Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

Bioactive compounds in *Hericium erinaceus* and their biological properties: a review

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ARTICLE INFO

Article history:
Received 24 November 2022
Received in revised form 29 December 2022
Accepted 13 February 2023

Keywords:
Hericium erinaceus
Bioactive compounds
Biological activities
Antioxidation
Neuroprotection
Immunoregulation

ABSTRACT

Hericium erinaceus is a nutritious edible and medicinal fungi, rich in a variety of functional active ingredients, with various physiological functions such as antioxidation, anticancer, and enhancing immunity. It is also effective in protecting the digestive system and preventing neurodegenerative diseases. In this review paper, we summarize the sources, structures and efficacies of the main active components in *H. erinaceus* fruiting body, mycelium, and culture media, and update the latest research progress on their biological activities and the related molecular mechanisms. Based on this information, we provide detailed challenges in current research, industrialization and information on the active ingredients of *H. erinaceus*. Perspectives for future studies and new applications of *H. erinaceus* are proposed.

1. Introduction

Hericium erinaceus, also known as Lion's mane mushroom, or Yamabushitake in Japan, belongs to the family Hericiaceae, in the order Russulales[1]. These species are found throughout the northern hemisphere in Europe, Asia, and North America. In the natural environment, *H. erinaceus* grows in deadwood or heartwood of living trees, and in large-scale artificial cultivation. The mature state of the fruiting body of *H. erinaceus* is easily discernible, with its basidiosome consisting of long branchless dangling spines that change in color from white to yellow and eventually, with aging, to brown[2].

As an edible and medicinal fungus, *H. erinaceus* not only tastes delicious, but also has high medicinal value, which has attracted the interest of many researchers and developers. More and more research results on the separation, identification, bioactivity evaluation and application of bioactive substances in *H. erinaceus* not only enrich the types of *H. erinaceus* products, but also reduce economic losses caused by difficult preservation, which is also important to broaden the market and promote the development of the *H. erinaceus* industry[3].

Studies have shown that in addition to functional macromolecules such as polysaccharides and proteins, *H. erinaceus* also contains small molecular active components such as terpenoids, cerebrosides, phenols and sterols[4]. These bioactive compounds enable *H. erinaceus* to have various physiological activities in health-care functions, such as antioxidant, anti-cancer, gastrointestinal protection, and immune regulation[2]. In addition, *H. erinaceus* also has neuroprotective effects and may be useful in preventing and treating neurodegenerative diseases[5], attracting extensive attentions.

Although there are numerous reports on the bioactive compounds and biological activities of *H. erinaceus*, a systematic summary of these studies is still lacking. In this paper, the source, chemical structures and bioactivities of reported components in *H. erinaceus* were systematically reviewed (as shown in Fig. 1), especially

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Peer review under responsibility of Tsinghua University Press.

Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2022.9250152

polysaccharides, hericenones, erinacines, proteins and peptides. The biological activities exhibited by *H. erinaceus*, especially the neuroprotective effects of *H. erinaceus* are also described. In addition, the challenges faced in the current research and industrialization were discussed, and we also provided new strategies for further in-depth studies on the bioactive compounds of *H. erinaceus* with its potential applications in food and medicine.

2. Bioactive compounds in *H. erinaceus*

2.1 Polysaccharides

Polysaccharides are the most well studied bioactive components of *H. erinaceus*[6]. The extraction methods of *H. erinaceus* polysaccharides reported to date mainly include water extraction, alkaline extraction, ultrasonic/microwave-assisted extraction, and enzyme-assisted extraction[7]. The water extraction method has the advantages of low equipment cost and simple operation, and is suitable for large-scale extraction and industrialization. However, it usually requires a long time, high temperatures and high liquid-solid ratios to obtain good yields[6]. In addition, due to the multi-layered cell wall structure of the fruiting body of *H. erinaceus*, some polysaccharides, especially *β*-glucans, often remain in the water-insoluble residue during water extraction, while using alkali extraction methods can further extract *α*/*β*-glucans from these residues[8]. Auxiliary strategies such as ultrasound, microwave and enzymes are often used to shorten extraction time and energy consumption. Ultrasonic processing has been shown to accelerate the dissolution of polysaccharides molecules into the extractant by disrupting cell walls and vacuolization[9-10]. Microwave has strong penetrability, and it can

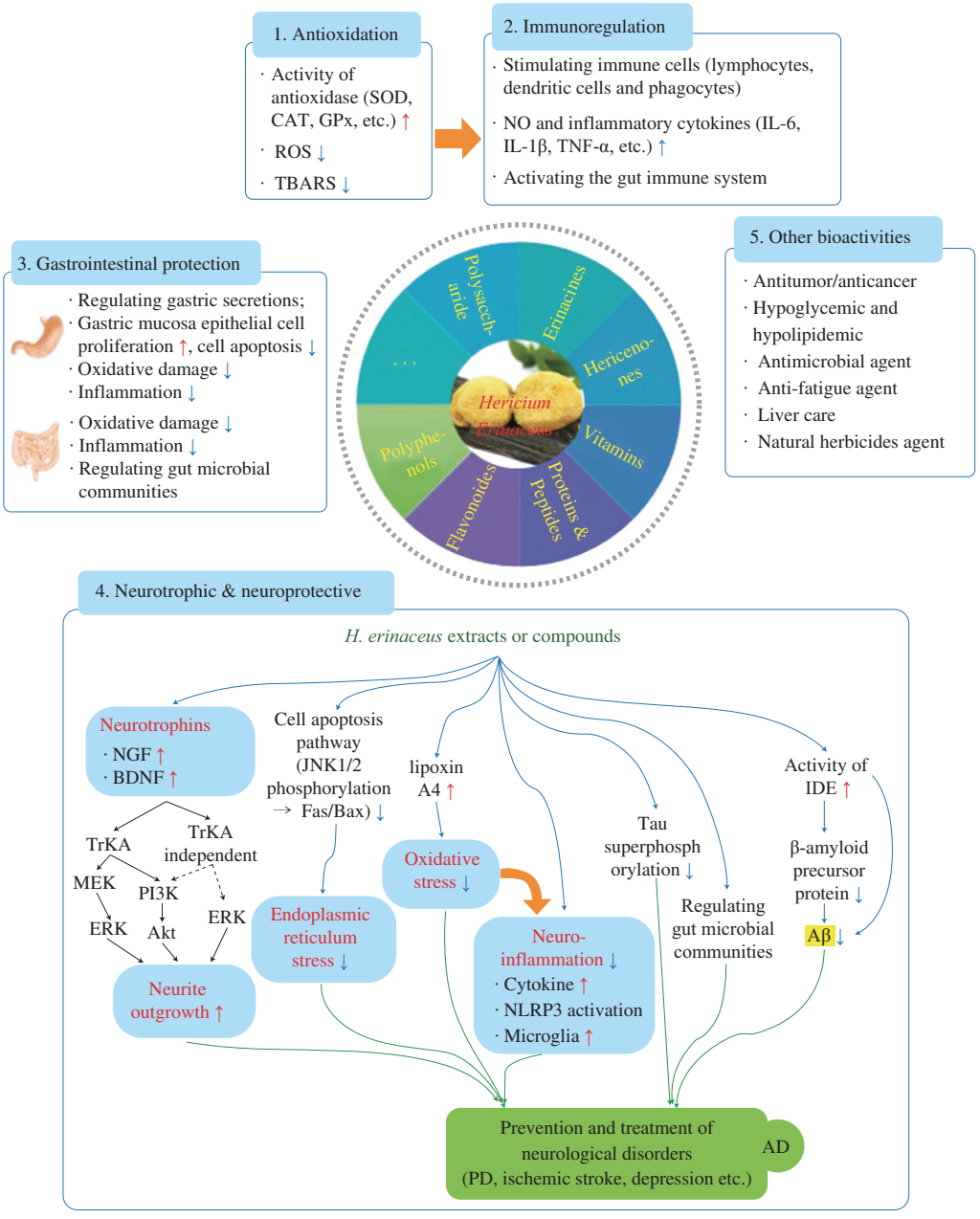


Fig. 1 A summary of active substances of *H. erinaceus* and their biological activities. PD, Parkinson's disease; AD, Alzheimer's disease.

also promote the release of intracellular substances by destroying the cell structure. The principle of enzymatic extraction is to destroy the cell wall of *H. erinaceus* by hydrolysis, thereby promoting the dissolution of polysaccharides molecules[9-12]. It has been reported that the enzymatic hydrolysis method relies on mild conditions but has a relatively high cost[13]. The extracted crude polysaccharides usually needs to be further purified for structural identification and biological activity research. Impurities (i.e., proteins, pigments, etc.) in crude polysaccharides can be removed by separation and purification methods such as alcohol precipitation, ultrafiltration, dialysis and column chromatography[14].

Generally, the structures of the polysaccharides are analyzed for molecular weight, monosaccharide composition, glycosidic bond type and configuration, by methods mainly including chemical analysis, chromatography and spectroscopic techniques. Different culture conditions and growth stages usually significantly impact the content, composition and structure of polysaccharides in *H. erinaceus*[6]. Polysaccharides from fruiting bodies, mycelia, or culture media usually have different structures. Most of the polysaccharides from fruiting bodies are heteropolysaccharides composed of two or more monosaccharides, and there are also glucans composed only of glucose, and a few glycoproteins, while only heteropolysaccharides and glycoproteins are typically found in mycelia[15]. Although the monosaccharide composition of polysaccharides from these two sources is primarily galactose, glucose and mannose, their composition ratios are not the same. Many different types of glycosyl linkages are present in the polysaccharides of fruiting bodies but relatively few glycosyl linkage types are present in polysaccharides from mycelium and culture medium[6]. These differences may affect the bioactivities of polysaccharides to some extent. Liu et al.[16] recently prepared high quality dietary fiber from *H. erinaceus* with blood lipid lowering and hypoglycaemic activity. High dose of the dietary fiber increased the superoxide dismutase and glutathione peroxidase activities, and decreased the activities of glutamic oxalacetic transaminase and glutamic-pyruvic transaminase in mice. It also could improve the lipid metabolism disorder of liver cells.

