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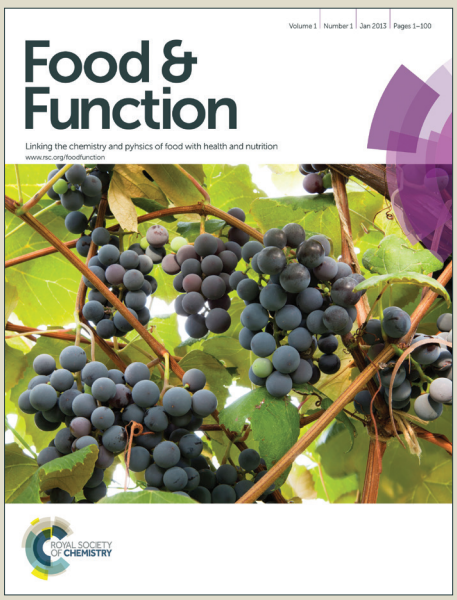

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Helicium erenaceus (Yamabushitake): A unique resource for developing functional foods and medicines

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Abstract

Helicium erinaceus (HE) is a fungus habiting in the mountainous areas of northeast territories. HE has been used in the traditional folk medicines and medicinal cuisine in China, Korea and Japan. It has been implicated in a variety of physiological functions such as anti-aging, anti-cancer, anti-gastritis, anti-metabolic diseases, etc. Hence, HE is an attractive target resource for developing not only medicines but also functional foods. Basic studies on the physiological functions and the chemical identification of its active ingredients have progressed in recent decades. In this article, we provide an overview of the biochemical and pharmacological studies of HE, especially of its antitumor and neural preserving functions, together with recent developments in the chemical analysis of its polysaccharides which comprise its major active components.

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Introduction

Many fungi are the familiar food resources frequently appearing on the daily dinning table. The reason why they are so popular is not only due to their taste, flavor and texture as an attractive food material but also is due to their health beneficial health effects. The fungus kingdom has a broad spectrum of biological functions, some of which are beneficial to human health; however, some are toxic. Many fungi and mushrooms have attracted much attention because of their medicinal functions such as immune modulation, anti-cancer and anti-aging as reviewed elsewhere [1, 2, 3, 4, 5]. The adjuvant effect has been acknowledged as one of the activities observed in fungal extracts, although the active principle(s) and their molecular mechanism of action have not been yet completely understood [6] . Such an indirect mode of action is sometimes described as the biological response modifier (BRM) function [7] and has been discussed as the possible function of polysaccharides, especially of β-glucans [8,9,10].

Recent progress in the studies of active components and their functions in fungi has revealed that both high and low molecular weight components play critical roles in their pharmacological functions[11]. The same occurs in *Hericium erinaceus* (HE), a precious fungous inhabiting the mountainous regions of northeast Asian countries such as China, Japan and Korea. Since many physiological functions due to HE have been implicated, such as anti-aging, anti-cancer, anti-gastritis, and anti-metabolic diseases, it has been used in traditional medicines and medicinal cuisines.

Early chemical studies were focused on polysaccharides such as β-glucan as the active component of HE in its immune modulation and anti-cancer activities[12]. However, more recent studies have revealed that small molecular weight components such as hericenone also play a role in the varied functions of HE such as neuroprotection through NGF modulation[13, 14]. Thus HE is attracting further attention as a novel resource for developing not only medicines but also functional foods for disease prevention and health promotion.

History and background of HE research

HE has been named Hou Tou Gu (Monkey Head Mushroom) in China and Yamabushitake in Japan. In the Western countries it is commonly referred to as Lion's Mane Mushroom. These names originated from the unique shape of its fruiting body

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(see Figure 1). It is listed as one of the "Four Famous Cuisines" of China, together with bear's paws, trepang and shark's fin. Although HE's health benefits have been known for some time, precise scientific studies on its physiological or pharmacological functions only began in the late 1990s to the early 2000s, mainly by Chinese researchers, and the results were reported in Chinese journals. They found that HE had immune modulating activities[15, 16, 17] and anti-cancer activities [16, 18] based on animal studies by analyzing aqueous extracts and its polysaccharides. A double-blind study was carried out in humans to evaluate the effect of HE intake on chronic atrophic gastritis [19]. Further, a few chemical studies on its low molecular weight components such as pyrone compounds were reported [20]. In addition to these early studies on the putative health benefits of HE, recent studies have identified several components such as hericenones which act as the active principles for the neuroprotective function of HE[21, 22, 23]. Thus HE became a promising target for studies on disease-preventive functional foods and medicines to help maintaining and extending human longevity. HE is a precious resource and rarely found in nature. With the improvement of artificial cultivation techniques, fruit body and mycelium of HE are currently manufactured as cuisine and medicinal resources[24], and thus basic studies on HE now underway is being accelerated.

