Hericium erinaceus, an amazing medicinal mushroom

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Abstract:	Medicinal mushrooms have become a compelling topic because the bioactive compounds they contain promise a plethora of therapeutic properties. Hericium erinaceus commonly known as "Houtou" or "Shishigashira" in China and "Yamabushitake" in Japan, has commonly been prescribed in Traditional Chinese Medicine (TCM), because its consumption has been shown to be beneficial to human health. The species is found throughout the northern hemisphere in Europe, Asia, and North America. Hericium erinaceus has been firmly established as an important medicinal mushroom and its numerous bioactive compounds have been developed into food supplements and alternative medicines. However, the correspondence of the active components that cause the observed effects is often not clear. The mushroom as well as the fermented mycelia have been reported to produce several classes of bioactive molecules, including polysaccharides, proteins, lectins, phenols, and terpenoids. Most interestingly, two classes of terpenoid compounds, hericenones and erinacines, from fruiting bodies and cultured mycelia, respectively, have been found to stimulate nerve growth factor (NGF) synthesis. In this review we examine the scientific literature to explore and highlight the scientific facts concerning medicinal properties of H. erinaceus. We provide up-to-date information on this mushroom, including its taxonomy and a summary of bioactive compounds that appear related to the therapeutic potential of H. erinaceus.

Hericium erinaceus, an amazing medicinal mushroom

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Abstract

Medicinal mushrooms have become a compelling topic because the bioactive compounds they contain promise a plethora of therapeutic properties. *Hericium erinaceus* commonly known as “Houtou” or “Shishigashira” in China and “Yamabushitake” in Japan, has commonly been prescribed in Traditional Chinese Medicine (TCM), because its consumption has been shown to be beneficial to human health. The species is found throughout the northern hemisphere in Europe, Asia, and North America. *Hericium erinaceus* has been firmly established as an important medicinal mushroom and its numerous bioactive compounds have been developed into food supplements and alternative medicines. However, the correspondence of the active components that cause the observed effects is often not clear. The mushroom as well as the fermented mycelia have been reported to produce several classes of bioactive molecules, including polysaccharides, proteins, lectins, phenols, and terpenoids. Most interestingly, two classes of terpenoid compounds, hericenones and erinacines, from fruiting bodies and cultured mycelia, respectively, have been found to stimulate nerve growth factor (NGF) synthesis.

In this review we examine the scientific literature to explore and highlight the scientific facts concerning medicinal properties of *H. erinaceus*. We provide up-to-date information on this mushroom, including its taxonomy and a summary of bioactive compounds that appear related to the therapeutic potential of *H. erinaceus.*

Keywords: *Hericium erinaceus*, ß-glucans, erinacines, hericenones, medicinal mushroom, nerve growth factor (NGF)

1. Introduction

Mushrooms have been traditionally used both as highly valued food and medicine for millennia, but only recently have scientists begun to understand molecular mechanisms and benefits of their bioactive constituents (De Silva et al. 2012a, b; Thawthong et al. 2014; Wasser 2011; Wisitrassameewong et al. 2012). Several classes of mushroom metabolites have been classified as effective immune boosting molecules, including proteins, polysaccharides, lipopolysaccharides, and glycoproteins (Wang et al. 2001b; Keong et al. 2007). Mushrooms also produce and accumulate several low-molecular secondary metabolites including phenols, polyketides, and terpenes that are effective medications (Wong et al. 2007; De Silva et al. 2013). For example, it has been found that mushroom phenolic compounds are outstanding antioxidants that lack mutagenic properties (Khatua et al. 2013). Important medicinal mushrooms, e.g. *Agaricus subrufescens*, *Ganoderma sichuanense*, *Grifola frondosa*, *Lentinula edodes*, *Phellinus linteus*, *Pleurotus ostreatus* and *Polyporus umbellatus* have been recommended for a variety of therapeutic treatments (Donatini 2011). Recently, many studies have shown that polysaccharides from mushrooms have substantial medicinal properties and no toxic side effects, unlike many existing chemotherapeutic anticancer drugs (Lee et al. 2010a). Edible mushrooms have therefore been used to develop alternative medicines for health care, especially as support in anti-cancer therapies (Ramberg et al. 2010). Scientists have also screened the antimicrobial properties of mushrooms to find a solution for antibiotic drug resistance in human pathogenic microorganisms (Anke et al. 1997; Lindequist et al. 2005; Suay et al. 2000).

In this review we focus on *Hericium erinaceus*, an edible-medicinal mushroom, which has a long history of use in traditional medicine in Asia and has received recent attention for its potential therapeutic and neuroprotective capabilities. The aim of this article is to gather and summarize available information on *H. erinaceus*, including its taxonomy, phylogeny, health promoting benefits, and medicinal properties.

2. Morphological characteristics and taxonomy of *Hericium erinaceus*

Hericium erinaceus (Bull.) Pers. 1797 is a basidiomycete belonging to the family Hericiaceae, order Russulales and class Agaricomycetes (Kirk et al. 2008). An overview on synonyms of *H. erinaceus* is given in **Table 1.** Even in the current literature, the epithet is often still being misspelt as the grammatically incorrect "*erinaceum*", in particular by non-specialists.

Etymology and trivial names: *erinaceus* literally means "hedgehog" in Latin. The name was proposed by Buillard, evidently as the fungus reminded him of this animal. This is also reflected by the German name "Igel-Stachelbart" and some English common names such as "Bearded Hedgehog" and "Hedgehog Mushroom". However, the fungus has been given many other common names, all of which are related to the conspicuous macromorphology of the basidiomes. In Japan, *H. erinaceus* is known as "Yamabushitake"; Yamabushi literally means "those who sleep in the mountains." In China, the mushroom goes by the name "猴頭菇", which means "lion's head," and "Houtou", which means "monkey head". This mushroom is also known as "Lion's Mane", "Monkey's Mushroom", "Bear's Head", "Hog's Head Fungus", "White Beard", "Old Man's Beard", "Pom Pom" and "Bearded Tooth" in other parts of the world.

In the mature state, *H. erinaceus* is easy to identify as its conspicuous basidiomes consist of numerous single, typically long, dangling, fleshy spines, that are at first white, becoming yellowish, then brownish with age. Species in the genus *Hericium* are distinguished macroscopically by the presence of branched vs. unbranched hymenophore structures supporting spines of various lengths, occurrence in single vs. multiple clumps, and microscopically by the presence of amyloid ornamented basidiospores (Ginns 1985; Harrison 1973). However, basidiomes of *Hericium* often begin to differentiate from primordia more or less as a single clump, and only develop their branches with age (Bernicchia and Gorjón 2010; Mas-Geesteranus 1971; Koski-Kotiranta 1987). Confusion stems from the fact that the long-spined species of *Hericium* may have short spines (1 cm in length or less) when they are at their youngest stage. The lobed tubercle of the basidiome is pendent from a tough rooting attachment arising within a woody substrate. The context is fleshy, tough, and watery; having a hint of seafood flavor reminiscent of crab or lobster. The spines are 1-4 cm long, pendent, arranged in a

beard-like manner in the basidiome. The macromorphology of *H. erinaceus* is usually sufficient for identification. It is however, by no means easy to differentiate certain growth forms of this species from *H. coralloides*, since the basidiospore sizes are highly similar in both species. As a rule, basidiomes of *H. coralloides* tend to be much more branched, but greatly contracted forms are known to exist in which the basidiome, instead of forming long and graceful branches, consists of a massive body, very much like that of *H. erinaceus*. However, host substrates can be used to aid identification, as *H. coralloides* is associated with conifers, whereas *H. erinaceus* occurs on deciduous trees. Basidiospores of both species are short ellipsoid to subglobose, 5.5-6.8 × 4.5-5.6 µm, white in mass, warty, amyloid; basidia are 4-spored 25-40 × 5-7 µm; gloeocystidia arising in subhymenium, up to 7 µm wide, with dense contents exuding as oily appearing droplets in KOH. Hyphae of the trama are 3-20 µm in diameter, inflated or not, thick-walled, at times the lumen almost closed, interwoven, giving rise to gloeocystidia in the spines (Harrison 1973, Koski-Kotiranta et al. 1987, Stamets 2005).

Notably, *H. erinaceus* has a long history of use in Traditional Chinese Medicine in Asia, but was first described in North America. As shown in Table 1, numerous synonyms have been used in the literature to describe this species, and several varieties and formae have been described, all of which are actually referring to the same fungal species (see Table 1). Most detailed descriptions and illustrations are from European countries and *H. erinaceus* is also commonly reported from the southern states of America. According to GBIF (http://www.gbif.org/species/5248508) the species was also recorded from Australia, but curiously there are no records from Asia, where it is being cultivated in large quantities. *Hericium* species are apparently not present in Africa, where only the related genus *Dentipellis* Donk, which forms hydnoid, resupinate crust-like basidiomes on dead wood, seems to be extant (cf. Hallenberg et al. 2012, Zhou & Dai 2013).