Table 1
The source, chemical, structural characteristics and biological activities of *H. erinaceus* polysaccharides

No.	Name	Source	Extraction methods	Molecular weight (Da)	Monosaccharide composition (Molar ratio)	Structure unit	Bioactivities	Reference
1	wHEP-1	Mycelium	Water extraction and alcohol precipitation	5.01×10^3	*D*-Man:*D*-Glc:*D*-Gal (1.2:16.9:1.1)	1→)-*D*-Man*p*,→3)-*D*-Glc*p*, →3)-*D*-Gal*p*, →3,4)-*D*-Glc*p*	Anti-inflammatory activity	[119]
2	wHEP-2	Mycelium	Water extraction and alcohol precipitation	1.81×10^3	*D*-Glc:*D*-Gal (3.2:1)	/	Anti-inflammatory activity	[119]
3	wHEP-3	Mycelium	Water extraction and alcohol precipitation	1.12×10^3	*D*-Glc:*D*-Gal (14.3:1)	/	Anti-inflammatory activity	[119]
4	Hep-2	Mycelium	Hot water extraction	1.08×10^3	*D*-Glc:*D*-Gal (1.0:0.4)	→1)-*D*-Gal*p*, (1→6)-*D*-Gal*p*, (1→4)-*D*-Gla*p*	Antioxidant activity	[120]
5	WEP-1	Mycelium	Water extraction and alcohol precipitation	4.01×10^3	*D*-Man:*D*-Glc:*D*-Gal (1.2:16.9:1)	Backbone structure: (1→3)-*α*-*D*-Glc*p*, (1→3)-*β*-*D*-Gal*p*, branches chain; *β*-*D*-Glc*p*-(1→3)-*β*-*D*-Man*p*	Protection against Caco-2 cells	[121]
6	EP-1	Mycelium	Water extraction and alcohol precipitation	3.10×10^3	/	/	Anti-ulcerative colitis activity	[65]
7	EP-1	Mycelium	Water extraction and alcohol precipitation	3.10×10^3	*D*-Glc:*D*-Man:*D*-Gal	(1→3)-*α*-*D*-Glc*p*-(1→)-*α*-*D*-Man*p*-(1→3,4)-*α*-*D*-Glc*p*-(1→3,4)-*β*-*D*-Gal*p*	Prevent hydrogen peroxide mediated oxidative stress	[122]
8	HEP-2	Mycelium	Compound enzyme extraction	/	*D*-Glc:*D*-Gal:*D*-Man:*L*-Fuc:*D*-Ara:*D*-Xyl:*L*-Rha	/	Inhibitory the growth of HeLa cells	[123]
9	EPS	Mycelium	Hot water extraction	/	*D*-Ara:*D*-Man:*D*-Gal:*D*-Glc (1:7:14:52)	/	Liver injury has a protective effect	[118]
10	IPS	Mycelium	Hot water extraction	/	*L*-Rha:*D*-Xyl:*D*-Man:*D*-Gal:*D*-Glc (3:4:7:14:137)	/	Liver injury has a protective effect	[118]
11	HEP-I	Fruiting body	Ultrasonic extraction and hot water extraction	1.72×10^4	*L*-Rha:*L*-Fuc:*D*-Glc:*D*-Gal (0.77:5.36:70.29:23.58)	*β*-*L*-Rhap-(1→3)-*β*-*L*-Fucp-(1 ↓ 4 →2)-*α*-*D*-Glcp-(1→6)-*α*-*D*-Galp-(1→2)-*α*-*D*-Galp-(1→3)-*β*-*D*-Glcp-(1→2)-*α*-*D*-Glcp-(1→	Significant inhibitory activity against hyaluronidase	[124]
12	HEP-II	Fruiting body	Ultrasonic extraction and hot water extraction	1.03×10^4	*L*-Rha:*L*-Fuc:*D*-Glc:*D*-Gal (2.74:3.14:82.33:11.79)	*β*-*D*-Galp-(1→3)-*α*-*L*-Fucp-(1→3)-*α*-*L*-Rhap-(1 ↓ 6 →4)-*β*-*D*-Glcp-(1→2)-*β*-*D*-Galp-(1→2)-*β*-*D*-Galp-(1→3)-*β*-*D*-Glcp-(1→4)-*β*-*D*-Glcp-(1→6)-*α*-*D*-Galp	Significant inhibitory activity against hyaluronidase	[124]
13	HEP- W	Fruiting body	Solvent extraction	5.98×10^5	*D*-Glc:*L*-Rha:*D*-Ara:*D*-Man:*D*-Gal (9.9:1.6:1.0:35.5:6.1)		Antioxidant activity	[7]
14	HEP-S	Fruiting body	Solvent extraction	4.49×10^5	*D*-Glc:*L*-Rha:*D*-Ara:*D*-Man:*D*-Gal (1.7:1.0:1.0:30.7:4.6)		Antioxidant activity	[7]
15	HEP-C	Fruiting body	Solvent extraction	2.30×10^5	*D*-Glc:*L*-Rha:*D*-Ara:*D*-Man:*D*-Gal (9.0:2.0:1.0:40.7:7.5)		Antioxidant activity, inhibition *α*-glycosidase and *α*-amylase activity	[7]
16	HEP-A	Fruiting body	Solvent extraction	2.57×10^5	*D*-Glc:*L*-Rha:*D*-Ara:*D*-Man:*D*-Gal (3.3:2.4:1.0:66.5:9.5)		Antioxidant activity	[7]

Table 1 (*Continued*)

No.	Name	Source	Extraction methods	Molecular weight (Da)	Monosaccharide composition (Molar ratio)	Structure unit	Bioactivities	Reference
17	HEP-S	Fruiting body	Water extraction and alcohol precipitation	1.83×10^4	*D*-Glc:*D*-Man:*L*-Fuc:*L*-*α*-Rha:*D*-Gal (8.68:1.36:0.93:1.47:4.08)	(1→)-*α*-*D*-Glc*p*, →3,4)-*α*-*D*-Glc*p*, →6)-*α*-*D*-Gal*p*, →3,4)-*β*-*D*-Man*p*, →3,6)-*α*-*L*-Rha*p*, →2)-*β*-*L*-Fuc*p*	Enhances immunity	[57]
18	WIP	Fruiting body	Alkali extraction	/	*D*-Glc:*D*-Gal:*D*-Man:*D*-Xyl:*L*-Rha:*D*-Rib (82.5:0.8:7.4:7.3:1.8:0.2)	(1→3)-*α*-*D*-Glc*p*	/	[125]
19	HEP	Fruiting body	Water extraction and alcohol precipitation	1.97×10^4	*L*-Fuc:*D*-Gal:*D*-Glc:*D*-Man: *D*-GlcA (1:2.87:0.09:0.12:0.01)	→4)-*α*-*L*-Fuc*p* and →6)-*α*-*D*-Gal*p*, →3,6)-*α*-*D*-Man*p*-(1→and→1,6)-*α*-*D*-Glc*p*,1→T-*α*-*D*-Glc*p*A	Antioxidant activity	[126]
20	HEP_N	Fruiting body	Water extraction and alcohol precipitation	1.27×10^4	*D*-Man:*D*-Glc:*D*-Gal (5.13:43.02:51.85)	→1)-*α*-*D*-Glc*p*, →4)-*α*-*D*-Glc*p*, →6)-*α*-*D*-Glc*p*, →6)-*α*-*D*-Man*p*, →3,6)-*α*-*D*-Man*p*, →6)-*α*-*D*-Gal*p*	Prevents hydrogen peroxide damage and promote cell proliferation	[127]
21	HEFPs	Fruiting body	Water extraction and alcohol precipitation	/	*L*-Ara:*D*-Gal:*D*-Glc:*D*-Man (8.99:11.15:1.2:1.97)	/	Induces apoptosis of colorectal cancer cells	[128]
22	HEP-C	Fruiting body	Solvent extraction	2.30×10^5	*L*-Rha:*L*-Ara:*D*-Man:*D*-Glc:*D*-Gal (9.0:2.0:1.0:40.7:7.5)	/	Hypoglycemic activity	[129]
23	HEP-W	Fruiting body	Water extraction and alcohol precipitation	1.59×10^4	*L*-Rha:*L*-Fuc:*D*-Man:*D*-Glc:*D*-Gal (0.98:1.59:0.89:5.60:7.06)	(1→)-*α*-*D*-Glc*p*, →3,6)-*α*-*D*-Glc*p*, →2,6)-*α*-*D*-Gal*p*, T-*β*-Gal*p*, →3,4)-*β*-*D*-Man*p*, →3)-*α*-*L*-Rha*p*, →2)-*β*-*L*-Fuc*p*	Promote phagocytic activity	[130]
24	HPB-3	Fruiting body	Ethanol extraction	1.50×10^4	*L*-Fuc:*D*-Gal:*D*-Glc (5.2:23.9:1)	Backbone structure: →6)-*α*-*D*-Glc*p*, →2,6)-*α*-*D*-Gal*p*; side chain: *O*-2-*α*-*L*-Fuc*p*	Macrophage stimulating activity	[131]

Note: Glc, glucose; Man, manose; Gal, galactose; Rha, rhamose; Fuc, fucose; Ara, arabinose; Xyl, xylose; GlcA, gluconic acid; *p* Represents pyranose. / Indicates unknown.

