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Review

Structures, biological activities, and industrial applications of the polysaccharides from *Hericium erinaceus* (Lion's Mane) mushroom: A review

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ABSTRACT

Hericium erinaceus (Bull.) Pers., also known as Yamabushitake, Houtou and Lion's Mane, is capable of fortifying the spleen and nourishing the stomach, tranquilizing the mind, and fighting cancer. Over the past decade, it has been demonstrated that *H. erinaceus* polysaccharides possess various promising bioactivities, including antitumor and immunomodulation, anti-gastric ulcer, neuroprotection and neuroregeneration, anti-oxidation and hepatoprotection, anti-hyperlipidemia, anti-hyperglycemia, anti-fatigue and anti-aging. The purpose of the present review is to provide systematically reorganized information on extraction and purification, structure characteristics, biological activities, and industrial applications of *H. erinaceus* polysaccharides to support their therapeutic potentials and sanitarian functions.

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1. Introduction

Hericium erinaceus (Bull.) Pers., also known as [1] Yamabushitake (Japanese), Houtou/猴头菇 (Chinese), Lion's Mane, Monkey's Mushroom, Bear's Head, Hog's Head Fungus, White Beard, Old Man's Beard, Pom Pom, and Bearded Tooth, used to belong to the

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Fig. 1. Fruiting bodies of *Hericium erinaceus* (Bull.) Pers. Photos taken by Henk Monster, in Holland (a); a CFDA approved drug named *H. erinaceus* extract granule (b); *H. erinaceus* in a growing room at Fungi Perfecti. Photos taken by Stuart Isett (c).

class Basidiomycetes, subclass Holobasidiomycetidae, order Hericiales, family Hericiaceae [2], while Index Fungorum [3] presents the currently adopted taxonomy of *Hericium erinaceus* (Bull.) Pers. as follows: Hericiaceae, Russulales, Incertae sedis, Agaricomycetes, Agaricomycotina, Basidiomycota, Fungi. *H. erinaceus* is mainly distributed through European countries and the southern states of America. However, there are no detailed descriptions and illustrations about the species from Asia, where its artificial cultivation has been developed in large quantities [4]. *H. erinaceus* which is considered as a saprotroph or weak parasite mostly occurs on dead wood, and sometimes on knotholes or cracks of living hardwoods [5–7]. The mature fruiting body is fleshy semi-spherical and whitish (Fig. 1a), and the color gradually becomes yellowish to brownish in age [8].

Studies on secondary metabolites have resulted in the isolation of an exceptionally large amount of structurally different and potentially bioactive components including erinacines, hericerins, steroids, alkaloids, and lactones [9]. Up to date, hericenones were reported only from the fruiting bodies of *H. erinaceus*, and erinacines were reported mainly from the mycelia derived from submerged cultures and were found in traces in fruiting bodies [10,11]. Every 100 g of dried *H. erinaceus* contains 61.3–77.5 g total sugar by proximate analysis [12–14], β-glucans, α-glucans and glucan-protein complexes are main representative polysaccharides [13]. In addition, it also has been reported that the total content of *H. erinaceus* polysaccharides in fruit bodies is higher than that in mycelium [15]. Up to date, a total of more than thirty-five polysaccharides have been isolated from *H. erinaceus*. Studies on pharmacological activities have revealed that *H. erinaceus* polysaccharides possess the potential to help prevent, alleviate, or treat major diseases including cancer, gastric ulcer, diabetes, hyperlipidemia, hepatic injury, and neurodegenerative diseases [16–20]. More recently, Khan [21] asserted the medical benefits of *H. erinaceus* polysaccharides by saying "This mushroom is rich in some physiologically important components, especially β-glucan polysaccharides, which are responsible for anti-cancer, immuno-modulating, hypolipidemic, antioxidant and neuro-protective activities of this mushroom". Therefore, *H. erinaceus* polysaccharides are very likely a kind of bioactive ingredients which could be proceeded to the development of pharmaceutical formulation. In facts, China Food and Drug Administration (CFDA) [22] has approved a large amount of patent health care products and medicines which all only contain *H. erinaceus* as the medicinal ingredient, including Hougu Yin, Hougu Pian, Houtoujun Pian, Weilexin Keli, Weilening Pian, Fufang Houtou Keli, Houtoujun Tiquwu Keli, etc. Some other patent products are reported from United States, Japan and South Korea [1]. It is worth mentioning that the efficacy of these products is capable of nourishing the stomach and harmonizing the middle energizer, and thus can be used for the treatment of epigastric pain caused by chronic superficial gastritis, gastric ulcer, or atrophic gastritis.

Up to date, no review concerning *H. erinaceus* polysaccharides is available. In this review, we intend to provide a comprehensive insight into the physiochemical and structural features and pharmacological effects of the polysaccharides obtained from *H. erinaceus* to provide knowledge to people for better utilization of polysaccharides, and to attract more scholars' attention on their anti-tumor and immunomodulatory, anti-gastric ulcer, hepatoprotective, hypoglycemic, hypolipidemic, neuroprotective and neuroregenerative activities. In addition, it is worth mentioning that the epithet "erinaceus" is still being misspelt as the grammatically incorrect "erinaceum" [1].

2. Extraction and purification

Over the past few years, methods about isolation and purification of potentially bioactive polysaccharides from *H. erinaceus* have gained much attention. The generally adopted polysaccharide extraction method is to stir the pulverized fruiting bodies in hot water for several hours, so it is very time-consuming. Microwave irradiation in water has an advantage for the extraction of polysaccharides from the fruiting body of *H. erinaceus* in terms of time duration. A study launched by Ookushi and colleagues [23] demonstrated that the extractability of microwave irradiation in water carried out at 140 °C for 5 mins was almost equivalent to that of using conventional external heating carried out at 100 °C for 6 h. The major polysaccharides obtained by microwave irradiation in water were β-D-glucans rich in $(1\rightarrow3)$ linkages, while polysaccharides obtained by traditional hot water extraction using conventional external heating were fucogalactans and β-D-glucans rich in $(1\rightarrow6)$ linkages, which was confirmed to be related to the removed heteropolysaccharides such as fucogalactan as depolymerized low molecular weight component [24].