Hericium erinaceus is considered as a saprotroph or weak parasite. The mushroom most often occurs on dead wood, but sometimes its fruiting bodies may emanate from knotholes or cracks of living hardwoods. This might be indicative of an endophytic lifestyle. In the UK, it is usually found on the central deadwood of trunks during September to December (Boddy et al. 2003, 2004, 2011). The fungus is certainly not commonly encountered in Nature. In 2003, *H. erinaceus* was red-listed in

13 of the 23 European countries because its natural habitats are beginning to disappear (Govaerts et al. 2011).

The fungus can also easily be discriminated from its closest relatives by molecular methods. A set of PCR primers specific to the ITS (internal transcribed spacer) nrDNA locus of *Hericium* species has been developed successfully, which can be used to quickly identify *H. erinaceus* (Lu et al. 2002, Parfitt et al. 2005). The taxonomy of the genus has not changed much in the past decades and seems to be rather settled, aside from the fact that *H. coralloides* has also been described under several synonyms. Also, the taxonomic position of *H. cirrhatum* still seems unsettled. This species is considered by some mycologists to represent a separate genus and is still often being referred to as *Creolophus cirrhatus*. Recently, three new species were described as a new to science with phylogenetic inference, viz. *H. bharengense* and *H. yumthangense* from Himalaya, India (Das et al. 2011, 2013) and *H. rajchenbergii* from Argentina (Hallenberg et al. 2012)**. Table 2** gives an overview of species in the genus *Hericium* that were published from the 19 – 20th century. Basidiomes of *H. erinaceus* in the natural habitat are shown in **Figs. 1a and 1b**.

3. Chemical composition of fruiting bodies vs. cultured mycelia

Numerous types of biologically active compounds from mushrooms have been demonstrated to have pharmaceutical activities and therapeutic properties. In particular, their bioactive polysaccharides have been extensively studied for potential and existing applications in pharmaceuticals and functional foods (Giavasis 2014; Mizuno and Nishitani 2013). However, bioactive secondary metabolites of medicinal mushrooms that can be obtained from submerged cultures may not be produced in fruiting bodies. Monitoring of nutrient consumption, respiration and metabolite production in the culture media under controlled process conditions is critical for optimizing the process. Several studies have tried to ascertain the best conditions for growing and fruiting mushrooms so that the fungi produce higher biomass and more of the valuable bioactive metabolites. Cui et al. (2010), Hu et al. (2008), Kulisic et al. (2004), Lee et al. (2010b), Malinowska et al. (2009) and Zhang et al. (2012b) explored the efficiency of *H. erinaceus* to grow on different

substrates including artificial media, but also cheap substrates such as agro wastes, and tofu whey. The fungus can be grown at large scale on inexpensive substrates, which is favorable for mass production. Li et al. (2015) have recently established that the state of development of the cultivated mushroom has a strong influence on the composition of the polysaccharides and hence the biological activity.

Even more striking are the different compositions of fruiting bodies and cultures with regard to their content of bioactive low-molecular metabolites. For instance, hericenones and erinacines, whose bioactivities will be treated in detail further below, are predominant in either the fruiting bodies or the mycelia of *H. erinaceus* (Ma et al. 2010). Submerged cultivation is the most promising alternative for high yields of mycelial biomass and erinacines, but not hericenones, which can so far only be obtained from the mushrooms! Many researchers have turned their attention to minimizing the fermentation time in submerged culture, while maximizing production. Recently, large-scale fermentation and use of analytical techniques such as mass spectrometry coupled with high performance liquid chromatography (HPLC-MS) and 2D-nuclear magnetic resonance (NMR) for the detection and identification of bioactive secondary metabolites have been developed (Bills and Stadler 2014). However, recently Shen et al. (2014) have developed an alternative immunological method for specific detection of the cyathane terpenoids in *H. erinaceus.*

In general, the bioactive metabolites from *H. erinaceus* and other mushrooms can be classified into a) high molecular weight compounds, such as polysaccharides, and b) low molecular weight compounds such as polyketides and terpenoids (Kawagishi et al. 1994; Ma et al. 2010; Mizuno et al. 1992). We will furst treat these two types of compounds in general, but many of their significant bioactivities will also be discussed in detail in the chapters further below.

a) **Polysaccharides** are found mainly in the cell walls of fungi, and they are present in large quantities (about 20% of the biomass, fide Dong et al. 2006 and Lee et al. 2009b) in the fruiting bodies, as well as the cultured mycelium. Five different polysaccharides that showed antitumor activity were isolated from basidiomes of *H. erinaceus.* These are xylans, glucoxylans, heteroxyloglucans, and galactoxyloglucans (Mizuno et al. 1992). Crude water-soluble polysaccharides were extracted and fractionated from the fruiting bodies by Lee et al. (2009b). yielding a β-1,3-

branched β-1,6-glucan with a laminarin-like triple helix conformation and a molecular mass of about 13 kDa. This compound activated macrophages in the immune system. Jia et al. (2004) isolated a heteropolysaccharide with molecular weight of 1.8×10^4 Da, which is composed of monosaccharides including, rhamnose, galactose, and glucose. Zhang et al. (2006, 2007) found a hetero-polysaccharide with a molecular weight 1.9×10^4 Da, which was mainly composed of fructose, galactose, and glucose, while 3-O-methyl rhamnose was determined to be a minor component. Other types of purified polysaccharides from alkaline extracts of the fruiting bodies include ß-(1-3)-linked D-glucopyranosyl residues with single galactose branches (Dong at el. 2006). Lee et al. (2009a) identified a β-1, 3-branched- β-1,2-mannan with a laminarin-like triple helix conformation from submerged mycelial cultures that is able to up regulate the functional events mediated by activated macrophages. As will be shown further below, several of these compounds possess significant biological and pharmacological activities, both *in vitro* and *in vivo*.

b) Numerous **low molecular secondary metabolites** have recently been isolated from mycelial cultures and fruiting bodies of *H. erinaceus*. In general, these metabolites have a poor water solubility and their extraction requires the use of organic solvents such as methanol or ethyl acetate. Aside from the above mentioned erinacines and hericenones, this concerns, e.g. the fruiting body metabolites, erinacerins A and B **(1-2**), of which no sigificant biological activities are known (Yaoita et al. 2005) (**Fig. 2)**. Several chlorinated aromatic compounds are also known from submerged cultures of the mushroom (Ueda et al. 2009). These metabolites are well-known to exhibit non-specific activities in biologial systems, and care should be taken that they are not present in significant amounts in the dietary supplements made from the mycelia of *H. erinaceus*. However, there seems to be no quality control, monitoring their occurrence. Some reactive pyranones (**3-6**) with cytotoxicity against HeLa S3 cells were also isolated from submerged cultures (Kawagishi et al. 1992; Mizuno 1999) (**Fig. 2)**. A summary of studies on low molecular weight secondary metabolites and organic extracts of *H. erinaceus* and their miscellaneous bioactivities is given in Table 3, and the chemical structures are depicted in **Figs. 2-11**. Many of these compounds are being treated below in the chapters about various bioactivities of *Hericium*.

Hericium erinaceus was selected as biotransformation model species, as it is well-known for efficient terpenoids productions of the unique cyathane type. So-called cyathadiene cyclases which do not follow the isoprene rule via intermediates of cyathane diterpenoids were also isolated from the mycelia of *H. erinaceus*, resulting in the *c*haracterization of cyatha-3, 12-diene **(8**) and its isomer **(9) (**Kenmoku et al. 2001) (**Fig. 4)**. Erinacine E has an unique structural feature as compared with other cyathane diterpenoids and was converted to CP-41258 **(7)** (Saito et al. 1998) (**Fig. 2)** by using *Caldariomyces fumago*. Detailed studies on the biosynthesis of erinacine-like metabolites were already conducted by Anke et al. (2002) based on herical, a derivative of this type that was so far only found in "*H. ramosum*" (current name *H. coralloides*) but not in *H. erinaceus*.

Some recent studies investigated *Hericium* growing on traditional medicinal plants. They claim that the fungus "biotransforms" active plant material, thereby attaining enhanced biological activity in the resulting extract. Other researchers are presently trying to combine preparations from mushrooms with Chinese herbs. Scoparone, for example, is a coumarin derivative found in the Chinese herb *Artemisia capillaries*. It activates the constitutive androstane receptor in the liver, and protects kidney functions in murine *in vivo* models (Huh et al. 2003). An ethanol extract from *H. erinaceus* cultivated on *Artemisia capillaries* inhibited gastric mucosal damage in rats in a dose-dependent-manner with an effective dose 50 (ED50) value of 22.6 mg/kg (Choi et al. 2012). In addition, the same extract significantly attenuated hepatic lipid deposits and reduced oxidative stress in the liver of male Sprague-Dawley rats (Choi et al. 2011). A methanolic extract from *H. erinaceus* cultured on *Artemisia iwayomogi*, another scoparone-containing plant was also studied for various bioactivities, including proliferation of vascular smooth muscle cells, interferon-inducing activity, and CCl_4-induced acute hepatotoxicity in rats (Lee et al. 2003; Choi et al. 2005). It remains unclear whether the observed effects are due to scoparone, its biotransformation products, or the genuine fungal metabolites. The same holds true for a study where a solid culture of *H. erinaceus* cultivated with *Morus alba* (white mulberry) was found to have anti-inflammatory activity, but no detailed analytical characterization was carried out (Kim et al. 2011a).