Fig.1: *Hericium erinaceus* in nature

Antitumor and immunomodulating functions of HE

Cancer is the major cause of human death worldwide[25]. The cancer morbidity is expected to reach approximately 18% in 2030 according to projections by the WHO [26]. Although some good progress has been made in cancer treatment and development of new anti-cancer drugs, it becomes more and more important now for the chemoprevention by natural products [27]. One of the important functions of HE is the

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anti-cancer effect that was firstly demonstrated by Chen ZY, *et al.* [18] They showed chemopreventative effects for 6 edible natural resources against carcinogen- induced liver cell injury, which included HE. The anti-mutagenic activity of HE was also shown *in vitro* by Wang JC *et al* [16].

The anti-cancer potential of fungi has frequently been discussed as an indirect mechanism such as through activation of the immune system [28], and polysaccharides have been implicated as the active component(s) involved in this activity[29]. Manipulation of intestinal microflora is an alternative mechanism of action by fungi[30]. Since enterobacterial flora are associated with immune activity[31], immune modulation may be attributable to fundamental biological properties of fungi. Therefore, immune modulation and antitumor activities of the polysaccharide fractions were reciprocally studied, even in the early stages of HE research. For example, Wang JC *et al.* [16] conducted mice studies to assess the immune-enhancing and antitumor activities of polysaccharides isolated from the broth of HE culture.. Other studies also focused on the immune modulating role of polysaccharides in the anti-cancer activity of HE, as described below. Xu HM *et al.* concluded that the immune modulating activity of HE is present in the polysaccharide fraction[15]. Yim MH *et al.* reported that the water-soluble component of HE activates NK cells indirectly through induction of IL-12 in splenocytes[32]. Son CG *et al.* reported macrophage activation and NO production activities of aqueous extracts of HE[33]. Lee JS *et al.* also reported that purified polysaccharides from the fruiting body activated macrophages and they discussed the structure of the active polysaccharide[34]. The immune stimulatory activity of HE was also demonstrated in other pathological systems such as *Salmonella typhimurium*-induced liver damage, in which the aqueous and 50% EtOH extracts stimulated innate immune cells to protect against the bacterial infection [28]. Sensitization of anti-cancer drug actions may be another mode for the BRM effect of HE. Lee and Hong[35] reported that HE enhanced doxorubicin (Dox)-mediated apoptosis of human hepatocellular carcinoma cells through the reduction of c-FLICE-inhibitory proteins (FLIP) expression via Jun N-terminal kinase (JNK) activation, and also enhanced intracellular Doxorubicin (Dox) accumulation via Nuclear factor kappa B (NfkB) inhibition. They suggested that HE in combination with Dox serves as an effective tool for treating drug-resistant human hepatocellular carcinoma.The direct cytotoxicity of HE extract has been recently demonstrated in several cancer cell models *in vitro*. For example, Gu and Belury[36] demonstrated the

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cytotoxicity of the EtOH extract of HE and the *Lentinula edodes* extract on murine skin carcinoma cells (CH72) [26]. Kim *et al.* [37] prepared several types of extracts from the fruiting body of HE using hot water, 50% EtOH, and acidic and alkaline solvents, respectively, and examined their cytotoxicity towards U937 human monocytic leukemia cells. The results showed that both the water and the aqueous EtOH extracts induced apoptosis. Further analysis indicated that growth inhibition of the cancer cells by HE was strictly related to apoptosis induced via the caspase 3, 9 pathway but not by caspase 8.