Considering that the use of organic toxic solvents is not conducive to food safety, the limitation of organic toxic solvents and the integral fractionation of raw materials are desirable. A sequence of stages [25] including microwave hydrogravity, supercritical CO_2 extraction was used to obtain soluble fractions from *H. erinaceus*, and remaining solid phase were subjected either to enzyme assisted extraction or to non-isothermal autohydrolysis with water. The proposed green processes resulted in a dissolution of more than 40% of *H. erinaceus* [25]. Enzyme-assisted extraction possesses the advantage of being environmentally friendly, highly efficient, and easily operated owing to the relatively mild reaction conditions. Enzymes could effectively degrade the cell wall to favor the release of bioactive polysaccharides existing as a structural component in fungal cell walls. Response surface methodology and the Box-Behnken design based on single-factor and orthogonal experiments [26] were applied to optimize the enzyme-assisted extraction of polysaccharides from fruiting bodies of *H. erinaceus*, which resulted in the highest yield of *H. erinaceus* polysaccharides with a value of 13.46%.

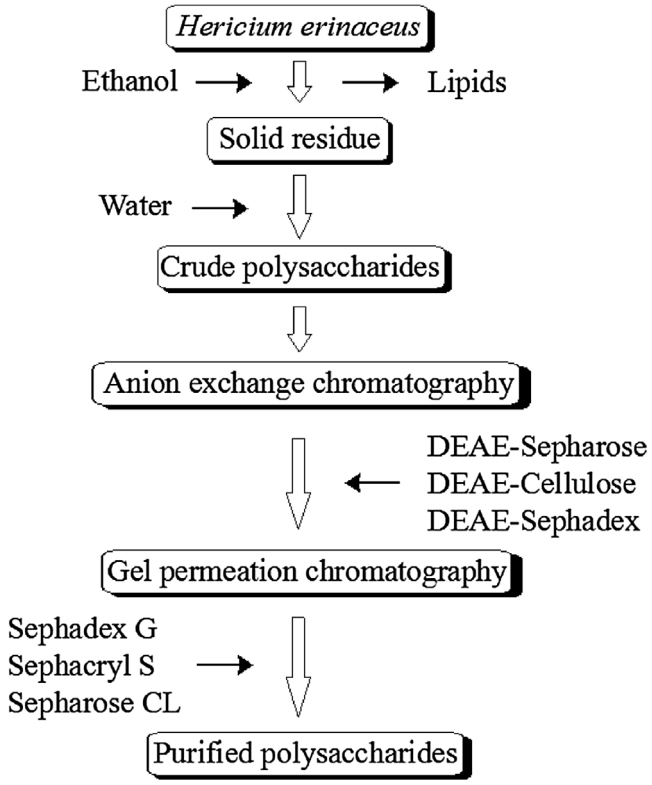

Fig. 2. Essential steps involved in the purification of *Hericium erinaceus* polysaccharides.

The general procedures for separating and purifying polysaccharides from *H. erinaceus* could be summarized as follows: The total fruiting bodies or mycelium of *H. erinaceus* were pre-extracted with ethanol under reflux to remove lipids. The remaining residues was dried and extracted with hot water, the solution of polysaccharides was collected after filtration and concentration. Crude polysaccharides were obtained through alcohol precipitation and afterwards the crude polysaccharides were dissolved in water and insoluble residues were removed by centrifugation. The supernatant was applied to different column chromatography as mentioned in Fig. 2, including anion exchange chromatography (DEAE-Sepharose, DEAE-Cellulose, DEAE-Sephadex) and gel permeation chromatography (Sephadex G, Sephacryl S, Sepharose CL) to obtain purified polysaccharides.

3. Submerged culture for polysaccharides biosynthesis

The artificial cultivation of *H. erinaceus* is firstly reported in China in 1988, and it is cultivated by artificial log using bottles and polypropylene bags [27]. However, due to the long cycle and low yield, artificial cultivation is not suitable for industrialized production. Submerged culture can obtain a large number of mycelium and fermentation products in a short period of time. Deep submerged culture can also break the growth environment factors to provide sufficient nutrients for bioactive substances' accumulation.

A study [28] carried out to evaluate the effect of carbon sources, nitrogen source, carbon/nitrogen ratio, promine Vitamin B_1, and pH value on the biosynthesis of *H. erinaceus* polysaccharides has shown that the effect sequence was: nitrogen source > carbon source > pH value > Vitamin B_1. The relatively suitable carbon sources, nitrogen source, pH value, and carbon/nitrogen ratio were glucose, complex nitrogen source (containing soybean powder, corn powder, and wheat bran powder), 5, and 26, respectively [29]. The optimum seed age was 84 h, the stability and polysaccharides production of the first generation was the highest, there was no significant difference between the second, third, and fourth generation, and the fifth generation showed obvious decline [30]. Further studies [31] revealed that *H. erinaceus* had little demand for monosaccharides in the process of fermentation, and the ability of *H. erinaceus* mycelium to synthesize intracellular polysaccharides decreased over time, while the ability to secrete extracellular polysaccharides is continuous. Malinowska and colleagues [32] optimized the culture medium composition so as to obtain simultaneously high yields of *H. erinaceus* mycelial biomass, exopolysaccharides, and intracellular polysaccharides by using a central composite rotatable design (CCRD) and a response surface methodology. It has been discovered that the process of biosynthesizing high molecular weight polysaccharides proceeded until nutritional sources in the culture medium were depleted.