In fact, the term "biotransformation" is normally used for the conversion of a certain, defined molecule to another. In classical biotransformation protocols, which have been extremely important in

biotechnology, the starting materials, as well as the end products, are very well defined by their chemical structures. This however, cannot be the case if *H. erinaceus*, a fungus capable of digesting lignin and cellulose, is incubated with plant material whose actual composition has not been determined. Since lignin peroxidases, manganese peroxidases and laccases and even the cellulolytic enzymes of basidiomycetes are well-known to destroy even complex and recalcitrant polymers, the fungal enzymes may modify or destroy the bioactive ingredients of the medicinal plants. Such processes should therefore be monitored very carefully by means of modern analytical chemistry, including HPLC-MS, in order to determine the composition of the "biotransformation" products. Perhaps the least alarming scenario for patients who consume such medicines would be that the fungus (i.e., *Hericium*) has destroyed all the plant biomass including 100% of the active ingredients, in order to produce its own mycelia and basidiomata. This, however, could easily be determined by comparing extracts from the fungus that has been grown under regular conditions with that derived from the same strain that was cultivated on the medicinal plant material. Unfortunately, the available studies do not follow these rules. In addition, the experiments have normally been carried out at a small scale, and straightforward reproducible scale-up of the procedures to allow for provision of sufficient material in order to obtain a drug that can be reliably distributed to patients is difficult to envisage. We have therefore included these papers in our review, in particular to point out potential drawbacks and can only encourage that further research on these matters should rely on an extensive analytical characterization of the samples.

Besides secondary metabolites, some enzymes have also been isolated from the fruiting bodies, such as an amylase with a molecular mass of 55 kDa and a laccase with molecular mass of 63 kDa (Du et al 2013; Wang et al. 2014). Recently, a novel fibrinolytic metalloprotease named herinase with a molecular mass of 51 kDa was identified from the fruiting bodies (Choi et al. 2013). Some of these studies actually associate such enzymes with health claims. The therapeutic potential of enzymes, however, remains obscure because it is difficult to conceive how they might act in the human body, especially with regard to their allergenic potential, and whether they are not destroyed by digestion. Enzymes from *Hericium* might nevertheless find interesting applications in the food industry, where substances derived from edible fungi will often be regarded safe and more easily

approved for industrial applications than enzymes from widely unknown organisms, or such ones with known toxic properties.

4. Traditional use and pharmaceutical properties

Until recently scientists have paid most attention to the therapeutic potential of medicinal mushrooms to be used as antimicrobial and antioxidant agents and as an alternative natural resource in chemo-prevention and diabetes prevention (De Silva et al. 2012a, b, 2013; Hiwatashi et al. 2010; Wasser 2002; Yang et al. 2003). *Hericium erinaceus* has been a traditional mushroom in Eastern Asia since ancient times for treating neurasthenia and general debility (Ying et al. 1987). The most important "modern" applications of this traditional medicinal mushroom are summarized further below.

a) Anti-tumor and immune-modulating activities

Various cancers can also possibly be treated by administering preparations based on *H. erinaceus*, for instance esophageal cancer, intestinal cancer, pancreatic cancers and stomach cancers. Cancer-patients who have been treated with *H. erinaceus* have reported significantly fewer side effects than those associated with radiotherapy and chemotherapy.

The crude water-soluble polysaccharides of *H. erinaceus* have been found effective against tumor cell lines *in vitro*, e.g. against malignant hepatocytes (HepG2), mammary carcinoma (MCF-7), lymphoma (EL4) and esophageal cancer (EC109), see **Table 4.** The results indicated an anti-tumor effect of polysaccharides of *H. erinaceus* via activation of different immune cells, such as expression of cytokines (IL-1ß and TNF-ß) and by activation production of nitric oxide. These experiments also revealed strong anti-tumor activity mediated by activation of the c-Jun-N-terminal kinases (JNKs) that are involved in apoptosis (programmed cell death), as well as increasing intracellular doxorubicin-mediated apoptotic signaling via suppression of nuclear factor kappa B (NF-κB) activity (Lee and Hong 2010a). Polysaccharides derived from submerged mycelial cultures of *H. erinaceus* have also been recognized as potential anti-cancer agents. Moreover, several studies showed aqueous and organic extracts to have immunomodulatory effects, and the mode of action of both mentioned activities seems to be based on the same biochemical targets. Han et al. (2009) and Lee and Hong

(2010) found that polysaccharides from aqueous extracts had anti-hepatocarcinoma activity and activated NK cells indirectly through induction of IL-12 in splenocytes (Yim et al. 2007; Xu et al. 1994). ß-glucans extracted from submerged mycelial culture of *H. erinaceus* showed significant anticancer properties in animal systems. Liu et al. (2000) reported significant effects on artificial pulmonary metastatic tumor in mice with imprinting control regions (ICRs), as well as on mice burdened with sarcoma 180 (S-180). The results showed immuno-enhancing activities by increasing the number of CD4+ cells, T lymphocytes (T cells) and macrophages, which are cytotoxic to tumor cells. The *H. erinaceus* glucanes had significantly higher response immunity in the test group than in the control group. The anticancer activity of an orally administered freeze dried hot water extract and a microwave extract, respectively, of *H. erinaceus* in Balb/c mice with CT-26 colon cancer cells intra-cutaneously transplanted on their backs was demonstrated by Kim et al. (2011c), (2013). The tumor weight was significantly decreased when injected daily for 2 weeks by 38 and 41%, respectively. The results highlight immune response through increased phagocytosis of cytokines such as Tumor Necrosis Factor-α (TNF-α), interleukin-1β, and interleukin-6 that enhanced the activity of natural killer cells (NK). A significant suppression of neo-angiogenesis inside the tumor was observed, mediated by a decrease of pro-angiogenic factors, vascular endothelial growth factor (VEGF), cyclooxygenase 2 (COX-2), and 5-lipoxygenase (5-LOX). In addition, restoration of nitric oxide (NO) production was observed in peritoneal macrophages up to 95-98% of normal levels. Polysaccharides isolated from different species of *Hericium,* i.e., *H. laciniatum* and *H. erinaceus* were investigated to compare their effects on humeral immunity. Polysaccharide components were mainly glucose in *H. erinaceus* with enhanced increase of T cells and macrophages in mice as compared to mainly galactose in *H. laciniatum* (Wang et al. 2001b).

Additionally these are some studies related to anticancer and immunosuppressive activities of small molecules and organic extracts that should be mentioned in this context. Kim et al. (2011b) demonstrated that ethanolic and aqueous extracts from fruiting bodies of *H. erinaceus* are able to inhibit the development of tumor cell growth by introducing apoptosis and to suppress the proliferation pathway in U937 human monocytic leukemia cells via caspase 3 and caspase 9 through cytochrome P450 release from mitochondria. However, the active principles were not identified and

therefore cumulative effects cannot be excluded. Recently, Erinacene D (**20**) showed significant anti-tumor activity on tumor necrosis factor alpha (TNF-α) and induced NF- kB inhibitory activity, which plays an important role in transcriptional regulation of adhesion molecules and numerous cytokines. Erinacene D was found to have NF- κB inhibitory activity with an IC_{50} value of 9.7 μM in human keratinocytes (Li et al. 2014a) (**Fig. 5)**. It remains to be seen whether these results can be reproduced *in vivo*, and the observed activity seems rather low as compared to marketed drugs and developmental candidates for cancer indications, which normally act in the low nanomolar range in similar in vitro tests.

Several studies have been carried out on toxicity of *H. erinaceus* and products derived from it, in order to evaluate potential side effects, or to determine the effective dosages to be employed for preclinical *in vivo* experiments. Aqueous extracts of *H. erinaceus* were devoid of significant cytotoxicity to the neuroblastoma-glioma cell line, NG108-15, and the human lung fibroblast MRC-5 (Lai et al. 2013). Toxicological studies also provided satisfactory preclinical safety evidence to launch clinical trials in rats via doses of up to 5000 mg/kg/day body weight of "MUNOPHIL" a preparation comprising a mixture of aqueous extracts of *H. erinaceus* and *Panax ginseng* (Park et al. 2008). In addition, a toxicological safety study of erinacine A, the major active ingredient from cultures of the fungus, has been performed in a 28-day oral administration study in Sprague-Dawley rats. All animals survived, and neither developmental abnormalities nor adverse urine analysis were observed (Choi et al. 2011; Li et al. 2014b). Chemotherapy is the main treatment for patients with cancer, but the toxicity is extensive. Fluorouracil (5-FU) is a chemotherapeutic drug used to treat several types of cancer. *Hericium erinaceus* extracts have shown potential in treating gastrointestinal cancer, during both *in vivo* and *in vitro* experiments that was superior to that of 5-FU (Li et al. 2014a). The standard drug was less efficient and more toxic than the fungal samples.

