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Review

Neuroprotective and Anticarcinogenic Properties of *Hericium* Mushrooms and the Active Constituents Associated with These Effects: A Review

Zhixia (Grace) Chen[1], Karen Suzanne Bishop[2,3], Jingying Zhang[1], Siew Young Quek[1,4*]

[1]Food Science, School of Chemical Sciences, The University of Auckland, Auckland 1010, New Zealand
[2]Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland 1010, New Zealand
[3]Discipline of Nutrition and Dietetics, School of Medical Sciences, Faculty of Medical and Health Sciences, The University of Auckland, Auckland 1010, New Zealand
[4]Riddet Institute, New Zealand Centre of Research Excellence for Food Research, Palmerston North 4474, New Zealand
E-mail: sy.quek@auckland.ac.nz

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Abstract: *Hericium* mushrooms are well known for their numerous medicinal benefits, of which neuroprotective and anticarcinogenic characteristics are two of the most reported properties. This review summarizes the research advances and techniques used to study these two advantages of *Hericium* mushrooms reported in the latest 20 years, namely between the years 2001 and 2021. Based on published research, the *Hericium*-unique compounds (e.g., hericenones and erinacines) and polysaccharides are the main active constituents associated with these two properties. It was reported that about 70 such secondary metabolites were characterized to help prevent or treat neurological and tumor diseases. We have collated the above information in order to provide insights for further studies aiming to maximize the application of *Hericium* mushrooms as functional ingredients for neuroprotection and anticarcinogenesis.

***Keywords*:** *Hericium*, mushrooms, neuroprotection, anticancer, compounds unique to *Hericium*, polysaccharides

1. Introduction

Mushrooms, recognized for various nutritional qualities, are gaining worldwide recognition for their nutritional value and health-promoting properties. Medicinal mushrooms have become a compelling topic due to the promising broad-spectrum of therapeutic effects from their bioactive constituents. Various mushroom metabolites contribute to their medicinal properties. These metabolites are bioactive compounds with varied molecular weights. They are produced by fungi in response to stress, helping the organism to survive, but are generally not essential for normal growth and reproduction [1]. Different primary and secondary bioactive metabolites are present in mushrooms, with polysaccharides being the most identified bioactive metabolites. Other bioactive metabolites include alkaloids, fatty acids, lectins, nucleic acids, nucleosides, peptides, phenolics, polyketides, proteins, statins, steroids, terpenoids, etc. [1].

Hericium is a group of edible mushrooms with multiple medicinal properties. According to the Integrated Taxonomic Information System [2], the position of *Hericium* mushrooms in classification is shown as follows: *Hericium*, *Hericiaceae*, Russulales, Agaricomycetes, Basidiomycota, Fungi. The genus *Hericium* contains mushrooms

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such as *H. erinaceus*, *H. coralloides*, *H. flagellum* and *H. caput-medusae*. *H. novae-zealandiae* is a new member of *Hericium* (Figure 1a) [3]. Among the species in *Hericium*, *H. erinaceus* is probably the most well-known (Figure 1b). In China, this mushroom is known as "Houtou", which means "monkey head". In Japan, *H. erinaceus* is named as "Yamabushitake", which means "mountain priest". It is also known as "Lion's Mane", "Bear's Head", "Hog's Head Fungus", "White Beard", "Old Man's Beard", "Pom Pom" and "Bearded Tooth" in other parts of the world [4]. This mushroom is predominantly found in East Asian countries and has a long history of usage in traditional Chinese medicine for the treatment of neurasthenia and general debility [5]. Other reported activities of the fruiting bodies and mycelium of *Hericium* mushrooms and their extracts include antibiotic, anticarcinogenic, neuroprotective, antioxidant, and antidiabetic properties [6]. *Hericium* mushrooms are considered to offer greater potential than other medicinal mushrooms for the treatment of neurodegenerative diseases [4, 7-14]. Another remarkable activity of *Hericium* mushrooms is inhibition of proliferation of many cancer cell lines such as human gastric cancer cell line SGC-7901 [15], breast cancer cell line MCF-7, and HeLa cells [16]. Along with the medicinal advantages, *Hericium* mushrooms are also known to contain various bioactive components. Many structurally different bioactive compounds have been isolated from *Hericium* mushrooms, such as polysaccharides, terpenoids, and low molecular weight proteins, glycoproteins, nucleosides etc. [17]. More impressively, dozens of low-molecular-weight metabolite compounds were identified only from the fruiting bodies and mycelium in *Hericium* mushrooms and these compounds unique to *Hericium* have shown various biological activities. In this review, we summarized the studies of the two most reported health properties of *Hericium* mushrooms, namely neuroprotective and anticarcinogenic effects with the majority of studies focusing on *H. erinaceus*. In addition, the active constituents that were shown to play a role in these bioactivities were also discussed. The purpose of this review is to demonstrate a link between the bioactivities of *Hericium* mushrooms and their corresponding active chemical constituents. The research areas of interest will emerge and will likely direct further studies. Pictures of two *Hericium* mushrooms could be found below.

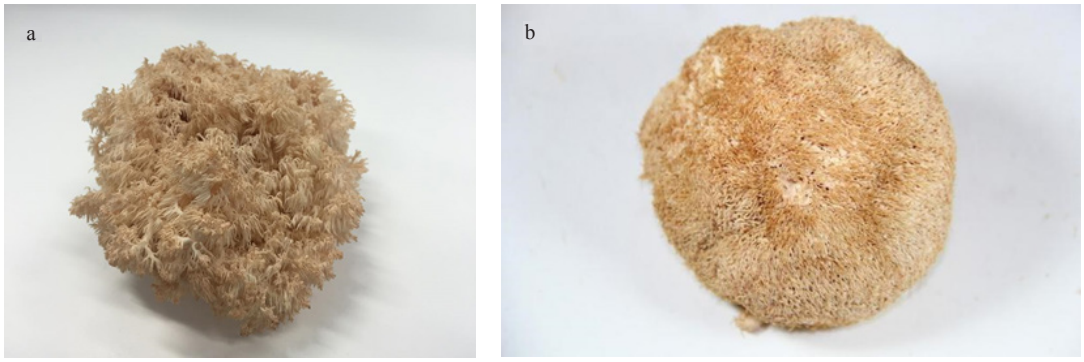


Figure 1. (a) Fruiting bodies of *H. novae-zealandiae* (b) Fruiting bodies of *H. erinaceus*

2. Health-promoting properties of *Hericium* mushrooms

2.1 *Neuroprotective activities*

2.1.1 *Neuroprotective effects observed in cell and animal studies*

Neurotrophic factors play an important role in organizing and maintaining the functionalities of neurons. As such, neurotrophic factor-like substances are promising to be used in the treatment of neurodegenerative related diseases [18]. A highly conserved protein, the Nerve Growth Factor (NGF), is found to be substantially involved in neuron function by supporting neuritis outgrowth, promoting synapse formation, preventing neuronal death, and strengthening memory function [19]. To investigate the neuroprotective properties of *Hericium*, numerous studies have explored the linkage between its application and NGF level. Neuroprotective effects *H. erinaceus* were observed by increasing the levels of NGF in both the striatum and cortex in a study performed on mice subjected to middle cerebral artery occlusion [20]. *H. ramosum*, a rare species from *Hericium*, was also reported to greatly increase concentrations of NGF in the

hippocampus of intact mice [21].