Table 1 lists the molecular weight, monosaccharide composition, structural characteristics and biological activities of some representative polysaccharides derived from *H. erinaceus* fruiting bodies, mycelia and cultures. It can be seen that the research strategies and technologies of polysaccharides in *H. erinaceus* have been initially established, which can provide reference for the study of other compounds that are still in the early investigation stage. Some advanced extraction technologies (such as pulsed electric fields assisted extraction, supercritical and subcritical fluid extraction, and subcritical water extraction) that have been successfully applied in plant polysaccharides isolation may further increase the yield and biological activity of polysaccharides in *H. erinaceus*.

2.2 Small bioactive molecules

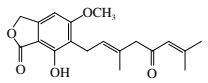
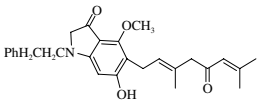
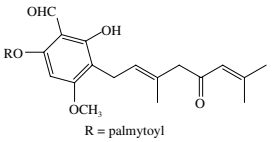
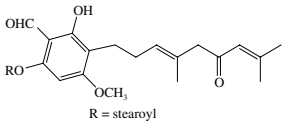
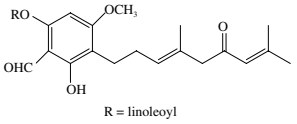
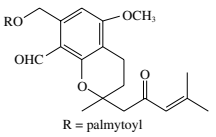
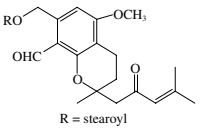
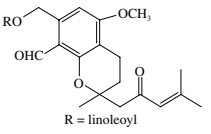
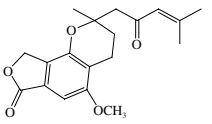
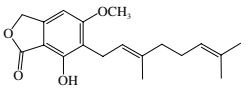
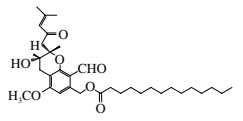
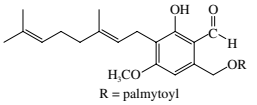
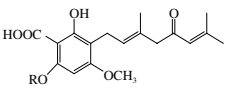
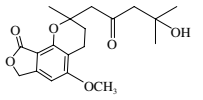
Approximately 150 small molecules from *H. erinaceus* have been separated and identified. Among them, the two most well-known categories are hericenones and erinacines, because many of them have neurotrophic and neuroprotective activities. The naming of most small molecules reported in *H. erinaceus* is not according to their chemical structure. Therefore, in this section, we focus on the research progress related to hericenones and erinacines, and then summarize other active small molecules in accordance with chemical classification.

2.2.1 Hericenones

In the 1990s, Kawagishi et al.[17-19] took the lead in successively extracting and purifying 8 benzyl alcohol derivatives from the fruiting bodies of *H. erinaceus*, and named these hericenones A, B, C, D, E, F, G and H. Ueda et al.[20] then isolated three compounds of hericenones I, J and 3-hydroxyhericenone F, and hericenone L and K were also discovered in subsequent studies[21]. Hericenones A-I can now be synthesized[22-23]. Table 2 lists the extraction methods, structures, and biological activities of the reported hericenones. The hericenones are not a strictly chemically classified. Hericenones C, D, E, and I are phenols, hericenones A, I, J, H, G, F are ketones, while hericenone B can be categorized as alkaloids. However, hericenones have commonalities in molecular structure. Most have a methoxyphenol core, but the phenolic hydroxyl groups in a few compounds (such as hericenones F, G and I) are reacted with olefinic bonds to form pyran structures. Studies have shown that hericenones C, D, E, H and 3-hydroxyhericenone F possessed neuroprotective activity, while hericenones F, G, I(1), J and K have been proved without such activity. In addition, hericenones A, B, I(2) and L exhibited cytotoxicity to carcinoma cell lines.

Kobayashi et al.[22] divided geranyl-resorcinols isolated from *H. erinaceus* into 4 types based on the degree of oxidation of a geranyl side chain and the involvement of the fatty acid chain. Although the original intention of this classification was to facilitate designing total synthesis strategies, we found an interesting thing that the hericenones belong to Type 4 (hericenones C, D, E, H and 3-hydroxyhericenone F), which possessed both fatty acid chain and oxygen on geranyl side chain, happened to have neuroprotective activity. However, it has not yet been confirmed whether this is the key structure of the neurological activity, which may be a breakthrough for the investigation of structure-activity relationship. There are no certified

Table 2
The chemical, structural characteristics and biological activities of hericenones.

No.	Name	Extraction methods	Characteristics	Structure	Bioactivities	Reference
1	Hericenone A	Acetone solvent extraction	Colorless crystals		Cytotoxicity (HeLa cells 100 μg/mL)	[17]
2	Hericenone B	Acetone solvent extraction	Colorless crystals		Cytotoxicity HeLa cells (6.3 μg/mL)	[17]
3	Hericenone C	Acetone extraction → chloroform and ethyl acetate extraction → ODS column	White crystals	 R = palmytoyl	Stimulate the synthesis of nerve growth factor (NGF) *in vitro*, non-toxic to HeLa cells (33 μg/mL, secreting NGF medium: 10.8 pg/mL)	[18]
4	Hericenone D	Acetone extraction → chloroform and ethyl acetate extraction → ODS column	White crystals	 R = stearoyl	Stimulate the synthesis of NGF *in vitro*, non-toxic to HeLa cells (33 μg/mL, secreting NGF medium: 23.5 pg/mL)	[18]
5	Hericenone E	Acetone extraction → chloroform and ethyl acetate extraction → ODS column	Colorless oil	 R = linoleoyl	Stimulate the synthesis of NGF *in vitro*, non-toxic to HeLa cells (33 μg/mL, secreting NGF medium: 13.9 pg/mL)	[18]
6	Hericenone F	Acetone extraction and ethyl acetate extraction	Light yellow oily compound	 R = palmytoyl	Stimulators of NGF synthesis (33 μg/mL, no activity)	[19]
7	Hericenone G	Acetone extraction and ethyl acetate extraction	Light yellow block	 R = stearoyl	Stimulating in NGF synthesis (33 μg/mL, no activity)	[19]
8	Hericenone H	Acetone extraction and ethyl acetate extraction	Pale yellow oily compound	 R = linoleoyl	Stimulate the synthesis of NGF (33 μg/mL, Secreting NGF medium: 45.1 pg/mL)	[19]
9	Hericenone I	Ethanol and acetone extraction → hexane-separation→ ethyl-acetate → ethanol → silica gel column →high-performance liquid chromatography (HPLC) →hericenone I	Colorless crystal		No protective effect on estrogen receptor stress-dependent cell death	[20]
10	Hericenone J	Ethanol and acetone extraction → hexane-separation→ ethyl-acetate → ethanol → silica gel column → HPLC →hericenone J	Colorless crystal		No protective effect on estrogen receptor stress-dependent cell death (cytotoxicity against HL-60 cell lines: IC_{50}: 4.1 μmol/L)	[20]
11	3-Hydroxyhericenone F	Ethanol and acetone extraction → chloroform separation → silica gel column separation → HPLC → 3-hydroxyericenone F	Brown oil		Protect neurons, protective activity against endoplasmic reticulum stress-dependent neuro2a cell death (10 μg/mL, significant dose-dependent protective action)	[20]
12	Hericenone I	Methanol extraction → chloroform-fractionation → column chromatography	White oil	 R = palmytoyl	Cytotoxic activity against Ec109 cell line (1×10^{-3}, 3×10^{-4}, 1×10^{-4} mol/L)	[29]
13	Hericenone L	Methanol extraction → chloroform-distribution → petroleum-ether/ethyl acetate elution → silica gel column → HPLC	White oil		Toxic activity against Ec109 cells (IC_{50}: 46 μg/L)	[21]
14	Hericenone K	Ethanol extraction→ethyl-acetate elution→silica gel, glucose gel, and semi preparation RP-HPLC	Colorless oil		No activity on PC12 cells	[132]

standard hericenones. The detection of the hericenones content in *H. erinaceus* and its processed products remains a technical bottleneck limiting their applications and products. In addition, the biological activity mechanism of hericenones is not yet clear, and the relationship between biological activity and chemical structure also requires further studies.

2.2.2 Erinacines

After isolating hericenones from fruiting bodies, Kawagishi and his research team attempted to extract hericenones by fermentation of *H. erinaceus* mycelium to increase yield and reduce cost. They accidentally discovered three diterpenoids with cyathane skeleton in 1994, named erinacines A, B and C, respectively[24]. These have neurotrophin-inducing activity similar to hericenones, of which erinacine A has also been found to have excellent antioxidant activity[25]. Subsequently, the research group and other researchers successively identified a series of erinacines, more than 19 kinds, whose molecular structures and biological activities are shown in Table 3. According to existing reports, erinacines mainly exist in the mycelium of *H. erinaceus*, mostly in the form of xylosides, and some of them can be transformed into each other. For example, erinacine P can be transformed into erinacine A and B through biotransformation[26], and erinacine Q can be transformed into erinacine C[27]. No studies have shown that whether this transformation implied the secondary metabolic pathway in *H. erinaceus*, or it has some special functions for the growth and reproduction of *H. erinaceus*. Understanding the molecular pathway may be able to artificially stimulate the synthesis of related compounds.

