. It induced IgM antibodies production against Lewis lung carcinoma cells. The polysaccharide increased antibody-mediated cytotoxicity and attenuated the production of tumor-associated inflammatory mediators (such as monocyte chemoattractant protein-1). The mice achieved a significant increment in the peritoneal B1 B-cell population, suggesting the polysaccharide-mediated anti-glycan IgM production [73]. *G. lucidum* polysaccharide was used to study the impact on miRNA differential expression of human hepatocarcinoma (HepG2) cells [74]. The microarray data indicated that among the 61 differential expressed miRNAs, 17 were regulated significantly. It came forth that the polysaccharide can inhibit HepG2 cells directly through the regulation of hepatocarcinoma genes [74]. Cytotoxicity assays revealed that the extracellular polysaccharides of *P. ostreatus* exhibited highest antitumor activity towards human endometrial RL95 carcinoma cell line [75]. Some polysaccharides exhibited SOD-like activity correlated to the anticancer effect [75]. *Pleurotus abalonus* polysaccharide fractions (PAP-1, PAP-2 and PAP-3) were tested for anti-proliferative activity in human breast cancer MCF-7 cells [76]. The largest PAP-3 (kDa), an acidic polysaccharide fraction, was the most active in inhibiting the cancer cells with an IC50 of 193 μg/mL. PAP-3 caused apoptosis by mitochondria-mediated pathway involving the loss of mitochondrial membrane potential, the increase of Bax/Bcl-2 ratio, caspase-9/3 activation, and poly (ADP-ribose) polymerase (PARP) degradation, as well as intracellular ROS production. PAP-3 also induced the up-regulation of p53, and cell cycle arrest at the S phase. Intracellular ROS generation was recognized significant for cell death [76]. *Pleurotus pulmonarius* fruiting body extract and mycelia extract (2 or 20 mg) administered for 80 days inhibited colitis-associated colon carcinogenesis in mice. It was gathered from the lowered instances of aberrant crypt foci and of microadenomas. The modulation of cell proliferation, induction of apoptosis, and inhibition of inflammation was recognized as the mechanism [77]. *In vitro* study revealed that the extracts induced apoptosis in a dose-dependent manner and modulated the expression of Bcl-2, Bax, and cytochrome c, and inhibited the expression of TNF-α. Four water-soluble polysaccharides (LSPa1, LSPb1, LSPb2 and LSPc1) with molecular weight 156, 134, 96 and 57 kDa, respectively, were extracted from the fruiting bodies of *Lepista sordida*. The components LSPb1, LSPb2 and LSPc1 composed of glucose, mannose, rhamnose and arabinose exerted anti-proliferative effect on human laryngocarcinoma (Hep-2) cells. Two week treatment with LSPc1 reduced the Hep-2 cells-implanted mice tumor [78]. The anti-proliferative activity of *Boletus edulis* polysaccharides and glycoproteins against human colon adenocarcinoma LS180 cells was screened. The biopolymer BE3 inhibited cancer cell proliferation, which was accompanied by cell cycle arrest in the G0/G1-phase. Growth inhibition was associated with the modulation of the p16/cyclin D1/CDK4-6/pRb pathway (G1 regulatory pathway commonly targeted in tumorigenesis) [79]. Purified polysaccharide, BSF-A, isolated from *Boletus speciosus* Frost was investigated, which at a dose of 40 mg/kg, inhibited 62.449% of S180 tumors in mice [80]. There was weak expression of the pro-inflammatory cytokines TNF-α, IL-6, IL-1β and iNOS mRNA in the untreated macrophages. BSF-A increased the above in the cancer cells significantly in a dose-dependent manner. Also, the fraction exerted a time- and dose-dependent inhibition of the Hep-2 cells, with the concentration of 400 μg/ml having the highest inhibitory rate [80]. Effect of *I. obliquus* polysaccharide extract on human neurogliocytoma U251 cell line was investigated [81]. MTT

assay showed reduced cell viability. The extract decreased the expression of Bcl-2 and increased the expression of caspase-3. Dose-dependent effect was evident [81]. A polysaccharide fraction from *Tricholoma matsutake* composed of glucose, galactose and mannose was evaluated for its antitumor efficacy [82]. Its anti-proliferative activities (at 4 mg/ml dose) on the growth of HepG2 and A549 cells were 67.98% and 59.04%, respectively [82]. *Poria cocos* polysaccharides and other derivatives possessed potential to be developed an adjuvant therapy for cancer. The successes so far and scopes ahead in this direction have been reviewed [83]. Five novel polysaccharides (SLNT1, SLNT2, JLNT1, JLNT2, and JLNT3) were isolated from the fruiting body of *L. edodes*. SLNT1 and JLNT1 treatment conferred significant antitumor effects on H22 cell-bearing mice, 65.41% and 61.07%, respectively. Both the components significantly increased the levels of serum IL-2 and TNF-α and induced tumor cell apoptosis [84].Sulfated β-glucan from *Phellinus linteus* exhibited growth inhibitory activity against human colon cancer SNU-C2A cells [85]. Two polysaccharides (GUMP-1-1 and GUMP-1-2) isolated from *Grifola umbellata* mycelia inhibited the growth of mouse hepatoma (H22) cell line implanted tumor. Also, the polysaccharides enhanced the spleen index and splenocyte proliferation of the test mice. The antitumor activity of the polysaccharides were linked to probable immune modulation [86]. HEG-5, a novel polysaccharide-protein from the fermented mycelia of *H. erinaceus* CZ-2 could induce apoptosis and cell cycle arrest of human gastric cancer cells SGC-7901 *via* caspase-8/-3-dependent, p53-dependent mitochondrial-mediated and PI3k/Akt signaling [178]. Schizophyllan from *S. commune* inhibited the development of mammary and hepatic carcinomas, decreasing their proliferation [180].

Only a few studies have investigated the synergistic anticancer effects elicited by combinations of MPs. The blended MPs are hypothesized to exhibit different cytotoxic effects on various tumor cells and thus be more effective. A study proved the theory as the mix of three commercial mushroom products exhibited stronger cytotoxic effects on human tumor cell lines [6]. Further, the combination of polysaccharides from *L. edodes* and *Tricholoma matsutake* improved the efficacy of 5-fluorouracil-mediated inhibition of mouse hepatoma H22 cell growth implanted in mice. The tumor mass significantly shrunk. Serum levels of TNF-α, IL-2, and IFN-γ, frequencies of CD4 + and CD8 + T cells in the spleen, and splenic NK and cyotoxic T lymphocytes (CTL) activities were significantly increased [87]. *Hericium erinaceus* polysaccharides could promote doxorubicin-mediated apoptosis of cancer cells, which might be exploited for drug-resistant human hepatocellular carcinoma treatment [177].

The anticancer mechanisms have not been deciphered optimally. Cancer propagates and subverts host immunity in multiple ways. Structures of the MPs decide the cancer pathways to intervene. MPs significantly enhanced the expression of p27(Kip) in human hepatocellular liver carcinoma HepG2 and Bel-7404 cells, while suppressing the activity of cyclin D1/CDK4 and/or cyclin E/CDK2. The polysaccharides suppressed protein kinase B (Akt) activity through the inhibition of Akt phosphorylation at Thr (308) and/or Ser (473). The growth of the studied cancer cells was suppressed by the up-regulation of PI3K (a subunit of phosphoinositide 3-kinase) and phospho-PTEN (phosphatase and tensin homolog), known to modulate Akt activity. Also, the MPs activated the mitochondria-mediated apoptosis pathway by stimulating the activation of Bcl-2 family proteins to release cytochrome c and Smac and cleave caspase-9 and caspase-3 in the cancer cells. These factors contribute to cell cycle arrest in G1 and/or S phase and induction of apoptosis [88]. Fig. 2 shows the cancer intervention pathways of MPs.

3.5. Immunomodulation

Countless research findings have reported the excellent immuomodulation potential of mushrooms. In fact, most of the studies attribute the polysaccharides to be bioactive components. The β-glucans have been validated as the biological response modifiers (BRMs). In this context, some important findings have been delineated below. The hot water extract from the fruiting body of *Termitomyces robustus* showed significant macrophage, splenocyte, and thymocyte activation potential. The polysaccharides containing water soluble PS I and water insoluble PS II (termitan) fractions were attributed to bestow the immune stimulation [89]. *H. serotina* polysaccharide (200 mg/kg) significantly promoted the proliferation of splenocytes and prevented the decline in blood WBC and hematopoietic function in irradiated mice [90]. The *in vivo* activity was further verified by the assay of monocyte phagocytosis [90]. Several studies indicated the immunomodulation activity of MPs is owing to the increased cytokine production. *I. obliquus* sclerotia and mycelia-derived polysaccharides showed immunomodulation by significantly stimulating the secretion of TNF-α, IFN-γ, IL-1β, and IL-2 in human peripheral blood mononuclear cells (PBMCs), in dose-dependent manner [91]. *Grifola frondosa* polysaccharide with a molecular mass of 2.6 kDa significantly enhanced the production of NO and secretion of cytokines (TNF-α, IL-1β, and IL-δ) from macrophages *in vitro* [92]. Another study found a water-soluble homogeneous polysaccharide 26.2 kDa from the fruiting body of same mushroom. It was effective inducer of TNF-α and IL-6 secretion in murine resident peritoneal macrophages RAW264.7 cells. It bound to dendritic cell-associated Dectin-1, leading to the activation of Syk (protein tyrosine kinase), NF-κB signaling and enhancement of TNF-α production [93]. Some fractions of *Hypsizigus marmoreus* exopolysaccharides, ranging from 6 to 150 kDa, and characterized as rhamnogalacturonan type I and arabinogalactan type II, exhibited significant macrophage stimulating activity [94]. Hot water extract of *G. lucidum* fruit bodies yielded a low-molecular-weight (5.1 kDa) polysaccharide (TB3-2-2), composed of galactose and glucose, which augmented the proliferation of mouse spleen lymphocytes and the expression of IL-6 [95].

A water-soluble glucan from the hot aqueous extract of *Calocybe indica* fruit bodies was investigated for its impact on immunity. This glucan stimulated the splenocytes and thymocytes [96]. Proliferation of splenocytes (cells present in spleen that include T cells, B cells, dendritic cells, *etc.*) and thymocytes (hematopoietic cells present in thymus responsible for generation of T cells) is an indicator of immunostimulation. The splenocyte and thymocyte stimulation tests were carried out with the polysaccharide in mouse cell culture medium by the MTT method [96].

The extracts from *A. bisporus* activate bone marrow-derived macrophages manifested in NO production, without activating enterocytes and thereby, stimulating the immune response in depressed states of immunity [13]. However, *A. blazei* Murill and *P. linteus* had no effect at all. Structural analysis of *A. bisporus* compared to *A. blazei* Murill suggests that the branching of the β-glucan chain is essential for immune-stimulating activity. Semi-purified polysaccharide extracts from *A. bisporus* mannogalactan and *A. brasiliensis* β-glucan species stimulated the production of pro-inflammatory cytokines and enzymes, while the polysaccharide extract of *A. brasiliensis* reduced the synthesis of these cytokines induced by LPS, suggesting programmable immunomodulation [97]. The extracts induced a comparable increment in the transcription of the pro-inflammatory cytokine genes IL-1β and TNF-α as well as of COX-2 in induced-differentiated THP-1 cells. Pro-inflammatory effects of bacterial LPS in this assay could be reduced significantly by the simultaneous addition of *A. brasiliensis* extract.

A water-soluble glucan, isolated from the alkaline extract of the fruit bodies of *Lentinus squarrosulus* could activate macrophages as well as splenocytes and thymocytes at 10 μg/mL [98]. *Cordyceps taii* polysaccharides composed of glucose, mannose, and galactose possessed potent antioxidant activity closely associated with immune function enhancement and free radical scavenging. The polysaccharides also significantly enhanced the antioxidant enzyme activities (SOD, CAT, and GSH-Px) and markedly decreased the MDA production of lipid peroxidation in a D-galactose-induced aging mouse model [99]. A novel

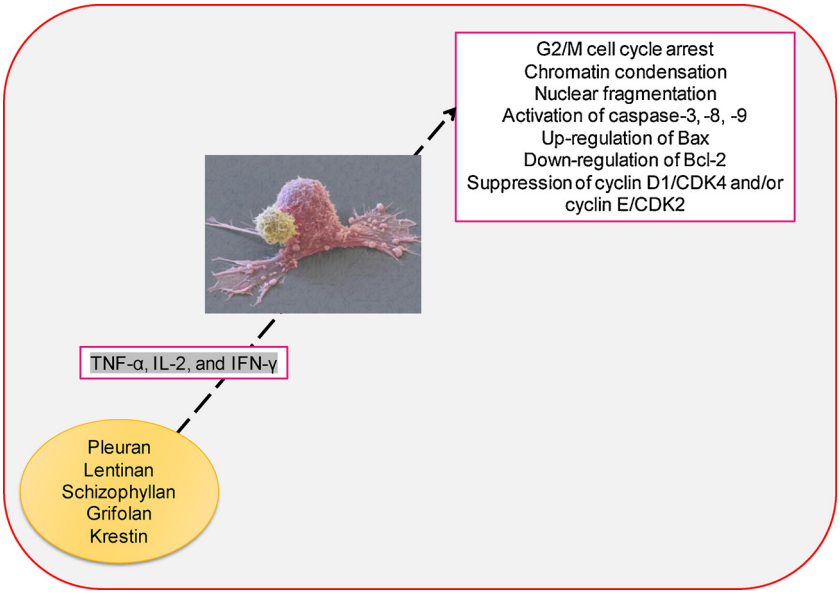

Fig. 2. Anticancer mechanism of mushroom polysaccharides.

polysaccharide (CP2-S) composed of glucose was purified from *Cordyceps militaris* fruit bodies. Immunostimulating experiments implied that CP2-S can stimulate NO production, phagocytosis, respiratory burst activity, and secretion of IL-1β and IL-2 of macrophages, suggesting immunomodulator prospects [100]. Soluble β-glucan preparation from *Sparassis crispa* was a six-branched 1,3-β-D-glucan. Leukocytes from DBA/2 mice are highly sensitive to this MP, producing cytokines *in vitro*. Oral administration of the MP to mice led to IFN-γ and IL-6 induction by the immune cells in Peyer's patches [101]. The immune activity of *Pleurotus tuber-regium* polysaccharide was investigated using the mice peritoneal macrophage model [31]. Both water and alkaline-extracted MPs showed a significant enhancement effect on the macrophage phagocytosis, and could activate the related enzymes, such as ATPases, lysozyme, and LDH, which are responsible for providing the maturation and proliferation process of macrophages with sufficient energy. Also, the levels of intracellular cytokines (IL-1, TNF-α, NO) were significantly increased after being treated with polysaccharides [31]. A water-soluble polysaccharide of *C. indica* var. APK2 (composed of D-glucose, D-galactose, and L-fucose) showed immunoenhancing (macrophage, splenocyte, thymocyte, and bone marrow activation) properties [102]. A water soluble β-glucan (195 kDa) was isolated from the alkaline extract *Russula albonigra*. This β-glucan showed *in vitro* macrophage activation by NO production as well as splenocytes and thymocytes proliferation [103]. The innate and adaptive immunity-eliciting effect of *L. edodes* polysaccharides has been reviewed [104]. Histology assays of the livers of mice infected with a sublethal dose of *Salmonella* Typhimurium showed that bioprocessed polysaccharide (BPP) from *L. edodes* liquid mycelial culture supplemented with black rice bran, administered daily through an intraperitoneal or oral route, protected against liver necrosis, a biomarker of *in vivo* salmonellosis [105]. The lifespan of mice infected with a lethal dose of *Salmonella* (1×10^5 CFU) was significantly extended by intraperitoneal injection or oral administration of the BPP without side effects. These results suggest that the activity of BPP against bacterial infection in mice occurs mainly through the activation of macrophage-mediated immune response, resulting from augmented Th1 immunity [105]. ELISA analysis on cytokine production by Th1 and Th2 immune cells from splenocytes of infected mice showed significant increment in the levels of the Th1 cytokines such as IL-1β, IL-2, IL-6, and IL-12. The immunopotentiation effects and immune receptors for *Coriolus versicolor* polysaccharides (CVP) were characterized. CVP can bind and induce B cell activation using membrane Ig and TLR4 as potential immune receptors. CVP activates mouse B cells through the mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways [106]. The immunomodulatory effect of *Antrodia camphorata* mycelia-derived polysaccharides on pathogen-free chickens was studied [107]. When fed 5 mg of the extract for 35 consecutive days, followed by sacrificing, it was observed that the immune organ indices (except for the thymus) were higher after 14 days. The higher rate of proliferation and positive T lymphocytes in blood implied immunomodulation in chickens [107].