In summary, these results appear promising, but notably, there is no anticancer drug based on *Hericium* on the market yet because clinical efficacy studies have not been conducted.

b) Metabolic syndromes: antihyperglucemic and antihypercholesterolemic activities

Mushrooms provide a healthy food source as they are rich in proteins, vitamins, fibers and minerals and low in carbohydrates, but contain low amounts of fat and cholesterol (Lau et al. 2012; Phillips et al. 2011; Thawthong et al. 2014; Ulziijargal and Mau 2011). Some species are therefore used as functional foods with anti-diabetic effects or for dietetic prevention of cardiovascular diseases, which are one of the major causes of death in both western and Asia-Pacific countries (Ali et al. 2012). Diabetes mellitus is a group of metabolic diseases with abnormal production of insulin and/or insulin dysfunction, recognized by high blood glucose (hyperglycemia) (De Silva et al. 2012b, 2013). Several studies have determined antihypoglycemic activities in fruiting bodies and mycelium from numerous medicinal mushrooms (Hikino et al. 1989, Sato et al. 2002, Teng et al. 2012, Badole et al. 2006). The potential anti-hyperglycemia effect of extracts from fruiting bodies and mycelia of *H. erinaceus* has also been reported in diabetic animals. Vertesy et al. (1999) tested the phthalaldehyde derivatives, hericenals A (21), B (22) and C **(23)** from submerged cultures for therapeutic treatment of Diabetes mellitus in particular disorders of glucose metabolism or other metabolic disorders of the human body. Furthermore, exo-polymers isolated from submerged cultures have shown beneficial effects in hypoglycemic rats by oral administration (Yang et al. 2003) **(Fig. 6)**. D-threitol, D-arabinitol and palmitic acid and α-D-glucan are major components from fruiting bodies of *H. erinaceus* that also have demonstrated antihyperglycemic effects in diabetic rats (Wang et al. 2005; Hiwatashi et al. 2010). These components also showed significant anti-hypercholesterolemic effects and reduced the plasma total cholesterol, LDL cholesterol, triglycerides, phospholipid, atherogenic index and hepatic HMG-CoA reductase activity. Rats given an oral administration of extract of *H. erinaceus* had increased plasma HDL cholesterol levels as compared to the control group fed with saline (Yang et al. 2002; Yang et al. 2003; Wang et al. 2005).

Several studies have demonstrated significant anti-hyperglycemic and anti-hyperlipidemic effects in streptozotocin-induced diabetic rats fed with methanol and acqueous extracts of *H. erinaceus* (Wang et al. 2005, Liang et al. 2013). Significantly lower elevation rates of blood glucose level and increased serum insulin level occurred in rats fed with HEM, as compared with untreated control groups. In another study, the mycelial ethanol extract of the mushrooms, significantly reduced serum content of low density lipoprotein-cholesterol (LDL-C) by 45.5% and effectively increased high density

lipoprotein-cholesterol (HDL-C) by 31.1% in serum of diabetic mice (Yang et al. 2003). In a similar study, ethanol extracts of *H. erinaceus* showed hypoglycemic action, which might affect activation of peroxisome proliferator-activated receptor alpha (PPARα) at EC_{50} = 40 µg/ml and could regulate lipid metabolic gene expression of C57BL/6 in mice with Diabetes mellitus (Hiwatashi et al. 2010). Even though clinical studies on humans are not yet available, the above studies indicate the great potential of *H. erinaceus* to treat metabolic disorders and prevent cardiovascular diseases.

The methanolic mycelial extracts of the fungus also showed protective effect on CCl_4-induced hepatic damage (Choi et al. 2005). It remains unclear whether the hydrophilic macromolecules or the more lipophilic secondary metabolites are responsible for this effect.

c) Neuroprotective activity

The Nerve growth factor (NGF) is a highly conserved protein critical for survival that is involved in preventing neuronal death and promoting neuritis outgrowth, supporting synapse formation, and enhancing memory function, and is also essential in maintaining and organizing neuron function (Obara and Nakahata 2002). Rita Levi-Montalcini and Stanley Cohen were awarded the 1986 Nobel Prize in Physiology/Medicine for discovering the NGF. The authors discovered an important biological effect of nerve growth factor on neuronal cells and on several non-neuronal cells and explained the possible mechanism of Nerve growth factor on cells of the immune system (Levi-Montalcini 1996; Aloe 2004).

It is assumed that functional deficiency of Nerve growth factor is related to Alzheimer's disease (AD) and is expected to be applied to the treatment of Alzheimer's disease patients (Allen et al. 2006). AD is a progressive neurodegeneration of the brain that is commonly diagnosed in the aging population over 65 years old and women have higher risk of this kind of disease (Shen 2004; Prine et al. 2014). AD is identified in patients by synaptic injury deficiency of neurotransmitters, un-functioning and/or death of neural cells, and possibly by interference with the process of adult neurogenesis in the hippocampus (Crews and Masliah 2010). AD patients have abnormal accumulation of amyloid-ß peptide containing neurofibrillary tangles composed of hyperphosphorylated tau proteins. (Murphy and Levine 2010). Symptoms of Alzheimer's disease

include confusion, memory forming loss and behavior changes. Neurotrophic factors are essential for maintenance and organization of neurons functionally. Hence, neurotrophic factor-like substances or their inducers are expected to be applied to cure neurodegenerative diseases such as AD. In addition, it is estimated that over 5 million Americans live with AD and this number will increase by an average of 50% by the year 2025 (Anonymous 2008; Gaugler 2014; World Alzheimer Report 2014). However, the efficacy of current drugs for the treatment of Alzheimer's disease patients is still unclear.

The endoplasmic reticulum is one of the important organelles triggering a specific program of cell death via induced apoptotic pathways with a signaling between ER and mitochondria and therefore also constitutes a valid target for neuroprotective drugs (Ueda et al. 2008). Endoplasmic reticulum stress causes brain cells to die which leads to development of neurodegenerative diseases. Dilinoleoyl-phosphatidylethanolamine (DLPE) isolated from *H. erinaceus* appears to reduce endoplasmic reticulum stress and amyloid-β peptide (A-β) toxicity by decreasing neuronal cell death of Neuro2a cells via the protein kinase C pathway (Nagai et al. 2006). Another strongly bioactive compound named 3-hydroxyhericenone (**29a**), showed protective activity against neuronal cell death of Neuro-2a caused by endoplasmic reticulum stress (Ueda et al. 2008). Furthermore, the Functional Independence Measure (FIM) score regarding disease progression of preliminary clinical trials showed improvement in patients with dementia (Kawagishi et al. 2008).

Myelin sheaths wrap neuronal axons and play important functions in the support and speed up the neural signal. Hence, injury of the myelin structure leads to an impairment and severe illness of the nerve system. *Hericium erinaceus* shows an action on the nerve tissue *in vitro* assay. Extracts from *H. erinaceus* showed abilities to promote normal development of cultivated cerebellar cells and demonstrated a regulatory effect on the process of myelin genesis (Kolotushkina et al. 2003). Many studies worldwide have reported that *H. erinaceus* may be appropriate for the prevention or treatment of dementia diseases. Organic extracts from fruiting bodies of *H. erinaceus* demonstrated neurotrophic effects enhancing the myelination process in the mature myelinating fibers *in vitro* assays (Moldavan et al. 2007). Mori et al. (2008) reported that ethanol extracts of *H. erinaceus* can stimulate nerve growth factor synthesis via activation of the c-Jun N-terminal kinases (JNKs)

pathway, in a concentration-dependent manner, by enhancing the nitrite outgrowth of PC12 cells in 1321N1 human astrocytoma. Mori et al. (2009) found significant prevention of cognitive impairment with *H. erinaceus* powder from air-dried fruit bodies. A double-blind, parallel-group, placebo-controlled clinical study was performed with oral administration of *H. erinaceus* on 50-80 year old individuals with mild cognitive impairment. The group treated with *H. erinaceus* showed significantly increased scores on the cognitive function scale compared with the placebo group. Dietary administration of 96% *H. erinaceus* powder 250 mg tablets also resulted in prevention of dementia and decreased cognitive impairment of spatial short term and memory deficits in ICR mice induced by amyloid-β peptide (Mori et al. 2009). Oral administrations of the aqueous extract from fruiting bodies of *H. erinaceus* promoted regeneration of injured adult female Sprague–Dawley rat nerve-injury during the early stage of recovery (Wong et al. 2009a; Wong et al. 2011).

Nerve growth factor is easily metabolized by peptidases and is also unable to cross the blood–brain barrier. Therefore, the low molecular weight compounds of *H. erinaceus* such as hericenones and erinacines were investigated for significant bioactivities that increase mRNA expression of Nerve growth factor biosynthesis. Hericenones and erinacines are low-molecular weight compounds that can easily cross the blood–brain barrier (Moldavan et al. 2007; Kawagishi et al. 2008; Shin et al. 2011). However, the detailed mechanism by which erinacines and hericenones induces Nerve growth factor biosynthesis remains unknown. Hericenones and erinacines had neurotrophic, but not neuroprotective activities when applied in combination of 10 ng/mL NGF with 1 μg/mL *H. erinaceus* extracts. *Hericium erinaceus* contained neuroactive compounds that showed the highest percentage increase of 60.6% on neurite outgrowth stimulation and induced Nerve growth factor synthesis in neuroblastoma-glioma cell line NG108-15 (Kenmoku et al. 2001; Lai et al. 2013).