Table 3
The chemical, structural characteristics and biological activities of erinacines.

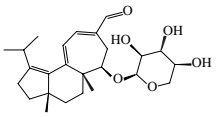
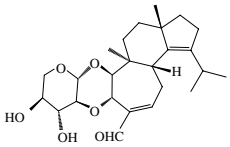
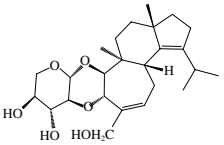
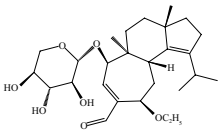
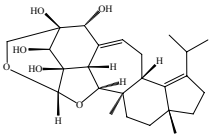
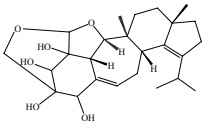
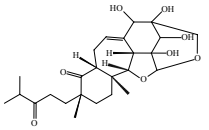
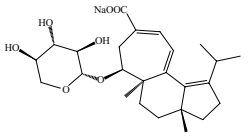
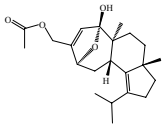
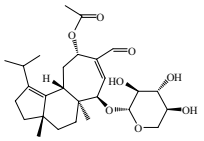
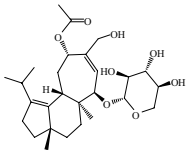
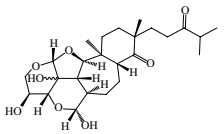
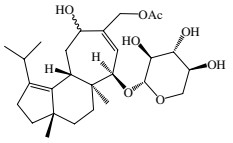
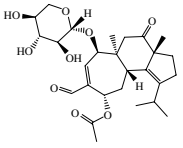
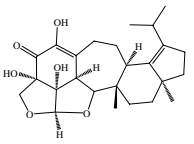
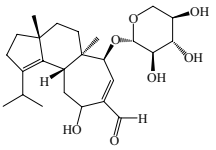
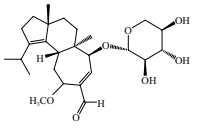
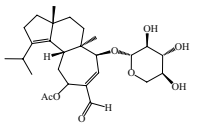
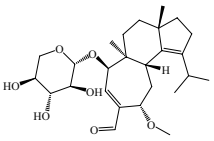
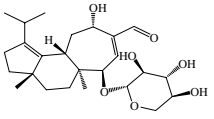
No.	Name	Characteristics	Structure	Bioactivities	Reference
1	Erinacine A	White crystals		Stimulator of nerve growth factor (NGF) synthesis *in vitro* ((250.1 ± 36.2) pg/mL at 1.0 mmol/L), weak cytotoxicity against PC12 cells (IC_{50}: 73.7 μmol/L), anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity	[24,79,133]
2	Erinacine B	White crystals		Stimulator of NGF synthesis *in vitro* ((129.7 ± 6.5) pg/mL at 1.0 mmol/L)	[24]
3	Erinacine C	White crystals		Stimulator of NGF synthesis *in vitro* ((299.1 ± 59.6) pg/mL at 1.0 mmol/L)	[24]
4	Erinacine D	White crystals		Stimulators of NGF synthesis (amount of NGF: 141.5 pg/mL at 1.67 mmol/L)	[74]
5	Erinacine E	White crystals		Stimulators of NGF synthesis by astrocytes (amount of NGF: (105.0 ± 5.2) pg/mL at 5.0 mmol/L)	[75]
6	Erinacine F	White crystals		Stimulators of NGF synthesis by astrocytes (amount of NGF: (175.0 ± 52.0) pg/mL at 5.0 mmol/L)	[75]
7	Erinacine G	White crystals		Stimulators of NGF synthesis by astrocytes (in this study, erinacine G has not been tested yet)	[75]
8	Erinacine H	Yellow amorphous residue		Obvious NGF stimulating activity, 33.3 g/mL, five times more NGF (31.5 pg/mL)	[78]

Table 3 (*Continued*)

No.	Name	Characteristics	Structure	Bioactivities	Reference
9	Erinacine I	Yellow oil		No stimulatory activity of NGF synthesis in astrocytes	[78]
10	Erinacine P	Light yellow amorphous solid		Significant neurotrophic effects (2.5−10 μmol/L, at 10 μmol/L: percentage of neurite-bearing cells: 48.3%)	[26]
11	Erinacine Q	Colorless amorphous solid		/	[27]
12	Erinacine J	Colorless crystal		Inactive against MRSA	[133]
13	Erinacine K	Light yellow oil		Anti-MRSA activity (500 μmol/L)	[133]
14	Erinacine R	Light yellow amorphous powder		/	[134]
15	Erinacine S	Colorless crystal		Elevated levels of insulin-degrading enzymes (2.395 g/kg BW (*H. erinaceus* mycelial extract equivalent to 50 mg/kg BW) the male Sprague-Dawley rats of pharmacokinetics: 15.13%)	[135]
16	Erinacine T	White powder		Promotion of PC12 cells differentiation and axonal growth (2.5−10 mol/L, at 10 μmol/L: percentage of neurite-bearing cells: 43.7%)	[79]
17	Erinacine U	/		Promote the neurite growth of PC12 cells (2.5−10 μmol/L, at 10 μmol/L: percentage of neurite-bearing cells: 76.31%)	[79]
18	Erinacine V	/		Promote the neurite growth of PC12 cells (2.5−10 μmol/L, at 10 μmol/L: percentage of neurite-bearing cells: 65.3%)	[79]
19	Erinacine Z1	Colorless oil		Promote PC12 cell differentiation and neurite growth (potent cytotoxicity against HL-60 cell lines: IC_{50}: 8.9 μmol/L)	[4,77]
20	Erinacine Z2	Colorless oil		Promote PC12 cell differentiation and neurite growth (potent cytotoxicity against HL-60 cell lines: IC_{50}: 0.5 μmol/)	[4,77]

2.2.3 Other bioactive ingredients

Table 4 shows some other bioactive ingredients.

1) Phenols: Hericenes A-D were observed as a class of phenolic compounds with long fatty acid chains similar in structure to hericenones mentioned in 2.2.1. All of them have nuclear factor κB (NF-κB) inhibitory activity[28-29]. The difference between hericenes and hericenones mainly lays in the oxidation level of the geranyl side chain[22]. Hericenal A-C were a serious compounds isolated from mycelium of *H. erinaceus*, which possessed hypoglycemic activity[30].

2) Ketones: Erinacerins A-N were a group of isoindolinone compounds, wherein erinacerins A, B, M and N are derived from *H. erinaceus* fruiting bodies[31], while erinacerins C-L are isolated from solid culture of *H. erinaceus* and possessed *α*-glucosidase inhibitory activity[32]. Ryu et al.[33] isolated four novel isoindolinone compounds with neurotrophic activity from the fruiting bodies of *H. erinaceus*, hericerin, isohericerinol A, *N*-de-phenylethyl isohericerin and corallocin A. Erinapyrones A, B[34] and C[28] are three *γ*-pyrones isolated from mycelium, of which erinapyrones A and B possess cytoxicity towards HeLa cells, while erinapyrone C is a *γ*-dihydropyrone with moderate activity against Gram-positive bacteria. Wu et al.[35] isolated three compounds (erinaceolactones A to C) from the culture broth of *H. erinaceus* with plant-growth regulatory activity. Subsequently, five isobenzofuranone derivatives, erinaceolactones D-F[36] and erinaceolactones G and H[37], were successively isolated from the fruiting bodies of *H. erinaceus*, but the authors did not report their biological activities.

3) Sterols: Erinarol A-G[38-39] were a group of sterol fatty acid esters isolated from the methanol extract of fruiting bodies of *H. erinaceu*m. Erinarols A and B have peroxisome proliferators-activated receptors α, γ transactivational effects, with EC_{50} values of 8.2 and 6.4 μmol/L, respectively, while erinarols H and J exhibited inhibitory activity against TNF-α secretion, with inhibition values ranging from 33.7% to 43.3% at 10 μmol/L. *H. erinaceus* also contains sterols with similar structures to phytosterols, such as ergosterol with antibacterial, anti-inflammatory and gastric mucosal protection activities[40].

4) Terpenoids: The discovery of erinacines has aroused extensive attention to cyathane-type diterpenoids in *H. erinaceus*, and studies have shown that most of them have strong NGF synthesis-inducing activities. However, three cyathane-type diterpenoids (named hericinoids A-C) isolated from *H. erinaceus* fermentation broth by Chen et al.[41], were incapable of the enhancement of NGF-induced neutrite outgrowth in PC-12 cells.

5) Fatty acids: Fatty acids with special activities are also found in *H. erinaceus*, such as octadecenoic acid derivatives reported by Kawagishi et al.[42], which exhibit growth inhibitory effects on tea pollen and cytotoxicity against HeLa cells.

Table 4
Structure and biological activity of other bioactive components.