A water-soluble polysaccharide was isolated from the aqueous extract of the fruit bodies of somatic hybrid PCH9FB, protoplast fusion of *Pleurotus florida* and *C. indica*. It contained galactose, fucose, and glucose, and it showed macrophage, splenocyte, thymocyte activation as well as antioxidant property [108]. A water-soluble heteropolysaccharide (PS-I) having molecular weight 201 kDa was isolated from the fruit bodies of hybrid mushroom pfle 1p, a protoplast fusion between *P. florida* and *L. edodes*. The heteropolysaccharide containing glucose, galactose, and mannose (4:2:1), showed *in vitro* macrophage activation by NO production and also stimulated splenocytes and thymocytes [109].

3.6. Antilipemic

The correlation between cholesterol and the risk of coronary heart disease has raised alarm among consumers. In this context, the cholesterol-lowering effect is another interesting aspect of mushroom polysaccharides. A 30–38 kDa purified polysaccharide from *P. eryngii* exerted strong inhibitory effect on lipid accumulation. This polysaccharide composed of mannose, glucose and galactose interfered with the development of macrophage-derived foam cells, which is recognized as the hallmark of early atherosclerosis, in foam-cell model [110]. *Catathelasma ventricosum* polysaccharides administration to streptozotocin (STZ)-induced diabetic mice for 30 days caused decrease in the concentrations of TC, TGs, LDL-C and increased the concentrations of HDL-C [111]. The crude polysaccharide fraction from the water extract of *A. bisporus, L. edodes*, and *P. ostreatus* contained mainly β-glucans along with other glucans [112]. The fermentability of β-glucans and the property to form viscous solutions in the human gut is implicated vital for the biological importance [26].

3.7. Antidiabetic

Diabetes mellitus has assumed epidemic proportion, with alarming

rise throughout the world. Inflammation-replete modern lifestyle is leading to insulin resistance [113]. The hypoglycemic activity of *G. frondosa* polysaccharide (GFP) on insulin resistance of HepG2 cell was investigated. The ameliorative role of GFP on insulin resistance was observed, which occurred by the promotion glucose metabolism and stimulation intracellular glycogen synthesis through Akt/GSK-3 pathway [114]. Recently, the antidiabetic effects of *I. obliquus* polysaccharides on high fat diet and STZ-induced type 2 diabetic mice were studied. Oral administration of the MP (900 mg/kg) exhibited significant antihyperglycemic effect, where the underlying mechanism might be the activation of phosphatidylinositol 3-kinase (PI3K) and Akt phosphorylation as well as the translocation of GLUT4 in diabetic mice [115]. The effect of *P. tuber-regium* extracellular polysaccharides on fatty acid composition and liver peroxisome proliferator-activated receptor-alpha (PPAR-α) expression in obese-diabetic rats was investigated. On oral administration of the MP (20 mg/kg body weight/8-week), the elevated fatty acid ratio n-6/n-3 in the liver and plasma of obese-diabetic rats attenuated. Also, the elevated serum TC, TG and LDL concentrations were controlled. The results suggested that the stable fatty acid components and activated PPAR-α by the MP might be ameliorating hyperglycemia [116]. The β-glucan rich polysaccharide of *Pleurotus sajor-caju* was investigated for *in vivo* efficacy against diabetes mellitus and inflammation in C57BL/6 J mice fed a high-fat diet for 16 weeks. The glucan-rich MP (240 mg/kg, body weight) improved glucose tolerance, attenuated hyperglycemia and insulin resistance, by up-regulating the expression of glucose transporter protein 4 (GLUT-4) and adiponectin genes, and down-regulating the expression of inflammatory markers (IL-6, TNF-α, SAA2, CRP and MCP-1) *via* the attenuation of NF-κB pathway [117].

P. florida polysaccharide was investigated for its hypoglycemic potential in induced-diabetic rats [118]. At 200 and 400 mg/kg doses, blood glucose, serum cholesterol, triglycerides, as well as urine glucose and ketones were lowered. Also, MDA level dipped and that of antioxidant enzymes SOD, CAT, and reduced glutathione were restored suggesting the potential of this MP in resolving hyperglycemia and hypercholesteremia associated with diabetes [118]. In a study, the polysaccharide from the fruiting body of *C. ventricosum* (CVP-1S) has showed antioxidant, hypolipidemic, and hypoglycemic activities along with protective action on the liver, kidney, and pancreas from diabetes-induced injuries in STZ-induced diabetic mice [119]. Furthermore, selenylation at C-6 position of the mycelial polysaccharide from *C. ventricosum* (mCVP-1Ss) significantly enhanced the antihyperglycemic, antihyperlipidemic and antidiabetic activities in STZ-induced diabetic mice [120].

3.8. Antibacterial/Antiviral/Nano

A crude polysaccharide from *Auricularia auricula-judae* showed *in vitro* activities against the food-borne pathogens *Escherichia coli* and *Staphylococcus aureus* [121]. The sulfated polysaccharide from *P. eryngii* also inhibited *E. coli* and *S. aureus* [122]. In an another study, a dose-dependent antimicrobial effect of sulfated polysaccharide from *G. lucidum* was observed against *E. coli*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Salmonella*, *Listeria monocytogenes*, *Shigella sonnei*, *Staphylococcus aureus*, *S. epidermidis*, and methicillin-susceptible-*S. aureus* ATCC 292123 [123]. The low molecular weight fraction from *L. edodes* displayed anti-adhesive properties towards the oral pathogens *Streptococcus mutans* and *Prevotella intermedia* [124]. Polysaccharide from spent mushroom substrate of *L. edodes* also displayed antibacterial activity against *E. coli, S. aureus* and *Sarcina lutea* [125].

The protective action of MPs against bacterial infections through the modulation of immune system has been evidenced by several *in vivo* studies. Polysaccharide from *L. edodes* with added black rice bran protected mice against *Salmonella* lipopolysaccharide-induced endotoxemia with the stimulation of innate immunity [126]. In another parallel study, the same *L. edodes* polysaccharide fraction protected against salmonellosis through the activation of macrophage-mediated immune response resulting from upregulation of the Th1 immunity. Polysaccharides were extracted from *A. auricula* and chemically modified by chlorosulfonic acid-pyridine method. Both native and sulfated polysaccharide exhibited inhibition towards *in vitro* culture of Newcastle disease virus, though the latter exerted superior efficacy [127]. The adjuvanticity of *G. lucidum* polysaccharide (GLP) for Newcastle disease vaccine was investigated *in vitro* and *in vivo*. This study demonstrated that GLP enhanced lymphocyte proliferation and humoral immunity, and upregulated expression of IFN-γ gene as well, suggesting its application as novel immune adjuvant [128]. A heteropolysaccharide from *P. abalones* (120 kDa), with alpha configuration inhibited HIV-1 reverse transcriptase [129]. Recently, the antiviral activity *G. frondosa* heteropolysaccharide (GFP1) and its mechanism of action against enterovirus 71 (EV71) has been reported [130]. GFP1 blocked EV71 viral replication and suppressed viral VP1 protein (immunodominant capsid protein) expression and genomic RNA synthesis. Moreover, GFP1 inhibited the EV71-induced apoptosis by decreasing the caspase-3 activation and by the downregulation of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) [130].

Silver nanoparticles (AgNPs) when conjugated to polysaccharides are reported to improve the latter's antibacterial efficacy. *P. florida* blue variant-derived glucan was used to synthesize silver nanoparticles (AgNPs) [131]. The nano-glucan conjugates exhibited antibacterial activity against multiple antibiotic resistant (MAR) bacterium *Klebsiella pneumoniae* YSI6A in a dose-dependent manner. The conjugate acted synergistically with four medicinal antibiotics (ampicillin, azithromycin, cefepime and tetracycline) to inhibit nearly 100% bacterial growth, indicating an effective way to control the MAR bacteria. The antibacterial activity was assumed to be due to the damage of cellular macromolecules by the generation of ROS [131]. In another study, AgNPs synthesized using a heteropolysaccharide from *L. squarrosulus* displayed antibacterial activity against MAR *E. coli* [132]. The nano-polysaccharide conjugate in combination with four antibiotics (ampicillin, azithromycin, kanamycin and netilmicin) to which *E. coli* was resistant, showed synergistic effect to inhibit complete bacterial growth. Therefore, it can be inferred that nanoparticle conjugated MPs are more effective than normal-sized particles in penetrating and destroying bacteria and viruses [132].

3.9. Prebiotics

Recent findings have reported the prebiotic prospects of certain mushroom polysaccharides. Prebiotics are non-digestible food ingredients that benefit host health by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon [133]. Fermentation of prebiotics in the colon results in a large number of physiologic effects which include the higher density of bifidobacteria and lactobacilli in the colon [134]. Recently, Singdevsachan et al. appraised in detail the prebiotic potential of mushroom polysaccharides coupled with their immunomodulation and anti-cancer effects [135]. Saman et al. evaluated edible mushrooms as a source of prebiotic with thorough explanation on its concept and application [136]. Literature reports that polysaccharides from *Pleurotus* sp., *L. edodes*, *T. fuciformis*, and *A. bisporus*, among others, have prebiotic activity. The branched β-1,3-1,6-glucan and linear α-1,3-glucan from *P. ostreatus* and *P. eryngii*, respectively, displayed prebiotic activity probiotic strains of *Lactobacillus*, *Bifidobacterium* and *Enterococcus* [137]. Currently, pleuran from *P. ostreatus* and lentinan from *L. edodes* are the most-frequently used β-glucans as prebiotics [135]. Furthermore, mushroom by-products owing to their richness in polysaccharides, sustain the growth of probiotic strains. The polysaccharides from *L. edodes* stripe, *P. eryngii* base and *F. velutipes* base enhanced the survival of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium longum* subsp. *longum* during cold storage. Also, the mushroom discards promoted the viability of the

probiotic strains in simulated gastric and bile juice conditions [138]. Contribution of fungal, mainly MPs in nutraceuticals have been comprehensively reviewed [139]. Recently, polysaccharides derived from mycelia and fruiting bodies of *G. lucidum* and *P. cocos* have also shown prebiotic potential by remodeling the gut microbiota composition. The water-extracted polysaccharides fed daily at a dose of 750 mg/kg to C57BL/6 J mice for 15 days reduced pathogenic bacteria, while augmenting beneficial bacteria [140].

4. Production, extraction and structural characterization of mushroom polysaccharides

4.1. Production

Submerged fermentation (batch, fed-batch and repeated fed-batch) has been used successfully for the efficient production of mushroom polysaccharides. In submerged fermentation of *G. lucidum*, structural features and the yield of produced polysaccharide were highly influenced by the medium culture conditions. Higher glucose levels in growth medium and pH 4–6 favored the formation of polysaccharide with a higher abundance of (1→3) linkages. In contrast, polysaccharide with higher branching degree was obtained with low levels of peptone in growth medium and pH 5 [141]. The ability of *Volvariella volvacea* for the production of biomass, lipids and polysaccharides in static liquid, submerged static and agitated cultures were studied. Agitation did not show any impact on the biomass, polysaccharide production, but it increased total lipid in dry weight quantities [142]. Another study involving static- and shake-flask fermentation using 11 different mushroom species revealed that the growth medium favorable for biomass production is not suitable for polysaccharide production and *vice versa* [143]. Conversely, in fed-batch fermentation of *G. lucidum*, sucrose enhanced the biomass and polysaccharide production by 62% and 50%, respectively [144]. Submerged fermentation of *Trametes trogii* in 5 l stirred-tank and airlift reactors for 5 days was investigated for the production of polysaccharides. Analysis of the morphological parameters of the pellet and viscosity of the broth suggested a positive correlation between pellet compactness and polysaccharide content [145]. Repeated fed-batch cultivation was reported to be better than that of submerged batch cultivation for polysaccharide production from *G. lucidum* [146]. The polysaccharides obtained from the mycelia of *P. ostreatus* in batch bioreactor also displayed significant antioxidant activities [30].

4.2. Improvement of polysaccharide production by gene manipulation

Gene manipulation has been successfully applied to improve the production of MPs. Phosphoglucomutase (PGM), UDP-glucose pyrophosphorylase (UGP) and β-1,3-glucan synthase (GLS) are important enzymes for the biosynthesis of the MPs [147]. PGM and UGP are involved in the biosynthetic pathway of nucleotide sugar precursors where PGM catalyzes the inter conversion of glucose-6-phosphate into glucose-1-phosphate, and UGP catalyzes the reversible conversion of glucose-1-phosphate and UTP into UDP-D-glucose. GLS catalyzes the repetitive addition of glucose from UDP-glucose to growing glycan chains [147]. The biosynthesis pathway and putative genes involved in polysaccharide (1,3-β-glucan and 1,6-β-glucan) from *Agrocybe aegerita* were identified using transcriptomic analysis [148]. In *A. aegerita*, UDP-glucose was the precursor and its biosynthesis involved glucokinase, PGM, and UGP. Five GLSs from *A. aegerita* transcriptome were also identified, playing an important role in 1,3-β-glucans biosynthesis. Genes encoding these enzymes were identified and their expression analysis revealed up-regulation in fruiting body. In addition, gene encoding the β-glucan biosynthesis-associated protein KRE6 was also discovered in A. aegerita transcriptome, which play key role in the biosynthesis of 1,6-β-glucans [148]. Thus, the manipulation of polysaccharide biosynthetic genes may be an important approach to improve polysaccharide production. Chai et al. improved the production of *P. ostreatus* β-glucan from 32% to 132% *via* promoter engineering. They replaced the promoter of 1,3-β-glucan synthase gene of *P. ostreatus* by the promoter of glyceraldehyde-3-phosphate dehydrogenase gene of *Aspergillus nidulans* using homologous recombination [149]. Ji et al. improved the polysaccharide production in *G. lucidum* by engineering its biosynthetic pathway through the overexpression of the homologous UGP gene. The intra- and extra-cellular polysaccharide production in *G. lucidum* overexpressing the UGP gene were higher by 42% and 36%, respectively, than those of the wild type strain [150]. In another parallel study, Xu et al. [149] improved the polysaccharide production in *G. lucidum via* the overexpression of PGM gene. The intra- and extra-cellular polysaccharide production in the engineered strain was enhanced by 40.5 and 44.3% when compared to the wild type [151]. Recently, Li et al. reported the improved polysaccharide production and up-regulation of polysaccharide biosynthetic genes in a submerged culture of *G. lucidum* by the heterologous expression of the gram-negative aerobic bacterium *Vitreoscilla* hemoglobin (VHb) gene [152]. One dimensional gel electrophoresis-based proteomic analysis revealed the stimulatory mechanism of Tween 80 on the mycelial growth and exopolysaccharide production by *P. tuber-regium* [153]. The up-regulation of ATP:citrate lyase isoform 2 might suppressed the activity of tricarboxylic acid cycle and, thereby stimulated exopolysaccharide production. These findings will provide an insight about inceptive mushroom proteomics [153].