The anti-cancer potential of mycelium was also demonstrated in animal systems. The hot water extract of mycelia, consisting primarily of polysaccharides, was shown to have anti-hepatocarcinoma activity[35]. Choi *et al.*[38] also reported a protective effect for the methanol (MeOH) extract of mycelia on carbon tetrachloride (CCl_4)-induced hepatic damage. Metastasis is a prime factor in cancer fatalities [39]. Han SS *et al.* [8] studied the anti-metastatic and immunomodulating effects of various mushrooms including HE, and found the water extract containing polysaccharides was the active fraction. Kim SP *et al.* [40] studied the antitumor effects of HE using mice bearing the murine colon carcinoma cell line CT-26 by observing tumor growth regression for four different HE extracts (hot water, 50% EtOH, acidic solvent, and alkaline solvent extracts), and found both the hot water and 50% EtOH extracts significantly suppressed tumor growth by daily intraperitoneal injections. They observed modulation of several cellular markers such as Natural Killer (NK), Cyclooxygenase-2 (COX-2) and Vascular Endothelial Growth Factor (VEGF), which relate to immune activation, inflammation, and angiogenesis, respectively. They suggested that such multifunctionality plays a critical role in the antitumor effects of HE. They extended their investigation of the anti-metastatic activity of HE to both *in vitro* studies and an allograft mice model[41]. In these studies, they showed that both the hot water and the microwaved 50% ethanol extracts of HE induced apoptotic death of CT-26 cells, decreased the expression of extracellular matrix degrading proteases, metalloproteinases (MMPs) and urokinase-type Plasminogen Activator (u-PA), and down-regulated phosphorylation of the cell growth regulating signal proteins Extracellular Regulated Kinase (ERK), JNK, p38 Mitogen-Activated Protein Kinase (MAPK), and other cell growth-related signals. Further, it was shown that dietary administration of these extracts indeed inhibited the migration of CT-26 cells to the lung in the allograft mice model.Determination of the antitumor component of HE has

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been rather limited to date. However, Mizuno[42] has isolated the polysaccharides xylan and glycoxylan as putative antitumor components of HE. Moreover, studies of the low molecular weight components of HE are sparse.The reports described above indicate that HE has high potential for chemoprevention strategies, and polysaccharides play a critical role in the biological activity of HE as well as of other fungi[43].

Protective functions of HE on brain and other neural systems

Degenerative brain diseases such as dementia are a major cause of decreased quality of life (QOL) in the longevity society[44]. Many efforts are focused on finding neuroprotective herbs and herbal components in nature[45], but HE research made an indelible mark on the neuroprotective function of mushrooms. For example, Mori *et al* studied the effects of HE (Yamabusitake) supplementation on patients with mild cognitive deficiency [46]. After consuming 5g of HE fruiting body daily in soup, 6 out of 7 patients showed improvement in cognitive function such as understanding, communication and memory, while all 7 showed improved Functional Independence Scores (FIS) such as eating, dressing and walking. Further study by a double-blind, parallel-group, placebo-controlled trial confirmed the beneficial effects of HE on dementia. Thirty patients with mild dementia at ages 50-80 were randomly grouped into treatment and control groups, respectively, and were given HE in tablet form at 3g/day for 16 weeks. A significant increase in cognitive function was observed in the treatment group. The HE effect lasted for four weeks after termination of the trial, followed by declining cognitive function scores.

Another clinical study of HE targeting brain function was reported by Nagano M *et al* [47]. They evaluated the effects of HE on depression, sleep quality and indefinite complaints in menopausal women using the Kupperman Menopausal Index (KMI), the Center for Epidemiologic Studies Depression Scale (CES-D), the Pittsburgh Sleep Quality Index (PSQI), and the Indefinite Complaints Index (ICI). Thirty females randomly assigned to either the HE group or the placebo group took HE containing cookies (0.5g/tablet) or placebo cookies for 4 weeks. The CES-D and the ICI scores for those ingesting HE was significantly lower than that for the placebo group, especially for the ICI "insensitive" and "palpitatio", indicating that HE intake is beneficial for reducing depression and anxiety.

These clinical observations have been supported by several *in vitro* and animal studies, and also by the finding that several active ingredients are related to the

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neuroprotective potential of HE. The preventive effects of HE against dementia was studied by Mori *et al.* [48] in an animal experimental system. Mice were fed diets containing HE (5% w/w) over 23 days and given 10 μg of amyloid β (25-35) intracerebroventricularly on days 7 and 14. Memory and learning functions were then evaluated by behavioral pharmacology methods. The results showed that HE prevented the impairment of short-term spatial and visual recognition memories induced by amyloid β (25-35). Mori K *et al.*[49] also studied the stimulative function of the EtOH extracts of four edible mushrooms, including HE, on Nerve Growth Factor (NGF) expression in the human astrocytoma cell line (1321N1) and also in animals. The results indicated that the HE extract promoted NGF expression at both the translational and transcriptional levels, and that the expression is regulated by JNK signaling. It was further shown that isolated hericenones such as C, D and E are not the active components.