An extract of *H. erinaceus* accelerated neurite outgrowth in dissociated cells of the spinal cord, retina, and brain in chicken embryos in an immunofluorescence study [14]. Nevertheless, the aqueous extract from the same species failed to protect neuroblastoma X glioma hybrid NG108-15 cells when they were exposed to oxidative stress in pre-treatment and co-treatment modes. Instead, it exhibited neurotrophic but not neuroprotective activities. These results might be due to the extract of *H. erinaceus* contained neuro-promoting compounds that promoted neurite outgrowth and induced NGF-synthesis [22]. In a related study, the aqueous extracts of the fruiting bodies and mycelium stimulated neurite outgrowth in cultured NG108-15 cells [23]. It was also observed in another study that the *H. erinaceus* extract improved the myelination process in mature myelinating fibers and exerted neurotropic action [24]. No toxic effects or nerve cell damage, nor nerve cell growth were observed in this study.

The rat pheochromocytoma PC12 cell model was frequently used to study neurogenesis of *H. erinaceus in vitro*. An oral preparation of fresh *H. erinaceus* fruiting bodies attenuated amyloid beta (Aβ)-triggered damage in PC12 cells by greatly increasing cell viability and decreasing the release of lactate dehydrogenase [11]. Another study conducted on PC12 cells provided experimental evidence that the aqueous extract of *H. erinaceus* was rich in polysaccharide. It exhibited neuroprotective effects by activating PC12 cell differentiation and it increased the concentrations of acetylcholine and choline acetyltransferase in both the hypothalamus and the serum in a dose-dependent manner in the alzheimer's disease mouse model [25]. The enzymatically hydrolyzed fruiting bodies of *H. erinaceus* extracts were reported to possess antioxidant activity on PC12 cells [26]. In another study [27] it was shown that the mycelia of *H. erinaceus* attenuated cerebral Aβ plaque burden in a mouse model. It also simultaneously diminished the number of plaque-activated microglia and astrocytes in the cerebral cortex and hippocampus and increased the ratio of NGF relative to its precursor.

The neuroprotective effects of *H. erinaceus* after nerve injuries were also reported. A hot aqueous extract of the fruiting bodies of *H. erinaceus* exhibited a higher neuroprotective activity than NGF in a mouse peripheral nerve injury model [28]. It was revealed that an extract of the fruiting bodies of *H. erinaceus* promoted neuroprotection after pilocarpine-induced Status Epilepticus (SE) in mouse hippocampi [29]. In another two studies, the effect of aqueous extracts of fruiting bodies on nerve injury were found to promote peripheral nerve regeneration following injury [30], [31]. In addition, an extract of mycelium acted against ischemic-injury-induced neuronal cell death via the inhibition of inducible nitric oxide (NO) synthase (iNOS)/p38 MAPK and nitrotyrosine [10]. Furthermore, an aqueous extract from the fruiting bodies boosted the rebirth of injured rat peroneal nerve in the early stage of recovery in another two studies [32, 33]. This effect was observed through the assessment of performance using an immunofluorescence analysis, as well as performance on a walking track. *H. erinaceus* also prevented impairments of spatial short-term and visual recognition memory induced by Aβ in mice. This was measured by behavioral pharmacological methods, including the Y-maze test and the novel-object recognition test [34]. In addition, daily administration of an aqueous extract from the fruit bodies had a beneficial effect on the recovery of injured rat peroneal nerves in the early stages of regeneration in adult female Sprague-Dawley rats [35].

A range of biological activities of *H. erinaceus* have been reported on many brain diseases and the role of *H. erinaceus* in major psychiatric disorders such as depression and anxiety have been investigated as follows. In a behavior test in wild-type mice, oral supplementation of *H. erinaceus* induced a meaningful improvement in recognition memory. Additionally, an increase in spontaneous and evoked excitatory synaptic current in the mossy fiber-CA3 synapse was observed in hippocampal slices [7]. Administration of *H. erinaceus* exerted anxiolytic and antidepressant-like effects on the brain in adult mice, possibly by enhancing hippocampal neurogenesis [36].

NGF levels were found to decrease in the frontal cortices of people with senile plaques and also in the basal forebrain of Alzheimer's patients. The above cited studies in cell and mice models implied a value of further exploration for their potential to prevent progress of Alzheimer Disease (AD). Another study model based on the cholinergic hypothesis [37], which claims that memory and learning impairment in AD patients are initiated by acetylcholine deficiency, confirmed that the ethanol extract of *H. novae-zealandiae* exerted a weak Acetylcholinesterase inhibitory activity.

2.1.2 *Neuroprotective effects observed in human studies*

In a human clinical study, Nagan *et al.* investigated the effects of *H. erinaceus* on brain function and on the autonomic nervous system [13]. The clinical effects were evaluated by 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. The results showed that the consumption of *H. erinaceus* reduced depression and anxiety and these results suggested a different mechanism from the enhancement of NGF activity. Additionally, Mori et al. reported that cognitive scores in research subjects were greatly increased, which showed that the fruiting bodies of *H. erinaceus* was effective in improving mild cognitive impairment [12] as follows: The subjects were given 1g tablets containing 96% *H. erinaceus* (dry powder) 3 times a day and the study lasted for 16 weeks. Thereafter the subjects were evaluated against the Revised Hasegawa Dementia Scale and compared with a placebo group.

The studies performed in cell, rodents and human indicated potential application of *Hericium* mushrooms in neurological disorders such as Alzheimer's, Parkinson, and depression etc. However, these results should be interpreted with caution: only if similar findings could be further validated by the coming studies, particularly those conducted in human clinical trials.

2.1.3 *Active constituents considered to account for neuroprotective activities*

Two categories of chemical constituents, i.e., compounds unique to *Hericium* and polysaccharides, were discovered to be the major active compounds involved in the neuroprotective effects of *Hericium*.