4.3. Extraction techniques

Extraction is an important step that influences downstream analysis. Studies have found that the extraction techniques have profound influence on the yield and structural characteristic of the polysaccharides, as well as the biological activities [90]. Different activity of aqueous and alkaline extracts was observed, with further variations in fractions. This is understandable as components of different polarity resolve into different fractions. The polysaccharides need to be effectively extracted for their bioactivities. Common extraction techniques used for mushroom polysaccharides include hot water, alkali, pressure, enzyme, ultrasonic wave, microwave, and supercritical fluid extraction [154]. A study reported that the alkaline extract of *P. tuber-regium* exerted better immunomodulation than that of water extract [31]. The hot aqueous and alkali extraction of polysaccharides from *P. tuber-regium* resulted in polysaccharides with different color, solubility, molecular weight and monosaccharide composition [31]. Water soluble polysaccharides of *P. linteus* were extracted using hot water, 1% ammonium oxalate [$(NH_4)_2C_2O_4$], and 1.25 M sodium hydroxide (NaOH)/sodium borohydride ($NaBH_4$) solutions. The hot water extraction resulted in maximum yield, but the alkali and acid extracted polysaccharides showed stronger antioxidant activities [155]. The effect of four extraction methods (hot water, enzyme assistance, ultrasonic assistance and ultrasonic-enzyme assistance) was studied on the yields, preliminary structure and antioxidant activities of *H. serotina* polysaccharides [90]. Among the four methods, ultrasonic-enzyme assistant extraction (UAEA) was found to be best with maximum yield of polysaccharides and highest antioxidant activities. However, no significant structural differences were observed with the different extraction procedures [156]. Polysaccharides from *F. velutipes* extracted by hot water, ultrasonic, microwave or enzymatic methods showed similar physicochemical properties. Enzymatic extraction demonstrated better antioxidant activities against hydroxyl radical as well as improved metal chelating activity. Ultrasonic-extracted MP showed higher DPPH scavenging activity, but hot water-extracted MP exhibited higher antioxidant activity in reducing power [157]. Five polysaccharides were obtained from *A. blazei* Murrill (ABM) through different extraction methods including hot water extraction, single enzyme extraction (pectinase, cellulase or papain) and compound enzymes extraction (cellulase:pectinase:papain) [158]. The polysaccharide yield with studied extraction methods follows the order;

compound enzymes extract > cellulase-enzyme extract > pectinase-enzyme extract > papain-enzyme extract > hot-water extract. Compound enzymes extracts had the strongest reducing power and highest scavenging effects on hydroxyl radical, DPPH free radical and 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) free radical, whereas, the hot water extracts exhibited antioxidant activities [158]. Smiderle et al. observed similar efficiency in microwave-assisted extraction (MAE) and pressurized liquid extraction of β-glucans from *P. ostreatus* and *G. lucidum* fruiting bodies [159]. In a comparative study, enzyme-assisted (cellulase, papain and pectinase)-extraction of polysaccharide from *L. edodes* displayed improved yield as compared to hot water extraction [160]. Ultrasonic-assisted extraction (UAE) is reported to be an inexpensive, environment-friendly, fast and efficient technology for the extraction of mushroom polysaccharides. Ultrasonic technique was an effective method to extract bioactive polysaccharides from *I. obliquus* [161]. The optimal ultrasonic conditions to obtain the highest recovery of polysaccharides were 80 min, 75 °C, and 100 W. While the optimal ultrasonic conditions to obtain the strongest DPPH scavenging activity of polysaccharide were 80 min, 95 °C, and 160 w. The structural analysis demonstrated that ultrasonic treatment might cause the physicochemical changes in MP conformation and changes in molecular weight distribution by the degradation of polysaccharide chain, but not the main groups [161]. Ultrasound-assisted extracted polysaccharides from the fruiting body of *H. serotina* also displayed differences in the surface morphology as revealed by scanning electron microscopy (SEM). The microscopic analysis demonstrated more spongy structure with a defined fracture of ultrasound-assisted extracted polysaccharides as compared with that of hot extracted polysaccharides. Ultrasonic vibration increases the number of cavitation formed as well as the mass transfer rates to prompt the migration of target compounds from the material to the surroundings, resulting in higher extraction efficiency of polysaccharides [162].

4.4. Purification

Following extraction, polysaccharides are subjected to several purification steps to remove proteins, phenolic compounds, monosaccharides, amino acids or other contaminants. Proteins can be removed by precipitation with trichloroacetic acid (20%, w/v), using Sevag method, by treatment with the enzyme protease or phenolic reagent. The use of two or three volumes of cold ethanol separates high molecular weight polysaccharides from the low molecular weight ones [163]. The partially-purified polysaccharide extracts are usually fractionated using size-exclusion chromatography (SEC) and ion-exchange chromatography (IEC), based on their size or charge, respectively. The serial combination of multiple SEC columns or sequential combination of weak IEC and SEC column allow higher separation of MPs. Sephadex and DEAE-cellulose columns have been successfully used to separate MPs using SEC and IEC. Ultrasound assisted extracted *Tricholoma matsutake* crude polysaccharide was purified by DEAE-cellulose 52 chromatography and Sephadex G-100 to afford two fractions, TMP-1 and TMP-2 [82]. Hot water extracted polysaccharide from *Coprinus comatus* was also fractionated by sequential weak anion-exchange (DEAE Sepharose CL-6B) and size-exclusion (Sepharose CL-4B) chromatography [164]. Some less frequently used techniques for the purification of MPs include treatment with Fehling solution, closed dialysis, ultrafiltration (MWCO, 5–1000 kDa), and nanofiltration [163].

Drying process (freeze-drying, oven-drying, spray-drying, vacuum-drying and microwave drying) significantly influences the physicochemical properties of polysaccharides such as chemical composition, molecular weight distribution, viscosity, and conformation. The polysaccharides from *I. obliquus* (IOPS) was prepared by hot air drying, vacuum drying and freeze-drying methods. The three dying methods acted differently on the physicochemical and antioxidant properties of IOPS. Freeze-drying resulted in the maximum polysaccharide yield, highest neutral sugar content and uronic acid content with lower molecular weight distribution, and a hyperbranched conformation with triple helix, higher antioxidant abilities on DPPH radical scavenging, ferric-reducing power and lipid peroxidation inhibition activity [57]. Another study also compared different drying methods for *A. blazei* Murrill polysaccharides (ABMP), where freeze-drying resulted in ABMP with higher neutral sugar, polysaccharide yield, uronic acid content, and stronger antioxidant abilities (hydroxyl radical, DPPH radical, ABTS radical scavenging and Fe^{2+}-chelating activities) [165]. Recently, the effects of freeze-drying, vacuum-drying and spray-drying methods were also investigated on chemical composition, morphology and antioxidant activity of the polysaccharide from spent *L. edodes* substrate. Freeze-drying was found to be the best with the highest polysaccharide yield and maximum antioxidant effects [166]. Thus, freeze-drying method serves as a better choice for the preparation of antioxidant polysaccharides.

4.5. Structure determination

Structure is an important decisive factor in biological specificity of a comound. A study reports that the antitumor traits of the polysaccharides heavily rely on their solubility, molecular weight, branching configuration, conformation, and chemical modifications [14]. MPs are present mostly as linear and branched glucans with diversified chemical structures. The most common type consists of a backbone of β-D-glucose (1→3)-linked frequently branched at O-6 by β-D-glucose residues as side chains. However, it is possible to distinguish α-, β- and mixed D-glucans. Further discrimination could be made, based on glycosidic bond position in a pyranoid ring, distribution of specific glycosidic bonds along the chain, branching and molecular weight. Some MPs are heteroglycans containing glucuronic acid, xylose, galactose, mannose, arabinose or ribose [12]. The polysaccharide preparations from the closely related species *A. bisporus* and *A. brasiliensis* can show major differences in their compositions. *A. bisporus* had high mannogalactan content, whereas *A. brasiliensis* had higher β-glucan [97]. In another study, the intra- and extra-cellular polysaccharides from *Ganoderma neojaponicum* showed differences in their β-glucan content. The intracellular polysaccharide had lower β-glucan level (3.57%) as compared to that of exopolysaccharide (9.41%) [167]. Water-insoluble β-glucans have stronger immunostimulating activities than their water-soluble counterparts [21]. Studies have shown that both soluble and insoluble β-D-glucans are able to bind to dectin-1 receptor, although only the insoluble ones were able to induce phagocytosis activity [168].

The linkage in the main chain and in the branches of β-glucan are decisive in biological relevance. The presence of (1→3) linkages in the main chain, and of (1→6) linkages on the branches are essential for antitumoral activity. Also, it has been reported that MPs containing β-glucose and α-mannose show antitumor effects *via* innate carbohydrate-recognizing receptor interactions [12]. Liao et al. postulated the importance of terminal fucose residue of *G. lucidum* polysaccharides in the antitumor activities [73]. In addition, the polysaccharides with varied degree of branching showed different effects. Low degree of branching between 0.20 and 0.33 have the most cogent antitumor properties [169]. *A. blazei* Murill β-glucan with poor branching failed to elicit adequate immune-stimulation whereas *A. bisporus* β-glucan with branching showed immune-modification property [13]. Furthermore, most of the MPs possessing antitumor activity are heteropolysaccharides [170].

Also, other therapeutic efficacies hinge on the above attributes. So, structural elucidation is important. Sophisticated tools like FTIR, NMR

(^{1}H, ^{13}C, 2D-COSY, 2D-HMQC, 2D-ROESY and 2D-HMBC), GC–MS, HPSEC-MALLS, HPAEC, coupled with chemical reactions such as methylation analysis, partial hydrolysis (acid or enzymatic), periodate oxidation and controlled Smith degradation are very crucial in this regard [163].

The *Phellinus mori* heteropolysaccharide (PM-EPS3), fractionated by gel filtration displayed hydroxyl radical scavenging activity and total SOD activities in a dose-dependent manner [171]. The heteropolysaccharide was composed of mannose, glucose, galactose, and rhamnose, as affirmed by HPAEC. ^{1}H and ^{13}C NMR spectroscopy revealed that PM-EPS3 had a (1→4)-linked mannopyranosyl backbone (main chain), with branches of (1→4)-linked glucosyl residues and (1→3,4)-linked galactopyranosyl residues. [171]. The FTIR, NMR (^{1}H, ^{13}C, 2D-COSY, 2D-HMQC, 2D-ROESY and 2D-HMBC) and methylation analyses revealed a novel (1→6)-linked and (1→2,6)-linked α-D-glucan substituted at C-6 with 6-deoxy-β-D-altrose and α-D-galactose moiety from the edible fruiting bodies of *Lactarius lividatus*. The polysaccharide consists of D-glucose, D-galactose and 6-deoxy-D-altrose in a molar ratio of 3.0:1.0:1.0 [172].

The cell wall polysaccharide from *P. tuber-regium* fruiting body were fractionated, and their chemical structures were investigated [173]. The cell wall of this mushroom fruiting body contains four main fractions: an outer fraction of polysaccharide and protein complex, which can be extracted using boiling water; a cold alkali-soluble fraction of heteropolysaccharides associated with a small amount of proteins; a hot alkali-soluble fraction of hyper-branched glucans; and an alkali-insoluble fraction of glucan-chitin complex with a normalized relative percentage of 3.6:21.9:55.7:18.8. IR spectroscopy revealed that all the polysaccharides had anomeric linkage of β type. Methylation and SEC-MALLS analyses demonstrated that the most-abundant mycelial cell wall polysaccharide (the hot alkali-soluble one, FHA-I) was an hyper-branched β-1,4-glucan with 52% degree of branching on the O-6 position, and had a molecular weight of 4.224×10^{6} Da [173].

Three polysaccharides were isolated from *Calocybe gambosa* fruiting bodies by cold water (PS-Cg fC), hot water (PS-Cg fH), and hot aqueous NaOH (PS-Cg fB) extractions. On the basis of acid hydrolysis, methylation analysis, size exclusion chromatography, NMR analysis and Congo red complexation, structure of the three polysaccharides appeared to be equivalent, all of them were composed of glucose, had molecular weight of 145 kDa, had β-(1→4),(1→6)-linked backbone with 4% degree of branching, and triple-strand helical conformation [174].

Two different glucans (PS-I, water-soluble; and PS-II, water-insoluble) were isolated from the alkaline extract of fruit bodies of the edible mushroom *C. indica*. On the basis of acid hydrolysis, methylation analysis, periodate oxidation, and NMR analysis, the structure of the repeating unit of these water-insoluble glucan calocyban were established [175]. Information on the complete structural characterization of MPs together with their bioactivities is scanty. So, Table 2 represents some recently characterized MPs, their bioactivities and mechanism of action. Fig. 3 shows the steps in recovery of the bioactive MPs.

5. Discussion

As shown by the myriad of studies, polysaccharides are one of the key bioactive components of the mushrooms, mediating biological functions. The biological activities of MPs are restricted to β-glucans with β-(1→3) or β-(1→6) linkages. It is important to appreciate that the functions are not discrete but related, as advocated by Systems biology. MPs are often present in complexation with other compounds in the form of proteoglycans (polysaccharide-proteins or polysaccharide-peptides), glycoproteins *etc.* High molecular weight (10–500 kDa) MPs are generally used for therapeutic application [176]. However, the high molecular weight MP extraction is expensive. Few reports have indicated that low molecular weight polysaccharides scored higher in biological activity than high molecular weight polysaccharides [95], and thus creating a window of opportunity to synthesize MPs for therapeutic application with low cost. The role of molecular weight, monosaccharide composition, solubility, and chain conformation in biological activity of MPs is still not understood adequately and requires further attention.

Another critical aspect is chemical modification of MPs *via* sulfation or selenylation at strategic points for biological effect enhancement. This aspect ought to be pursued for different MPs. Furthermore, recovery of bioactive polysaccharides from spent mushroom has also been suggested based on effective antibacterial activities [125]. The combination of MPs for wider therapeutic scope has generated some encouraging results which should be pursued further. For safer usage, requisite toxicity and mutagenicity studies must be conducted. Several of the MPs are at various stages of clinical trials. The findings discussed above suggest that the fungal abundance can be exploited to mitigate a range of infectious, inflammatory, metabolic, and degenerative diseases in mankind. In this context, the screening of mushrooms from the biodiversity (bioprospecting) in sustainable manner is suggested.

Despite their high therapeutic potential, the MP industry is still in rudimentary stage. Very few mushroom species have been explored commercially for manufacturing MPs (β-glucans) with potential health benefits which include *P. ostreatus* (Pleuran), *L. edodes* (Lentinan), *I. obliquus* (β-glucan), *H. erinaceus* (β-glucan), *G. lucidum* (Ganoderan), *T. versicolor* (krestin), *G. frondosa* (Grifolan, maitake D-fraction) and *F. veluptis* (Flammulin). The marketing perspects of MPs has been impeded by the limitations in their extraction and purification, as well as complex structure-function relationships. These bottlenecks can be surmounted through a detailed investigation of the complex structure of MPs in relation to their bioactivities, supported by analytical, *in vitro*, *in vivo* and clinical studies. It is also important to note that the high polysaccharide content in a mushroom does not guarantee its high therapeutic/biological potential. Furthermore, the composition of MPs also varies with the medium and stage (mycelium or fruiting body) of the mushroom. Henceforth, clear legislation for the quality control to ascertain the efficacy and safety of commercial products containing MPs is imperative.