Kolotushkina *et al* [50] studied the effect of HE extract on nerve myelination *in vitro* and found that HE extract stimulated myelin genesis without any pathologic or toxic effect to nerve and glial cells in culture, suggesting its beneficial effects on neuronal network formation and the recovery of damaged neurons. The effect on myelination process was also studied by Moldavant *et al* [51] using HE extract from fruiting body. They observed pulse reactions in hippocampal cells by a patch clump method, and found the extract exerted a neurotropic effect and improved the myelination process in mature myelinating fibers without affecting cell growth.

Park YS *et al.* [52] reported that an exo-polysaccharide purified from the liquid culture broth of HE mycelium enhanced the growth of rat adrenal nerve cells and also improved the extension of neurites of PC12 cells. The enhanced neurite extension was found to be stronger than that induced by NGF and Brain-Derived Nerve Factor (BDNF). Recently, Lai PL *et al.* [13] studied the synergistic effects of an aqueous extract of HE and exogenous NGF on neurite outgrowth in a neuroblastoma-glioma cell line (NG108-15), together with preventative properties against oxidative stress. They concluded that the HE extract contains certain neuroactive components that induce NGF synthesis and promote neurite outgrowth, but they do not protect cells against oxidative stress. Moreover, the extract was essentially non-toxic to the human lung fibroblast cell lines MRC-5 and NG 108-15.

The stimulative effect of HE ingredients on NGF production also suggests a beneficial function for HE in recovery of the peripheral nervous system. Wong KH *et*

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al.[53] investigated the effect of oral intake of the aqueous extract of the HE fruiting body on recovery from axonotmetic peroneal nerve injury in female Sprague-Dawley rats. They showed that daily administration of the extract promoted regeneration of injured rat peroneal nerves in the early stages of recovery by stimulating NGF production.

The search for neuroprotective species has progressed in parallel, and several components such as benzyl alcohol and chroman derivatives (termed hericenones C-H) have been determined in the fruiting body of HE by Kawagishi *et al.*[54] to stimulate NGF production in the cultured astroglial cells of mice. They also isolated another group of cyathane derivatives from the mycelium, named erinacines A-I, that also induce NGF production.Since Endoplasmic Reticulum (ER) stress is involved in neuronal cell death and thus is implicated in many types of neurodegenerative diseases, those compounds inhibiting ER stress-induced cell death were screened against HE extracts. Ueda K *et al.*[55] isolated new types of hericenones termed F, I, and J from HE and showed that 3-hydroxy hericenone F was the most effective in preventing ER stress-dependent Neuro2 cell death[9]. Nagai K *et al.*[56] reported that a lipid ingredient, dilinoleoyl-phosphatidylethanolamine (DLPE), has the same effect. Four new compounds having this activity were further isolated from not only HE but also from the scrap cultivation beds of HE cultures, and all of them prevented ER stress-dependent cell death[57]. In addition, Mori K *et al.*[58] searched for inhibitors of platelet activation among the EtOH extracts of several mushroom species and identified hericinone B from HE as the active component inhibiting collagen-induced activation of platelets that were isolated from both rabbit and human. They suggested that HE may be effective for antithrombotic therapy against post-neurotraumatic injury, for example. The studies described above indicate the novel functions of HE in functional preservation and protection of the brain. HE is a food, having been served without any adverse effects, and thus HE has become a target for developing functional foods and medicines against neurodegenerative diseases.