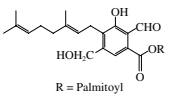
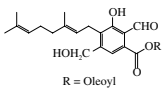
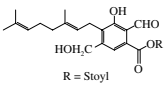
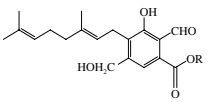
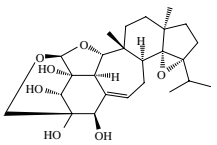
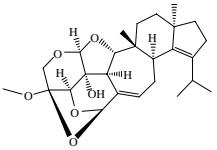
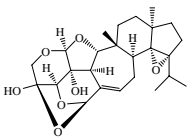
No.	Name	Source	Structure	Bioactivities	Reference
1	Hericene A	Mycelium /Fruiting body	 R = Palmitoyl	Nuclear factor-κB (NF-κB) inhibitory activity, and *α*-glucosidase inhibitory activity (IC_{50}: 6.7 μmol/L)	[4,28]
2	Hericene B	Mycelium /Fruiting body	 R = Oleoyl	NF-κB inhibitory activity	[4,28]
3	Hericene C	Mycelium	 R = Stoyl	NF-κB inhibitory activity	[28]
4	Hericene D	Fruiting body	 R = Linecoyl	NF-κB inhibitory activity, Weak *in vitro* antibacterial activity, and *α*-glucosidase inhibitory activity (IC_{50}: 3.9 μmol/L)	[4,28-29]
5	Hericinoid A	Fermentation broth		/	[41]
6	Hericinoid B	Fermentation broth		Cytotoxicity (HL60 cell lines, IC_{50}: 18.3 μmol/L)	[41]
7	Hericinoid C	Fermentation broth		/	[41]

Table 4 (*Continued*)

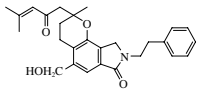
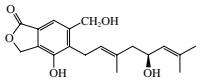
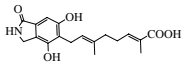
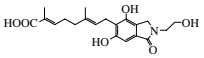
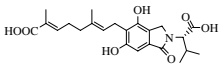
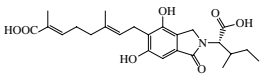
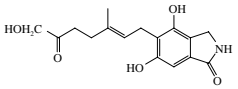
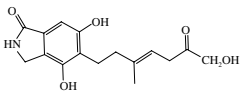
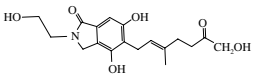
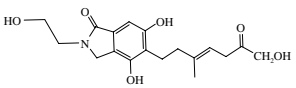
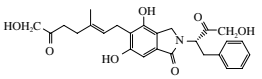
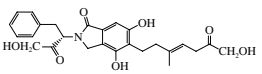
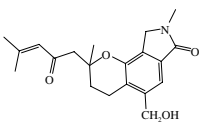
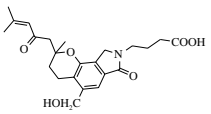
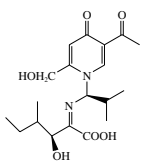
No.	Name	Source	Structure	Bioactivities	Reference
8	Erinacerin A	Fruiting body		/	[31,136]
9	Erinacerin B	Fruiting body		/	[136]
10	Erinacerin C	Mycelium		α-Glucosidase inhibitory activity	[32]
11	Erinacerin D	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
12	Erinacerin E	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
13	Erinacerin F	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
14	Erinacerin G	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
15	Erinacerin H	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
16	Erinacerin I	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
17	Erinacerin J	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
18	Erinacerin K	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
19	Erinacerin L	Mycelium		α-Glucosidase inhibitory activity (IC_{50} values ranging from 5.3 to 145.1 μmol/L)	[32]
20	Erinacerin M	Fruiting body		Anticancer cell activity *in vitro*	[31]
21	Erinacerin N	Fruiting body		Anticancer cell activity *in vitro*	[31]
22	Erinacerin O	Solid culture		Moderate cytotoxicity of wild K562 cells (IC_{50}: 11.4−18.2 μmol/L)	[106]

Table 4 (*Continued*)

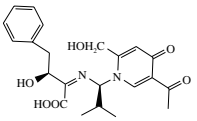
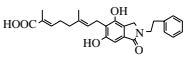
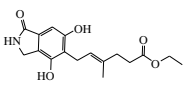
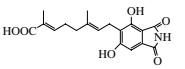
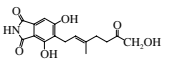
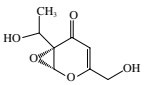
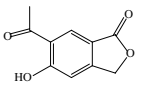
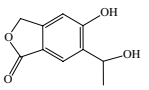
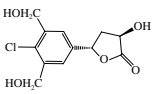
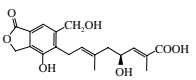
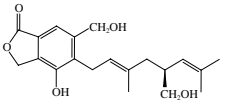
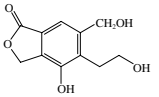
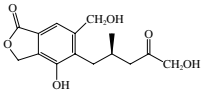
No.	Name	Source	Structure	Bioactivities	Reference
23	Erinacerin P	Solid culture		Moderate cytotoxicity of wild K562 cells (IC_{50}: 11.4−18.2 μmol/L)	[106]
24	Erinacerin Q	Solid culture		Inhibitory activities against PTP1B (IC_{50}: 29.1 μmol/L), and α-glucosidase inhibitory activity (IC_{50}: 12.7 μmol/L)	[106]
25	Erinacerin R	Solid culture		Inhibitory activities against PTP1B (IC_{50}: 42.1 μmol/L), and α-glucosidase inhibitory activity (IC_{50}: 23.3 μmol/L)	[106]
26	Erinacerin S	Solid culture		Inhibitory activities against PTP1B (IC_{50}: 28.5 μmol/L), and α-glucosidase inhibitory activity (IC_{50}: 19.5 μmol/L)	[106]
27	Erinacerin T	Solid culture		Inhibitory activities against PTP1B (IC_{50}: 24.9 μmol/L), and α-glucosidase inhibitory activity (IC_{50}: 20.1 μmol/L)	[106]
28	Erinapyrone A	Mycelia culture		Cytotoxicity (HeLa cells: 0.88 mmol/L), and stimulator of NGF synthesis, inhibiting the growth of lettuce hypocotyl (1 μmol/paper−100 nmol/paper)	[28,34-35]
29	Erinapyrone B	Mycelia culture		Cytotoxicity (HeLa cells: 1.76 mmol/L), and stimulator of NGF synthesis, inhibiting the growth of lettuce hypocotyl (1 μmol/paper−100 nmol/paper)	[28,34-35]
30	Erinapyrone C	Mycelium		Moderate activity against Gram-positive bacteria	[28]
31	Erinaceolactone A	Culture broth		Suppressed the growth of lettuce	[35]
32	Erinaceolactone B	Culture broth		Suppressed the growth of lettuce	[35]
33	Erinaceolactone C	Culture broth		Suppressed the growth of lettuce	[23,35]
34	Erinaceolactone D	Fruiting body		/	[36]
35	Erinaceolactone E	Fruiting body		/	[36]
36	Erinaceolactone F	Fruiting body		/	[79]
37	Erinaceolactone G	Fruiting body		/	[37]

Table 4 (*Continued*)

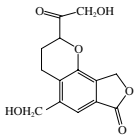
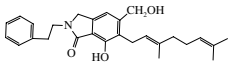
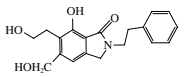
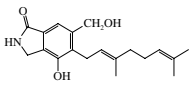
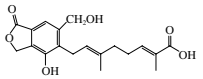
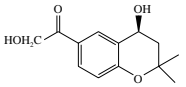
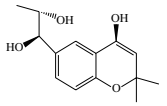
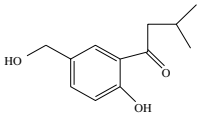
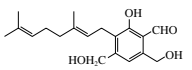
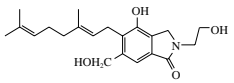
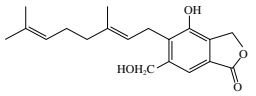
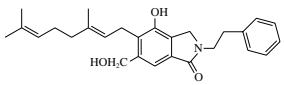
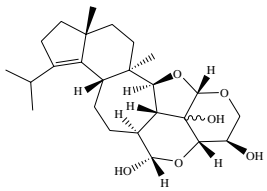
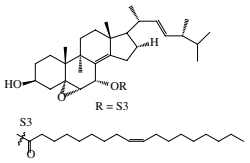
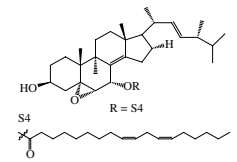
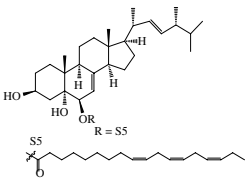
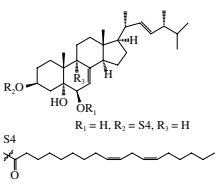
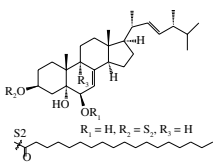
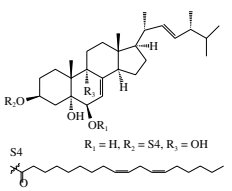
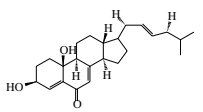
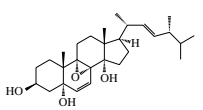
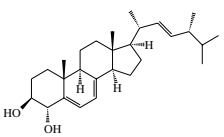
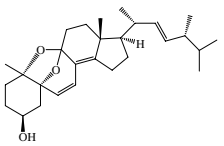
No.	Name	Source	Structure	Bioactivities	Reference
38	Erinaceolactone H	Fruiting body		/	[37]
39	Hericerin	Fruiting body		Promotion of axonal growth in N2a neuronal cells and cytotoxicity (HeLa cells, IC_{50}: 62.24 μmol/L)	[33,110]
40	Isohericerinol A	Fruiting body		Stimulator of NGF synthesis	[33]
41	*N*-De-phenylethyl isohericerin	Fruiting body		Promotion of axonal growth in N2a neuronal cells and cytotoxicity (HeLa cells, IC_{50}: 4.10 μmol/L)	[33,110]
42	Corallocin A	Fruiting body		Stimulator of NGF synthesis	[33]
43	Erinachromane A	Culture broth		Suppressed the growth of lettuce	[115]
44	Erinachromane B	Culture broth		Suppressed the growth of lettuce	[115]
45	Erinaphenol A	Culture broth		Suppressed the growth of lettuce	[115]
46	4-[3',7'-Dimethyl-2',6'-octadienyl]-2formyl-3-hydroxy-5-methyoxybenzylalcohol	Fruiting body		Cytotoxicity (HeLa cells, IC_{50}: 4.28 μmol/L) and *α*-glucosidase inhibitory activity (IC_{50}: 7.5 μmol/L)	[105,110]
47	Hericerin A	Fruiting body		Cytotoxicity (HeLa cells, IC_{50}: 3.06 μmol/L) and *α*-glucosidase inhibitory activity (IC_{50}: 6.7 μmol/L)	[105,110]
48	Isohericenone J	Fruiting body		Cytotoxicity (HeLa cells, IC_{50}: 59.74 μmol/L)	[110]
49	Isoericerin	Fruiting body		Cytotoxicity (HeLa cells, IC_{50}: 5.47 μmol/L)	[110]
50	CJ-14,258	Mycelium		Antimicrobial activity against methicillin resistant *Staphylococcus aureus* (MRSA) (MIC: 62.5 μmol/L)	[133]
51	2-Chloro-1,3-dimethoxy-5-methyl benzene	Mycelial culture		Antibacterial activity (*C. albicans* and *C. neoformans,* MIC: 31.3–62.5 μg/mL)	[109]