Other investigations' results [33] showed that the most suitable carbon, nitrogen, mineral sources, and cofactors for mycelial biomass and exopolymer production were: corn flour combined with 1% glucose, yeast extract, KH_2PO_4 and corn steep liquor. In the 15-l scale-up fermentation [33], the optimized medium brought about a maximum yield of 20.5 g/L in mycelial biomass. In addition, seven days incubation in tofu whey with temperature at 27 °C, pH value at 5.5, and rotation rate at 180 were found to be relatively optimized condition for the production of *H. erinaceus* polysaccharides [34]. Another optimal liquid culture condition for maximum polysaccharide production was determined to be 23 °C, 200 rpm, and a 10% inoculum size, at an uncontrolled initial pH value. In addition, the modified medium contained 20 g/L glucose, 10 g/L yeast extract, and 2.0 g/L ascorbic acid [35].

4. Structure features

Since *Hericium* polysaccharides were reported by Mccracken and Dodd in 1971 [36], a large number of studies on their isolation and structural identification have been carried out, which have resulted in a total of more than 35 polysaccharides from cultured/wild-growing/fermentative mycelia and fresh/dried fruiting bodies of *H. erinaceus*. Their structure characteristics have been investigated using a combination of fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR), field desorption mass spectroscopy (FD-MS), gas chromatography-mass spectrography (GC–MS), methylation analysis, periodate oxidation-Smith degradation, partial acid-hydrolysis, and enzymatic degradation. Herein, we have listed the reported *H. erinaceus* polysaccharides over the past few decades and have provided a comprehensive information with regard to their molecular weight, monosaccharide composition, and associated references in Table 1.

Six polysaccharides (FI_0-a, FI_0-a-α, FI_0-a-β, FI_0-b, FII-1, FIII-2b) were isolated from the fresh fruiting bodies of *H. erinaceus*. These were xylans, glucoxylans, heteroxyloglucans, and galactoxyloglucans. IR and NMR spectra showed that FI_0-a-α and FI_0-a-β had β-(1→3) and (1→6) glucan chains, FII-1 and FIII-2b had β-(1→3) and (1→6) glucosidic linkages [37]. Two polysaccharides (AF2S-2, BF2S-2) isolated from fruiting bodies of *H. erinaceus* were composed of a backbone of β-(1→6)-linked D-glucopyranosyl residues, and had β-(1→3) and β-(1→6) glucosidic linkages [15]. Three heteropolysaccharides (HEPA1, HEPA4, HEPB2) isolated from the mycelium of *H. erinaceus* were mainly composed of glucose. HEPA4 was a heteropolysaccharide peptide with a 3.8% of protein fraction, and the main glucosidic bond configuration between all the homogeneous monosaccharides was α-linkage [38]. The difference of the chemical composition between fruiting bodies and mycelia was further analyzed using UV, IR, and HPLC, the results [39] showed that both hfp-1 (from fruiting bodies) and hmp-2 (from mycelia) were homogeneous. Gas chromatography

Table 1
The polysaccharides isolated from *H. erinaceus.*

No.	Name	Monosaccharide composition	M.W. (Da)	Reference
1	Fl_0-a	Glc, Xyl, Man, Gal in a ratio of 10.0:33.3:3.40:0.40	1.2×10^5	[37]
2	Fl_0-a-α	Xyl, Man in a ratio of 10.0:0.40	8.9×10^4	[37]
3	Fl_0-a-β	Glc, Xyl, Man, Gal in a ratio of 10.0:23.3:5.80:1.30	1.8×10^5	[37]
4	Fl_0-b	Glc, Xyl, Man, Gal in a ratio of 10.0:10.4:1.00:1.50	5.7×10^5	[37]
5	FII-1	Glc, Xyl, Gal in a ratio of 10.0:17.9:1.70	1.6×10^5	[37]
6	FIII-2b	Glc, Xyl, Gal in a ratio of 10.0:5.10:3.20	3.0×10^4	[37]
7	AF2S-2	Glc, Man, Fuc in a ratio of 96.3:2.8:0.9	1.3×10^4	[15]
8	BF2S-2	Glc, Man, Fuc in a ratio of 95.7:3.1:0.6	2.2×10^4	[15]
9	$HEPA_1$	Glc, Ara, Xyl in a ratio of 33.1:1.7:1.0	6.2×10^4	[38]
10	$HEPB_2$	Glc, Ara, Xyl, Man in a ratio of 50.7:2.1:1.0:2.4	1.2×10^4	[38]
11	$HEPA_4$	Glc, Ara, Xyl, Man, Gal in a ratio of 3.6:2.3:3.5:1.0:1.7	2.6×10^4	[38]
12	hfp-1	Ara, Man, Gal, Glc in a ratio of 0.12:0.04:1.00:0.71	5.4×10^4	[39]
13	hmp-2	Glc, Xyl, Man, Gal, Glc in a ratio of 0.25:0.41:0.31:1.00:0.29	6.8×10^4	[39]
14	HPA	Glc, Gal, Fuc in a ratio of 10.00:21.10:4.23	5.0×10^4	[40]
15	HPB	Glc, Gal in a ratio of 115.29:10.00	3.0×10^4	[40]
16	HEP-1	Rha, Gal, Glc in a ratio of 1.19:3.81:1.00	1.8×10^4	[41]
17	HEP-2	Ara, Man, Glc in a ratio of 1.00:8.37:27.24	1.8×10^4	[42]
18	HPP	Glc	6.5×10^4	[43]
19	HPI	Fuc, Glc, Gal in a ratio of 4.23:10.00:21.10	5.0×10^4	[44
20	HEP-1	Rha, Gal, Glc in a ratio of 1.00:3.20:0.84	1.8×10^4	[45]
21	HEP-2	Glc, GlcA in a ratio of 4.0:1.0	1.2×10^4	[45]
22	HEP-3	Glc	$>1.0 \times 10^6$	[45]
23	HEP-4	Rha, Xyl, Man in a ratio of 1.00:2.40:4.60	Unknown	[45]
24	HEP-5	Glc	Unknown	[45]
25	HEPF1	Fuc, Gal, Glc in a ratio of 1.0:4.0:1.0	1.9×10^4	[46]
26	HEPF2	Fuc, Gal, Glc in a ratio of 1.00:3.69:5.42	1.7×10^4	[47]
27	HEPF3	Fuc, Gal in a ratio of 1.00:4.12	1.9×10^4	[48]
28	HEPF4	3-*O*-methyl-Rha, Fuc, Gal, Glc in a ratio of 0.12:1.00:3.27:0.28	2.0×10^4	[49]
29	HEPF5	Glc	4.2×10^5	[50]
30	HEF-AP Fr II	Glc, Gal, Man in a ratio of 91.11:6.09:2.80	1.3×10^4	[51]
31	HEB-AP Fr I	Man	4.6×10^4	[52]
32	HMP-w1. 1	Man, Glc, Gal, Fuc in a ratio of 10.16:15.43:117.03:10.00	3.6×10^4	[53]
33	HMP-a1. 1	Man, GalA, Glc, Gal, Fuc in a ratio of 13.49:10.00:37.26:20.11:16.44	4.3×10^4	[57]
34	EP-1	Glc, Man, Gal in a ratio of 67.87:6.42:1.00	3.1×10^3	[54]
35	HPB-3	Fuc, Gal, Glc in a ratio of 5.2:23.9:1.0	1.5×10^4	[55]