Hericenones A **(24)** and B **(25)** were originally isolated from the fruiting bodies of *H. erinaceus* and showed significant cytotoxicity against HeLa cells (Kawagishi et al. 1990a). Hericenones C **(27),** D (**28),** E **(29)** and H **(31)** exhibited stimulating activity in the synthesis of Nerve growth factor *in vitro.* The hericenones F **(30)** and G did not stimulate Nerve growth factor synthesis under the same conditions (Kawagishi et al. 1991, 1993; Mizuno 1999). Furthermore, hericenones I **(32),** J **(33)** and L were also identified, and hericenone L showed cytotoxic activity against EC109

tumor cells (Ma et al. 2012) (**Fig. 7**). There is debate as to whether hericenones are active components stimulating biosynthesis of Nerve growth factor. Other studies have reported that hericenones C and D do not increase Nerve growth factor biosynthesis in cell line 1321N1 (Mori et al. 2008). Hericenone E was able to stimulate Nerve growth factor synthesis in rat pheochromocytoma (PC12) cells when investigated using several pharmacological inhibitors. Hericenone E was able to stimulate Nerve growth factor secretion which was two-fold higher than that of the positive control (50 ng mL^{-1} of NGF) and increased phosphorylation on mitogen-activated protein kinases or extracellular signal-regulated kinases (MEK/ERKs) pathway and also increased protein kinase B (PKB) (Phan et al. 2014).

Erinacine derivatives are potential medicines for degenerative neuronal disorders and peripheral nerve regeneration. Several erinacines from submerged culture with unique ability to promote activity of Nerve growth factor synthesis have already been found. Erinacines A (**34**), B (**35**), C (**36**), D (**37**), E (**38**) F (**39**), G (**40**), H (**41**), and I (**42**) showed a stronger biological activity that stimulates Nerve growth factor synthesis than epinephrine used as a positive control on murine astroglial cells (Kawagishi et al. 1994, 1996a, 1996b; Lee et al. 2000) (**Fig. 8**). All these diterpenoids possess a cyathane skeleton consisting of angularly condensed five-, six-, and seven-membered rings. Additionally, erinacine A significantly increased the level of Nerve growth factor in the rat's locus caeruleus and hippocampus, but not in the cerebral cortex in an oral administration study (Shimbo et al. 2005). A cyathane-xyloside, erinacine P (**43**) and its biomimetic conversions into erinacine A and erinacine B, was also found to induce the Nerve growth factor -syntheses compared with epinephrine as a positive control (Kenmoku et al. 2000) (**Fig. 9**).

Kenmoku et al. (2002) isolated erinacine Q **(44)** and its biosynthetic route to erinacine C. A cyatha-3,12-dien-14-β-ol named erinacol (**45**) and 11-O-acetylcyathin A3 (**46**), both of which are probably biosynthetically related to erinacine Q were isolated by Kenmoku et al. (2004) and also reported to have Nerve growth factor -enhancing activities. The stereochemistry of erinacine R (**47)** was elucidated by Ma et al. 2008 (**Fig. 9**). Several studies were conducted on the mechanisms involved in the neuroprotection process of the brain from extracts from *H. erinaceus* (Hazekawa 2010; Mori et al. 2008, 2009; Phan et al. 2014). Lee et al. (2014) found the effects of erinacine A,

which is capable of preventing ischemic injury to neurons; possibly act as an anti-inflammatory agent to bring about neuroprotection using a model of global ischemic stroke and the mechanisms involved. Rats were treated with erinacine A. The extracts reduced the total infracted volumes by 22% and 44% at a concentration of 50 and 300 mg/kg, by oral administration of erinacine A, respectively, compared to the stroke animal model group. Erinacine A showed potent nerve-growth enhancing properties and effectively inhibited neuronal cell death via reduced levels of nitrotyrosine-containing proteins, phosphorylation of p38 MAPK and CCAAT enhancer-binding protein (C/EBP) and homologous protein (CHOP).

Investigations of the effectiveness of the bioactive compounds based on clinical trials in patients are now receiving much attention in Asia, e.g., China, Japan, Korea, and Malaysia. Specifically, these reports support promising potential of hericenones and erinacines that enhance Nerve growth factor synthesis. However further studies need to determine the mechanism of hericenones and erinacines whether the compounds are able to stimulate Nerve growth factor in the brain *in vivo*. Furthermore, clinical trials of patients treated with extracts of *H. erinaceus* indicated a significant effect on reduced depression and anxiety in 30 randomly selected females. Examples of clinical trials of patients treated with hericenones and erinacines from *H. erinaceus* are listed in **Table 5**.

d) Antimicrobial activity

Medicinal mushrooms are rich sources of secondary metabolites with activity against a wide range of microorganisms including bacteria, yeasts and filmentous fungi. These substances include diterpenoids, such as pleuromutilin from the genus *Clitopilus*, which led to the discovery of the marketed drug retapamulin (Kilaru et al. 2009). Other antibiotics have been isolated from *Ganoderma* (Richter et al. 2014) and many other species. It is hoped that further research on antimicrobial agents from basidiomycetes will lead to alternative antibiotic drugs on the market (De Silva et al. 2013, Stadler and Hoffmeister 2015). Even *H erinaceus* has been shown to be a source of a number of antimicrobial agents. Phenol-like and fatty acid-like compounds from the extracts of *H. erinaceus* were shown to have antifungal and antibacterial activity. 4-Chloro-3,5-dimethoxybenzyl alcohol, 4-chloro-3,5-dimethoxylbenzaldehyde and chlorinated orcinol from mycelial extracts possessed

antimicrobial activity (Okamoto et al. 1993). The submerged cultures contained hericene A (**48**), B (**49**), C (**50**) and erinapyrone C (**51**), which showed moderate bioactivities against Gram-positive bacteria (Alberto et al. 1995; Kawagishi et al. 1992) **(Fig. 10).**

In the 2000's other antimicrobial compounds from *H. erinaceus* were reported to be active against fungi, and protozoa, as well as various pathogenic gram-positive and gram-negative bacteria (Lindequist et al. 2005; Wong et al. 2009b). Methicillin-resistant *Staphylococcus aureus* (MRSA) is a gram-positive bacterium that currently causes illness worldwide. The mycelium extract of *H. erinaceus* exhibited a minimal inhibitory concentration (MIC) with EC_{50}value of 5.5 µl/ml against *Staphyloccocus aureus* (Kim et al. 2000). Furthermore, cyathane derivatives named erinacines J (**52**) and K (**53**) were tested for their effectiveness against MRSA. Only erinacine K showed anti-MRSA activity in the direct drop and minimum inhibitory concentration (MIC) bioassays. This was attributed due to chemical substitutions present in the three-ring skeleton of the aglycon in biologically active compounds expressing anti-MRSA activity (Kawagishi et al. 2005; Kawagishi et al. 2006) **(Fig. 10).** In clinical tests conducted by the Japanese group, MRSA were reported to have disappeared in a percentage of patients whose diet was supplemented with extracts of both fruiting body and mycelium of *H. erinaceus* (Kawagishi et al. 2005).

More recently, Kim et al. (2012) metabolites from the fruiting body of *H. erinaceus* with effective antimicrobial activity in an *in vivo* assay against the growth of *Salmonella* via stimulation of the immune system. A direct inhibitory effect of ethanol and ethyl acetate extracts of *H. erinaceus* fruiting bodies against *Helicobacter pylori* was found in patients associated with chronic gastritis and gastric ulcers (Shang et al. 2013). Several studies indicate that extracts of biologically active compounds from *H. erinaceus* possess significant anti-microbial effects that could be improved for pharmacological properties. Even the immunomodulatory effect of secondary metabolites mentioned above could help to overcome bacterial infections by boosting the immune system of the human host.

e) Antioxidant and anti-ageing activities

Reactive oxygen species (ROS) derived from oxygen can cause oxidative stress which leads to a variety of diseases including cancer, Alzheimer's disease (AD), cardiovascular disease, and the aging process (Ames et al. 1993; Halliwell et al. 2012). This mechanism can produce free radicals or various reaction oxygen species capable of damaging tissues, and functional cell components such as DNA, protein and lipids of host organisms. Antioxidant molecules are beneficial as they inhibit oxidation reactions and eliminate free radicals (Krishnaiah et al. 2010; Valko et al. 2007).

Many studies have been carried out to investigate antioxidant properties of *H. erinaceus* (Abdullah et al. 2012; Fu et al 2002; Malinowska et al. 2009; Mau et al. 2002; Mujić et al. 2011). An investigation of phenolics from mycelium extracts in hot water of *H. erinaceus* has been reported to evaluate the *in vitro* antioxidant by Abdullah et al. (2012). The Folin-Ciocalteu method used to estimate the total phenolics, being expressed as gallic acid equivalents (GAEs) that reflected the phenolic content as the amount of gallic acid (mg) in 1 g of extract (Ferreira et al. 2009).