A great number of low-molecular weight secondary metabolites were identified from extracts of fruiting bodies and mycelial of *H. erinaceus*. Among them, compounds such as erinacines and hericenones were found to be unique to *Hericium*. These compounds were examined to determine if they were responsible for the neuroprotective activities of the species. Erinacine A acted against ischemia-injury-induced neuronal cell death via the inhibition of iNOS/p38 MAPK and nitrotyrosine [10]. Both erinacine A and S reduced Alzheimer's Disease (AD) pathology via reducing amyloid deposition and promoting neurogenesis. Erinacine A also inhibited aβ production to ameliorate AD-related pathologies in APP/PS1 transgenic mice [38]. The mycelium, enriched in erinacine A, produced antidepressant-like effects through modulating BDNF/PI3K/Akt/GSK-3β signaling in mice [8]. Another cell-based screening for bioactivity showed that erinacine A not only potentiated NGF-induced neurite outgrowth, but also protected neuronally-differentiated cells against deprivation of NGF in PC12 cells [39]. In addition, erinacine A induced neurogenesis in neurons in the primary rat cortex [39]. Erinacines also played a role as neuroprotective adjuvants by inhibiting apoptosis induced by glucose-insult in PC-12 cells [40]. Four erinacine derivatives, isolated from the mycelia of *H. erinaceus,* induced the biosynthesis of NGF. Two compounds, hericerin and isohericerinol A increased the neurite outgrowth by NGF synthesis [41]. In addition to erinacines (erinacines A to I), a series of benzyl alcohol derivatives, hericenones C to H, greatly induced the synthesis of NGF [42-47]. Another compound, 3-hydroxyhericenone F, showed protective activity against endoplasmic reticulum stress-dependent Neuro-2a cell death [48, 49].

Regarding the safety of erinacine A, Li et al. evaluated the safety of consuming *H. erinaceus* [50]. The toxicity of the mycelium, enriched with 5 mg/g erinacine A, was assessed by implementing a 28-day repeated oral administration in Sprague-Dawley rats. The result showed no observed adverse effect at a dosage of greater than 3 g/kg body weight/day of erinacine A-enriched *H. erinaceus*.

Polysaccharides were generally recognized as the other active constituents in *H. erinaceus*, accounting for neuroprotective activities. In a study by Cheng et al., the polysaccharides (extracted from the fruiting bodies by ethanol) were purified and found to consist of two high molecular weight polysaccharides (1.7×10^5 Da and 1.1×10^5 Da) [51]. These compounds showed protective effects on Aβ-induced neurotoxicity in PC12 cells. Wong et al. observed an accelerated sensory functional recovery of nerve injuries in peroneal nerve crush in Sprague-Dawley rats after the treatment with *H. erinaceus* polysaccharides [52]. Park et al. purified an exo-biopolymer (Molecular weight 1,000,000, molar ratio of glucose: galactose: xylose: mannose: fructose as 1.5:1.7:1.2:0.6:0.9), which enhanced the growth and differentiation of rat adrenal nerve cells [53].

Three other compounds, ergosterol peroxide, cerevisterol, and 3β,5α,9α-trihydroxy-ergosta-7,22-dien-6-one isolated from the fruiting body of *H. erinaceus*, exerted a large increase in neurite-bearing cells in the presence of NGF at a concentration of 20 ng/mL [54]. Yao et al. revealed that amycenone isolated from *H. erinaceus* showed

antidepressant effects in an LPS-induced inflammation model of depression in rats [55]. More remarkably, in a human study, amycenone was also observed to restore cognitive function in three patients with mild neurocognitive disorders [56].

2.2 *Anticarcinogenic properties*

Carcinogenesis is a steady multistage cellular process comprising tumor initiation, tumor promotion, and tumor progression. Phytonutrients are promising sources for cancer prevention and suppression [57]. Relevant studies on *Hericium* mushrooms are summarized in this review based on mammalian cells and rodent models.

2.2.1 *Selected report on anticarcinogenic properties*

Water was one of the commonly used solvents in the preparation of *H. erinaceus* extract for investigating anticancer activities. Two water extracts of *H. erinaceus* were obtained using a combination of macro-porous resin with silica gel. They were observed to give active effect against the proliferation of various cancer cell lines, including liver cancer (HepG2 and Huh-7), colon cancer (HT-29) and gastric cancer (NCI-87 cells) [58]. In another study, a hot water extraction of the fruiting bodies inhibited the growth of intramuscularly transplanted sarcoma 180 ascitic cells but did not inhibit the proliferation of human cervical cancer HeLa 229 cells. This anti-tumor activity was not likely due to the direct cytotoxic action on tumor cells [59]. Jin et al. reported that a hot water extract possessed anti-tumor and anti-inflammatory effects via the modulation of Nrf2/ARE and inflammatory signaling pathways [60].

Organic solvents were also used to obtain *H. erinaceus* extracts for assessment of their anticarcinogenic activity. The antitumor effects were reported on an extract obtained by microwaving the fruiting bodies in 50% ethanol/water [61]. The extract was then administered to mice intracutaneously transplanted with CT-26 colon cancer cells. Treatment with the extracts was associated with a statistically significant reduction in tumor size, which was attributed to the induction of NK activity, activation of macrophages, and inhibition of angiogenesis. In a similar study, hot water and microwaved 50% ethanol extracts of powdered dry fruiting bodies have shown to induce apoptosis in the U937 human monocytic leukemia cells [62]. Similarly, there was a report that the hot water and microwaved 50% ethanol extracts inhibited metastasis of cancer cells to the lung in the CT-26 colon cancer-transplanted mice. Water and ethanol extracts of both the mycelium and fruiting body, respectively, have shown to exhibit anti-mutagenic effects against five mutagens, as determined by the Ames test using *Salmonella typhimurium* TA98 [63]. Compared to the water extracts, the ethanol extract exhibited stronger antimutagenic effects. Furthermore, the extract from the fruiting body showed stronger antimutagenic effects than that of the mycelium. The ultrasound assisted ethanol extract of *H. erinaceus* of dried fruiting bodies was further observed to possess antiangiogenic and anti-inflammatory activities. These two effects were related to the anticancer property of the extract through modulation of the MMP-9/NF-B and Nrf2-antioxidant signaling pathways [64].

2.2.2 *Active Constituents associated with anticarcinogenic properties*

A number of constituents from *H. erinaceus* have been identified to account for the anticarcinogenic properties. Among them, the compounds unique to *Hericium*, and polysaccharides, both stand out for their anticarcinogenic effects. Table 1 summarizes the bioactive compounds isolated from *Hericium* including the two important classes of compounds as mentioned above.

Along with the summary in Table 1, a polysaccharide with a molecular weight larger than 1×10^5 k Da was reported to display anti-artificial pulmonary metastatic tumor and immune-enhancing effects in a mouse model [65]. A water extract of the fruiting bodies of *H. erinaceus*, mainly consisted of pachyman and β-glucan, inhibited against lung metastasis after intravenous injection of colon 26-L5 cells [66]. The fractions of chloroform and n-hexane from the methanol extract of *H. erinaceus* showed potent activity of proteasome inhibitors. The investigations of the active compounds in the same study pointed to ericenones C, D and ergosterol peroxide as the associated compounds [67]. Furthermore, polysaccharides and lipophilic constituents such as ergosterol peroxide extracted from the fruiting bodies of a new *Hericium* species, i.e., *H. novae-zealandiae*, exhibited synergistic effects in suppressing the cell proliferation of three prostate cancer cell lines, DU145, LNCaP and PC3 [37, 68].