6. Conclusion

The findings discussed above testify that mushrooms display diverse bioactive repertoires. Their polysaccharides, namely β-glucans, have attracted most attention. A great extent of their immune elicitation mechanism has been unraveled over the years of mutlti-paradigm studies. Biological significance of other mushroom polysaccharides has also been validated. With techniques like genetic engineering, fermentation, extraction, and structural modification, the yield, and biological efficacy of mushroom polysaccharides can be enhanced and implicated in nutraceuticals and pharmaceuticals ingredients. Beta-glucan-based mycotherapy has the potencial to serve as adjunct treatment options to alleviate many of the ailments. As the demand for benign and effective therapeutic agents soars, the above suggested aspects should get due priority. Time is ripe for translating the folk medicine and laboratory findings to incorporate in mainstream medical regimen. The insights gleaned from the recent findings herald that mushroom polysaccharides are multifaceted bioactive compounds. This review is expected to be instrumental in fueling further research in this field.

Table 2
Some recent findings on detailed structure, bioactivities and mechanism of action of mushroom polysaccharides.

Mushroom (Common name) & Source	Extraction & Purification	Structural Characteristics	Bioactivities	Study	Mechanism
Paxillus involutus (Brown roll-rim) & Fruiting body	Hot water extraction; Ethanol precipitation; DEAE-Cellulose 52 (5.0 × 30 cm) and Sephadex G-100 (2.6 × 60 cm) column fractionation; Freeze-drying.	**PIP2-1** Heteroglycan; Man:Glu:Gal:Fuc (2.8:62.5:25.4:9.4); 32 kDa; 1-linked-fuc*p*, (1→3)-linked-man*p*, 1-linked-glc*p*, (1→4)-linked-glc*p*, (1→6)-linked-glc*p*, 1-linked-gal*p*, 1,6-linked-gal*p*, 1,4,6-linked-gal*p* and 1,2,6-gal*p* glycosidic bonds.	Antioxidant; Immuno-modulation	*In vitro*	**Antioxidant:** Scavenging DPPH, ABTS, OH and superoxide radicals. **Immunomodulation:** ↑ TNF-α and IL-6 production.
Agaricus bisporus (Button mushroom) & Fruiting body	Water (cold and hot) and alkaline extraction; Ethanol precipitation; Dialysis (12-14 kDa MWCO); Freeze-thawing fractionation; Treatment with Fehling solution; Closed dialysis (100 kDa MWCO).	**RK2-Ab** Mannogalactoglucan; Man:Gal:Glc (27.3:24.4:48.3); 18 kDa; Backbone composed of (1→6)-linked α-D-Gal*p* (32.8%) and β-D-Glc*p* (37.0%) units, with terminal β-D-Man*p* (14.6%) units, side chains substituted at O-2 (α-D-Gal*p* units; 3.3%) and O-2 and O-4 (β-D-Glc*p* units; 3.6%). (1→2)-linked β-D-Glc*p* (2.7%) and β-D-Man*p* (6.0%).	Anticancer	*In vitro*	Apoptosis *via* mitochondrial death pathway (↓ HepG2 cell viability, ↑ cytochrome c release, ↓ ATP content).
Lentinus fusipes (Baunsa chattu) & Dried fruiting body	Hot water extraction; Ethanol precipitation; Dialysis; Sepharose 6B column fractionation; Freeze-drying.	**PS-II** Heteroglycan; Galactose:Glucose (1:1); ~60 kDa; Backbone composed of (1→6)-linked-α-D-Gal*p* and (1→6), (1→3,6)-linked and terminal β-D-Glu*p* units (3:1:1:1).	Antioxidant; Immunomodulation	*In vitro*	**Antioxidant:** ROS and DPPH scavenging ability, ↑ reduced GSH level, **Immunomodulation:** Macrophage activation (↑ NO production), Proliferation of splenocyte.
Trametes versicolor (Yun zhi) & Mycelia	Aqueous extraction; Ethanol precipitation; Enzymatic deproteination; Dialysis (12 kDa MWCO); Sephacryl S-300 column (1.6 × 90 cm) fractionation.	**Tramesan** Heteroglucan; Fuc:Man:Gal:Glc (1:2.25:2.22:0.26); 23 kDa; Backbone composed of linear (α-1→6-Gal*p*)$_n$ with Man*p*-(1→2)-Man*p*-(1→3)-Fuc*p* residues in side chain.	Antioxidant	*In vitro*	ROS scavenging ability
Hohenbuehelia serotina (Late fall oyster) & Fruiting body	Ultrasound assisted extraction; Deproteination by Sevag method; DEAE-52 cellulose (1.6 × 40 cm) and Sephadex G-100 (2.5 × 100 cm) column fractionation; Freeze-drying.	**NTHSP-A1** Heteroglycan; Ara:Man:Glu:Gal (4:16:28:11); 8.09 kDa; Backbone composed of (1→3,6)-linked-α-D-Glc*p*, side chain with 1-linked-α-L-Ara*p*, 1-linked-α-D-Man*p* units at C-3 and (1→6)-linked-β-D-Gal*p* units at C-6 (28:4:16:11).	Antioxidant	*In vitro*	ABTS and OH scavenging ability.
Pleurotus cystidiosus (Brown oyster mushroom) & Whole mushroom	Hot water extraction; Ethanol precipitation; Dialysis (> 12.4 kDa MWCO); Sepharose–6B column (92 × 2.1 cm) fractionation; Freeze-drying.	**PCPS** Heteroglycan; Glu:Gal:Man (6:2:1); Backbone composed of (1→6)-β-D-Glu*p*, (1→3)-β-D-Glu*p*, (1→3)-α-D-Glu*p*, (1→6)-α-D-Glu*p*, and (1→6)-α-D-Gal*p* units (1:2:1:1:2), out of which one (1→3)-β-D-Glu*p* residue was branched at O-6 with terminal β-D-Glu*p* moiety and another (1→6)-α-D-Gal*p* residue was branched at O-2 with terminal β-D-Man*p* moiety.	Antioxidant	*In vitro*	↑ Reduced GSH level; ↓ MDA
Polyporus rhinoceros (Tiger milk mushroom) & Sclerotia	Hot water extraction; Ultrafiltration (MWCO 1 kDa & 50 kDa); Freeze-drying.	**PRW1** Polysaccharide-protein complex β-D-mannoglucan; Polysaccharide (45.7%) and Protein (44.2%); Glu (91.2%) and Man (8.8%); < 50 kDa; Backbone composed of →1)-D-Man*p*-(2→, →1)-D-Glc*p*-(6→ and →1)-D-Glc*p*-(4→ linkages (3:2:2) with branching points at the O-3 and/or O-6 positions and had a degree of branching (DB) of 0.62.	Immunomodulation	*In vitro*	Macrophage activation *via* phosphorylation of ERK and Akt, and iNOS (without NF-κB) ↑ NO production, ↑ cytokine secretion (G-CSF, GM-CSF, IL-6, IL12p40/70, MCP-1, MCP-5, MIP-1-α, MIP-2, RANTES, sTNFRI, and TNF-α).
Armillaria ostoyae (Honey mushroom) & Whole mushroom	Hot water extraction followed by alkali extraction; Ethanol precipitation; fractionation by DEAE Cellulose 52 (2.6 × 27 cm) and Superdex G-75 (2.6 × 60 cm) column fractionation; Freeze-drying.	**AkPS1V-2** Galactoglucan; Glucose:Galactose (6:1); 15.3 kDa; Backbone composed of β-(1→6)-linked Glc*p*, β-(1→3)-linked Glc*p*, α-(1→3)-linked Gal*p* and β-(1→3,6)-linked Glc*p* residues (3:1:1:1) and side chain of (1→3)-D-Glc*p* unit.	Antioxidant	*In vitro*	Trolox equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP), and ferrous ion Fe^{2+} chelating activity.
			Immunomodulation	*In vitro*	Macrophage activation (↑ NO production).

(*continued on next page*)

Table 2 (*continued*)

Mushroom (Common name) & Source	Extraction & Purification	Structural Characteristics	Bioactivities	Study	Mechanism
Hericium erinaceus (Lion's mane mushroom) & Fruiting body	Hot water extraction; Ethanol precipitation; Dialysis (3.5 kDa); Sephacryl S-300 column (26 × 100 cm) fractionation.	**HBP3** Heteroglycan; Fuc:Gal:Glu (5.2:23.9); 11.5 kDa; Backbone composed of α-(1→6)-linked Gal*p* with a side chain of α-l-Fuc*p* unit at the O-2 position.			
Lentinus giganteus (Zhudugu) & Whole mushroom.	Ultrasound assisted hot water extraction; Deproteination by Sevag method; Ethanol precipitation; DEAE Cellulose 52 (2.6× 30 cm) and Sephadex G-100 (2.6 × 60 cm) column fractionation; Freeze-drying.	**LGPS-1** Neutral heteroglycan; Man:Glc:Gal (3:4.1:7.1); 154.7 kDa; Backbone composed of (1→6)-α-D-Gal*p* and (1→3,6)-α-D-Man*p* whereas the branches were composed of (1→6)-α-D-Glc*p* and 1-α-D-Glc*p*.	Anticancr	*In vitro*	Induced apoptosis *via* intrinsic mitochondrial apoptosis and PI3K/Akt signaling pathways (activation of caspase-3, cleavage of PARP-1, ↓ mitochondrial membrane potential, ↑ Bax/Bcl-2, ↑ cytochrome c, ↓ phosphorylation of Akt).
Catathelasma ventricosum & Whole mushroom	Hot water extraction; DEAE-52 (3.5 × 20 cm) and Sephadex G-100 column (2.6 × 80 cm) fractionation; Freeze-drying	**CVP-1S** Heteroglycan; Glu (94.2%), Gal (3.51%) and Fuc (1.3%); 15 kDa; Backbone composed of mainly (1→6)-β-D-Glc*p* linkages and branches are attached to the backbone through (1→3)-linked glycosidic bonds.	Antidiabetic	*In vivo*	↑ Hepatic glycogen, ↑ insulin level, ↑ body weight, ↓ blood glucose; ↑ Antioxidant enzymes (GSH-Px, SOD, CAT), ↓ MDA level; Lipid metabolism (↓ Total cholesterol, ↓ triglycerides, ↑ HDL-C, and ↓ LDL-C levels).
Grifola frondosa (King of mushroom) & Mycelia	Hot water extraction; Ethanol precipitation; Deproteination by Sevag method; De colorized with AB-8 macroporous adsorbent resin; DEAE Sephadex A-50 (1.6 cm × 50 cm) and Sephadex G-200 (2.5 cm × 60 cm) column fractionation; Dialysis; Freeze-drying.	**GFP1** Heteroglycan; Glu:Fuc (2.3:0.5); 40.5 kDa; Backbone composed of (1→6)-β-D-Glu*p* with a single (1→3)-α-D-Fuc*p* side-branching unit.	Antiviral	*In vitro*	↓ Viral replication; ↓ Protein expression and RNA synthesis; Inhibition of virus induced apoptosis (↓ caspase-3 cleavage activity and ↓ IκBα regulation).
Pleurotus eryngii (King oyster mushroom) & Whole mushroom	Hot water extraction followed by alkali extraction; Deproteination; DEAE-Cellulose (2.0 × 40 cm) and Sephadex G-200 (2.5 × 100 cm) column fractionation; Freeze-drying.	**KOMAP** Linear β-glucan; Glu:Man:Ara (6.2:2.1:2.0); 21 kDa; Backbone composed of (1→4)-linked Glc*p*, β-(1→3,6)-linked Man*p* with terminal α-1-linked Ara*f* unit at C-6 position of β-(1→3,6)-linked man*p* moeity (3.1:1).	Antitumor; Immunomodulation	*In vivo*	**Antitumor:** Suppression of tumor growth. **Immunomodulation:** ↑ Relative spleen and thymus weight, ↑ Con A- and LPS-induced lymphocyte proliferation, ↑ activities of NK cell and cytotoxic T lymphocytes in spleen, and ↑ levels of serum cytokines (IL-2, TNF-α, and IFN-γ).

Ara, Arabinose; Fuc, Fucose; Gal, Galactose; Glu, Glucose; Man, Mannose; Ara*f*, Arabinofuranosyl; Fuc*p*, Fucopyranosyl; Gal*p*, Galactopyranosyl; Glc*p*, Glucopyranosyl; Man*p*, Mannopyranosyl; G-CSF, Granulocyte colony stimulating factors, GM-CSF, Granulocyte macrophage colony stimulating factor; MCP, Monocyte chemoattractant protein-1; MCP-5, monocyte chemoattractant protein-5; MIP-1α, Macrophage inflammatory protein-1 alpha; RANTES, Regulated on activation, normal T cell expressed and secreted; Soluble TNF receptor 1 (*s*TNFRI); ERK, Extracellular signal-regulated kinase.

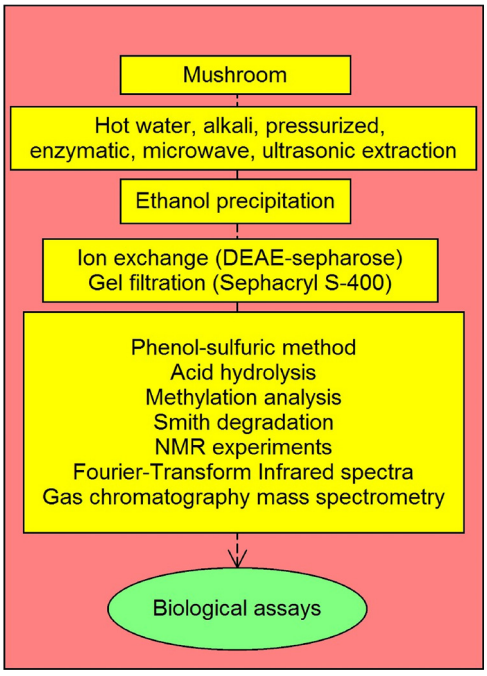

Fig. 3. The sequence and the types of techniques used to extract, purify, and characterize muchroom polysaccharides.

Conflict of interest

There is no conflict in submission of this manuscript.

References

[1] A. Ganeshpurkar, G. Rai, A.P. Jain, Medicinal mushrooms: towards a new horizon, Pharmacogn. Rev. 4 (2010) 127–135, http://dx.doi.org/10.4103/0973-7847.70904.

[2] A.D.L. Lima, R. Costa Fortes, M.R. Carvalho Garbi Novaes, S. Percário, Poisonous mushrooms: a review of the most common intoxications., Nutr. Hosp. 27 (n.d.) 402–408. doi:https://doi.org/10.1590/S0212-16112012000200009.

[3] W.-S. Jo, M.A. Hossain, S.-C. Park, Toxicological profiles of poisonous, edible, and medicinal mushrooms, Mycobiology 42 (2014) 215–220, http://dx.doi.org/10.5941/MYCO.2014.42.3.215.

[4] M. Bas, M. Yurttagul, Mushroom toxins and mushroom poisoning, SENDROM 16 (2004) 60–65 http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L39062025.

[5] S. Patel, A. Goyal, Recent developments in mushrooms as anti-cancer therapeutics: a review, 3 Biotech 2 (2012) 1–15, http://dx.doi.org/10.1007/s13205-011-0036-2.

[6] K. Durgo, M. Koncar, D. Komes, A. Belscak-Cvitanovic, J. Franekic, I. Jakopovich, N. Jakopovich, B. Jakopovich, Cytotoxicity of blended versus single medicinal mushroom extracts on human cancer cell lines: contribution of polyphenol and polysaccharide content, Int. J. Med. Mushrooms 15 (2013) 435–448 (Accessed February 21, 2015), http://www.ncbi.nlm.nih.gov/pubmed/24266369.