Table 4 (*Continued*)

No.	Name	Source	Structure	Bioactivities	Reference
52	Erinarol A	Fruiting body		Significantly activated the transcriptional activity of peroxisome proliferators-activated receptors (PPARs) in a dose-dependent manner (EC_{50}: 8.2−6.4 μmol/L)	[38]
53	Erinarol B	Fruiting body		Significantly activated the transcriptional activity of PPARs in a dose-dependent manner (EC_{50}: 8.2−6.4 μmol/L)	[38]
54	Erinarol C	Fruiting body		/	[38]
55	Erinarol D	Fruiting body		/	[38]
56	Erinarol E	Fruiting body		/	[38]
57	Erinarol F	Fruiting body		/	[38]
58	Erinarol G	Fruiting body		Moderate inhibitory activity of tumor necrosis factor α (TNF-α) secretion (inhabition ranging from 24.6%−26.3%)	[39]
59	Erinarol H	Fruiting body		Inhibitory activity against TNF-α secretion (inhibition values ranging from 33.7% to 43.3% at 10 μmol/L)	[39]
60	Erinarol I	Fruiting body		Anti-inflammatory	[39]
61	Erinarol J	Fruiting body		Inhibitory activity against TNF-α secretion (inhibition values ranging from 33.7% to 43.3% at 10 μmol/L)	[39]

"/" Indicates unknown.

2.3 Protein and peptides

It is gradually coming to light that mushrooms are a promising source of new proteins and peptides[43]. Chen et al.[44] reported that a single-band protein (HEP3) isolated from *H. erinaceus* by chemical separation combined with pharmacodynamic evaluation, which exhibited immunomodulatory activity both in macrophages and mice. The research group recently further evaluated the auxiliary antitumor activity of immunomodulatory proteins from *H. erinaceus*[45]. They identified 1 455 proteins and observed that *H. erinaceus* proteins enhanced the antitumor efficacy of 5-fluorouracil by improving the microbiota, immune inflammatory response, and homeostasis. An active peptide Lys-Ser-Pro-Leu-Tyr (KSPLY) isolated by Yu et al.[46] have also been proved to have immunomodulatory activity in macrophages at a concentration of 100 μmol/L. *H. erinaceus* polypeptide with molecular weight of 5−10 kDa prepared by an ultrasound-microwave assisted enzymatic method was recently reported to have strong antioxidant and hypolipidemic activities[47].

H. erinaceus has a high protein and low-fat content, like the majority of edible fungus[46]. However, the research on protein and bioactive peptides in *H. erinaceus* is still in its infancy. Zeng et al.[48] studied proteins that participated in bioactive metabolites in *H. erinaceus* through proteome analysis, and identified 2 543 unique proteins using *H. erinaceus* genome. After annotated them in database, 722 proteins were observed to be differently expressed in fruiting body compared with mycelium. Interestingly, proteins related to polyketide biosynthesis were up-regulated in the fruiting body, while proteins involved in terpenoid biosynthesis were generally up-regulated in mycelium. This study not only revealed that differential regulation of biosynthesis genes could obtain various bioactive metabolites, but also implied the high research and development value of proteins in *H. erinaceus*. In addition, it may also explain why the currently reported terpenoid were almost all obtained from the mycelium. What's more, the report suggested the potential that the omics technique may greatly promote the investigation of bioactive ingredients in *H. erinaceus*.

3. Biological activities of *H. erinaceus*

A large number of studies have shown that *H. erinaceus* has various biological activities, such as antioxidant, anti-cancer, protection of digestive tract, immune regulation, antibacterial, neuroprotection, hypoglycemic, and antifatigue activities[2,4]. This section reviews these physiological functions of *H. erinaceus*, especially its neurotrophic and neuroprotective activities.

3.1 Antioxidation

H. erinaceus is rich in a variety of antioxidant active ingredients, among which the antioxidant mechanism of polysaccharides is relatively well studied. *H. erinaceus* polysaccharides performed well on both enzymatic and non-enzymatic oxidations[49]. *H. erinaceus* polysaccharides has ferrous ion chelating and reducing ability, and its inhibitory effect on lipid peroxidation has also been widely confirmed[50]. Moreover, *H. erinaceus* polysaccharides can effectively scavenge a variety of free radicals, such as ABTS, DPPH, hydroxyl radicals and superoxide anions[51], and acetylation modification improves the free radical scavenging ability of *H. erinaceus* polysaccharides[52]. In addition to the antioxidant effects *in vitro*, *H. erinaceus* polysaccharides also have substantial impact on the maintenance of redox homeostasis *in vivo*. *H. erinaceus* polysaccharides can effectively reduce the production of reactive oxygen species (ROS), regulate the activity of antioxidases (i.e., superoxide dismutase, catalase, and glutathione peroxidase, etc.), thereby alleviating tissue and organ damage caused by oxidative stress[53]. Oligosaccharides, proteins, flavonoids, terpenes, phenols, alkaloids and vitamins (carotenoids, vitamin C, vitamin E) in *H. erinaceus* also have excellent antioxidant effects[25,54]. For example, erinacine A has been reported to prolong lifespan in *Drosophila melanogaster* and aged mice by reducing lipid oxidation levels, inducing superoxide dismutase, catalase and glutathione peroxidase activities[55].

3.2 Immunoregulation

The immunomodulatory effects of *H. erinaceus* have also been widely reported, and polysaccharides have been suggested as possible key components. The reported immunomodulatory mechanisms of polysaccharides in *H. erinaceus* can be summarized as 2 types: 1) regulating the content of cytokines and other related molecules. The polysaccharides extracted from the fruiting bodies and the culture medium of *H. erinaceus* have been found to activate splenic lymphocytes and stimulate the production of interleukins and interferons[56]. *H. erinaceus* polysaccharides also enhance the pinocytosis and phagocytosis of macrophages and promote the production of nitric oxide (NO) and pro-inflammatory cytokines[57]. Ren et al.[58] found that hydroxyethylated modification could increase the induction activity of NO, IL-6 and TNF-α in macrophages RAW264.7 compared with unhydroxyethylated *H. erinaceus* polysaccharides. 2) Regulating the mitogen-activated protein kinase (MAPK) pathways. In recent years, researchers have also found that *H. erinaceus* polysaccharides can up-regulate the secretion of intestinal immunoglobulin A in mice and activate the expression of MAPK and AKT cell signaling pathways, thereby playing a role in immune regulation mediated by the intestinal immune system[1,59]. According to a recent review about immunomodulatory effects of polysaccharides from edible fungus[60], polysaccharides can also display immunomodulatory activity through affecting NF-κB signal pathways, pattern recognition receptors, oxidative stress and intestinal microflora. These mechanisms have not been reported in studies of *H. erinaceus* polysaccharides. In addition to polysaccharides, some proteins and polypeptides in *H. erinaceus* have also been confirmed to have immunomodulatory activities[46]. For example, Lys-Ser-Pro Leu-Tyr (KSPLY) mentioned in section 2.4 is a potent immunomodulatory peptide that can promote the secretion of NO, IL-1β, IL-6 and TNF-α in macrophages[46].