Another study reported on the antioxidant properties of phenolic compounds from fruiting bodies and mycelia. Mycelial extracts contained the highest total phenolic content and the highest ferric reducing antioxidant power (FRAP). Both fresh and oven-dried fruiting body extracts contained phenolic compounds with antioxidant activities. However, possibly due to the generation and accumulation of Maillard's reaction products (MRPs) during the dry processing, the potential antioxidant capacity of oven-dried fruiting bodies was higher than the freeze-dried extract (Wong et al. 2009b).

The lipopolysaccharides (LPS) from mycelia showed significant anti-oxidative activities in BALB/C mice through the elevation of hepatic glutathione levels (Jang et al. 2010). Han et al. (2013) showed significant antioxidant activity against ischemia reperfusion induced renal oxidative injury damage in mice. The results of pre-administration of the β-glucans from *H. erinaceus* showed increased antioxidant enzymes activities as well as decreased lipid peroxidation levels. Zhang et al. (2012a) isolated endo-polysaccharides from ethanolic mycelium extracts of *H. erinaceus* grown on tofu whey that exhibited extremely high antioxidant effect *in vitro* assays. These results suggested that *H. erinaceus* extracts can be a good source for increasing antioxidant enzyme activities in humans. Xu et al. (2010) also found that β-glucanes from *H. erinaceus* showed significant anti-skin aging

properties, due inhibition of matrix metalloproteinase (MMP)-1, and tissue inhibitor of matrix metalloproteinase (TIMP)-1 activities in aged rat models. These date, however, were so far not corroborated by activities during *in-vivo* experiments.

f) Other therapeutic uses and biological activities of *Hericium* metabolites

Different bioactive metabolites derived from *H. erinaceus* are supposed to be safe to be used as pharmaceutical products and dietary supplements due to the minimum side effects of compounds of natural origin. Most of the potential properties of *H. erinaceus* extracts from fruiting bodies have been studied in animal models for nearly three decades. The cytoprotective effects of *H. erinaceus* freeze dried fruiting bodies have been shown to be effective against ethanol-induced gastric mucosal injury in rats (Abdulla et al. 2008). In addition, the aqueous extract from fruiting bodies of *H. erinaceus* enhanced the acceleration of wound healing in experimentally wounded and dressed male Sprague–Dawley rats (Abdulla et al. 2011). *Hericium erinaceus* can be useful in patients who are suffering from gastric ulcers as well as those of the oesophagus and appear to suppress and prevent Crohn's disease, characterized by the inflammation of the gut walls (Abdulla et al 2008; Wong et al. 2013).

A *Hericium erinaceus* extract was investigated for acute respiratory distress syndrome in a case study of a 63-year-old man who was admitted to the hospital for intensive care of severe acute respiratory failure with diffuse infiltration in both lungs. Lymphocytes stimulation test showed a strong reactivity against *H. erinaceus* extract daily for four months (Nakatsugawa et al. 2003). Inhibitors of platelet aggregation are preventive or therapeutic agents of various vascular diseases, including myocardial infarction and stroke, as platelet aggregation in the blood vessel causes thrombosis. The bioactive activity of hericenone B from fruiting body also exerts anti- platelet action. Hericenone B showed stimulating activity releasing of arachidonic acid as mediates receptor thrombosis via collagen through α2/β1 in tested rabbit. Specifically, only hericenone B showed inhibition of collagen-induced platelet aggregation when compared with hericenone C, D and E with inhibition at 30 μM similar to 5 μM aspirin as a reference investigated in *vivo* (Farndale 2004; Mori et al. 2010).

Hericium erinaceus also contained a biologically active substance which showed activities on plant-growth. Hericerin (**54**), for instance, showed activity against pine pollen germination and tea pollen growth (Kimura et al. 1991) **(Fig.11).** The recently isolated erinaceolactones A (**55**), B (**56**) and C (**57**) isolated from fruiting bodies have shown plant-growth regulatory activity (Wu et al. 2015) **(Fig. 11)**.

5-. *Hericium erinaceus* containing products

Scientists have established the components of medicinal mushrooms, including various polysaccharides, such as lentinan from *Lentinula edodes*, ganoderic acids from *Ganoderma lucidum*, polysaccharopeptide krestin (PSK) in *Trametes versicolor*, and a protein-bound polysaccharide complex in *Macrocybe lobayensis*. Hyde et al. (2010) also reported on some cosmetics containing mushroom products, made from *A. subrufescens* as the main bioactive ingredient. Recently, numerous commercial medicinal products and nutritional food with pharmaceutical properties have been derived from medicinal mushrooms. Biologically active compounds isolated from other fungi could provide a novel kind of cosmeceuticals with significant immune enhancement. Almost all pharmaceutical products have been derived from commercial fruiting bodies, as compared to those extracted from mycelia, approximately 80-85% vs. 15%, respectively.

Gastric cancer is the second most common cancer worldwide. In the United States (US) the National Cancer Institute documented a significant increase of about 25% in all common cancer forms of gastrointestinal (GI) cancers such as liver, gastric and colorectal cancers in recent years (Anand et al. 2008; Dicken et al.2005). It is appears likely that the culture extracts of *H. erinaceus* processed into medications have been brought into production on a large scale, mainly for healing chronic gastricism and gastric-cancer (Li et al. 2010).

The nutritional values and important medicinal properties of *H. erinaceus* are well-known in Asia, Europe, and North America. *H. erinaceus* normally requires temperatures of 22°C to 25°C for optimal mycelial growth and 18°C to 24°C to produce fruiting bodies. The mycelium of *H. erinaceus* from artificial media and fruiting body from artificial cultivation are illustrated in **Fig. 12**. The first publication on the cultivation of this mushroom on artificial logs and polypropylene bags was documented in 1988 (Suzuki and Mizuno 1997). However, the cultivation conditions did not affect

selected bioactive properties of this mushroom grown in tropical Malaysia (Wong et al. 2009b; Abdulla et al. 2008; Abdulla et al. 2011). The comparison of chemical components and biological activity of *H. erinaceus* fruiting body and mycelial extracts have been evaluated. The polysaccharide content of fruiting body extracts with protective effect on the gastric mucosa was 7.92% higher than that of mycelial extracts, while monosaccharide and protein contents were similar (Yang et al. 2003). Therefore, medicinal properties from cultures and fruiting bodies may also provide different and undiscovered therapeutic benefits.

Many promising novel drugs and commercial products in variable forms of *H. erinaceus* have served as remarkable finds in the history of disease treatments, especially immunosuppressive agents. Sandwich biscuits with the fruiting bodies of *H. erinaceus* were used in the prevention and therapeutic treatment for nutritional anemia of preschool children (Liu et al. 1992). The extract of dried fruiting bodies and mycelial culture were prepared for healthy beverages such as a sport drink (11^{th} Asian Sport Festival in China, 1990) and tea that can be used for improving liver function and preventing diabetes in China (Imtiaj et al. 2008; Qin et al. 2015; Wang et al. 2005). In the hospitals of China, tablets of *H. erinaceus* were found to be an effective treatment of anti-aging, inflammation, chronic gastric, esophageal carcinoma, and digestive tract ulcer and their use extended the life of cancer patients (Chen 1992; Li et al 2014a; Liu 1992; Poucheret et al. 2006; Ying et al. 1987). Capsule supplements of 100% pure powder of *H. erinaceus* are marketed in Malaysia to promote regeneration after peripheral nerve injury (Wong et al. 2013). Such effects reflect that *H. erinaceus* can be a good candidate for promoting health through combination with extracts of other herbal and medicinal mushrooms, which can be made available in variable forms, such as beverages, powder, capsules, or pills (Lakhanpal and Rana 2005; Smith et al 2002; Wong et al. 2012; Zhuang et al. 2009). An interesting future application for glucanes from medicinal mushrooms may be their use in pharmaceuticaltechnology. Polysaccharides derived from *H. erinaceus* were used to encapsulate curcumin nanoparticles for use in antitumor drug delivery, employing nanoprecipitation techniques (Huong et al. 2011).

Moreover, exciting recent research has claimed biological activities of these compounds at the level of clinical trials. Thus, *H. erinaceus* is now being used as food supplement and medicinal

nutrition therapy with enhancement of the immune function of the whole human body. However the therapeutic potential and development of pharmaceutical standards for extraction of compounds from the fruiting bodies and even standardisation of producton through mycelial cultures (e.g. by GMP facilities) still constitutes a future challenge.

Available commercial products from *H. erinaceus* that provided beneficial effects in prevention of various diseases, and supplementary foods that improve health showed no side effects are shown in **Table 6**. These products are mostly being sold over the counter (some are distributed via the Internet) and do not constitutedrugs, but rather can be categorised as nutraceuticals. This also means that their production does not necessarily meet the standards of pharmaceutical drugs. Nevertheless, *H. erinaceus* has been on the list of 'Nature's Nutrient for the Neurons' which refers to its potential to stimulate nerve growth factor synthesis (Kawagishi et al. 2004). Recent inventions relating to hericenones and erinacines as medicine through nutraceutical products or medicinal products for patients suffereing from neurological diseases have been claimed in patent applications. Pharmaceutical compositions containing erinacerins A and B have been recently claimed in patents as excellent brain protective agents for preventing dementia disease (Fan 2014; Kim et al. 2014; Noh et al. 2014). Promising innovations in nutraceuticals as well as pharmaceuticals refer to stimulators of nerve growth factor by erinacines, which can only be isolated from cultured mycelia is still extremely interesting because of better outcomes.