[7] M. Stajić, J. Vukojević, A. Knežević, S.D. Laušević, I. Milovanović, Antioxidant protective effects of mushroom metabolites, Curr. Top. Med. Chem. 13 (2013) 2660–2676 (Accessed March 20, 2015), http://www.ncbi.nlm.nih.gov/pubmed/24083793.

[8] M.E. Valverde, T. Hernández-Pérez, O. Paredes-López, Edible mushrooms: improving human health and promoting quality life, Int. J. Microbiol. 2015 (2015) 376387, http://dx.doi.org/10.1155/2015/376387.

[9] V. Popović, J. Živković, S. Davidović, M. Stevanović, D. Stojković, Mycotherapy of cancer: an update on cytotoxic and antitumor activities of mushrooms, bioactive principles and molecular mechanisms of their action, Curr. Top. Med. Chem. 13 (2013) 2791–2806 (Accessed February 21, 2015), http://www.ncbi.nlm.nih.gov/pubmed/24083788.

[10] O. Rop, J. Mlcek, T. Jurikova, Beta-glucans in higher fungi and their health effects, Nutr. Rev. 67 (2009) 624–631, http://dx.doi.org/10.1111/j.1753-4887.2009.00230.x.

[11] K.M. Bashir, J.-S. Choi, Clinical and physiological perspectives of β-glucans: the past, present, and future, Int. J. Mol. Sci. 18 (2017) 1906, http://dx.doi.org/10.3390/ijms18091906.

[12] S.P. Wasser, Medicinal mushroom science: current perspectives, advances, evidences, and challenges, Biomed. J. 37 (2014) 345–356, http://dx.doi.org/10.4103/2319-4170.138318.

[13] J.J. Volman, J.P.F.G. Helsper, S. Wei, J.J.P. Baars, L.J.L.D. van Griensven, A.S.M. Sonnenberg, R.P. Mensink, J. Plat, Effects of mushroom-derived beta-glucan-rich polysaccharide extracts on nitric oxide production by bone marrow-derived macrophages and nuclear factor-kappaB transactivation in Caco-2 reporter cells: can effects be explained by structure? Mol. Nutr. Food Res. 54 (2010) 268–276, http://dx.doi.org/10.1002/mnfr.200900009.

[14] L. Ren, C. Perera, Y. Hemar, Antitumor activity of mushroom polysaccharides: a review, Food Funct. 3 (2012) 1118–1130, http://dx.doi.org/10.1039/c2fo10279j.

[15] M. Bobovčák, R. Kuniaková, J. Gabriž, J. Majtán, Effect of Pleuran (β-glucan from *Pleurotus ostreatus*) supplementation on cellular immune response after intensive exercise in elite athletes, Appl. Physiol. Nutr. Metab. 35 (2010) 755–762, http://dx.doi.org/10.1139/H10-070.

[16] M.-L. Ng, A.-T. Yap, Inhibition of human colon carcinoma development by lentinan from shiitake mushrooms (*Lentinus edodes*), J. Altern. Complement. Med. 8 (2002) 581–589, http://dx.doi.org/10.1089/107555302320825093.

[17] L. Vannucci, J. Krizan, P. Sima, D. Stakheev, F. Caja, L. Rajsiglova, V. Horak, M. Saieh, Immunostimulatory properties and antitumor activities of glucans (Review), Int. J. Oncol. 43 (2013) 357–364, http://dx.doi.org/10.3892/ijo.2013.1974.

[18] C.J. Torkelson, E. Sweet, M.R. Martzen, M. Sasagawa, C.A. Wenner, J. Gay, A. Putiri, L.J. Standish, Phase 1 clinical trial of *Trametes versicolor* in women with breast cancer, ISRN Oncol. 2012 (2012) 251632, http://dx.doi.org/10.5402/2012/251632.

[19] J. Herre, S. Gordon, G.D. Brown, Dectin-1 and its role in the recognition of β-glucans by macrophages, Mol. Immunol. 40 (2004) 869–876, http://dx.doi.org/10.1016/j.molimm.2003.10.007.

[20] K.M. Dennehy, G. Ferwerda, I. Faro-Trindade, E. Pyz, J.A. Willment, P.R. Taylor, A. Kerrigan, S.V. Tsoni, S. Gordon, F. Meyer-Wentrup, G.J. Adema, B.-J. Kullberg, E. Schweighoffer, V. Tybulewicz, H.M. Mora-Montes, N.A.R. Gow, D.L. Williams, M.G. Netea, G.D. Brown, Syk kinase is required for collaborative cytokine production induced through Dectin-1 and Toll-like receptors, Eur. J. Immunol. 38 (2008) 500–506, http://dx.doi.org/10.1002/eji.200737741.

[21] D.H. Lee, H.W. Kim, Innate immunity induced by fungal β-glucans via dectin-1 signaling pathway, Int. J. Med. Mushrooms 16 (2014) 1–16 (Accessed February 3, 2015), http://www.ncbi.nlm.nih.gov/pubmed/24940900.

[22] S. Batbayar, D.H. Lee, H.W. Kim, Immunomodulation of fungal β-glucan in host defense signaling by Dectin-1, Biomol. Ther. (Seoul) 20 (2012) 433–445, http://dx.doi.org/10.4062/biomolther.2012.20.5.433.

[23] M.K. Mansour, J.M. Tam, N.S. Khan, M. Seward, P.J. Davids, S. Puranam, A. Sokolovska, D.B. Sykes, Z. Dagher, C. Becker, A. Tanne, J.L. Reedy, L.M. Stuart, J.M. Vyas, Dectin-1 activation controls maturation of β-1,3-glucan-containing phagosomes, J. Biol. Chem. 288 (2013) 16043–16054, http://dx.doi.org/10.1074/jbc.M113.473223.

[24] D.M. Underhill, E. Rossnagle, C.A. Lowell, R.M. Simmons, Dectin-1 activates Syk tyrosine kinase in a dynamic subset of macrophages for reactive oxygen production, Blood 106 (2005) 2543–2550, http://dx.doi.org/10.1182/blood-2005-03-1239.

[25] G.D. Brown, Dectin-1: a signalling non-TLR pattern-recognition receptor, Nat. Rev. Immunol. 6 (2006) 33–43, http://dx.doi.org/10.1038/nri1745.

[26] D. El Khoury, C. Cuda, B.L. Luhovyy, G.H. Anderson, Beta glucan: health benefits in obesity and metabolic syndrome, J. Nutr. Metab. 2012 (2012) 851362, http://dx.doi.org/10.1155/2012/851362.

[27] M.E. Obrenovich, Y. Li, K. Parvathaneni, B.B. Yendluri, H.H. Palacios, J. Leszek, G. Aliev, Antioxidants in health, disease and aging, CNS Nurol. Disord. Drug Targets 10 (2011) 192–207 (Accessed 20 March 2015), http://www.ncbi.nlm.nih.gov/pubmed/21226664.

[28] M. Kozarski, A. Klaus, D. Jakovljevic, N. Todorovic, J. Vunduk, P. Petrović, M. Niksic, M.M. Vrvic, L. Van Griensven, Antioxidants of edible mushrooms, Molecules 20 (2015) 19489–19525, http://dx.doi.org/10.3390/molecules201019489.

[29] Y. Zhang, L. Dai, X. Kong, L. Chen, Characterization and in vitro antioxidant activities of polysaccharides from *Pleurotus ostreatus*, Int. J. Biol. Macromol. 51 (2012) 259–265, http://dx.doi.org/10.1016/j.ijbiomac.2012.05.003.

[30] E. Vamanu, Antioxidant properties of polysaccharides obtained by batch cultivation of *Pleurotus ostreatus* mycelium, Nat. Prod. Res. 27 (2013) 1115–1118, http://dx.doi.org/10.1080/14786419.2012.704376.

[31] G.-H. Wu, T. Hu, Z.-L. Huang, J.-G. Jiang, Characterization of water and alkali-soluble polysaccharides from *Pleurotus tuber-regium* sclerotia, Carbohydr. Polym. 96 (2013) 284–290, http://dx.doi.org/10.1016/j.carbpol.2013.03.036.

[32] R. You, K. Wang, J. Liu, M. Liu, L. Luo, Y. Zhang, A comparison study between different molecular weight polysaccharides derived from *Lentinus edodes* and their antioxidant activities in vivo, Pharm. Biol. 49 (2011) 1298–1305, http://dx.doi.org/10.3109/13880209.2011.621960.

[33] A. Zhang, N. Xiao, P. He, P. Sun, Chemical analysis and antioxidant activity *in vitro* of polysaccharides extracted from *Boletus edulis*, Int. J. Biol. Macromol. 49 (2011) 1092–1095, http://dx.doi.org/10.1016/j.ijbiomac.2011.09.005.

[34] F. Yan, B. Wang, Y. Zhang, Polysaccharides from *Cordyceps sinensis* mycelium ameliorate exhaustive swimming exercise-induced oxidative stress, Pharm. Biol. 52 (2014) 157–161, http://dx.doi.org/10.3109/13880209.2013.820197.

[35] J.K. Gusman, C.-Y. Lin, Y.-C. Shih, The optimum submerged culture condition of the culinary-medicinal white jelly mushroom (Tremellomycetes) and its antioxidant properties, Int. J. Med. Mushrooms 16 (2014) 293–302 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24941170.

[36] W. Zhong, N. Liu, Y. Xie, Y. Zhao, X. Song, W. Zhong, Antioxidant and anti-aging activities of mycelial polysaccharides from *Lepista sordida*, Int. J. Biol. Macromol. 60 (2013) 355–359, http://dx.doi.org/10.1016/j.ijbiomac.2013.06.018.

[37] P. Maity, S. Samanta, A.K. Nandi, I.K. Sen, S. Paloi, K. Acharya, S.S. Islam,