The preventative effects of HE on oxidative stress and inflammation-related diseases

Oxidative stress and chronic inflammation are common pathologies characteristic of almost all diseases such as metabolic syndromes, cancers, dementia and aging[59] and thus are implicated as targets for the study of the physiological

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functions of mushrooms. The polyphenolics are major antioxidant molecules found in nature[60] and several polyphenolic ingredients isolated from various fungi have demonstrated antioxidant activities both *in vitro* and *vivo*, such as *Inonotus obliquus* (Chaga)[61,62], *Plourotus ostreatus*[63] and *Armillaria mellea* [64]. HE also contains considerable levels of polyphenols and phenolic amino acids, which are also found in other mushroom species[65]. Fu HY *et al.*[66] studied the antioxidant and free radical scavenging activities of several edible mushrooms commercially available in Taiwan, including HE, and showed that the antioxidant activity essentially consisted of the total polyphenol content. The same line of *in vitro* antioxidant assessment was reported by Maua JL *et al.*[67]. Both studies indicated that neither the polyphenolic content nor the antioxidant activity of HE were especially high among the edible mushrooms examined. Abcullah *et al.*[68] examined both antioxidant and Angiotensin Converting Enzyme (ACE)-inhibitory activities of aqueous extracts of 16 culinary mushrooms with putative medicinal effects, including HE. The hot water extract of the HE fruiting body showed relatively high antioxidant activity, which was also evident for *Ganoderma lucidum* and *Schizophyllum commune*, but the polyphenolic contents among them did not strictly coincide with the antioxidant activities. Interestingly, the HE extract had the highest ACE inhibitory activity among them, indicating the beneficial effects of HE on hypertension control. The direct scavenging potential of polysaccharide fractions from 11 mushroom species, including HE, was demonstrated against free radicals such as superoxide and hydroxyl radicals using the phenazin methosulphate-NADH-nitroblue tetrazolium system and the ascorbic acid-Cu^{2+}-cytochrome C system, respectively, but the results were variable because of the presence of proteins in the polysaccharide extracts which also showed free radical scavenging activity[69]. Zhang Z *et al.*[70] studied the antioxidant activities of ex-polysaccharides fractionated by EtOH precipitation from HE grown on Tofu whey both *in vitro* and *vivo*. They found that the 80% EtOH fraction had the strongest activity *in vitro* and also had hepatoprotective properties *in vivo*. Han ZH *et al.*[71] administered the polysaccharide from HE to mice orally at a dose of 300mg/Kg for 15 days and observed the antioxidant effect using a renal ischemia reperfusion model for mice and concluded that HE polysaccharide improves the antioxidant status of animals as evaluated by antioxidant enzyme levels.

Gastritis is a pathology characterized by oxidative stress and chronic inflammation. IHE has been used for treating gastritis as a folk medicine or in the Traditional

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Chinese Medicine prescriptions but its mechanism of action has remained unclear. Therefore, several studies have focused on anti-gastric ulcer and cancer prevention. For example, Abdulla M.A *et al.*[72] have reported on the cytoprotective effect of freeze-dried fruiting bodies in EtOH-induced gastric mucosal injury in rats. Currently, Wong JY[73] has also observed the protective effects of an aqueous extract of HE on the same ulcer model in rats and found that HE inhibited EtOH-induced oxidative stress by modulating the expression of antioxidant enzymes, as well as by up-regulating Heat Shock 70 kDa Protein (HSP70) and down-regulating BCL2-Associated X Protein (BAX). He also conducted an acute toxicity study and found that the extract was not toxic in rats at 5g/Kg. Yu CG *et al.*[19] reported on the protective effects of HE on gastric mucosa in rats. The anti-gastritis effect was also studied in humans by Xu CP *et al* [17]. Certain improvements in chronic atrophic gastritis were shown by a double-blind study in patients aged 30 to 60 after taking HE tablets; unfortunately, the HE contents in the tablet were not provided in the article.

Helicobacter pylori is the bacterium implicated as the major factor for the increased incidence of human gastric cancer and peptic ulceration. It causes chronic inflammation, leading to carcinogenic transformation of gastric epithelial cells. Therefore, many natural products have been studied for their anti-*H. pylori* effects[74,75]. Shang *et al.* [76] studied the inhibitory effects of HE extract on either laboratory or clinically isolated strains of *H. pylori* together with 13 other mushroom species. They found that the EtOH extract of 12 mushrooms, including HE, effectively inhibited *H. pylori* growth with the Minimum Inhibitory Concentration (MIC) of < 3mg/mL. The AcOEt extract of HE inhibited the growth of 9 clinically isolated *H. pylori* species in the concentration range of 62.5 to 250 mg/mL. The authors suggested that besides polysaccharide-mediated immunomodulation, a direct mode of action by such as cyathane derivatives, one of the active ingredients in HE, may play a role in the anti-bacterial action of HE. Metabolic syndromes are now known to be associated with many diseases adversely affecting the Quality of Life (QOL), including dementia, stroke and cancer. Therefore, dietary control of metabolic syndromes has become a major social goal and much attention has been focused on identifying functional food resources and related ingredients having anti-metabolic disease activity. HE is one of the attractive resources for developing functional foods.