Conclusion

H. erinaceus is distinguished as an edible-medicinal mushroom and also a delicacy for food supplement and has earned much attention as a potential source of various pharmaceutical properties. It has been used for more than 1000 years in China and for many decades in other oriental countries (Mizuno et al. 1999; Jia et al. 2004; Ying et al. 1987). Pharmacological effects of *H. erinaceus* have been examined over the last 20 years. Polysaccharides isolated from fruiting bodies of *H. erinaceus* have shown significant suppression of various tumor cells in both *in vitro* and *in vivo* based experiments (Lee & Hong, 2010a; Mizuno et al. 1992; Wang et al. 2001a). Mycelial cultures of *H. erinaceus* are used to extract bioactive compounds and are processed in tablets, and are now produced

in large scale, mainly for curing gastric ulcer and chronic gastricism and esophagus cancers (Xu et al. 1985; Li et al. 2014). Extracts containing erinacines from mycelium and hericenones from fruiting bodies have provided evidence that *H. erinaceus* can stimulation nerve growth factors (NGF).

Studies have identified the effectiveness of bioactive compounds from *H. erinaceus* that may be able to pass through the brain- blood barrier into the brain to stimulate NGF synthesis, while harmful effects have not been reported. Worldwide clinical trial data have verified beneficial properties of this mushroom and provided dietary supplements of high market value. Several bioactive compounds thought to be excellent therapeutic agents offer solutions for future drug discovery. However, uncharacterized polysaccharides must still be determined for their potential health benefits. Additionally, the potential pathways and mechanisms that different compounds affect to stimulate human immune responses still remain to be elucidated.

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List of Figure legends

Fig.1

Fig. 2 Chemical structures of erinacerins and erinapyrones

Fig 3.Chemical structurs of chlorinated aromatic compounds, benzopyrans, benzofurans and an ergosterol derivative isolated from *Hericium erinaceus*

Table 1 Overview of taxonomic synonyms for *Hericium erinaceus.* For details see Index Fungorum (http://www.indexfungorum.org/) and Mycobank (http://www.mycobank.org/)

Hericium erinaceus (Bull.) Pers. 1797 **Varieties and formae (all currently regarded assynonyms)** *Hericium erinaceus* f. *caput-medusae* (Bull.) Nikol.
Hericium erinaceus subsp. *erinaceo-abietis* Burds., O.K. Mill. and Nishij.
Hericium erinaceus subsp. *unguiculatum* Pers.
Hericium erinaceus var. *sulphureum* Pers.
Hericium erinaceus var. *viridescens* Pers. **Synonyms** *Clavaria erinaceus* (Bull.) Paulet. *Dryodon erinaceus* (Bull.) P. Karst.
Clavaria conferta Paulet
Dryodon caput-medusae (Bull.) Quél.
Dryodon juranus Quél.
Hericium caput-medusae (Bull.) Pers.
Hericium echinus (Scop.) Pers.
Hericium grande Raf.
Hericium hystrix Pers.
Hericium unguiculatum (Pers.) Legon and A. Henrici
Hydnum caput-medusae Bull.,
Hydnum echinus (Scop.) Fr.
Hydnum erinaceus Bull.

Hydnum grande (Raf.) Steud.
Hydnum hystricinum Batsch,
Hydnum hystrix (Pers.) Fr.
Hydnum juranum (Quél.) Sacc. and D. Sacc.
Hydnum omasum Panizzi
Hydnum unguiculatum (Pers.) Streinz
Manina cordiformis Scop.
Martella echinus Scop.
Martella hystricinum (Batsch) Kuntze
Martella hystrix (Pers.) Lloyd
Merisma caput-medusae (Bull.) Spreng.
Merisma hystrix (Pers.) Spreng.
Steccherinum quercinum Gray

Table 2 Overview of some species accepted in the genus *Hericium* and their distribution

Name	**Basidiome morphology**	**Basidiospores size/ characteristics**	**Host**	**Locality**
Hericium abietis (Weir ex Hubert) K.A. Harrison	Compact branched structure from which long spines hanging down of teeth with cream white shades	4.5–5.5×4–4.5 µm	coniferous wood	Northwest America
Hericium alpestre Pers.	Branches, hymenophore hydnoid, with branched spines up to 2 cm long with cream shades	5-6.5 x 4.5-5.5 µm,	*Abies alba*	Europe
Hericium americanum Ginns	Branches stout and branching repeatedly, white, becoming cream-colored in age	5-7 x 4.5-6 µm	*Fagus, Acer, Carya* and *Quercus*	North America
Hericium bharengense K. Das, Stalpers and U. Eberh.	Hymenophoral , sterile and fertile branching pattern, presence of moderately long spines, white shades	4.9×4.0 µm, low ornamentation (0.2 µm high)	*Tsuga dumosa*	Sikkim, India
Hericium cirrhatum Nikol.	Pileate basidiomes Spines are pointed and usually little more than 1 to 1.5cm long, with little or no real stem with cream shades	inamyloid 3.5-4.5 x 3-3.5µm	dead wood of *Fagus*	Europe

Hericium clathroides Nikol.	Consisting of few to several main branches springing from a rooting base which enters the wood of a tree.	3.5-4 x 2.6-3.4 µm	*Betula, Fagus* and *Quercus*	New Zealand
Hericium rajchenbergii Robledo and Hallenb.	Orbicular and coralloid, repeatedly branched from a common base, laterally attached to the substrate, pale flesh-coloured pink when fresh	4.5–5.0× 3.0–4.0 µm	*Lithraea molleoides*	Argentina
Hericium yumthangense K. Das, Stalpers and Stielow	the stipe-like small rooting base, intricate three tier branching system, 8–13 mm long spines, white to pale yellow	5.3–6.5 × 4.0–5.5 µm, smooth to slightly roughened	*Abies densa*	India

Table 3 Bioactive compounds from the fruiting bodies of *H. erinaceus*. Why the 3 first molecules are not drawn ?

Bioactive compound	**Biological activity**	**Reference**
4-chloro-3,5-dimethoxybenzoic acid -O-arabitol ester	Immunomodulatory	Qian et al. 1990
2-hydroxymethyl-5-α-hydroxy-ethyl-γ-pyranone	Immunomodulatory	Qian et al. 1990
6-methyl-2,5-dihydroxymethyl-γ-pyranone	Immunomodulatory	Qian et al. 1990
4-chloro-3,5-dihydroxybenzaldehyde (**10**)	Anti-microbial	Qian et al. 1990
4-chlro-3,5- dihydroxybenzyl alcohol (**11**)	Anti-microbial	Okamoto et al. 1993
2,3,4,7-Tetrahydro-5-methoxy-2-methyl-2-(4-methyl-2-oxo-3-pentenyl)-9*H*-furo[3,4-*h*]-1-benzopyran-9-one **(12)**	Immunomodulatory	Qian et al. 1990
2,6-dimethoxy-4-methyl-chlorobenzene (**13**)	Anti-microbial	Okamoto et al. 1993
3,5-dimethoxy-4-chloro-benzyl alcohol (**14**)	Anti-microbial	Okamoto et al. 1993
3,5-dimethoxy-4-chloro-benzaldehyde (**15**)	Anti-microbial	Okamoto et al. 1993
5-dihydroxy-6-β-methoxyergosta-7,22-diene (**16**)	Anti-microbial	Bycroft and Hall 1988
Isobenzofuranone **(17)**	Anti-microbial	Yaoita et al. 2005
Benzopyran **(18)**	Anti-microbial	Yaoita et al. 2005

Table 4 Anti-tumor activities of *H. erinaceus* demonstrated *in vivo* and *in vitro*.