Structure elucidation and antioxidant properties of a soluble β-D-glucan from mushroom *Entoloma lividoalbum*, Int. J. Biol. Macromol. 63 (2014) 140–149, http://dx.doi.org/10.1016/j.ijbiomac.2013.10.040.
[38] T.G. Pillai, P. Uma Devi, Mushroom beta glucan: potential candidate for post irradiation protection, Mutat. Res. 751 (2013) 109–115, http://dx.doi.org/10.1016/j.mrgentox.2012.12.005.
[39] J. Joseph, T.P.P. Smina, K.K. Janardhanan, Polysaccharide protein complex isolated from mushroom *Phellinus rimosus* (berk.) Pilat alleviates γ radiation-induced toxicity in mice, Cancer Biother. Radiopharm. 26 (2011) 299–308, http://dx.doi.org/10.1089/cbr.2010.0905.
[40] A.A. Soares, A.B. de Sá-Nakanishi, A. Bracht, S.M.G. da Costa, E.A. Koehnlein, C.G.M. de Souza, R.M. Peralta, Hepatoprotective effects of mushrooms, Molecules 18 (2013) 7609–7630, http://dx.doi.org/10.3390/molecules18077609.
[41] S.A. Nada, E.A. Omara, O.M.E. Abdel-Salam, H.G. Zahran, Mushroom insoluble polysaccharides prevent carbon tetrachloride-induced hepatotoxicity in rat, Food Chem. Toxicol. 48 (2010) 3184–3188, http://dx.doi.org/10.1016/j.fct.2010.08.019.
[42] Y. Zhang, H. Li, T. Hu, H. Li, G. Jin, Y. Zhang, Metabonomic profiling in study hepatoprotective effect of polysaccharides from *Flammulina velutipes* on carbon tetrachloride-induced acute liver injury rats using GC–MS, Int. J. Biol. Macromol. 110 (2018) 285–293, http://dx.doi.org/10.1016/j.ijbiomac.2017.12.149.
[43] J. Joseph, S.N. Panicker, K.K. Janardhanan, Protective effect of polysaccharide-protein complex from a polypore mushroom, *Phellinus rimosus* against radiation-induced oxidative stress, Redox Rep. 17 (2012) 22–27, http://dx.doi.org/10.1179/1351000211Y.0000000018.
[44] L. Fu, Y. Wang, J. Wang, Y. Yang, L. Hao, Evaluation of the antioxidant activity of extracellular polysaccharides from *Morchella esculenta*, Food Funct. 4 (2013) 871–879, http://dx.doi.org/10.1039/c3fo60033e.
[45] Q. Liu, G. Tian, H. Yan, X. Geng, Q. Cao, H. Wang, T.B. Ng, Characterization of polysaccharides with antioxidant and hepatoprotective activities from the wild edible mushroom *Russula vinosa* Lindblad, J. Agric. Food Chem. 62 (2014) 8858–8866, http://dx.doi.org/10.1021/jf502632c.
[46] Q. Liu, M. Zhu, X. Geng, H. Wang, T.B. Ng, Characterization of polysaccharides with antioxidant and hepatoprotective activities from the edible mushroom *Oudemansiella radicata*, Molecules 22 (2017), http://dx.doi.org/10.3390/molecules22020234.
[47] N. Xu, Z. Ren, J. Zhang, X. Song, Z. Gao, H. Jing, S. Li, S. Wang, L. Jia, Antioxidant and anti-hyperlipidemic effects of mycelia zinc polysaccharides by *Pleurotus eryngii* var. tuoliensis, Int. J. Biol. Macromol. 95 (2017) 204–214, http://dx.doi.org/10.1016/j.ijbiomac.2016.11.060.
[48] R.P. Tracy, The five cardinal signs of inflammation: Calor, Dolor, Rubor, Tumor … and Penuria (Apologies to Aulus Cornelius Celsus, De medicina, c. A.D. 25), J. Gerontol. A Biol. Sci. Med. Sci. 61 (2006) 1051–1052 (Accessed 15 October 2016), http://www.ncbi.nlm.nih.gov/pubmed/17077197.
[49] T.A. Wilgus, S. Roy, J.C. McDaniel, Neutrophils and wound repair: positive actions and negative reactions, Adv. Wound Care 2 (2013) 379–388, http://dx.doi.org/10.1089/wound.2012.0383.
[50] B. Muszyńska, A. Grzywacz-Kisielewska, K. Kała, J. Gdula-Argasińska, Anti-inflammatory properties of edible mushrooms: a review, Food Chem. 243 (2018) 373–381, http://dx.doi.org/10.1016/j.foodchem.2017.09.149.
[51] Y. Masuda, D. Nawa, Y. Nakayama, M. Konishi, H. Nanba, Soluble beta-glucan from *Grifola frondosa* induces tumor regression in synergy with TLR9 agonist via dendritic cell-mediated immunity, J. Leukoc. Biol. 98 (2015) 1015–1025, http://dx.doi.org/10.1189/jlb.1A0814-415RR.
[52] D. Akramiene, C. Aleksandraviciene, G. Grazeliene, R. Zalinkevicius, K. Suziedelis, J. Didziapetriene, U. Simonsen, E. Stankevicius, E. Kevelaitis, Potentiating effect of β-glucans on photodynamic therapy of implanted cancer cells in mice, Tohoku J. Exp. Med. 220 (2010) 299–306, http://dx.doi.org/10.1620/tjem.220.299.
[53] Y. Nishitani, L. Zhang, M. Yoshida, T. Azuma, K. Kanazawa, T. Hashimoto, M. Mizuno, Intestinal anti-inflammatory activity of Lentinan: influence on IL-8 and TNFR1 expression in intestinal epithelial cells, PLoS One 8 (2013), http://dx.doi.org/10.1371/journal.pone.0062441.
[54] I. Lavi, D. Levinson, I. Peri, L. Nimri, Y. Hadar, B. Schwartz, Orally administered glucans from the edible mushroom *Pleurotus pulmonarius* reduce acute inflammation in dextran sulfate sodium-induced experimental colitis, Br. J. Nutr. 103 (2010) 393–402, http://dx.doi.org/10.1017/S0007114509991760.
[55] B. Schwartz, Y. Hadar, Possible mechanisms of action of mushroom-derived glucans on inflammatory bowel disease and associated cancer, Ann. Transl. Med. 2 (2014) 19, http://dx.doi.org/10.3978/j.issn.2305-5839.2014.01.03.
[56] F.R. Smiderle, C.H. Baggio, D.G. Borato, A.P. Santana-Filho, G.L. Sassaki, M. Iacomini, L.J.L.D. Van Griensven, Anti-inflammatory properties of the medicinal mushroom *Cordyceps militaris* might be related to its linear (1→3)-β-D-glucan, PLoS One 9 (2014), http://dx.doi.org/10.1371/journal.pone.0110266.
[57] L. Ma, H. Chen, W. Zhu, Z. Wang, Effect of different drying methods on physicochemical properties and antioxidant activities of polysaccharides extracted from mushroom *Inonotus obliquus*, Food Res. Int. 50 (2013) 633–640, http://dx.doi.org/10.1016/j.foodres.2011.05.005.
[58] F.R. Smiderle, G. Alquini, M.Z. Tadra-Sfeir, M. Iacomini, H.J. Wichers, L.J.L.D. Van Griensven, *Agaricus bisporus* and *Agaricus brasiliensis* (1 → 6)-β-D-glucans show immunostimulatory activity on human THP-1 derived macrophages, Carbohydr. Polym. 94 (2013) 91–99, http://dx.doi.org/10.1016/j.carbpol.2012.12.073.
[59] V.C. Castro-Alves, J.R.O. do Nascimento, α- and β-d-glucans from the edible mushroom *Pleurotus albidus* differentially regulate lipid-induced inflammation and foam cell formation in human macrophage-like THP-1 cells, Int. J. Biol. Macromol. 111 (2018) 1222–1228, http://dx.doi.org/10.1016/j.ijbiomac.2018.01.131.
[60] A.C. Ruthes, E.R. Carbonero, M.M. Córdova, C.H. Baggio, G.L. Sassaki, P.A.J. Gorin, A.R.S. Santos, M. Iacomini, Fucomannogalactan and glucan from mushroom *Amanita muscaria*: structure and inflammatory pain inhibition, Carbohydr. Polym. 98 (2013) 761–769, http://dx.doi.org/10.1016/j.carbpol.2013.06.061.
[61] A. Ganeshpurkar, G. Rai, Experimental evaluation of analgesic and anti-inflammatory potential of Oyster mushroom *Pleurotus florida*, Indian J. Pharmacol. 45 (2013) 66–70, http://dx.doi.org/10.4103/0253-7613.106438.
[62] A.C. Ruthes, E.R. Carbonero, M.M. Córdova, C.H. Baggio, A.R.S. Santos, G.L. Sassaki, T.R. Cipriani, P.A.J. Gorin, M. Iacomini, *Lactarius rufus* (1→3),(1→6)-β-D-glucans: structure, antinociceptive and anti-inflammatory effects, Carbohydr. Polym. 94 (2013) 129–136, http://dx.doi.org/10.1016/j.carbpol.2013.01.026.
[63] D. Wu, W. Duan, Y. Liu, Y. Cen, Anti-inflammatory effect of the polysaccharides of golden needle mushroom in burned rats, Int. J. Biol. Macromol. 46 (2010) 100–103, http://dx.doi.org/10.1016/j.ijbiomac.2009.10.013.
[64] Mda S. Nascimento Santos, J.Ede M. Magalhães, L.S.E.P.W. Castro, T. de Sousa Pinheiro, D.A. Sabry, L.T.D.B. Nobre, J.P.M.S. Lima, I.G. Baseia, E.L. Leite, Effect of glucans from *Caripia montagnei* mushroom on TNBS-induced colitis, Int. J. Mol. Sci. 15 (2014) 2368–2385, http://dx.doi.org/10.3390/ijms15022368.
[65] F. Balkwill, A. Mantovani, Cancer and inflammation: implications for pharmacology and therapeutics, Clin. Pharmacol. Ther. 87 (2010) 401–406, http://dx.doi.org/10.1038/clpt.2009.312.
[66] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (2008) 436–444, http://dx.doi.org/10.1038/nature07205.
[67] B. Schwartz, Y. Hadar, Possible mechanisms of action of mushroom-derived glucans on inflammatory bowel disease and associated cancer, Ann. Transl. Med. 2 (2014) 19, http://dx.doi.org/10.3978/j.issn.2305-5839.2014.01.03.
[68] T.S. Ivanova, T.A. Krupodorova, V.Y. Barshteyn, A.B. Artamonova, V.A. Shlyakhovenko, Anticancer substances of mushroom origin, Exp. Oncol. 36 (2014) 58–66 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24980757.
[69] S.C. Jeong, S.R. Koyyalamudi, Y.T. Jeong, C.H. Song, G. Pang, Macrophage immunomodulating and antitumor activities of polysaccharides isolated from *Agaricus bisporus* white button mushrooms, J. Med. Food. 15 (2012) 58–65, http://dx.doi.org/10.1089/jmf.2011.1704.
[70] F.T.G.S. Cardozo, C.M. Camelini, M.N.S. Cordeiro, A. Mascarello, B.G. Malagoli, I.V. Larsen, M.J. Rossi, R.J. Nunes, F.C. Braga, C.R. Brandt, C.M.O. Simões, Characterization and cytotoxic activity of sulfated derivatives of polysaccharides from *Agaricus brasiliensis*, Int. J. Biol. Macromol. 57 (2013) 265–272, http://dx.doi.org/10.1016/j.ijbiomac.2013.03.026.
[71] Y. Zeng, Z. Han, P. Qiu, Z. Zhou, Y. Tang, Y. Zhao, S. Zheng, C. Xu, X. Zhang, P. Yin, X. Jiang, H. Lu, G. Yu, L. Zhang, Salinity-induced anti-angiogenesis activities and structural changes of the polysaccharides from cultured *Cordyceps militaris*, PLoS One 9 (2014) e103880, http://dx.doi.org/10.1371/journal.pone.0103880.
[72] Q. Hu, H. Wang, T.B. Ng, Isolation and purification of polysaccharides with antitumor activity from *Pholiota adiposa* (Batsch) P. Kumm. (higher Basidiomycetes), Int. J. Med. Mushrooms 14 (2012) 271–284 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/22577977.
[73] S.-F. Liao, C.-H. Liang, M.-Y. Ho, T.-L. Hsu, T.-I. Tsai, Y.S.-Y. Hsieh, C.-M. Tsai, S.-T. Li, Y.-Y. Cheng, S.-M. Tsao, T.-Y. Lin, Z.-Y. Lin, W.-B. Yang, C.-T. Ren, K.-I. Lin, K.-H. Khoo, C.-H. Lin, H.-Y. Hsu, C.-Y. Wu, C.-H. Wong, Immunization of fucose-containing polysaccharides from Reishi mushroom induces antibodies to tumor-associated Globo H-series epitopes, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 13809–13814, http://dx.doi.org/10.1073/pnas.1312457110.
[74] J. Shen, H. Park, Y. Xia, G. Kim, S.W. Cui, The polysaccharides from fermented *Ganoderma lucidum* mycelia induced miRNAs regulation in suppressed HepG2 cells, Carbohydr. Polym. 103 (2014) 319–324, http://dx.doi.org/10.1016/j.carbpol.2013.12.044.
[75] S. Silva, S. Martins, A. Karmali, E. Rosa, Production, purification and characterisation of polysaccharides from *Pleurotus ostreatus* with antitumour activity, J. Sci. Food Agric. 92 (2012) 1826–1832, http://dx.doi.org/10.1002/jsfa.5560.
[76] X. Shi, Y. Zhao, Y. Jiao, T. Shi, X. Yang, ROS-dependent mitochondria molecular mechanisms underlying antitumor activity of *Pleurotus abalonus* acidic polysaccharides in human breast cancer MCF-7 cells, PLoS One 8 (2013) e64266, http://dx.doi.org/10.1371/journal.pone.0064266.
[77] I. Lavi, L. Nimri, D. Levinson, I. Peri, Y. Hadar, B. Schwartz, Glucans from the edible mushroom *Pleurotus pulmonarius* inhibit colitis-associated colon carcinogenesis in mice, J. Gastroenterol. 47 (2012) 504–518, http://dx.doi.org/10.1007/s00535-011-0514-7.
[78] S. Miao, X. Mao, R. Pei, S. Miao, C. Xiang, Y. Lv, X. Yang, J. Sun, S. Jia, Y. Liu, Antitumor activity of polysaccharides from *Lepista sordida* against laryngocarcinoma *in vitro* and *in vivo*, Int. J. Biol. Macromol. 60 (2013) 235–240, http://dx.doi.org/10.1016/j.ijbiomac.2013.05.033.
[79] M.K. Lemieszek, C. Cardoso, F.H. Ferreira Milheiro Nunes, A.I. Ramos Novo Amorim de Barros, G. Marques, P. Pożarowski, W. Rzeski, *Boletus edulis* biologically active biopolymers induce cell cycle arrest in human colon adenocarcinoma cells, Food Funct. 4 (2013) 575–585, http://dx.doi.org/10.1039/c2fo30324h.
[80] Y. Hou, X. Ding, W. Hou, B. Song, T. Wang, F. Wang, J. Li, Y. Zeng, J. Zhong, T. Xu, H. Zhu, Pharmacological evaluation for anticancer and immune activities of a novel polysaccharide isolated from *Boletus speciosus* Frost, Mol. Med. Rep. 9 (2014) 1337–1344, http://dx.doi.org/10.3892/mmr.2014.1976.
[81] X. Ning, Q. Luo, C. Li, Z. Ding, J. Pang, C. Zhao, Inhibitory effects of a polysaccharide extract from the Chaga medicinal mushroom, *Inonotus obliquus* (higher Basidiomycetes), on the proliferation of human neurogliocytoma cells, Int. J. Med. Mushrooms 16 (2014) 29–36 (Accessed 21 February 2015), http://www.ncbi.nlm.