3.3 Gastrointestinal protection

H. erinaceus has a positive therapeutic impact on chronic atrophic gastritis and superficial gastritis and has been used as a stomach nourishing food. *H. erinaceus* aqueous extract has been reported to protect ethanol-induced gastric ulcers in rats and effectively reduce the ulcer area compared with the control

group[61]. Polysaccharides are thought to be possibly the main active components showing the gastroprotective effect of *H. erinaceus*[49]. *H. erinaceus* polysaccharides can regulate gastric secretions, defensive factors release and redox homeostasis, and have anti-inflammatory activity and enhance gastric mucosa epithelial cells repair[62-63]. Hou et al.[64] investigated the structure and protective effect on alcohol-induced gastric mucosal injury of polysaccharides from *H. erinaceus* mycelium and fruit bodies. The results indicated that the impact of mycelium polysaccharides was greater, and the authors speculated that conformational stability polysaccharides in *H. erinaceus* was more related to gastric-protecting activity. *H. erinaceus* polysaccharides may also exert gut protective effects by modulating oxidative stress, gut microbiota composition, and anti-inflammatory effects. It has been reported that *H. erinaceus* polysaccharides can be used to treat ulcerative colitis and inflammatory bowel disease[65]. Ren et al.[66] found that *H. erinaceus* polysaccharides could effectively reverse the changes in intestinal microbiota composition and oxidative stress caused by dextran sulfate sodium in C57BL/6 mice, and regulate the inflammatory signaling pathway, alleviating the colitis induced by dextran sulfate sodium accordingly.

3.4 Neurotrophic and neuroprotective activity

The promotion of nervous system and brain health is another important pharmacological effect of *H. erinaceus*, which was the result of its neurotrophic and neuroprotective activities. Although this effect has not been clinically demonstrated, all *in vivo* and *in vitro* data suggested that containing of *H. erinaceus* in diet might be a potential solution to ameliorating neurological diseases such as ischemic stroke, Parkinson's disease (PD), Alzheimer's disease (AD), and depression[67].

3.4.1 Neurotrophins-inducing and neurite outgrowth stimulation activity

Neurotrophins (neurotrophic factors) play a key role in the growth, maintenance and repair of neurons in the nervous system. However, neurotrophins are proteins, of molecular weight too large to pass through the blood-brain barrier and are easily metabolized by peptidases. Thus, it was considered difficult to apply to such molecules in the prevention and treatment of neurological diseases[68]. Therefore, finding small molecules with neurotrophic properties and/or enhancing the effect of endogenous neurotrophic factors may represent the breakthrough required to address this problem[69]. Studies have shown that the neurotrophic activity of *H. erinaceus* is not a direct effect, but is instead achieved by inducing the expression of neurotrophic factors, especially nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Ethanol extract of *H. erinaceus* fruiting bodies can stimulate NGF mRNA and protein levels in human astrocytoma cell line 1321-N1, and promote the neurite outgrowth in pheochromocytoma (PC12) cells by inhibiting c-Jun N-terminal kinase[70]. *H. erinaceus* mycelium and its ethanol extract were also found to promote NGF synthesis[71]. Hericenones from fruiting bodies and erinacines from mycelium were considered as stimulators of NGF biosynthesis in *H. erinaceus*[72].

Kawagishi et al.[18] reported NGF stimulation of hericenones C-E as early as 1991, of which hericenone D was the most promising, comparable to epinephrine (a potent NGF stimulator). The authors suggested that the change in this activity depended on the length of the chain and the double bond of the fatty acid. Hericenone E could increase the phosphorylation of extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) and enhance NGF-induced neuritogenesis in PC12 cells through the allosteric mitogen-activated protein kinase/extracellular-signal regulated kinases (MEK/ERK) and phosphoinositide-3-kinase /protein kinase B (PI3K/Akt) pathways[73]. The subsequently discovered hericenone H was also shown to promote the secretion of NGF in astrocytes[19,72].

Erinacines isolated from *H. erinaceus* mycelium are also excellent NGF stimulators. Kawagishi et al.[24,74-75] systematically studied the NGF-inducing effect of Erinacines A-G in three reports, and results showed that the Erinacines A-F all had potent stimulating activity of NGF. When erinacines A, B, and C were present (1 mmol/L), the contents of NGF secreted by astrocytes were (250.1 ± 36.2), (129.7 ± 6.5), and (299.1 ± 59.6) pg/mL, respectively, which were significantly more effective than epinephrine (positive control, a well-known NGF stimulator, 69.2 pg/mL at 1.0 mmol/L)[24]. Moreover, in the presence of erinacine D (1.7 mmol/L), the concentration of NGF secreted into the medium was (141.5 ± 18.2) pg/mL[74]. The synthesis of astrocytic NGF was (105.0 ± 5.2) and (175.0 ± 52.0) pg/mL when erinacines E and F were 5.0 mmol/L, respectively[75]. However, in other reports that was not the case. Zhang et al.[76] revealed that erinacines A enhanced NGF-induced neurite outgrowth in the presence of NGF, but did not stimulated NGF synthesis in PC12 cells. They found that the enhancement of NGF-induced neurite outgrowth by erinacines A was completely TrkA-mediated and partially Erk1/2-dependent. Rupcic et al.[77] showed that erinacine C possesses both NGF and BDNF neurotrophic factor-inducing activities. In this study, erinacine E did not stimulate NGF or BDNF, but the metabolites of 1321N1 cells incubation with erinacine E had strong PC12 differentiation activity. The authors speculated that erinacine E induced NGF or BDNF expression in 1321N1 cells with a lag phase or produced some unknown factor with PC12 differentiation-inducing activity[77]. These different results may be due to different cell lines or doses of erinacines used by different investigators. Furthermore, erinacine H, at a concentration of 33.3 μg/mL, resulted in a 4-fold increase the synthesis of NGF by astrocytes[78], and, recently discovered erinacines T-V in the range of 2.5−10 μmol/L can also significantly increase the percentage of differentiation of PC12 cells[79].

In addition to Hericenones and Erinacines, isohericerinol A isolated from *H. erinaceus* fruiting bodies could significantly increase NGF production in C6 glioma cells and further promote axonal growth in N2a cells[33]. Isohericerinol A has also been reported to increase the expression of BDNF[33], which was essential for central nervous system development and neuronal plasticity[80]. Park et al.[81] found that a *H. erinaceus* mycelium polysaccharides also promoted the growth of neurites in PC12 cells *in vitro*, but like many components in *H. erinaceus* that have been determined to have neurotrophic activity, and the specific mechanism has not yet been clarified and need to be further investigated.

3.4.2 Prevention and treatment of Alzheimer's disease (AD)

Neurodegeneration is the slow and progressive dysfunction and loss of neurons and axons in the central nervous system, which is the

main pathological feature of acute and chronic neurodegenerative diseases, such as AD, Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS)[82]. *H. erinaceus* contains a variety of active ingredients that could act on therapeutic targets of neurodegenerative diseases, so it has been regarded as a potential therapeutic agent.

AD has become the fifth leading cause of death among adults aged 65 and older[83]. As a neurodegenerative disease, the essence of AD was progressive dysfunction of neurons. Thus, stimulating nerve cell development and regeneration will aid in its prevention and treatment. *H. erinaceus* and its bioactive components can induce the production of neurotrophins, and promote the growth and differentiation of nerve cells (as mentioned in section 3.4.1). *In vitro* studies found that *H. erinaceus* extract supported the development of cerebellar nerve cells by stimulating the regulatory process of myelination[84]. *In vivo* studies also showed that oral administration of *H. erinaceus* could stimulate doublecortin immunohistochemistry and cell nuclear antigen proliferation in the hippocampus and cerebellum of mice to exert a positive effect on neurogenesis and recognition memory[85]. Wong et al.[86] found that *H. erinaceus* was beneficial to the functional recovery of axonotmetic peroneal nerve injury in rats, and promoted the regeneration of injured nerves in the early stage of recovery. A 30 days short-term administration of erinacine A and S could effectively ameliorate AD-related pathologies, including attenuating cerebral plaque loading by inhibiting plaque growth, reducing glial activation and promoting hippocampal neurogenesis[87].

Although the exact pathogenesis of AD has not yet been clarified, a large number of studies have shown that the formation of β-amyloid (Aβ) plaque was a typical pathological feature of AD[88]. Therefore, inhibiting the production of Aβ or preventing the aggregation of Aβ into amyloid plaques has been considered to be an ideal preventive and therapeutic target for AD[67]. Mori et al.[89] showed that *H. erinaceus* prevented $A\beta_{25-35}$-induced learning and memory deficits in mice. Aβ was derived from the continuous action of β and γ secretases on Aβ precursor protein. *H. erinaceus* can reduce the abnormal overexpression of Aβ precursor protein[90], and act as an inhibitor of β-secretase (also known as BACE1) to reduce the formation of Aβ plaques[44]. In addition, *H. erinaceus* and its active components can reduce the formation of Aβ plaques by increasing the level and activity of insulin-degrading enzyme (IDE)[71]. IDE has a direct degradation effect on Aβ and can also reduce the production of Aβ by inhibiting γ-secretase[91] or degrading the intracellular domain of Aβ precursor protein[92]. Tzeng et al.[87] found that the mycelium of *H. erinaceus* improved AD-related pathology in AD model mice, and showed that erinacine A increased the expression of IDE and reduced the C-terminal fragment of Aβ precursor protein and the level of Aβ, which was not mediated by erinacine S. The therapeutic effect of erinacine A on AD was also confirmed in a clinical study[93]. *H. erinaceus* could also alleviate AD by reducing the hyperphosphorylation of tau-protein. *H. erinaceus* might be involved in the regulation of tau-protein phosphorylation by increasing the level or activity of IDE that could stimulate Akt/PKB signaling pathway[90].