Wang JC *et al.*[77] studied the effects of a MeOH extract of HE on the stereptozosin (STZ)-induced diabetic model in rats and found that administration of the extract

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suppressed the STZ-induced increase in plasma glucose levels and the elevation of serum triglycerides and total cholesterol levels. The hypolipidemic effects of an exo-biopolymer (polysaccharides) produced by a submerged mycelial culture of HE was reported by Yang BK *et al.*[78], in which the polymer given orally inhibited dietary-induced hyperlipidemia in rats in a dose-dependent manner.

Hiwatashi K *et al.*[79] examined the effects of dietary intake of Yamabushitake mushroom (HE) on lipid metabolism and showed that intake of the EtOH extract improved lipid metabolism in high fat diet-supplemented mice through the activation of Peroxisome Proliferator Activated Receptors-α(PPARα). Liang B *et al.*[80] studied the antihyperglycemic and antihyperlipidemic effects of the aqueous extract of HE on the STZ-diabetic rat model and reported that administration of the extract for 28 days significantly decreased plasma glucose and lipid levels and was accompanied by a significant increase in serum insulin. At the same time, liver oxidative stress was inhibited with increased levels of GSH and antioxidant enzymes including Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GSH-Px).

Polysaccharides and other active components of HE

In parallel with the functional studies described above, the chemical analysis of the active ingredients present in HE has progressed significantly in recent years. Polysaccharides have been implicated as major active components of mushrooms or fungi[9] such as HE, which has a wide variety of pharmacological functions such as anti-microbial, anti-diabetic and anti-hypertension, as reviewed by Khan *et al* [81]. Several bioactive polysaccharides have been isolated from both the fruiting bodies and the mycelia of HE[75]. Table 1 summarizes the structures determined for the polysaccharides isolated from HE in recent years.

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Table 1: Sugar composition of polysaccharides purified from *Hericium erinaceus*

Name of polysaccharide	Major sugar components and molar ratio	Molecular weight (Da)
HPA[82]	Glc:Gal:Fuc=1.00:2.11:0.423	5.0×10^4
HPB[82]	Gal:Glc=1.00:11.5	3.0×10^4
HEP-1[83]	Rhm:Gal:Glc=1.19:3.18:1.00	1.8×10^4
HEP-3[84]	β-D-glucan	/
HEPF1[85]	Fuc:Gal:Glc=1:4:1	1.94×10^4
HEPF3[86]	Fuc:Gal=1.00:4.12	1.9×10^4

Wang Z *et al.*[82] isolated a polysaccharide consisting of two diverse structural moieties termed HPA and HPB from the fruiting body of HE by boiling-water extraction, EtOH precipitation, and DEAE-Sepharose CL-6B column chromatography. The polysaccharides of HPA consisted of Glucose (Glc), Galactose (Gal) and Fucose (Fuc) in the ratios 1.00:2.11:0.423, and HPB contained monosaccharides of Gal and Glc in the molar ratio of 1.00:11.5. Further structural analysis by methylation, GC-MS, periodate oxidation-Smith degradation, and partial acid hydrolysis revealed the polysaccharide was composed of repeating units of HPA and HPB. Jia M *et al.*[83] isolated a new heteropolysaccharide (HEP-1) with a molecular weight of 1.8×10^4 Da from the fruiting body extract. Structural analysis revealed that the polysaccharide is composed of rhamnose (Rha):Gal:Glc in the ratio of 1.19:3.18:1.00 and has a (1→6)-linked α-D-galactopyranosyl backbone to which Rha and Glc attached through O-2.