nih.gov/pubmed/24940902.
[82] L. You, Q. Gao, M. Feng, B. Yang, J. Ren, L. Gu, C. Cui, M. Zhao, Structural characterisation of polysaccharides from *Tricholoma matsutake* and their antioxidant and antitumour activities, Food Chem. 138 (2013) 2242–2249, http://dx.doi.org/10.1016/j.foodchem.2012.11.140.
[83] Y. Sun, Biological activities and potential health benefits of polysaccharides from *Poria cocos* and their derivatives, Int. J. Biol. Macromol. 68 (2014) 131–134, http://dx.doi.org/10.1016/j.ijbiomac.2014.04.010.
[84] K. Wang, Q. Zhang, Y. Liu, J. Wang, Y. Cheng, Y. Zhang, Structure and inducing tumor cell apoptosis activity of polysaccharides isolated from *Lentinus edodes*, J. Agric. Food Chem. 61 (2013) 9849–9858, http://dx.doi.org/10.1021/jf403291w.
[85] I.Y. Bae, J.-Y. Shin, H.G. Lee, Preparation of Black Hoof medicinal mushroom *Phellinus linteus* (Berk. et M.A. Curt.) Teng (Aphyllophoromycetideae) beta-glucan sulfate and *in vitro* tumor cell growth inhibitory activity, Int. J. Med. Mushrooms 13 (2011) 115–120 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/22135887.
[86] Y. Bi, Y. Miao, Y. Han, J. Xu, Q. Wang, Biological and physicochemical properties of two polysaccharides from the mycelia of *Grifola umbellate*, Carbohydr. Polym. 95 (2013) 740–745, http://dx.doi.org/10.1016/j.carbpol.2013.03.002.
[87] M. Ren, L. Ye, X. Hao, Z. Ren, S. Ren, K. Xu, J. Li, Polysaccharides from *Tricholoma matsutake* and *Lentinus edodes* enhance 5-fluorouracil-mediated H22 cell growth inhibition, J. Tradit. Chin. Med. 34 (2014) 309–316 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24992758.
[88] F. OuYang, G. Wang, W. Guo, Y. Zhang, W. Xiang, M. Zhao, AKT signalling and mitochondrial pathways are involved in mushroom polysaccharide-induced apoptosis and G1 or S phase arrest in human hepatoma cells, Food Chem. 138 (2013) 2130–2139, http://dx.doi.org/10.1016/j.foodchem.2012.10.047.
[89] S.K. Bhanja, C.K. Nandan, S. Mandal, B. Bhunia, T.K. Maiti, S. Mondal, S.S. Islam, Isolation and characterization of the immunostimulating β-glucans of an edible mushroom *Termitomyces robustus* var, Carbohydr. Res. 357 (2012) 83–89, http://dx.doi.org/10.1016/j.carres.2012.04.007.
[90] X. Li, L. Wang, Effect of extraction method on structure and antioxidant activity of *Hohenbuehelia serotina* polysaccharides, Int. J. Biol. Macromol. 83 (2016) 270–276, http://dx.doi.org/10.1016/j.ijbiomac.2015.11.060.
[91] X. Xu, J. Li, Y. Hu, Polysaccharides from *Inonotus obliquus* sclerotia and cultured mycelia stimulate cytokine production of human peripheral blood mononuclear cells *in vitro* and their chemical characterization, Int. Immunopharmacol. 21 (2014) 269–278, http://dx.doi.org/10.1016/j.intimp.2014.05.015.
[92] C. Zhou, Y. Qiao, Q. Tang, W. Jia, Y. Liu, A. Wu, Purification and characterization of a novel small-molecule polysaccharide from the Maitake medicinal mushroom *Grifola frondosa* (higher Basidiomycetes), Int. J. Med. Mushrooms 15 (2013) 145–152 (Accessed February 21, 2015), http://www.ncbi.nlm.nih.gov/pubmed/23557366.
[93] Y. Wang, J. Fang, X. Ni, J. Li, Q. Liu, Q. Dong, J. Duan, K. Ding, Inducement of cytokine release by GFPBW2, a novel polysaccharide from fruit bodies of *Grifola frondosa*, through dectin-1 in macrophages, J. Agric. Food Chem. 61 (2013) 11400–11409, http://dx.doi.org/10.1021/jf4029915.
[94] B.-Z. Zhang, K.T. Inngjerdingen, Y.-F. Zou, F. Rise, T.E. Michaelsen, P.-S. Yan, B.S. Paulsen, Characterisation and immunomodulating activities of exo-polysaccharides from submerged cultivation of *Hypsizigus marmoreus*, Food Chem. 163 (2014) 120–128, http://dx.doi.org/10.1016/j.foodchem.2014.04.092.
[95] L. Zhu, X. Luo, Q. Tang, Y. Liu, S. Zhou, Y. Yang, J. Zhang, Isolation, purification, and immunological activities of a low-molecular-weight polysaccharide from the Lingzhi or Reishi medicinal mushroom *Ganoderma lucidum* (higher Basidiomycetes), Int. J. Med. Mushrooms 15 (2013) 407–414 (Accessed February 21, 2015), http://www.ncbi.nlm.nih.gov/pubmed/23796222.
[96] E.K. Mandal, K. Maity, S. Maity, S.K. Gantait, B. Behera, T.K. Maiti, S.R. Sikdar, S.S. Islam, Chemical analysis of an immunostimulating (1→4)-, (1→6)-branched glucan from an edible mushroom, *Calocybe indica*, Carbohydr. Res. 347 (2012) 172–177, http://dx.doi.org/10.1016/j.carres.2011.10.040.
[97] F.R. Smiderle, A.C. Ruthes, J. van Arkel, W. Chanput, M. Iacomini, H.J. Wichers, L.J.L.D. Van Griensven, Polysaccharides from *Agaricus bisporus* and *Agaricus brasiliensis* show similarities in their structures and their immunomodulatory effects on human monocytic THP-1 cells, BMC Complement. Altern. Med. 11 (2011) 58, http://dx.doi.org/10.1186/1472-6882-11-58.
[98] S.K. Bhunia, B. Dey, K.K. Maity, S. Patra, S. Mandal, S. Maiti, T.K. Maiti, S.R. Sikdar, S.S. Islam, Isolation and characterization of an immunoenhancing glucan from alkaline extract of an edible mushroom, *Lentinus squarrosulus* (Mont.) Singer, Carbohydr. Res. 346 (2011) 2039–2044, http://dx.doi.org/10.1016/j.carres.2011.05.029.
[99] J.-H. Xiao, D.-M. Xiao, D.-X. Chen, Y. Xiao, Z.-Q. Liang, J.-J. Zhong, Polysaccharides from the medicinal mushroom *Cordyceps taii* show antioxidant and immunoenhancing activities in a D-galactose-induced aging mouse model, Evid. Based. Complement. Altern. Med. 2012 (2012) 273435, http://dx.doi.org/10.1155/2012/273435.
[100] L. Zhu, Q. Tang, S. Zhou, Y. Liu, Z. Zhang, X. Gao, S. Wang, Z. Wang, Isolation and purification of a polysaccharide from the caterpillar medicinal mushroom *Cordyceps militaris* (Ascomycetes) fruit bodies and its immunomodulation of RAW 264.7 macrophages, Int. J. Med. Mushrooms 16 (2014) 247–257 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24941166.
[101] T.H. Hida, H. Kawaminami, K.-I. Ishibashi, N.N. Miura, Y. Adachi, N. Ohno, Oral administration of soluble β-glucan preparation from the cauliflower mushroom, *Sparassis crispa* (Higher Basidiomycetes) modulated cytokine production in mice, Int. J. Med. Mushrooms 15 (2013) 525–538 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24266377.
[102] E.K. Mandal, K. Maity, S. Maity, S.K. Gantait, S. Maiti, T.K. Maiti, S.R. Sikdar, S.S. Islam, Structural characterization of an immunoenhancing cytotoxic heteroglycan isolated from an edible mushroom *Calocybe indica* var. APK2, Carbohydr. Res. 346 (2011) 2237–2243, http://dx.doi.org/10.1016/j.carres.2011.07.009.
[103] A.K. Nandi, S. Samanta, S. Maity, I.K. Sen, S. Khatua, K.S.P. Devi, K. Acharya, T.K. Maiti, S.S. Islam, Antioxidant and immunostimulant β-glucan from edible mushroom *Russula albonigra* (Krombh.) Fr, Carbohydr. Polym. 99 (2014) 774–782, http://dx.doi.org/10.1016/j.carbpol.2013.09.016.
[104] X. Xu, H. Yan, J. Tang, J. Chen, X. Zhang, Polysaccharides in *Lentinus edodes*: isolation, structure, immunomodulating activity and future prospective, Crit. Rev. Food Sci. Nutr. 54 (2014) 474–487, http://dx.doi.org/10.1080/10408398.2011.587616.
[105] S.P. Kim, S.O. Park, S.J. Lee, S.H. Nam, M. Friedman, A Polysaccharide isolated from the liquid culture of *Lentinus edodes* (Shiitake) mushroom mycelia containing black rice bran protects mice against salmonellosis through upregulation of the Th1 immune reaction, J. Agric. Food Chem. 62 (2014) 2384–2391, http://dx.doi.org/10.1021/jf405223q.
[106] S.-F. Yang, T.-F. Zhuang, Y.-M. Si, K.-Y. Qi, J. Zhao, *Coriolus versicolor* mushroom polysaccharides exert immunoregulatory effects on mouse B cells via membrane Ig and TLR-4 to activate the MAPK and NF-κB signaling pathways, Mol. Immunol. 64 (2015) 144–151, http://dx.doi.org/10.1016/j.molimm.2014.11.007.
[107] A.-R. Song, D. Qin, C. Zhao, X.-L. Sun, F. Huang, C. Kong, S. Yang, Immunomodulatory effect of polysaccharides extracted from the medicinal mushroom *Antrodia camphorata* (higher Basidiomycetes) in specific pathogen-free chickens, Int. J. Med. Mushrooms 16 (2014) 95–103 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24940908.
[108] K. Maity, E. Kar Mandal, S. Maity, S.K. Gantait, D. Das, S. Maiti, T.K. Maiti, S.R. Sikdar, S.S. Islam, Structural characterization and study of immunoenhancing and antioxidant property of a novel polysaccharide isolated from the aqueous extract of a somatic hybrid mushroom of *Pleurotus florida* and *Calocybe indica* variety APK2, Int. J. Biol. Macromol. 48 (2011) 304–310, http://dx.doi.org/10.1016/j.ijbiomac.2010.12.003.
[109] S. Maity, S.K. Bhunia, I.K. Sen, E.K. Mandal, K. Maity, B. Behera, T.K. Maiti, P. Mallick, S.R. Sikdar, S.S. Islam, A heteropolysaccharide from an edible hybrid mushroom pfle 1p: structural and immunostimulating studies, Carbohydr. Res. 374 (2013) 89–95, http://dx.doi.org/10.1016/j.carres.2013.04.007.
[110] J. Chen, Y. Yong, M. Xing, Y. Gu, Z. Zhang, S. Zhang, L. Lu, Characterization of polysaccharides with marked inhibitory effect on lipid accumulation in *Pleurotus eryngii*, Carbohydr. Polym. 97 (2013) 604–613, http://dx.doi.org/10.1016/j.carbpol.2013.05.028.
[111] Y. Liu, J. Sun, S. Rao, Y. Su, Y. Yang, Antihyperglycemic, antihyperlipidemic and antioxidant activities of polysaccharides from *Catathelasma ventricosum* in streptozotocin-induced diabetic mice, Food Chem. Toxicol. 57 (2013) 39–45, http://dx.doi.org/10.1016/j.fct.2013.03.001.
[112] M. Palanisamy, L. Aldars-García, A. Gil-Ramírez, A. Ruiz-Rodríguez, F.R. Marín, G. Reglero, C. Soler-Rivas, Pressurized water extraction of β-glucan enriched fractions with bile acids-binding capacities obtained from edible mushrooms, Biotechnol. Prog. 30 (2014) 391–400, http://dx.doi.org/10.1002/btpr.1865.
[113] A.B. Olokoba, O.A. Obateru, L.B. Olokoba, Type 2 diabetes mellitus: a review of current trends, Oman Med. J. 27 (2012) 269–273, http://dx.doi.org/10.5001/omj.2012.68.
[114] X. Ma, F. Zhou, Y. Chen, Y. Zhang, L. Hou, X. Cao, C. Wang, A polysaccharide from *Grifola frondosa* relieves insulin resistance of HepG2 cell by Akt-GSK-3 pathway, Glycoconj. J. 31 (2014) 355–363, http://dx.doi.org/10.1007/s10719-014-9526-x.
[115] J. Wang, C. Wang, S. Li, W. Li, G. Yuan, Y. Pan, H. Chen, Anti-diabetic effects of *Inonotus obliquus* polysaccharides in streptozotocin-induced type 2 diabetic mice and potential mechanism via PI3K-Akt signal pathway, Biomed. Pharmacother. 95 (2017) 1669–1677, http://dx.doi.org/10.1016/j.biopha.2017.09.104.
[116] H.-Y. Huang, M. Korivi, H.-T. Yang, C.-C. Huang, Y.-Y. Chaing, Y.-C. Tsai, Effect of *Pleurotus tuber-regium* polysaccharides supplementation on the progression of diabetes complications in obese-diabetic rats, Chin. J. Physiol. 57 (2014) 198–208, http://dx.doi.org/10.4077/CJP.2014.BAC245.
[117] G. Kanagasabapathy, U.R. Kuppusamy, S.N. Abd Malek, M.A. Abdulla, K.-H. Chua, V. Sabaratnam, Glucan-rich polysaccharides from *Pleurotus sajor-caju* (Fr.) Singer prevents glucose intolerance, insulin resistance and inflammation in C57BL/6J mice fed a high-fat diet, BMC Complement. Altern. Med. 12 (2012) 261, http://dx.doi.org/10.1186/1472-6882-12-261.
[118] A. Ganeshpurkar, S. Kohli, G. Rai, Antidiabetic potential of polysaccharides from the white oyster culinary-medicinal mushroom *Pleurotus florida* (higher Basidiomycetes), Int. J. Med. Mushrooms 16 (2014) 207–217 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/24941162.
[119] D. Chen, Y. Liu, D. Chen, Y. You, S. Zeng, Y. Hu, X. Duan, A. Liu, H. Chen, X. Hu, S. Chen, C. Li, Structural characterization and antidiabetic activity of a glucopyranose-rich heteropolysaccharide from *Catathelasma ventricosum*, Carbohydr. Polym. 149 (2016) 399–407, http://dx.doi.org/10.1016/j.carbpol.2016.04.106.
[120] Y. Liu, Y. You, Y. Li, L. Zhang, L. Yin, Y. Shen, C. Li, H. Chen, S. Chen, B. Hu, D. Chen, The characterization, selenylation and antidiabetic activity of mycelial polysaccharides from *Catathelasma ventricosum*, Carbohydr. Polym. 174 (2017) 72–81, http://dx.doi.org/10.1016/j.carbpol.2017.06.050.
[121] M. Cai, Y. Lin, Y.L. Luo, H.H. Liang, P.L. Sun, Extraction, antimicrobial, and antioxidant activities of crude polysaccharides from the wood ear medicinal mushroom *Auricularia auricula-judae* (higher basidiomycetes), Int. J. Med. Mushrooms 17 (2015) 591–600, http://dx.doi.org/10.1615/IntJMedMushrooms.v17.i6.90.
[122] S. Li, N.P. Shah, Antioxidant and antibacterial activities of sulphated polysaccharides from *Pleurotus eryngii* and *Streptococcus thermophilus* ASCC 1275, Food Chem. 165 (2014) 262–270, http://dx.doi.org/10.1016/j.foodchem.2014.05.110.
[123] W.A.A.Q.I. Wan-Mohtar, L. Young, G.M. Abbott, C. Clements, L.M. Harvey,