Table 1. Active constituents isolated from *Hericum* exhibiting anticarcinogenic properties

Constituent	Cancer type/cell line	Mechanism of action	References
Erinacine A	Gastric cancer cells (TSGH 9201)	Activating the FAK/AKT/p70S6K/PAK1 pathway and upregulating proteins 1433S and MTUS2	[69]
Erinacine A	Colorectal cancer cell lines, HCT-116 and DLD-1	Up regulating the activation of PI3K/mTOR/p70S6K and production of ROS	[70]
Diastereomer of erinacine E in the sugar part	human cancer cell lines, K562, LNCaP and HEP2	-	[71]
Hericerin A and hericerin	human acute promyelocytic leukaemia cell (HL-60)	down-regulation of *p-AKT* and *c-myc* concentrations	[41, 72]
Hericenone L	human Esophageal Squamous Cell Carcinoma (ESCC) EC109 cell line	-	[73]
Cerebroside E	LLC-PK1 cells, Human Umbilical Vascular Endothelial Cells (HUVECs)	-	[74]
Polysaccharides	human hepatocellular carcinoma cells	reducing *c-FLIP* expression via JNK activation and enhancing intracellular Dox accumulation via the inhibition of NF-κB activity	[75]
Polysaccharide-protein	human gastric cancer cell line (SGC-7901)	promoting apoptosis and cell cycle arrest at S phase	[15]
Polysaccharides	breast cancer cells (MCF-7) and HeLa cells	-	[16]
Polysaccharide	precancerous human gastric cells	apoptosis-associated pathway by modulating the expression of *Bax, Bcl-2*, and *caspase-3*	[76]
Ergosterol peroxide	HUVECs	reducing senescence associated β-galactosidase (SA-β-gal) activity	[77]
Four alkaloids	chronic myelogenous leukemia K562 cells	-	[78]
Sambutoxin	various cancer cells such as human breast cancer MDA-MB-231 and MCF-7cells	activating the mitochondrial apoptosis pathway through an increased *Bax/Bcl-2* ratio, loss of mitochondrial membrane potential (m), Cytochrome (Cyt) c release, caspase-9 and caspase-3 activation, and poly (ADP-ribose) polymerase (PARP) degradation	[79]

-indicates mechanism unknown

3. Compounds unique to *Hericium* and polysaccharides isolated from *Hericium* sp.

As discussed in section 2, compounds unique to *Hericium* and polysaccharide are the two main categories of active constituents identified as responsible for the neuroprotective and anticarcinogenic properties of *Hericium* sp. through various studies. This justified further exploration of these two chemical categories.

3.1 *Compounds unique to Hericium*

Studies of low molecular weight secondary metabolites in *Hericium* led to the isolation of many small molecular

compounds [6]. These compounds were highly bioactive, and they were exclusively found in *Hericium*. From literature, *H. erinaceus* is the most well-studied species and most of the compounds unique to *Hericium* have been firstly isolated from this species. As many as 70 different metabolites have been biosynthesized in *H. erinaceus*, e.g. hericenones and erinacines [6]. Hericenones are present only in the fruiting bodies, while erinacines were found in trace amounts in the fruiting bodies but in higher concentrations in the mycelia [80, 81]. The chemical structures of these compounds are shown in Figure 2.

3.1.1 *Erinacines*

Erinacines are cyathane diterpenoids. They were isolated from the mycelium of *Hericium*. These compounds include erinacine A, B, C [43]; erinacine D [42]; erinacine E, F, G [82, 83]; erinacine H, I [84]; erinacine J, K [85]; erinacine P [86]; erinacine Q [87]; erinacine R [88]; and erinacine T, U, V [89]. In addition to the list, two new erinacines, namely erinacine Z1 and Z2 were isolated from mycelial cultures of *H. erinaceus* and the rare species *H. flagellum* [90].

3.1.2 *Erinacenes*

Erinacenes are the other type of cyathane diterpenoids isolated from both the mycelia and fruiting bodies of *Hericium* mushrooms. All erinacines possess a cyathane skeleton consisting of angularly condensed five-, six-, and seven-membered rings. Erinacene A, B and C were isolated from the mycelium of *H. erinaceus* [91] and erinacene D was isolated from the fruiting body of *H. erinaceus* [92].

3.1.3 *Erinacerins*

Erinacerin A and B were isolated from the fruiting bodies [93]. Ten new isoindolin-1-ones, named erinacerins C-L were isolated from solid culture [94]. Three novel compounds, erinachromane A, erinachromane B and erinaphenol A were isolated from the culture broth [95].

3.1.4 *Erinaceolactones*

Erinaceolactone A, B, C [96]; D, E, F [97]; G, H [98] were isolated from the culture broth of *H. erinaceus*.

3.1.5 *Hericenones*

From the fruiting body of *Hericium,* aromatic compounds, hericenones were isolated. These compounds include hericenone A, B [99], C, D, E [45, 100], F, G, H [46], hericenone I and hericenone J [101], hericenone K [54], hericenone L [78]. Hericenone derivatives have also been isolated from *Hericium*, including 3-hydroxyhericenone F [48] and five new isoindolinones called erinaceolactams A-E [102].

3.1.6 *Hericerins*

Hericerin [103] and isohericerins [77] were isolated from the fruiting bodies of *H. erinaceus* by acetone and methanol, separately. Five other compounds were isolated from the ethyl acetate extraction of *H. erinaceus* as isohericerin, *N*-De phenylethyl isohericerin, 1-d-arabinitol-monolinoleate, hericene A and 4-[3′,7′-dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol [41, 104]. Later, a new isoindolinone derivative named isohericerinol A was isolated from the fruiting bodies of the same species [41].

3.1.7 *Hericenes*

The isolation of hericenes was first reported by Arnone *et al.* in 1994 [91] and Hericene A, B and C were isolated from the fruiting bodies of *H. erinaceus* in their study. Almost 20 years later, hericene A and C were also isolated from the fruiting bodies of another species, *H. coralloides* [105]. More recently, hericene B was also isolated from a newly identified species, *H. novae-zealandiae* [106]. Hericene A and D were also isolated from the fruiting bodies of *H.*

erinaceus in another study in 2010 [107].

3.1.8 *Erinarols*

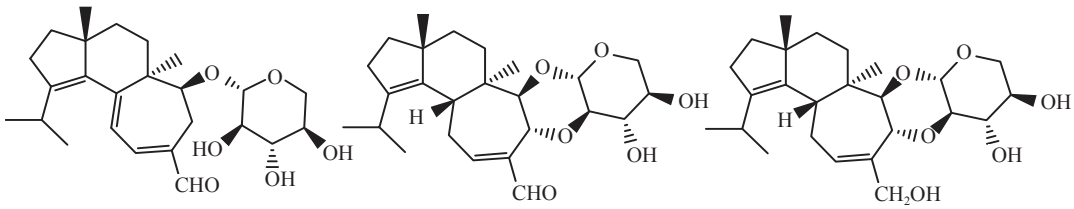
Erinarol H and J, as well as two of the ergostane-type sterols, were isolated from a methanol extract of *H. erinaceus* [108].