(GC) showed that hfp-1 was composed of arabinose, mannose, galactose, and glucose in a molar ratio of 0.12:0.04:1.00:0.71, and hmp-2 was composed of arabinose, xylose, mannose, galactose, and glucose in a molar ratio of 0.25:0.41:0.31:1.00:0.29. In addition, β-glycoside linkage appeared in hfp-1, but not in hmp-2 [39]. Jia and colleagues revealed that HEP-1 isolated from the fruiting bodies of *H. erinaceus* had a (1 → 6)-linked α-D-galactopyranosyl backbone with branches that were composed of rhamnose and glucose attached to *O*-2 [41]. Aqueous extract of *H. erinaceus* contained predominantly two types of water extractable polysaccharides (HPA and HPB) which were mainly composed of glucose and galactose [40]. A water soluble polysaccharide (HPI) isolated from the *H. caput-medusae* was mainly composed of glucose and galactose [44]. Two neutral heteropolysaccharides (HEP-1 and HEP-4), two glucans (HEP-3 and HEP-5) together with one acidic polysaccharide (HEP-2) containing uronic acid were isolated from fruiting bodies of *H. erinaceus*. Among them, the chemical compositions of HEP-1 and HEP-2 are rare in fungal polysaccharides [45]. A heteropolysaccharide (HEPF1) was isolated from the fruiting bodies of *Hericium erinaceus*. It was composed of fucose, galactose, glucose, and a minor proportion of 3-*O*-methyl rhamnose. HEPF1 had a (1 → 6)-linked α-D-galactopyranosyl backbone with branches that were composed of fucose attached to *O*-2 and contained 6-*O*-substituted-β-D-oligoglucosyl units and a minor terminal 3-*O*-methyl rhamnose residue [46]. Lee and colleagues reported a polysaccharides (HEF-AP Fr II) with a laminarin-like triple helix conformation of β-1, 3-branched-β-1, 6-glucan [43]. A heteropolysaccharide (HEPF2) containing a small amount of 3-*O*-methylrhamnose was further showed to posess (1 → 4)-, (1 → 6)-linked glucosyl, and (1 → 6)-linked galactosyl residues. In addition, the configuration of (1 → 4)-linked glucosyl was β-linkage, while the configuration of (1 → 6)-linked galactosyl, (1 → 2, 6)-linked galactosyl together with the terminal fucosyl residues were all α-linkage [47]. Another heteropolysaccharide (HEPF4) containing a small amount of 3-*O*-methylrhamnose and D-glucose was composed of a tetrasaccharide repeating unit [49]. A heteropolysaccharide (EP-1) with a small molecular weight of 3.1 kDa had an α-D-Glc(1 → 3) and β-D-Glc(1 → 3) backbone with branches

that were composed of mannose, glucose, and galactose attached to O-4 [54]. A heteropolysaccharide (HPB-3) with a molecular weight of 15 kDa was isolated from the maturating-stage IV, V, and VI fruiting body of *H. erinaceus*. Sugar, methylation, and NMR analysis showed that it contained an α-(1 → 6)-linked-D-galactopyranosyl backbone with branches that were composed of α-L-fucopyranose attached to *O*-2 [55].

In addition to the above heteropolysaccharides, there are also several homopolysaccharides obtained from *H. erinaceus*. For example, a neutral glucan (HPP) [43] was isolated from the fermentative mycelia of *H. erinaceus*, it had a (1 → 6)-linked-Glc backbone with branches that were composed of (1 → 3)-linked-Glc residues attached to *O*-3, and the main glucosidic bond configuration between monosaccharides was α-linkage. Zhang and colleagues [50] reported a neutral α-D-glucan (HEPF5) which was composed of a multibranch tetrasaccharide repeating unit. The sequence of the residues in the multibranch tetrasaccharide was established from NOESY spectrum. The complete structure of the repeating unit was established using chemical and NMR analysis. Lee and colleagues [52] reported a polysaccharides (HEB-AP Fr I) with a laminarin-like triple helix conformation of *β*-1, 3-branched-*β*-1, 2-mannan. Two glucans (HEP-3, HEP-5) were isolated from fruiting bodies of *H. erinaceus*, the characteristic absorption of IR showed that HEP-3 was mainly *β*-glucan, while HEP-5 was mainly α-glucan [45]. Furthermore, there are also several glycoproteins obtained from *H. erinaceus*. Cui and colleagues [56] isolated an acidic glycoprotein (HEG-5) with a molecular weight of 14.4 kDa from cultured mycelia of *H. erinaceus*. The protein/polysaccharide ratio of HEG-5 is 10:1 (%/%), and it contained D-glucose, L-rhamnose, D-galactose, and D-mannose in a molar ratio of 1.00:1.09:2.45:7.14. FT-IR and NMR analysis revealed that HEG-5 contained the protein and carbohydrate portions with (1 → 4)-linked *β*-galactose and *β*-glucose residues. Analysis using circular dichroism then showed that HEG-5 was a predominantly *β*-sheet glycoprotein. The complete three-dimensional structure was obtained by protein sequencing and modeling using MALDI-TOFMS, NCBI blast search, and online SWISS-MODEL Workplace service. Kawagishi and colleagues [57] isolated a sialic acid-binding lectin (HEL) with a molecular weight of 54 kDa and a blocked N-terminal from the fresh fruiting bodies of *H. erinaceus*. In addition, another lectin (HEA) with a molecular weight of 51 kDa and distinctly different N-terminal amino acid sequences was isolated from the dried fruiting bodies of *H. erinaceus* [58]. A sulfated glycoprotein (HEP-2) with a protein/polysaccharide/sulfated group/metal ion ratio of 7.49:62.52:18.50:12.64 was isolated from cultured mycelia of *H. erinaceus*. The polysaccharide fraction was composed of arabinose, mannose, and glucose in a ratio of 1.00:8.37:27.24 [42].