B. McNeil, Antimicrobial properties and cytotoxicity of sulfated (1,3)-β-D-glucan from the mycelium of the mushroom *Ganoderma lucidum*, J. Microbiol. Biotechnol. 26 (2016) 999–1010, http://dx.doi.org/10.4014/jmb.1510.10018.
[124] C. Signoretto, A. Marchi, A. Bertoncelli, G. Burlacchini, A. Papetti, C. Pruzzo, E. Zaura, P. Lingström, I. Ofek, J. Pratten, D.A. Spratt, M. Wilson, P. Canepari, The anti-adhesive mode of action of a purified mushroom (*Lentinus edodes*) extract with anticaries and antigingivitis properties in two oral bacterial phatogens, BMC Complement. Altern. Med. 14 (2014), http://dx.doi.org/10.1186/1472-6882-14-75.
[125] H. Zhu, K. Sheng, E. Yan, J. Qiao, F. Lv, Extraction, purification and antibacterial activities of a polysaccharide from spent mushroom substrate, Int. J. Biol. Macromol. 50 (2012) 840–843, http://dx.doi.org/10.1016/j.ijbiomac.2011.11.016.
[126] S.P. Kim, S.O. Park, S.J. Lee, S.H. Nam, M. Friedman, A polysaccharide isolated from the liquid culture of *Lentinus edodes* (Shiitake) mushroom mycelia containing black rice bran protects mice against a Salmonella lipopolysaccharide-induced endotoxemia, J. Agric. Food Chem. 61 (2013) 10987–10994, http://dx.doi.org/10.1021/jf403173k.
[127] T.L. Nguyen, J. Chen, Y. Hu, D. Wang, Y. Fan, J. Wang, S. Abula, J. Zhang, T. Qin, X. Chen, X. Chen, S.K. Khakame, B.K. Dang, *In vitro* antiviral activity of sulfated *Auricularia auricula* polysaccharides, Carbohydr. Polym. 90 (2012) 1254–1258, http://dx.doi.org/10.1016/j.carbpol.2012.06.060.
[128] P. Zhang, R. Ding, S. Jiang, L. Ji, M. Pan, L. Liu, W. Zhang, X. Gao, W. Huang, G. Zhang, L. Peng, H. Ji, The adjuvanticity of *Ganoderma lucidum* polysaccharide for Newcastle disease vaccine, Int. J. Biol. Macromol. 65 (2014) 431–435, http://dx.doi.org/10.1016/j.ijbiomac.2014.01.067.
[129] C.R. Wang, T.B. Ng, L. Li, J.C. Fang, Y. Jiang, T.Y. Wen, W.T. Qiao, N. Li, F. Liu, Isolation of a polysaccharide with antiproliferative, hypoglycemic, antioxidant and HIV-1 reverse transcriptase inhibitory activities from the fruiting bodies of the abalone mushroom *Pleurotus abalonus*, J. Pharm. Pharmacol. 63 (2011) 825–832, http://dx.doi.org/10.1111/j.2042-7158.2011.01274.x.
[130] C. Zhao, L. Gao, C. Wang, B. Liu, Y. Jin, Z. Xing, Structural characterization and antiviral activity of a novel heteropolysaccharide isolated from *Grifola frondosa* against enterovirus 71, Carbohydr. Polym. 144 (2016) 382–389, http://dx.doi.org/10.1016/j.carbpol.2015.12.005.
[131] I.K. Sen, A.K. Mandal, S. Chakraborti, B. Dey, R. Chakraborty, S.S. Islam, Green synthesis of silver nanoparticles using glucan from mushroom and study of antibacterial activity, Int. J. Biol. Macromol. 62 (2013) 439–449, http://dx.doi.org/10.1016/j.ijbiomac.2013.09.019.
[132] D.K. Manna, A.K. Mandal, I.K. Sen, P.K. Maji, S. Chakraborti, R. Chakraborty, S.S. Islam, Antibacterial and DNA degradation potential of silver nanoparticles synthesized via green route, Int. J. Biol. Macromol. 80 (2015) 455–459, http://dx.doi.org/10.1016/j.ijbiomac.2015.07.028.
[133] S. Patel, A. Goyal, The current trends and future perspectives of prebiotics research: a review, 3 Biotech 2 (2012) 115–125, http://dx.doi.org/10.1007/s13205-012-0044-x.
[134] J. Chow, Probiotics and prebiotics: a brief overview, J. Ren. Nutr. 12 (2002) 76–86 (Accessed 19 March 2015), http://www.ncbi.nlm.nih.gov/pubmed/11953920.
[135] S.K. Singdevsachan, P. Auroshree, J. Mishra, B. Baliyarsingh, K. Tayung, H. Thatoi, Mushroom polysaccharides as potential prebiotics with their antitumor and immunomodulating properties: a review, Bioact. Carbohydr. Diet. Fibre 7 (2016) 1–14, http://dx.doi.org/10.1016/j.bcdf.2015.11.001.
[136] P. Saman, A. Chaiongkarn, S. Moonmangmee, J. Sukcharoen, C. Kuancha, B. Fungsin, Evaluation of prebiotic property in edible mushrooms, Biol. Chem. 3 (2016) 75–85 Res.
[137] A. Synytsya, K. Míčková, A. Synytsya, I. Jablonský, J. Spěváček, V. Erban, E. Kovářříková, J. Čopíková, Glucans from fruit bodies of cultivated mushrooms *Pleurotus ostreatus* and *Pleurotus eryngii*: structure and potential prebiotic activity, Carbohydr. Polym. 76 (2009) 548–556, http://dx.doi.org/10.1016/j.carbpol.2008.11.021.
[138] W.-T. Chou, I.-C. Sheih, T.J. Fang, The applications of polysaccharides from various mushroom wastes as prebiotics in different systems, J. Food Sci. 78 (2013), http://dx.doi.org/10.1111/1750-3841.12160 M1041-8.
[139] I. Giavasis, Bioactive fungal polysaccharides as potential functional ingredients in food and nutraceuticals, Curr. Opin. Biotechnol. 26 (2014) 162–173, http://dx.doi.org/10.1016/j.copbio.2014.01.010.
[140] I. Khan, G. Huang, X. Li, W. Leong, W. Xia, W.L.W. Hsiao, Mushroom polysaccharides from *Ganoderma lucidum* and *Poria cocos* reveal prebiotic functions, J. Funct. Foods 41 (2018) 191–201, http://dx.doi.org/10.1016/j.jff.2017.12.046.
[141] I. Fraga, J. Coutinho, R.M. Bezerra, A.A. Dias, G. Marques, F.M. Nunes, Influence of culture medium growth variables on *Ganoderma lucidum* exopolysaccharides structural features, Carbohydr. Polym. 111 (2014) 936–946, http://dx.doi.org/10.1016/j.carbpol.2014.05.047.
[142] P. Diamantopoulou, S. Papanikolaou, E. Katsarou, M. Komaitis, G. Aggelis, A. Philippoussis, Mushroom polysaccharides and lipids synthesized in liquid agitated and static cultures. Part II: study of *Volvariella volvacea*, Appl. Biochem. Biotechnol. 167 (2012) 1890–1906, http://dx.doi.org/10.1007/s12010-012-9714-8.
[143] P. Diamantopoulou, S. Papanikolaou, M. Kapoti, M. Komaitis, G. Aggelis, A. Philippoussis, Mushroom polysaccharides and lipids synthesized in liquid agitated and static cultures. Part I: screening various mushroom species, Appl. Biochem. Biotechnol. 167 (2012) 536–551, http://dx.doi.org/10.1007/s12010-012-9713-9.
[144] Z.H. Wei, L. Liu, X.F. Guo, Y.J. Li, B.C. Hou, Q.L. Fan, K.X. Wang, Y. Luo, J.J. Zhong, Sucrose fed-batch strategy enhanced biomass, polysaccharide, and ganoderic acids production in fermentation of *Ganoderma lucidum* 5.26, Bioprocess Biosyst. Eng. 39 (2016) 37–44, http://dx.doi.org/10.1007/s00449-015-1480-x.
[145] C. Xu, L. Geng, W. Zhang, Production of extracellular polysaccharides by the medicinal mushroom *Trametes trogii* (higher Basidiomycetes) in stirred-tank and airlift reactors, Int. J. Med. Mushrooms 15 (2013) 183–189 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/23557370.
[146] J. Habijanic, M. Berovic, B. Boh, B. Wraber, V. Petravic-Tominac, Production of biomass and polysaccharides of Lingzhi or Reishi medicinal mushroom, *Ganoderma lucidum* (W.Curt. :Fr.) P. Karst. (higher Basidiomycetes), by submerged cultivation, Int. J. Med. Mushrooms 15 (2013) 81–90 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/23510287.
[147] M. Li, T. Chen, T. Gao, Z. Miao, A. Jiang, L. Shi, A. Ren, M. Zhao, UDP-glucose pyrophosphorylase influences polysaccharide synthesis, cell wall components, and hyphal branching in *Ganoderma lucidum* via regulation of the balance between glucose-1-phosphate and UDP-glucose, Fungal Genet. Biol. 82 (2015) 251–263, http://dx.doi.org/10.1016/j.fgb.2015.07.012.
[148] M. Wang, B. Gu, J. Huang, S. Jiang, Y. Chen, Y. Yin, Y. Pan, G. Yu, Y. Li, B.H.C. Wong, Y. Liang, H. Sun, Transcriptome and proteome exploration to provide a resource for the study of *Agrocybe aegerita*, PLoS One 8 (2013) e56686, http://dx.doi.org/10.1371/journal.pone.0056686.
[149] R. Chai, C. Qiu, D. Liu, Y. Qi, Y. Gao, J. Shen, L. Qiu, β-glucan synthase gene overexpression and β-glucans overproduction in *Pleurotus ostreatus* using promoter swapping, PLoS One 8 (2013), http://dx.doi.org/10.1371/journal.pone.0061693.
[150] S.-L. Ji, R. Liu, M.-F. Ren, H.-J. Li, J.-W. Xu, Enhanced production of polysaccharide through the overexpression of mhomologous uridine diphosphate glucose pyrophosphorylase gene in a submerged culture of Lingzhi or Reishi medicinal mushroom, *Ganoderma lucidum* (Higher Basidiomycetes), Int. J. Med. Mushrooms 17 (2015) 435–442, http://dx.doi.org/10.1615/IntJMedMushrooms.v17.i5.30.
[151] J.W. Xu, S.L. Ji, H.J. Li, J.S. Zhou, Y.Q. Duan, L.Z. Dang, M.H. Mo, Increased polysaccharide production and biosynthetic gene expressions in a submerged culture of *Ganoderma lucidum* by the overexpression of the homologous α-phosphoglucomutase gene, Bioprocess Biosyst. Eng. 38 (2015) 399–405, http://dx.doi.org/10.1007/s00449-014-1279-1.
[152] H.J. Li, D.H. Zhang, T.H. Yue, L.X. Jiang, X. Yu, P. Zhao, T. Li, J.W. Xu, Improved polysaccharide production in a submerged culture of *Ganoderma lucidum* by the heterologous expression of *Vitreoscilla* hemoglobin gene, J. Biotechnol. 217 (2016) 132–137, http://dx.doi.org/10.1016/j.jbiotec.2015.11.011.
[153] B.-B. Zhang, L. Chen, P.C.K. Cheung, Proteomic insights into the stimulatory effect of Tween 80 on mycelial growth and exopolysaccharide production of an edible mushroom *Pleurotus tuber-regium*, Biotechnol. Lett. 34 (2012) 1863–1867, http://dx.doi.org/10.1007/s10529-012-0975-7.
[154] I. Aguiló-Aguayo, J. Walton, I. Viñas, B.K. Tiwari, Ultrasound assisted extraction of polysaccharides from mushroom by-products, LWT – Food Sci. Technol. 77 (2017) 92–99, http://dx.doi.org/10.1016/j.lwt.2016.11.043.
[155] Z. Bin Wang, J.J. Pei, H. Le Ma, P.F. Cai, J.K. Yan, Effect of extraction media on preliminary characterizations and antioxidant activities of *Phellinus linteus* polysaccharides, Carbohydr. Polym. 109 (2014) 49–55, http://dx.doi.org/10.1016/j.carbpol.2014.03.057.
[156] D.-L. Qiao, F. Zhao, H.-Z. Huang, C.-C. Fan, L. Han, Ultrasonic-assisted extraction and *in vitro* antioxidant activity of polysaccharides from *Agaricus bisporus*, Zhong Yao Cai 35 (2012) 1340–1347 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/23320369.
[157] Z. Zhang, G. Lv, W. He, L. Shi, H. Pan, L. Fan, Effects of extraction methods on the antioxidant activities of polysaccharides obtained from *Flammulina velutipes*, Carbohydr. Polym. 98 (2013) 1524–1531, http://dx.doi.org/10.1016/j.carbpol.2013.07.052.
[158] S. Jia, F. Li, Y. Liu, H. Ren, G. Gong, Y. Wang, S. Wu, Effects of extraction methods on the antioxidant activities of polysaccharides from *Agaricus blazei* Murrill, Int. J. Biol. Macromol. 62 (2013) 66–69, http://dx.doi.org/10.1016/j.ijbiomac.2013.08.031.
[159] F.R. Smiderle, D. Morales, A. Gil-Ramírez, L.I. de Jesus, B. Gilbert-López, M. Iacomini, C. Soler-Rivas, Evaluation of microwave-assisted and pressurized liquid extractions to obtain β-D-glucans from mushrooms, Carbohydr. Polym. 156 (2017) 165–174, http://dx.doi.org/10.1016/j.carbpol.2016.09.029.
[160] Y. ming Zhao, J. Wang, Z. gang Wu, J. ming Yang, W. Li, L. xia Shen, Extraction, purification and anti-proliferative activities of polysaccharides from *Lentinus edodes*, Int. J. Biol. Macromol. 93 (2016) 136–144, http://dx.doi.org/10.1016/j.ijbiomac.2016.05.100.
[161] L. Fu, H. Chen, P. Dong, X. Zhang, M. Zhang, Effects of ultrasonic treatment on the physicochemical properties and DPPH radical scavenging activity of polysaccharides from mushroom *Inonotus obliquus*, J. Food Sci. 75 (2010) C322–C327, http://dx.doi.org/10.1111/j.1750-3841.2010.01590.x.
[162] X. Li, Z. Wang, L. Wang, E. Walid, H. Zhang, Ultrasonic-assisted extraction of polysaccharides from *Hohenbuehelia serotina* by response surface methodology, Int. J. Biol. Macromol. 51 (2012) 523–530, http://dx.doi.org/10.1016/j.ijbiomac.2012.06.006.
[163] A.C. Ruthes, F.R. Smiderle, M. Iacomini, d-Glucans from edible mushrooms: a review on the extraction, purification and chemical characterization approaches, Carbohydr. Polym. 117C (2015) 753–761, http://dx.doi.org/10.1016/j.carbpol.2014.10.051.
[164] B. Li, J.M. Dobruchowska, G.J. Gerwig, L. Dijkhuizen, J.P. Kamerling, Structural investigation of water-soluble polysaccharides extracted from the fruit bodies of *Coprinus comatus*, Carbohydr. Polym. 91 (2013) 314–321, http://dx.doi.org/10.1016/j.carbpol.2012.08.045.
[165] S. Wu, F. Li, S. Jia, H. Ren, G. Gong, Y. Wang, Z. Lv, Y. Liu, Drying effects on the antioxidant properties of polysaccharides obtained from *Agaricus blazei* Murrill,

Carbohydr. Polym. 103 (2014) 414–417, http://dx.doi.org/10.1016/j.carbpol.2013.11.075.
[166] H. Zhu, L. Tian, L. Zhang, J. Bi, Q. Song, H. Yang, J. Qiao, Preparation, characterization and antioxidant activity of polysaccharide from spent *Lentinus edodes* substrate, Int. J. Biol. Macromol. 112 (2018) 976–984, http://dx.doi.org/10.1016/j.ijbiomac.2018.01.196.
[167] N.H.N. Ubaidillah, N. Abdullah, V. Sabaratnama, Isolation of the intracellular and extracellular polysaccharides of *Ganoderma neojaponicum* (Imazeki) and characterization of their immunomodulatory properties, Electron. J. Biotechnol. 18 (2015) 188–195, http://dx.doi.org/10.1016/j.ejbt.2015.03.006.
[168] H.S. Goodridge, C.N. Reyes, C.A. Becker, T.R. Katsumoto, J. Ma, A.J. Wolf, N. Bose, A.S.H. Chan, A.S. Magee, M.E. Danielson, A. Weiss, J.P. Vasilakos, D.M. Underhill, Activation of the innate immune receptor Dectin-1 upon formation of a ▫ Phagocytic synapse-TM, Nature 472 (2011) 471–475, http://dx.doi.org/10.1038/nature10071.
[169] Y. Zhang, H. Kong, Y. Fang, K. Nishinari, G.O. Phillips, Schizophyllan: a review on its structure, properties, bioactivities and recent developments, Bioact. Carbohydr. Diet. Fibre 1 (2013) 53–71, http://dx.doi.org/10.1016/J.BCDF.2013.01.002.
[170] A.C. Ruthes, F.R. Smiderle, M. Iacomini, Mushroom heteropolysaccharides: a review on their sources, structure and biological effects, Carbohydr. Polym. 136 (2016) 358–375, http://dx.doi.org/10.1016/j.carbpol.2015.08.061.
[171] C. Cao, F. Peng, B.-K. Cui, Chemical characterization and structure of exopolysaccharides from submerged culture of new medicinal mushroom from China, *Phellinus mori* (higher Basidiomycetes), Int. J. Med. Mushrooms 15 (2013) 57–69 (Accessed 21 February 2015), http://www.ncbi.nlm.nih.gov/pubmed/23510285.
[172] M. Tako, Y. Dobashi, J. Shimabukuro, T. Yogi, K. Uechi, Y. Tamaki, T. Konishi, Structure of a novel α-glucan substitute with the rare 6-deoxy-D-altrose from *Lactarius lividatus* (mushroom), Carbohydr. Polym. 92 (2013) 2135–2140, http://dx.doi.org/10.1016/j.carbpol.2012.11.010.
[173] L. Chen, P.C.K. Cheung, Mushroom dietary fiber from the fruiting body of *Pleurotus tuber-regium*: fractionation and structural elucidation of nondigestible cell wall components, J. Agric. Food Chem. 62 (2014) 2891–2899, http://dx.doi.org/10.1021/jf500112j.
[174] A. Villares, Polysaccharides from the edible mushroom *Calocybe gambosa*: structure and chain conformation of a (1→4), (1→6)-linked glucan, Carbohydr. Res. 375 (2013) 153–157, http://dx.doi.org/10.1016/j.carres.2013.04.017.
[175] S. Mandal, K.K. Maity, S.K. Bhunia, B. Dey, S. Patra, S.R. Sikdar, S.S. Islam, Chemical analysis of new water-soluble (1→6)-, (1→4)-α, β-glucan and water-insoluble (1→3)-, (1→4)-β-glucan (Calocyban) from alkaline extract of an edible mushroom, *Calocybe indica* (Dudh Chattu), Carbohydr. Res. 345 (2010) 2657–2663, http://dx.doi.org/10.1016/j.carres.2010.10.005.
[176] L. Zhang, C.G. Li, H. Liang, N. Reddy, Bioactive mushroom polysaccharides : immunoceuticals to anticancer agents, J. Nutraceutic. Food Sci. 2 (2017) 6.
[177] J.S. Lee, E.K. Hong, *Hericium erinaceus* enhances doxorubicin-induced apoptosis in human hepatocellular carcinoma cells, Cancer Lett. 297 (2010) 144–154, http://dx.doi.org/10.1016/j.canlet.2010.05.006.
[178] X. Zan, F. Cui, Y. Li, Y. Yang, D. Wu, W. Sun, L. Ping, *Hericium erinaceus* polysaccharide-protein HEG-5 inhibits SGC-7901 cell growth via cell cycle arrest and apoptosis, Int. J. Biol. Macromol. 76 (2015) 242–253, http://dx.doi.org/10.1016/j.ijbiomac.2015.01.060.
[179] A. Klaus, M. Kozarski, M. Niksic, D. Jakovljevic, N. Todorovic, I. Stefanoska, L.J.L.D. Van Griensven, The edible mushroom *Laetiporus sulphureus* as potential source of natural antioxidants, Int. J. Food Sci. Nutr. 64 (2013) 599–610, http://dx.doi.org/10.3109/09637486.2012.759190.
[180] A. Mansour, A. Daba, N. Baddour, M. El-Saadani, E. Aleem, Schizophyllan inhibits the development of mammary and hepatic carcinomas induced by 7,12 dimethylbenz(α)anthracene and decreases cell proliferation: comparison with tamoxifen, J. Cancer Res. Clin. Oncol. 138 (2012) 1579–1596, http://dx.doi.org/10.1007/s00432-012-1224-0.