3.1.9 *Erinacol*

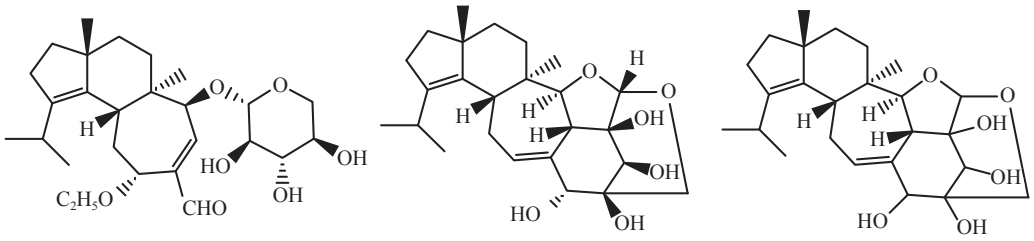
Erinacol was first isolated from the mycelia of *H. erinaceus* by Kenmoku et al. in 2004 [109].

3.1.10 *Hericinoids*

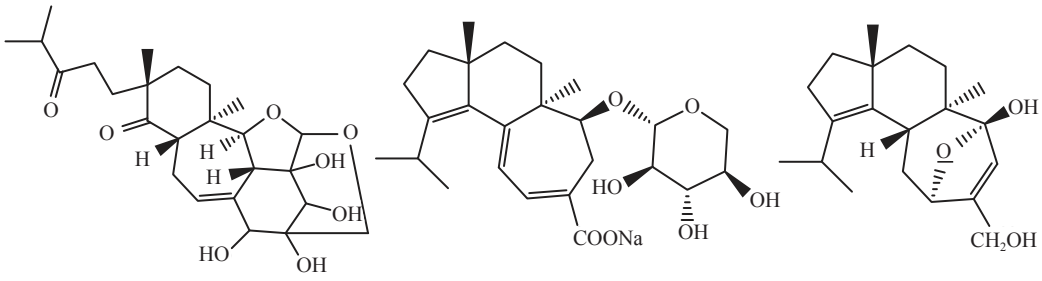
Three cyathane-type diterpenoids, hericinoid A-C have been isolated from fermentation broth of *H. erinaceus* [110].



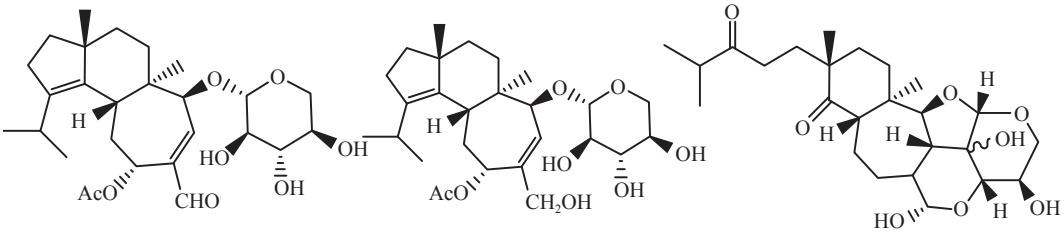
Erinacine A (1) Erinacine B (2) Erinacine C (3)



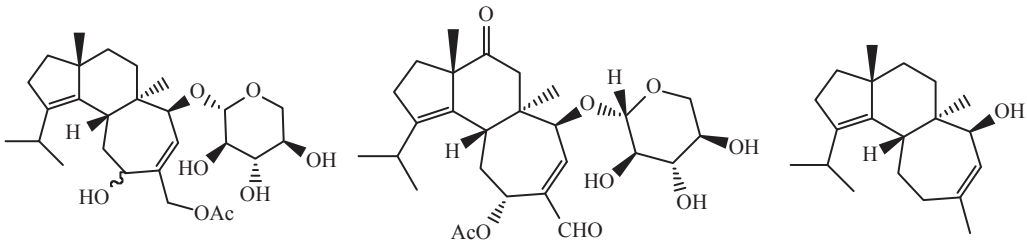
Erinacine D (4) Erinacine E (5) Erinacine F (6)



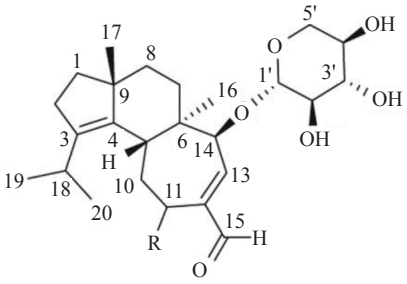
Erinacine G (7) Erinacine H (8) Erinacine I (9)



Erinacine P (10) Erinacine Q (11) Erinacine J (12)

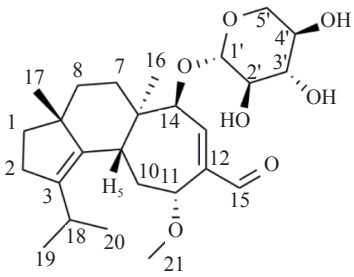


Erinacine K (13) Erinacine R (14) Erinacol (15)

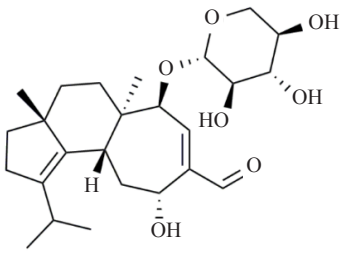


1 R = α OH
2 R = α OCH_3
3 R = β OCH_3

Erinacine T-V (16-18)



Erinacine Z1 (19)



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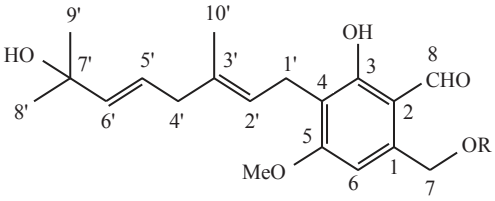

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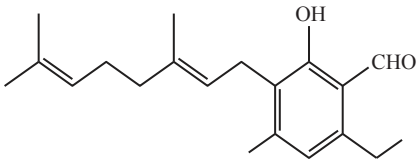
Erinacene B (R = S2) (23)
Erinacene C (R = R3) (24)



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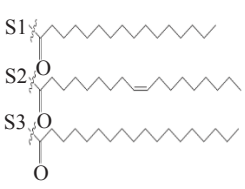

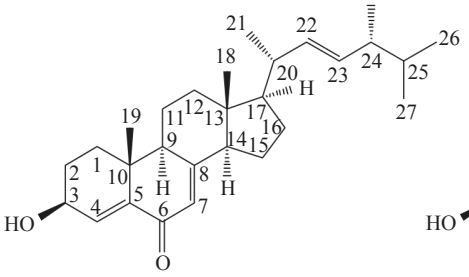

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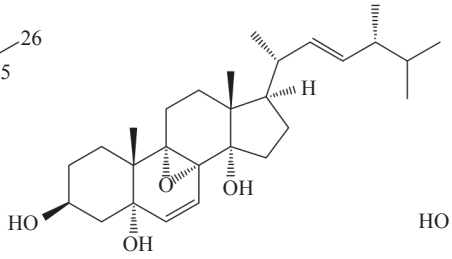