5. Biological activities

5.1. Antitumor and immunomodulatory activities

World Health Organization has reported that cancer causes 8.2 million deaths each year and results in 13% of all deaths worldwide [59]. Mushroom polysaccharides' antitumor activity has been demonstrated to be related to the activation of different immune responses in the host to some extent. For example, *β*-Glucans which have a backbone of glucose residues linked by *β*-(1 → 3)-glucosidic bonds with additional *β*-(1 → 6) branch points present distinct affinities toward dectin-1, CR3, LacCer, and scavenger receptors to trigger different host responses, thus resulting in the boosting of immune responses in affected cells by activating multiple signal pathways to achieve the antitumor effect to some extent [60]. In addition, it also has been postulated that mushroom polysaccharides containing glucose and mannose show antitumor effects via immune system because a receptor which manifest high specificity for glucose and mannose is found on human macrophages [61]. Reviewing available literatures, besides the direct induction of tumor cell apoptosis and cell cycle arrest, *H. erinaceus* polysaccharides also have been proven to be able to act on various cell receptors to play a promising antitumor effect (Fig. 3).

Early in 1992, Mizuno and colleagues [37] have reported that five polysaccharides (10 mg/kg, *i.p.*) isolated from cultivated fruiting body of *H. erinaceus* showed high antitumor activity, these polysaccharides could not only prolong the longevity, but significantly reduce the mortality of the hosts. Another recent study [58] demonstrated that *H. erinaceus* agglutinin (lectin) with high stability in a wide range of pH value and high heat stability exhibited antiproliferative activity toward hepatoma and breast cancer cells with IC_{50} values of 56.1 and 76.5 μmol/L, respectively. In addition, it [58] manifested strong mitogenic activity toward mouse splenocytes and showed HIV-1 reverse transcriptase inhibitory activity with an IC_{50} value of 31.7 μmol/L. *H. erinaceus* polysaccharide also has been reported to exhibit the highest 1, 1-diphenyl-2-picrylhydrazyl radical-scavenging capacity and strongest inhibitory activity on HeLa cells among several polysaccharides from eight medicinal mushroom species [62]. According to Zan and colleagues, glycoprotein (HEG-5) purified from fermented mycelia of *H. erinaceus* was capable of inducing apoptosis and cell cycle arrest as evidenced by markedly inhibiting the proliferation (IC_{50} value of 46.7 μg/mL) and colony formation of SGC-7901 cells, via: (a) down-regulating the expressions of Bcl2, PI3 K, and AKT1, (b) up-regulating the expressions of Caspase-8, Caspase-3, p53, CDK4, Bax, and Bad [63].

Macrophages provide the defense line against tumor cells and somatic cells infected with parasite or fungus in host defense system [64]. Purified *H. erinaceus* polysaccharides were demonstrated to be able to stimulate the functional activation of macrophages. For example, either HEB-AP Fr I or HEF-AP Fr II could strongly trigger the expression of pro-inflammatory cytokines like tumor necrosis factor (TNF)-α and interleukin (IL)-1*β*, which indicated that *H. erinaceus* polysaccharides could elicit innate immune responses in macrophages via regulating the expression of pro-inflammatory cytokines [51,52]. Furthermore, it has been demonstrated that WEHE containing 28% polysaccharides which are mainly *β*-glucan was able to stimulate IL-1*β* expression in macrophages at a transcriptional level via enhancing the activation of transcription factors such as NF-*κ*B, NF-IL6, and AP-1 [65]. As for the induction of NO production in macrophages, different studies have revealed that macrophage-like RAW264.7 cells incubated with 1000 μg/mL of HEB-AP Fr I or HEF-AP Fr II produced great larger amounts of nitric oxide (NO) than untreated cells [51,52]. HPB-3 (50–800 μg/mL) obtained from fruiting body of *H. erinaceus* at different maturating-stage could effectively stimulate macrophage-like RAW264.7 cells to produce NO in a dose-dependent manner [55]. Further in-depth research revealed that WEHE induced macrophages activation leading to iNOS gene expression followed by NO production through the activation of transcription factor NF-*κ*B [66]. Specifically, WEHE increased DNA binding activity of the transcription factor NF-*κ*B, and its trans-acting activity was confirmative as determined by *in vitro* transfection assay. p(NF-*κ*B)$_3$-CAT expression was solely regulated by NF-*κ*B, and WEHE significantly reduced intracellular IκBα level accompanied with NF-*κ*B activation [66].