Growing evidence suggested that dysregulation of the antioxidant system and oxidative stress-driven neuroinflammation might be an important cause of neurodegenerative diseases[94]. *H. erinaceus* has been proven to play a role in AD prevention and treatment by regulating oxidative stress and inflammatory pathways. Oral administration of *H. erinaceus* reduced oxidative stress and NLRP3 inflammasome activation managed the characteristics of AD, including behavioral changes, phosphorylated Tau levels, and Aβ precursor protein overexpression, Aβ accumulation, and neuronal degeneration[90]. In another study, *H. erinaceus* promoted resolution of AD-related inflammation by modulating redox status and enhancing lipoxin A4 expression in rat cortex, hippocampus, substantia nigra, striatum and cerebellum[95]. *H. erinaceus* mycelium has also been reported to prevent and alleviate AD by blocking the activation of microglia, the central drivers of neuroinflammation[71].

3.4.3 Other neurological disorders

PD is the second most common neurodegenerative disease, and its pathogenesis is closely related to the dysfunction of dopaminergic neurons in the substantia nigra pars compacta region of the brain. *H. erinaceus* mycelium was found to play a neuroprotective role by inhibiting endoplasmic reticulum stress and significantly improves dopaminergic lesions and oxidative stress in the substantia nigra[96]. Ueda et al.[20] demonstrated that 3-hydroxyhericenone F in the fruiting body of *H. erinaceus* has a similar effect, inhibiting neuronal cell damage caused by endoplasmic reticulum stress by inducing apoptosis pathway.

Excessive reactive oxygen species and oxidative stress are closely related to the pathogenesis of ischemic brain injury[97]. *H. erinaceus* mycelium could alleviate ischemic stroke in rats by targeting the iNOS/RNS and MAPK/CCAAT enhancer-binding protein homologous protein pathways[98]. Defective transmission within the monoamine system and chronic restraint stress usually lead to reduced hippocampal BDNF expression and depression-like behavior. *H. erinaceus* played a part in the treatment of depression by regulating monoamine neurotransmitters and promoting the expression of BDNF[99]. *H. erinaceus* polysaccharides can accelerate the recovery of sensory function after peripheral nerve injury in Sprague-Dawley rats by up-regulating the expression of Akt and p38 MAPK in dorsal root ganglia and restoring the blood-nerve barrier[100]. *H. erinaceus* also improved cognitive impairment by modulating gut microbiota[101].

3.5 Other biological activities

With the improvement of living standards, the number of patients with hyperglycemia and hyperlipidemia continues to increase, and diabetes has become a major social problem that threatens human health. Studies have shown that *H. erinaceus* was of great significance for the treatment of hyperlipidemia, obesity and diabetes. Both alcohol[102] and water extracts[103] of fruiting bodies of *H. erinaceus* have been reported to increase serum insulin levels and reduce blood glucose, serum triglyceride and total cholesterol levels in diabetic model rats. Zhang et al.[104] revealed that *H. erinaceus* significantly increased the activity of antioxidant enzymes and inhibited lipid peroxidation in model rats. The authors suggested that enhancing the host antioxidant system may be responsible for the amended diabetic neuropathy by *H. erinaceus* extract. A recent study has shown that *H. erinaceus* fruiting body polysaccharides also have hypoglycemic and

hypolipidemic activities. Molecular mechanism analysis showed that *H. erinaceus* polysaccharides maintained the balance of blood glucose and blood lipids by activating the PI3K/Akt signal transduction pathway to positively mediate glycogen synthesis and inhibit lipid peroxidation in diabetic rats[49]. Hericenone D, hericene A and D, and 4-[3′,7′–dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol[105] from fruiting body of *H. erinaceus*, and erinacerins Q-T[106] from mycelium of *H. erinaceus* all had inhibitory activity of α-glucosidase inhibition, and played a hypoglycemic effect by reducing carbohydrate absorption. Erinacerins Q-T also showed inhibitory activity on PTP-1B, a key negative regulator in the insulin signaling pathway, thereby reducing blood glucose and inducing increased fat metabolism by blocking insulin receptor phosphorylation and enhancing leptin signaling[106].

In recent years, drug-resistant bacteria have become the focus of modern medicine, and *H. erinaceus* could be used as an important source of new natural antibacterial agents. Active ingredients with antibacterial effects were found in the fruiting body, mycelium and culture medium of *H. erinaceus*. Wang et al.[107] reported that *H. erinaceus* alcohol extract not only exhibited *in vitro* growth inhibitory effect on *Helicobacter pylori*, but also reduced its colonization in stomach by reducing adhesion in C57BL mice. Researchers also found substances that inhibited *Helicobacter pylori* and bacterial urease in the mycelium and culture medium of *H. erinaceus*[108]. CJ14258 (a small molecular extracted from mycelium of *H. erinaceus*) and erinacine C isolated from mycelium exhibited antibacterial activity against methicillin-resistant *Staphylococcus aureus*[4], and 2-chloro-1,3-dimethoxy-5-methyl benzene was reported to inhibit *Candida albicans* and *Cryptococcus neoformans* growth and biofilm formation[109].

As an important source of novel metabolites with unique structural and functional characteristics, many of the natural products identified in *H. erinaceus* also have anticancer/antitumor effects. Hericerin A, isohericenone J, isoericerin, hericerin, *N*-de-phenylethyl isohericerin, hericenone J and 4-[3′,7′-dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol isolated from alcohol extracts of *H. erinaceus* fruiting bodies all showed cytotoxicity against human myelocytic leukemia cell HL-60[110]. Erinacine A in mycelium could induce apoptosis in human colon cancer cell lines DLD-1 and HCT-116 by stimulating extrinsic apoptotic activation pathways (TNFR, Fas, FasL and caspases)[111]. Erinacine S has also been reported to induce ROS production and apoptosis in gastric cancer cells by increasing FasL and tumor necrosis factor-related apoptosis-inducing ligand protein[112]. HTJ5 (a water extract from the culture broth of *H. erinaceus*) and HTJ5A (obtained from HTJ5 after further polysaccharides and proteins separation process) isolated from liquid cultures of *H. erinaceus* have cytotoxic activity against liver cancer (HepG2 and Huh-7), colon cancer (HT-29) and gastric cancer (NCI87) cells[113]. Hericinoid B, erinacine Z1 and erinacine Z2 shows cytotoxicity against HL-60 cell line[41]. Erinacerins M-P extracted from solid culture of *H. erinaceus* showed moderate cytotoxicity against human chronic myeloid leukemia cell line K562[106]. A recent report showed that erinacerin P increased the apoptosis rate of U87 cells through the Bax/capase-3 pathway[114]. Immunomodulatory fungal proteins from *H. erinaceus* can contribute to the antitumor efficacy of chemotherapy drug 5-fluorouracil by improving gut microbiota composition, immune-inflammatory response and homeostasis[45].

H. erinaceus also has some other biological activities. Researchers found some components with herbicidal activity in *H. erinaceus*, such as erinachromanes A and B, erinaphenol A, 4-chloro-3,5-dimethoxybenzaldehyde, methyl 4-chloro-3,5-dimethoxybenzoate, which could be used as natural herbicides agent[115]. Hericenone B in fruiting bodies of *H. erinaceus* prevented platelet adhesion and thrombosis by inhibiting platelet aggregation[116]. Liu et al.[117] reported that the extract of *H. erinaceus* can act as an anti-fatigue agent by reducing the level of serum urea nitrogen, blood lactate, malondialdehyde or increasing glycogen content and superoxide dismutase activity, thereby significantly prolonged swimming time of mice. Intracellular and extracellular polysaccharides from *H. erinaceus* can effectively alleviate carbon tetrachloride-induced liver injury in mice[118].

4. Future perspectives and conclusion

H. erinaceus has attracted much attention due to its rich nutritional components, physiological activities and its medicinal and edible properties. Researchers have carried out various studies on the bioactive components and their biological efficacy of *H. erinaceus* fruiting bodies, mycelium and even their cultures (Fig. 1). However, the extraction, structure identification, activity and mechanism of these bioactive ingredients have not formed a relatively systematic theoretical and technical system, which greatly limits their industrial application. Thus, the most of the commercially available *H. erinaceus* products were functional foods containing fruiting bodies. The main reasons for this situation were as follows:

1) The composition, structure and biological activity of active components in *H. erinaceus* fruiting body, mycelium and culture medium are quite different, and the relationship between source, chemical structure and biological activity is not yet clear. Even for the more well-studied polysaccharides, there are only some preliminary discussions on the structure-activity relationship. However, most studies related to biological activity stop at the cell and/or animal level, and few preclinical and/or clinical studies have been performed, and the mechanism of the biological activity remains to be further confirmed. These problems restrict the movement of the bioactive ingredients of *H. erinaceus* from the laboratory to the market.

2) Existing extraction, purification or synthesis methods are difficult to achieve in industrial production. Most products, including some commercialized polysaccharides, are still crude. Some small-molecule active ingredients are still in the stage of laboratory structure identification and activity verification. Their classification and naming are confusing, and no standard material is available, which makes it difficult to control the quality of products between batches, so that the safety and stability of the products cannot be guaranteed.

3) Many components in *H. erinaceus* are chemically unstable. The current research lacks consideration of the activity changes during processing and digestion, as well as the development of corresponding activity protection technologies.

Therefore, it is necessary to further carry out fundamental and applied research on the bioactive compounds and biological activities of *H. erinaceus*, and establish corresponding deep processing technology systems and quality standards to promote the application of *H. erinaceus* in the fields of food, health care products and clinical medicine.

Declaration of competing interest

There are no conflict of interest.

Acknowledgement

This project is supported by the fund from Natural Science Foundation of Zhejiang Province, China (LY17C200017).

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