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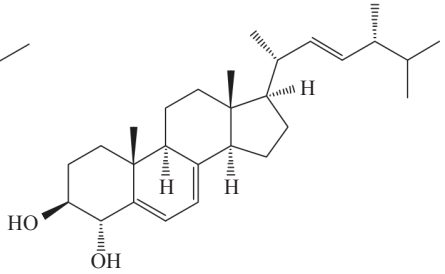

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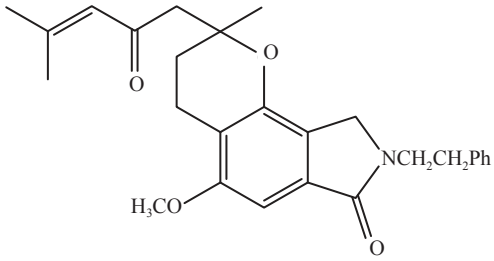

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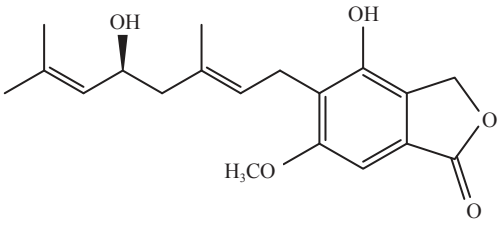
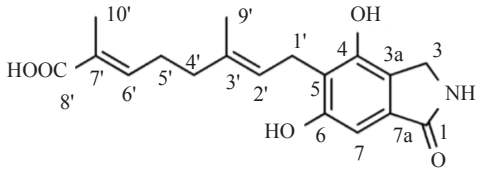
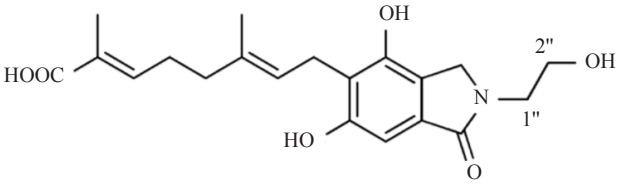


Erinacerin B (29)



Erinacerin C (30)



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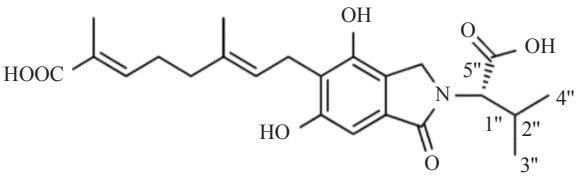
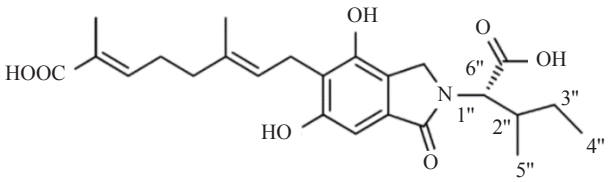


Erinacerin E (32)



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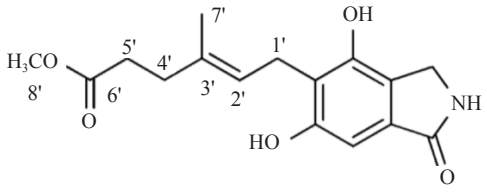

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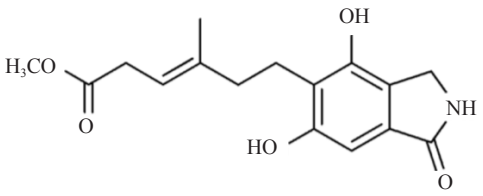

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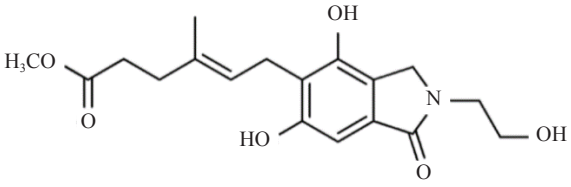

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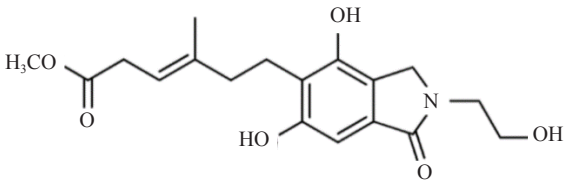

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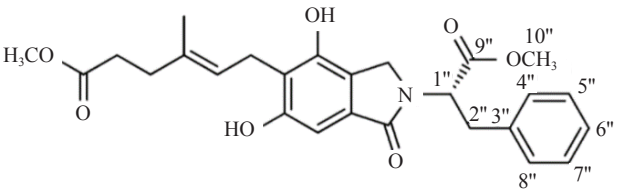
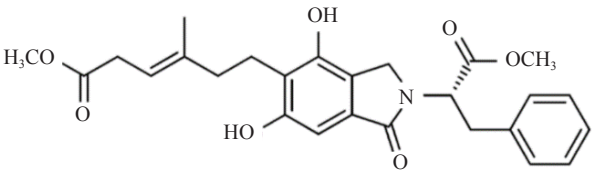
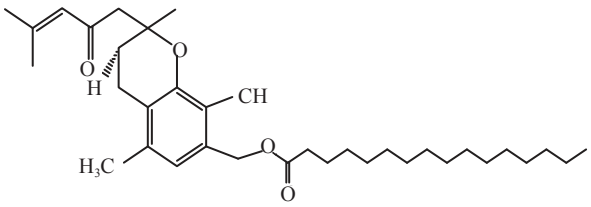


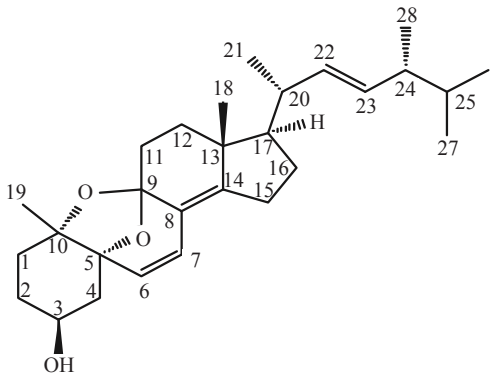
Erinacerin K (38)



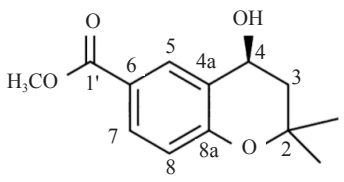
Erinacerin L (39)



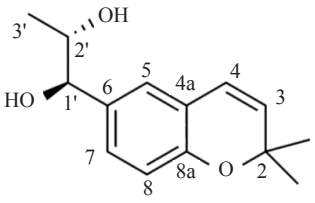
3-Hydroxyhericenone F (40)



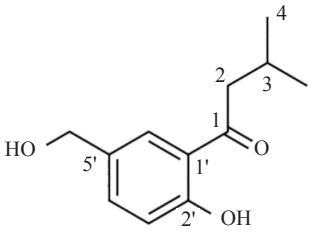
Erinarol J (41)