It is well known that dendritic cells (DCs) as the most powerful antigen presenting cells of the immune system play a pivotal role in initiating T cell responses against microbial pathogens and tumors [67]. *H. erinaceus* polysaccharide (HE-PS) containing *β*-glucan derivatives at a concentration of 50 μg/mL has been reported to be able to induce dendritic cells (DCs) maturation in parallel with a 2-fold increase in marrow hematopoietic cell (MHC) class II and CD80/86 surface antigens [68]. In addition, HE-PS (100 μg/mL) could significantly reduce endocytosis of FITC-dextran

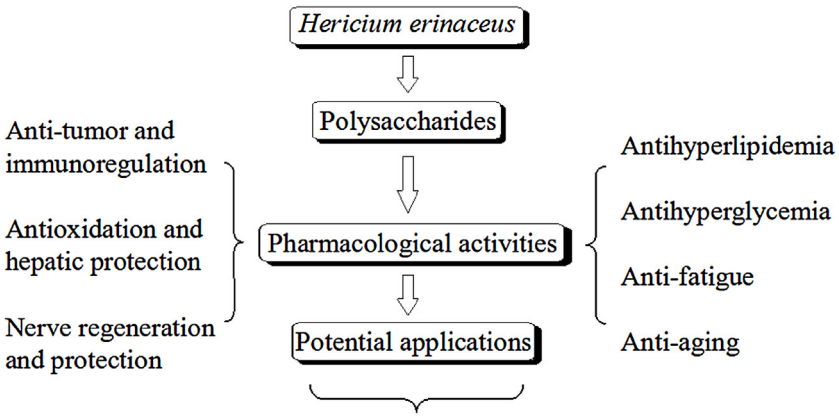

Fig. 3. Biological properties and potential industrial uses of *Hericium erinaceus* polysaccharides.

by BMHC-imDCs, and stimulate the secretion of IL-12, IFN-γ, and IL-10 in a dose-dependent manner. These results to some extent indicated that *H. erinaceus* polysaccharide might contribute to the T_h1 response [68].

It has been demonstrated that both *H. laciniatum* polysaccharide (mainly galactose) and *H. erinaceus* polysaccharide (mainly glucose) isolated from culture broth showed anti-artificial pulmonary metastatic tumor effects in ICR mice and could enhance the increase of T cells and macrophages [69]. NK cells are potent antitumor killer cells capable of killing not only circulating tumor cells, but well-established micro metastases [70]. Further study [71] has revealed that WEHE indirectly activated the cytolytic ability of NK cells via the induction of IL-12 in total splenocytes and possibly via other immuno-mediators or cellular components as evidenced by the facts that: (a) WEHE significantly increased the cytolytic activity of total splenocytes towards Yac-1 cells. However, there was no enhancement of cytotoxicity in NK cell-depleted splenocytes, (b) splenocytes treated with IL-12 were strongly activated to lyse Yac-1 cells, while the effect was abolished by the treatment with antibodies against IL-12, and (c) WEHE increased the expression of IL-12 and IFN-γ in splenocytes.

Chemotherapeutic resistance to drugs is a major obstacle to the successful treatment of human hepatocellular carcinoma. Lee and colleagues [17] demonstrated that the combination of low doses of crude water-soluble polysaccharide (HE) obtained from the fruiting body of *H. erinaceus* and 1 μg/mL of doxorubicin significantly caused a greater dose-dependent growth-inhibitory effect on HepG2 cells than that of using HE or doxorubicin alone. In the treatment group, the typical morphology of apoptotic cells, including cell shrinkage, chromatin condensation, and formation of apoptotic bodies all appeared. Further experiments [17] demonstrated that HE as an enhancer sensitized doxorubicin-induced apoptotic signaling by down-regulating c-FLIP expression via JNK activation and modulating intracellular accumulation of doxorubicin via the inhibition of NF-κB activation.

5.2. Effect on gastrointestinal mucosa

Shao [72] has demonstrated that *H. erinaceus* polysaccharides (17 and 68 mg/kg, *p.o.*, 500 μg/mL), can: (a) inhibit ethanol-induced acute gastric mucosal injury, (b) reduce indomethacin-induced rats gastric ulcer area and increase expressions of prostaglandin E_2 (PGE_2) and epidermal growth factor (EGF) in gastric mucosa of model rats, (c) reduce acetic acid-induced rats gastric ulcer area and increase expressions of basic fibroblast growth factor (bFGF) and mRNA of transforming growth factor-alpha (TGF-α) in gastric mucosa of model rats, (4) reduce rats gastric ulcer area induced by water immersion stress and elevate gastric mucosal blood flow in model rats, and (5) inhibit the secretion of pro-inflammatory cytokines IL-6, IL-8, IL-12 and promote the secretion of anti-inflammatory cytokine IL-10 in co-culture system of Caco-2 cells and Caco-2/RAW264.7 cells under LPS stimulation.

In addition, it was also suggested that *H. erinaceus* polysaccharides were effective against *Helicobacter pylori* which is responsible for many gastric disorders, and Bi^{3+}-*H. erinaceus* polysaccharide (BiHEP) complexes with a small amount of Bi^{3+} exhibited strong inhibitory effects on *H. pylori* with a MIC value of 20 μg/mL equivalent to that of colloidal bismuth subcitrate (the most utilized bismuth preparation in eradication treatment of *H. pylori*) with high-content of Bi^{3+} [73].

5.3. Anti-oxidative and hepatoprotective activities

H. erinaceus has been reported to possess hepatoprotective effect, which is related to its anti-oxidative activity to some extent. For example, Zhang and colleagues [20] demonstrated that one of the endo-polysaccharides from three fractions of *H. erinaceus* grown on tofu whey protected mice from carbon tetrachloride-induced liver damage *in vivo*, and showed strong *in vitro* hydroxyl radical scavenging activity, DPPH scavenging activity, iron chelating ability, and reducing power. Another related study [74] performed *in vivo* with CCl_4-induced hepatic injury-bearing mice has suggested that supplement of extracellular and intracellular polysaccharides were capable of not only reducing the aspartate aminotransferase and glutamic pyruvic transaminase activities as well as the triglyceride level in serum, but increasing the levels of cholesterol and albumin. In addition, the contents of lipid peroxidation and malondialdehyde largely decreased, and the superoxide dismutase and catalase activities significantly increased in liver tissue. Histopathological observation in treatment group showed that hepatocytes' structure recovered and there were less hydropic degeneration, lobular necrosis, and lipid droplets.