Dong Q *et al.*[84] isolated HEP3, a slightly water soluble β-D-glucan from the alkaline extract of the fruiting body of HE. Structural analysis revealed that HEP3 has a main chain composed of β-(1→3)-linked D-glucopyranosyl residues with single unit Glc branches attached to O-6 of every third backbone residue. Viscometry and Congo red reaction indicated that HEP3 has a highly ordered hydrogen-bonded conformation in aqueous solution, and this conformation was unstable in strongly alkaline solution. Zhang AQ *et al.*[85] isolated a novel heteropolysaccharide HEPF1 with a molecular weight of 1.94×10^4 Da from the fruiting body of HE. It was composed of Fuc, Gal and Glc in the ratio of 1:4:1, and 3-O-methyl Rha was determined to be a minor component. It was further revealed that HEPF1 has a (1→6)-linked

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α-D-galactopyranosyl backbone with branches that are composed of Fuc attached to O-2. It also contained 6-O-substituted-β-D-oligoglucosyl units and a minor terminal 3-O-methyl Rha residue. Zhang AQ *et al.*[86] also isolated a novel heteropolysaccharide, HEPF3, from the fruiting body of HE. HEPF3 has a molecular weight of 1.9×10^4 Da and is composed of Fuc and Gal in a ratio of 1.00:4.12. It is suggested that HEPF3 consists of a branched pentasaccharide repeating unit.

Analysis of polysaccharide composition may be appropriate for the quality control of HE resources. Such assays have been reported by Keong C.Y *et al.*[87], and Guan J and Li PS [88] in which characteristic polysaccharide profiles of enzyme hydrolysates were used as markers.

Besides polysaccharides, many low molecular weight ingredients have been isolated from HE, as described in the preceding sections, such as a series of Erinacines[14,53,89,90], hericenones[91,92,93], Erinacerines[23], and anti-ER stress protective dilinoleoyl-phosphatidylethanolamine (DLPE)[55]. Further, isohericenone[22], geranylated isoindolinone, together with ergosterols[94] and ergosterol peroxide[95] , have been isolated from HE. Recent developments in mass spectrometry have allowed for the quantitation of the secondary metabolites of HE, such that the distribution of terpenoid ingredients including erinacine type metabolites have been imaged by MALDI-MS[96].

A few enzymes have also been identified in the fruiting body of HE, such as amylase with a molecular mass of 55 kDa[97] and laccase with a novel *N*-terminal sequence[98]. Laccase has a molecular mass of 63 kDa and showed considerable inhibitory activity toward HIV-1 reverse transcriptase (IC_{50} = 9.5μM). It is interesting to note that a novel fibrinolytic metalloprotease termed herinase was recently isolated from HE[99]. This enzyme of 51kDa molecular mass was able to degrade fibrin clot directly and activated plasminogen. Its fibrinolytic function might in part explain the medicinal functions of HE, although it is uncertain whether this enzyme is absorbed into the blood circulation without loss of activity.

A variety of chemical constituents are thus present in HE, including polysaccharides, terpenoids and their glycosides, alkaloids, proteins, amino acids and benzotriazole pyrrolidone derivatives, as reviewed elsewhere such as by Avtonomova AV *et al.*[100] and by Mizuno T[42]. The beneficial health effects of HE have been recently discussed in the context of bioactive compounds and their cognate functions by Khan SP *et al.*[81].

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Conclusion and prospects

Besides the broad spectrum of physiological functions described above, there are several additional functions that have been reported for HE, such as stimulation of wound healing[101]. Therefore, HE is an attractive resource to be studied for the development of functional foods and medicines. In spite of a long history of usage in the medicinal cuisine of Oriental countries, until about a decade ago only a limited number of studies have been done to prove the implicated functions. However, the recent development of technologies to culture mycelium has allowed for sufficient sample sizes to conduct basic research. Such progress has thus stimulated both functional and chemical studies of HE. In addition to discovering biologically active low molecular weight ingredients, the development and refinement of structural and functional analysis of polysaccharides isolated from HE, especially from mycelium, has afforded new insights into polysaccharides with specific structures and sugar composition that are pharmacologically active. These developments supplement the traditional concept of the indirect action mode, such as immune modulation. Further structural and functional studies of HE polysaccharides will permit structural modifications of polysaccharides, yielding improved medical therapies and a further understanding of the bioavailability and metabolic fate of polysaccharides. The low toxicity of HE, in both fruit body and mycelium form and even of its chemical components, will be an additional advantage for the dietary application of HE for the prevention and amelioration of diseases in the form of functional foods.

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This article provided valuable scientific information of Hericium erinaceus and showed its possibility of developing new functional foods and drugs.

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