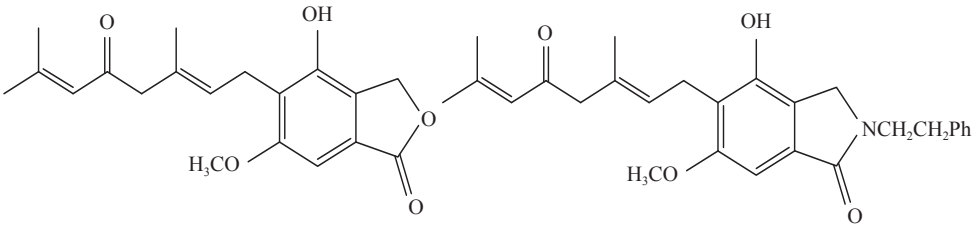
Erinachromane A (42)



Erinachromane B (43)

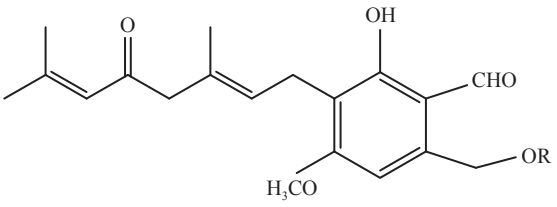


Erinaphenol A (44)



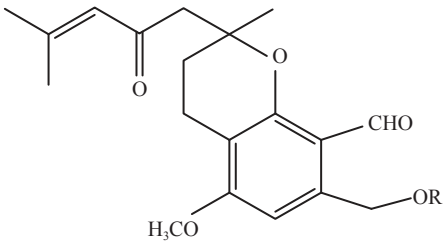
Hericenone A (45)

HHericenone B (46)



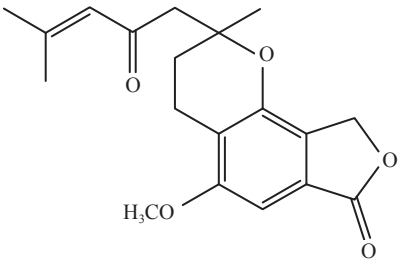
Hericenone C R = palmitoyl (47)

Hericenone E R = stearoyl (49)
Hericenone G R = linoleoyl (51)

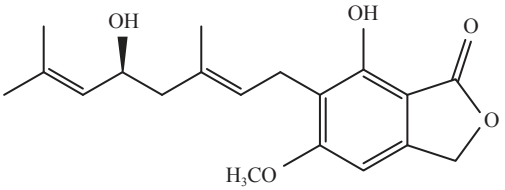


Hericenone D R = palmitoyl (48)

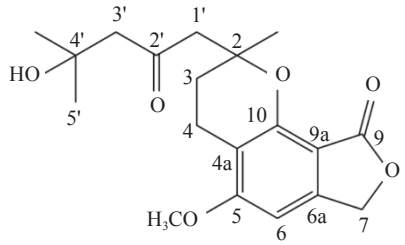
Hericenone F R = stearoyl (50)
Hericenone H R = linoleoyl (52)



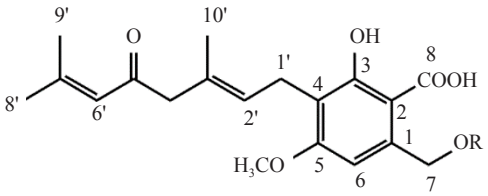
Hericenone I (53)



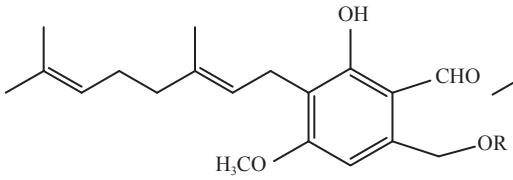
Hericenone J (54)



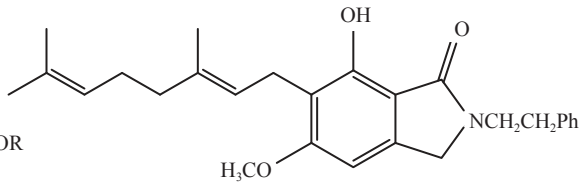
Hericenone K (55)



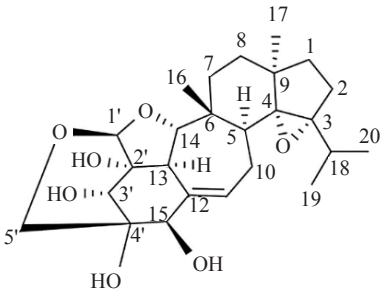
Hericenone L (56)



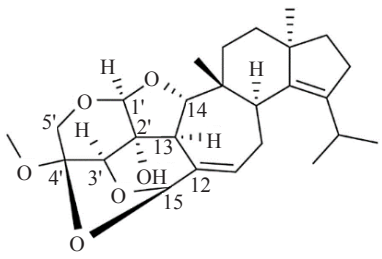
Hericene A R = palmytoyl (57)
Hericene B R = oleoyl (59)
Hericene C R = stearoyl (60)
Hericene D R = linoleoyl (61)



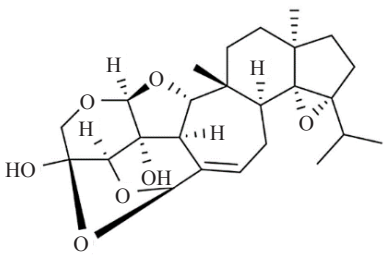
Hericerin (58)



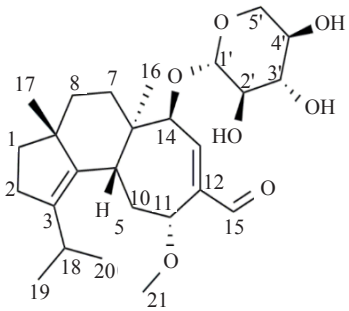
Hericinoid A (62)



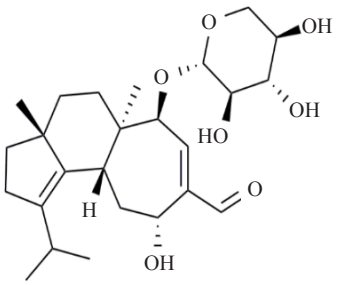
Hericinoid B (63)



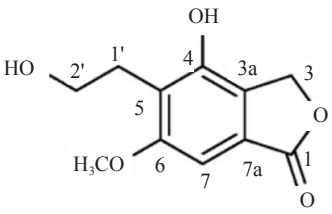
Hericinoid C (64)



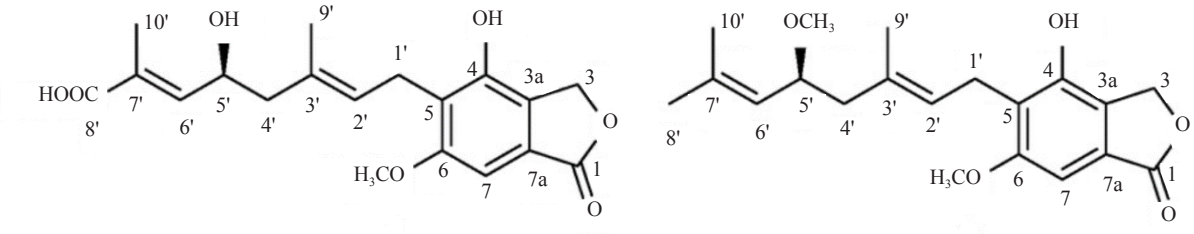
Erinaceolactone G (65)