Experimental work [16] performed *in vitro* with PC12 cells have suggested that HEPS (1 mg/mL) from fresh fruiting bodies of *H. erinaceus* was capable of decreasing ROS production and showed a free radical scavenging rate of 90%. It [75] also has been demonstrated that a *H. erinaceus* polysaccharide named HEP displayed strong antioxidant activity and was able to decrease ischemia/reperfusion (IR)-induced oxidative injury in kidney as evidenced by the facts that HEP (300 mg/kg, *i.g.*) can: (a) significantly cause decrease in blood urea nitrogen and serum creatinine, and cause increase in creatinine clearance levels, (b) significantly up-regulate malondi-

Table 2
Patents list of products containing *H. erinaceus* polysaccharides and their claimed pharmacological properties.

Application	Main composition	Pharmacological properties	Publish number
Meal replacement powder	*H. erinaceus* polysaccharides, konjaku flour, soybean polypeptide, resistant starch, capsaicin, L-carnitine	Weight loss and lipid lowering	CN 103404865A
Solid beverage	*H. erinaceus* polysaccharides, soybean powder, red bean powder, fructo-oligosaccharides	Improving gastrointestinal function	CN 103478792A
Chewable tablet	*H. erinaceus* polysaccharides, bifidobacteria and lactobacillus, fruit and vegetable freeze dried powder	Nourishing the stomach and intestine	CN 104770639A
Health product	*H. erinaceus* polysaccharides, fermented turmeric powder, Puerariae Lobatea Radix extracts, Polygonati Rhizoma extracts, Dioscoreae Rhizoma extracts	Liver protection, alleviating a hangover, expelling toxins	CN 104223107A
Health product	*H. erinaceus* polysaccharides, ganoderan, *Cordyceps sinensis* polysaccharides, astragalan, *Lycium barbarum* Polysaccharides	Enhancing immunity function	CN 1762236B
Health product	*H. erinaceus* polysaccharides, Fermented turmeric powder, *Poria cocos* extracts, Crataegi Fructus extracts, *Dioscorea opposita* extracts, Amomi Fructus powder	Strengthening the spleen and promoting digestion	CN 104256592A
Health product	*H. erinaceus* polysaccharides, Crataegi Fructus powder, inulin, fructo-oligosaccharide powder, xylo-oligosaccharide powder	Nourishing the stomach and intestine	CN 102172270A
Health product	*H. erinaceus* polysaccharides and their by-products, glycopeptide, oleanolic acid, taurine	Nourishing the stomach and intestine	CN 101574513A
Pharmaceutical	*H. erinaceus* polysaccharides	Relieving epigastric pain caused by chronic superficial gastritis, gastric ulcer, or atrophic gastritis	CN 1453295A

aldehyde level, and down-regulate the reduced glutathione level in renal IR rats. Besides, it [76] is also worth mentioning that *H. erinaceus* polysaccharide was able to significantly enhance derma antioxidant enzymes MMP-1 and TIMP-1, and up-regulate collagen protein levels.

5.4. Neuroprotective and neuroregenerative activities

It has been reported that a series of benzyl alcohol derivatives hericenones from fruiting bodies and diterpenoid derivatives erinacines from mycelium are promising bioactive substances which are capable of promoting nerve growth factor (NGF) synthesis *in vitro* and *in vivo* [77]. However, there is also debate as to whether hericenones are active components stimulating biosynthesis of NGF and recent result have shown that hericenone C, D and E did not increase NGF mRNA expression in 1321N1 human astrocytoma cells [78]. It has long been speculated that *H. erinaceus* polysaccharides to some extent underlie regenerative effect on peripheral nerve following crush injury in aqueous extract of fruiting bodies which contain erinacines in traces [11,79].

Experimental work [16] performed *in vitro* with rat pheochromocytoma PC12 cells have suggested that a *H. erinaceus* polysaccharide named HEPS was capable of protecting PC12 cells from amyloid beta$_{1\text{-}40}$-induced neurotoxicity, promoting cell viability under amyloid beta$_{1\text{-}40}$-induced toxic conditions, decreasing amyloid beta$_{1\text{-}40}$-induced high mitochondrial membrane potentials, and preventing amyloid beta$_{1\text{-}40}$-induced cell shrinkage and nuclear degradation. Another *in vitro* experimentation [80] demonstrated that exo-biopolymer from the liquid culture medium of *H. erinaceus* mycelium was capable of enhancing the growth of rat adrenal nerve cells, improving the extension of neurites in PC12 cells, maintaining relatively constant number of neurite-bearing cells even though the cell growth started to decreased, and preventing PC12 cells' apoptosis via dramatically reducing the ratio of apoptotic cells. In addition, the efficacy on the growth of PC12 cells was found to be greater than NGF and brain-derived nerve factor (BDNF) [80]. Additional animal studies [81] further illuminated the restoration of sensory dysfunction following peripheral nerve injury by *H. erinaceus* polysaccharides associated with the activation of protein kinase signaling pathways and the restoration of blood-nerve barrier as evidenced by the facts that: (a) the time taken for rats to withdraw its hind limb from contacting with the hot plate significantly reduced, (b) expressions of Akt and p38 MAPK in the dorsal root ganglia strongly up-regulated, (c) the intensity of endothelial cells antigen-1 that recognized endothelial cells in the blood vessels of distal segments in crushed nerves increased.

5.5. Hypolipidemic activity

Experimental studies performed in dietary-induced hyperlipidemic rats have suggested that exo-polymers produced in submerged mycelial culture of *H. erinaceus* were capable of significantly reducing not only the levels of total cholesterol, low-density lipoprotein cholesterol, liver total cholesterol, lasma triglyceride, and phospholipid [19], but also atherogenic index and hepatic HMG-CoA reductase activity [82]. Additional animal studies [83] further illuminated that the cholesterol-lowering effect might be related to the increase in bacterial count and short chain fatty acids production in the large intestine, and the accelerated rate of catabolism of cholesterol to bile acids as evidenced by the facts that: (a) dietary HFCP (polysaccharides from the submerged fermentation concentrate of *H. caput-medusae*) decreased the levels of total cholesterol, triglyceride, and low-density lipoprotein cholesterol in serum, and increased high-density lipoprotein cholesterol level, (b) the caecum *Escherichia coli* count and pH value decreased linearly and quadratically, while the caecum lactobacilli count, bifidobacteria count, and propionic acid concentration increased with increasing levels of dietary HFCP, and (c) cholesterol content in liver, thigh, and breast muscle decreased, while the bile acid excretion increased. In addition, dietary supplementation with HFCP [84] showed lipid-lowering effect, thus bringing about lower fat deposition in broilers.

5.6. Hypoglycemic activity

Animal studies [85] have clearly demonstrated that *H. erinaceus* polysaccharides had a wide prospect for the treatment of diabetes due to their low effective dose, oral effective and sustained efficacy with no side effects as evidenced by the facts that: (a) *H. erinaceus* polysaccharides at a low dosage of 6 mg/kg significantly reduced blood glucose level in normal mice and alloxan-induced diabetic mice, (b) Normal mice and diabetic mice upon intragastrical administration of *H. erinaceus* polysaccharides (25 mg/kg) both resulted in a reduce of nearly 50% in blood glucose level, (c) mice treated with *H. erinaceus* polysaccharides before alloxan injection significantly reduced the blood glucose level, and (d) *H. erinaceus* polysaccharides enhanced the sugar tolerance of alloxan-induced diabetic mice.

5.7. Anti-fatigue and anti-aging activities

H. erinaceus polysaccharides have been shown to be able to increase the flying ability of *D. melanogaster* [86]. Additional animal studies [87] further illuminated that *H. erinaceus* polysaccharides (50, 100, and 200 mg/kg, *i.g.*) were capable of extending exhaustive swimming time, increasing tissue glycogen content and antioxidant enzyme activity, and decreasing the contents of certain biochemical parameters related to fatigue, including blood lactic acid, serum urea nitrogen, and malondialdehyde. Lipofuscin is waste product of human and animal aging metabolism, it is constantly accumulating in cells with the increase of age, thereby bringing about cell atrophy. Evidence [86] suggested that administration of *Drosophila melanogaster* and mice with *H. erinaceus* polysaccharides significantly reduced lipofuscin content. As the age increases, SOD content decreases significantly. *H. erinaceus* polysaccharides (50 and 100 mg/kg, *i.p.*) have been shown to be capable of increasing the activity of SOD in brain and liver.

5.8. Others

H. erinaceus was shown to has the potential to inhibit metal elements loss in rat skull [88] as evidenced by the facts that: (a) Se-enriched *H. erinaceus* polysaccharides improved bone mineral density and bone mineral content in experimental rat skull, (b) the lower elastic deformation, elastic load, maximum deformation, and maximum load in Se-enriched *H. erinaceus* polysaccharides-treated groups were dose-dependently enhanced, femur weight was significantly reduced, and there was no significant change in the femur length, and (c) Se-enriched *H. erinaceus* polysaccharides significantly increased blood P level, and decreased Ca^{2+} level, blood and skull alkaline phosphatase activities.

6. Industrial applications

According to the record in "*Zhonghua Bencao*" (中华本草) [89], *H. erinaceus* is capable of fortifying the spleen and nourishing the stomach, tranquilizing the mind, and fighting cancer, thus can be widely used for the treatment of various diseases, including body deficiency and weakness, dyspepsia, insomnia, gastric and duodenal ulcer, chronic gastritis, and digestive tract tumor. As mentioned above, Lion's Mane mushroom shows much promise in supporting the immune system, nervous system and digestive system with its unique ingredient polysaccharides to some extent.

Polysaccharides are the main bioactive constituents in *H. erinaceus* oral liquid [90]. Commercial health products namely fresh *H. erinaceus* oral liquid have served for health-care and for the promotion of learning and memory [91]. Likewise, *H. erinaceus* oral liquid also has certain effects on gastric mucosal injury [92]. Furthermore, *H. erinaceus* polysaccharides-encapsulated curcumin nanoparticles were successfully prepared by nanoprecipitation. These particles exhibited good solubility in water and increased drug delivery efficiency and biological effect, thereby bringing about better *in vitro* antitumor activity compared to free curcumin [93–95].

A large number of listed drugs which only contain *H. erinaceus* extracts as the medicinal ingredient have penetrated into many aspects of protecting human health, especially nourishing the stomach and intestine and enhancing immunity function. Some patent health products, meal replacement powder, chewable tablet, and solid beverage containing *H. erinaceus* polysaccharides that improve health without side effects are shown in Table 2.

7. Conclusion and future prospects

H. erinaceus is distinguished as an edible medicinal mushroom and also a delicacy for food supplement, therefore has earned much attention as a potential source of various pharmaceutical properties. Over the past decade, *H. erinaceus* has been made into many patent health care products and medicines to treat epigastric pain caused by chronic superficial gastritis, gastric ulcer, or atrophic gastritis. However, besides antitumor and immunomodulatory activities, further in-depth studies about the potential mechanism for the promotion of learning and memory and for the protection on gastric mucosa injury of *H. erinaceus* polysaccharides still need to vigorously increase. There is debate as to whether hericenones are active components stimulating NGF biosynthesis, and the other kind of well-known NGF-promoting compounds namely erinacines are in traces in fruiting bodies. Therefore, *H. erinaceus* polysaccharides are very likely a kind of bioactive ingredients due to the facts that crude extracts of *H. erinaceus* fruiting bodies have been reported to be capable of inducing NGF biosynthesis and protecting neuronal cells. *H. erinaceus* polysaccharides are orally effective, the possible role in corresponding receptor molecules on the surface of intestinal cells is worth investigating. In addition, bioactivities of polysaccharides are closely correlated with their physicochemical properties, while reliable evaluation for the characterization of polysaccharides from *H. erinaceus* collected from different regions has seldom been carried out. Likewise, the relationship between bioactivities and chemical structures are still not well established.

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