Erinaceolactone H (66)



Erinaceolactone F (67)



Erinaceolactone D (68)

Erinaceolactone E (69)

Figure 2. Chemical structures of compounds unique to *Hericium*

3.2 *Polysaccharides*

Polysaccharides (also known as glycans) are polymers comprised of large numbers of monosaccharides (glycoses) which are mutually joined by O-glycosidic linkages. Glycosidic linkage is built by the glycosyl moiety of hemiketal (or hemiacetal) and a hydroxyl group of another unit as an acceptor molecule, or by aglycone [111]. Biologically active polysaccharides are present in most higher Basidiomycete mushrooms in the cultured broth, mycelia and fruit bodies [112]. All mushroom polysaccharides contain a common β-linked glucose backbone but the pattern and degree of branching varies among species [113]. More than thirty-five polysaccharides have been isolated from *Hericium* mushrooms. The bioactivities of polysaccharides are often related to their chemical composition, molecular weight and conformation, and glycosidic linkages. As a result, polysaccharides have been evaluated with regard to their monosaccharide components, molecular weight, methylation, and spectra as summarised in Table 2.

Full names of the monosaccharides are as follows: Rha, D-Rhamnose; Fuc, D-Fucose; Man, D-Mannose; Glc, D-Glucose; Gal, D-Galactose; Xyl, D-Xylose; Rib, D-Ribose; Ara, D-Arabinose; -indicates data not available. -indicates data not available. MW = molecular weight.

4. Conclusion and outlook

Edible mushrooms have gained increasing attention from health-conscious consumers due to their reported health benefits, resulting in their use in a wide range of functional foods. *Hericium* species are good examples of medicinal foods, and they have been used in traditional diets to promote wellbeing, taking advantage of the bioactive compounds present therein. In this review, we presented scientific evidence of the biomedical properties of *Hericium* species as observed in cell and in rodent models, and to some extent in humans, and the chemical profiling of *Hericium* species. *Hericium* have been extensively documented on their neuroprotective activities. Many experiments have demonstrated that polysaccharides and compounds unique to *Hericium*, such as erinacines and hericenones, accounted for these activities, which have been described in detail in this review. In addition to neuroprotective properties, the anticarcinogenic properties of *Hericium* have been demonstrated from numerous studies. These properties were attributed to the presence of two categories of compounds found in *Hericium*, namely the compounds unique to *Hericium* and the polysaccharides. These bioactive compounds may be candidates as therapeutic agents, offering potential for future drug discovery. In addition, majority of research on *Hericium* species has focused on *H. erinaceus*. It would be of interest to evaluate the chemical composition of the phylogenetically related species and it is believed that these efforts would contribute to the improvement of human nutrition and health.

Table 2. Characterization of polysaccharides isolated from *H. erinaceus* (and from one other *Hericium* species as indicated)

Fungus part	MW (Da)	Monosaccharide Composition	Glycosidic Linkage	References
Fruiting body	1.83×10^4	Rha:Fuc:Man:Glc:Gal 1.47:0.93:1.36:8.68:4.08	(1→)-α-Glc, (1→3,4)-α-Glc, (1→6)-α-Gal, (1→3,4)-β-Man, (1→3,6)-α-Rha and (1→2)-β-l-Fuc	[115]
Fruiting body	5.16×10^3	Fuc:Glc:Gal 7:2.28:21.59	α-(1→2)-linked Man	[116]
Fruiting body	1.59×10^4	Rha:Fuc:Man:Glc:Gal 0.98:1.59:0.89:5.60:7.06	(1→)-α-Glc, (1→3,6)-α-Glc, (1→2,6)-α-Gal, T-β-Gal, (1→3,4)-β-Man, (1→3)-α-Rha, and (1→2)-β-L-Fuc	[117]
Fruiting body	-	Man:Xyl:Rha:Gal:Rib 4.1:4.1:1:45.8:1	Predominantly Glu linked by a-glycosidic bonds	[118]
Fruiting body	1.5×10^4	Fuc:Gal:Glc 5.2:23.9:1	A (1/6)-linked galactopyranosyl backbone, partially with a side chain composed of α-l-fucopyranose at the O-2 position	[119]
Mycelium	3.1×10^3	Glc:Man:Gal 6.4:67.9:1	Mainly (1→3)-linked Glcp with approximately 10% each of (1→)-manp units and (1→3,4)-Glcp units and 1.5% of (1→3,4)-galp units	[120]
Mycelium	1.44×10^4	Glc:Rha:Gal:Man 1:1.1:2.4:7.1	(1→4)-linked β-Gal residues and β-linked Glc residues	[121]
Fruiting body	2.0×10^4	3-O-Me-Rha:Fuc:Gal:Glc 1:8.3:27.2:2.3	A (1→6)-linked-d-Gal backbone and branches composed of Glc and Rha	[122]
Fruiting body	4.2×10^5	Glc	2,3,4,6-tetra-O-Me-Glu, 2,6-di-O-Me-Glc	[123]
Fruiting body	1.94×10^4	Fuc:Gal:Glc 1:4:1	(1→6)-linked α-d-Gal backbone with branches that are composed of Fuc attached to O-2; it also contains 6-O-substituted-β-d-oligoglucosyl units and a minor terminal 3-O-Me-Rha residue	[124]
Fruiting body	$> 1.0 \times 10^6$	Glc	Main chain composed of β-(1→3)-linked d-glucopyranosyl residues, with single unit glucosyl branches attached to O-6 of every third backbone residue	[125]
Fruiting body	1.9×10^4	Fuc:Gal 1:4.1	A branched pentasaccharide repeating unit and a minor proportion of 3-O-Me-Rha that is thought to terminate the polymer main chain	[126]
Fruiting body	1.8×10^4	Rha:Gal:Glc 1.2:3.8:1	A (1→6)-linked α-d-Gal backbone with branches that are composed of Rha and Glc attached to O-2	[127]
Fruiting body	5.0×10^4	Glc:Gal:Fuc 1:2.1:0.4	A backbone composed of (1→6)-linked-Gal with branches attached to O-2 of some Gal	[128]
Fruiting body	3.0×10^4	Gal:Glc 1:11.5	Mainly of terminal Glc, 1,3-linked Glc, 1,6-linked Glc, 1,6-linked Gal, and 1,3,6-linked Glc	[128]
Mycelium	6.2×10^4 2.6×10^4 1.2×10^4	Glc - Glc	α-linkage	[129]
Fruiting body of *H. caput-medusae*	6.5×10^4	Fuc:Glc:Gal 1:2.4:5	Not available	[130]

Conflict of interest

The authors declare that they have no conflicts of interest.

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