Target organ	**Source of extracts**	**Test**	**References**
Breast carcinoma (MCF-7)	Fruiting bodies	*in vitro*	Zhang et al. 2009, 2010 Li et al. 2010
Cervical carcinoma	Fruiting body	*in vitro*	Kawagishi et al. 1990a, 1990b
Colon carcinoma (CT-26), (HT-29)	Fruiting bodies and mycelial culture	*in vivo*	Kim et al. 2011c, 2012, 2013 et al.
Esophageal carcinoma (EC109)	Fruiting bodies	*in vitro*	Ma et al. 2012
Gastric carcinoma (NCI-87)	Mycelial cultures	*in vivo* and *in vitro*	Li et al. 2014a
Liver carcinoma (HepG2), (Huh-7)	Fruiting bodies and mycelial culture	*in vitro*	Huong et al. 2011; Lee et al. 2010 ; Li et al. 2014a
Lymphoma carcinoma (EL4)	Fruiting bodies	*in vitro*	Suzuki et al. 2010
Pulmonary carcinoma (NCI-H460)	Mycelial culture	*in vivo*	Wang et al.2001b
Sarcoma 180 (S-180)	Mycelial culture	*in vivo*	Liu et al. 2000 Mizuno et al. 1992
Stomach (MKN-45)	Mycelial culture	*in vitro*	Kim et al. 2010
U973 human cell	Fruiting bodies	*in vitro*	Kim et al. 2011b

Table 5. Pharmacological effect of extracts from *H. erinaceus* demonstrated in human double blind clinical trials

Clinical trial	**Source**	**Protective and treatment functions**	**References**
63 years males	Fruiting bodies	respiratory distress syndrome	Nakatsugawa et al. 2003
50-80 years	Fruiting bodies	improving cognitive impairment	Mori et al. 2009
35.7-46.9 years	Fruiting bodies	brain functions and autonomic nervous systems	Nagano et al. 2010
75-77.2 years	Fruiting bodies	dementia disease	Kasahara et al. 2001, Ootomo 2005

Table 6 Examples of patented products of mushroom extracts with claimed biological and pharmacological properties

Claimed product / extract name[a]	**Description**	**Patent Application No**	**Inventors**
Induce production of nerve growth factor (NGF), preventing and treating senile dementia such as Alzheimer's	A composition comprising *Phellinus baumii*, *Hericium erinaceus* and *Zea mays* for activating and protecting brain function, and its preparation method Anti-dementia substrate from Hericium erinaceus and method extraction	JP 09019270 US 20090274720	Rho et al. 2005 Zhang et al. 2009
An agent for antioxidant, suppress hair and skin aging	Production of *Hericium erinaceus* mycelia and fruit body with improved antioxidation activity, immunocompetence, and antitumor effect Health food with antioxidation function and its manufacture method	KR 1066429 CN 101518339	Jang et al. 2011 Wang et al.2009

Claimed product / extract name[a]	**Description**	**Patent Application No**	**Inventors**
Preventing and treating hyperglycemia and cardiovascular diseases.	Traditional Chinese medicine tea for nourishing lung and reducing blood pressure	CN 102018896	Jing 2011
	Method for manufacturing traditional Chinese medicine liquor for resisting aging and reducing blood sugar	CN 101940714	Wang 2011
Preventing and treating digestive tract function	Ecological medicinal liquid for treating esophagus and gastric cancer and digestive diseases	CN 202166150	Hu and Pang 2010
	Method for manufacturing traditional Chinese medicine composition for treating acute gastroenteritis	CN 102058858	Song and Fuzhi 2011
Preventing and treating cancer	Traditional Chinese medicine composition for treating malignant tumor	CN 102441065	Jing and Qinian 2012

Claimed product / extract name[a]	**Description**	**Patent Application No**	**Inventors**
	Mixed powder of *Panax notoginseng* and *Hericium erinaceus*	JP 2009298762	Arakawa 2009

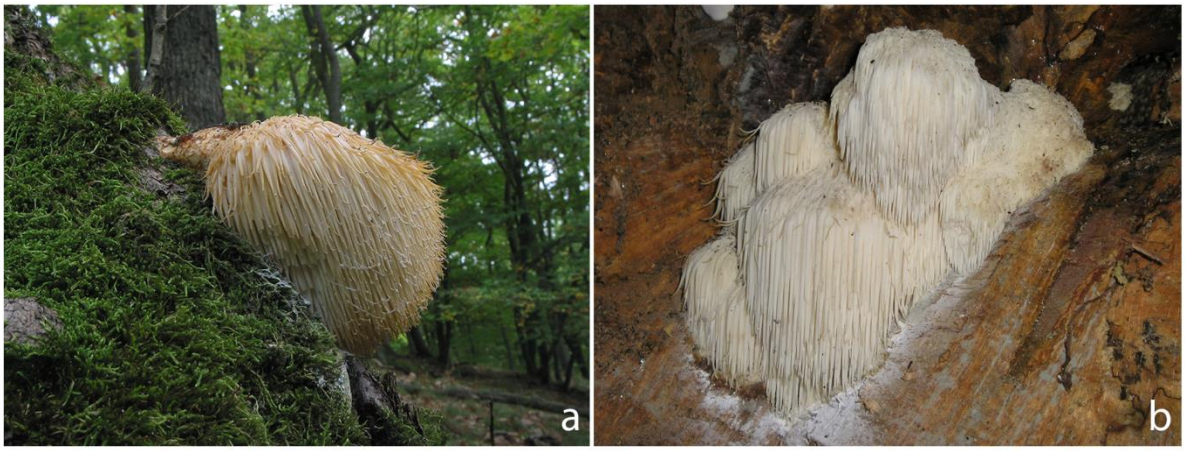


Fig. 1 Fruiting bodies of *H. erinaceus*; a. mature fruiting body on deadwood; b. mature fruiting body on heartwood of living trees. Photo taken by Bettina Haberl (a) and Vivien Bedregal (b), respectively, in Germany.

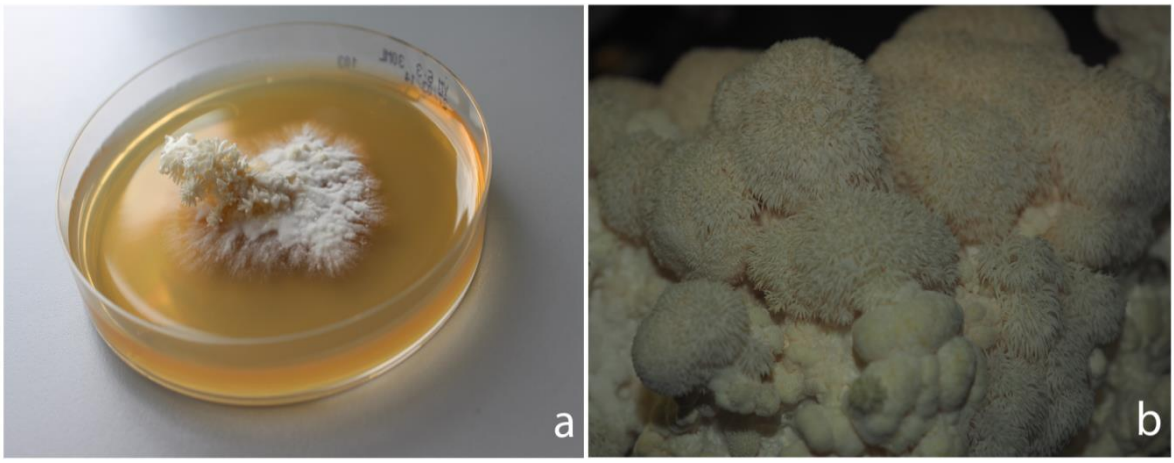
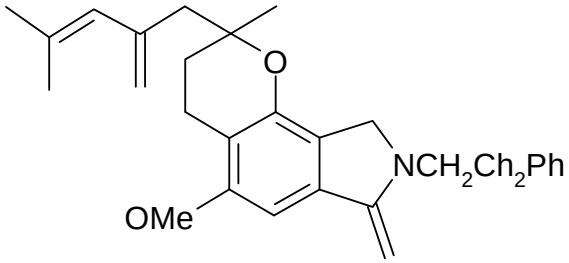
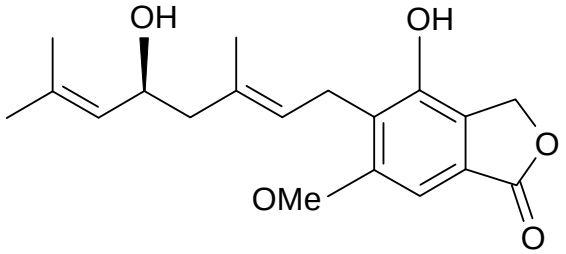


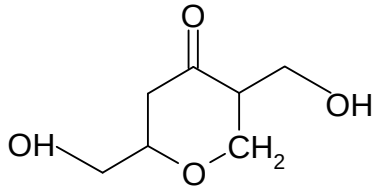
Fig. 12 a. Mycelium of *H. erinaceus* from artificial media; b. fruiting body from artificial culture. Photos taken by Eduard Löwen and Peter Karasch, respectively in Germany, 2013



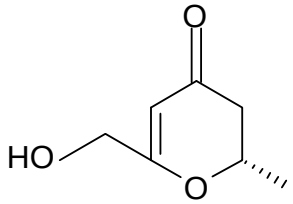
(1) erinacerin



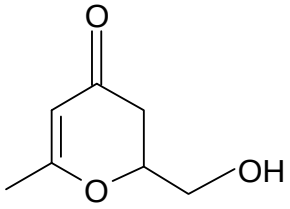
(2) erinacerin B



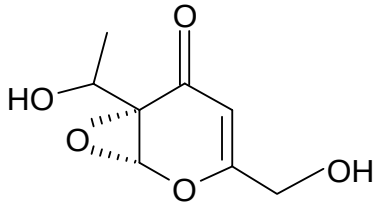
(3) pyranones



(4) erinapyrone A

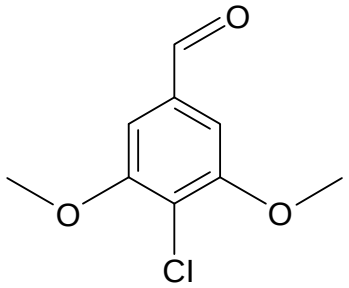


(5) erinapyrone B

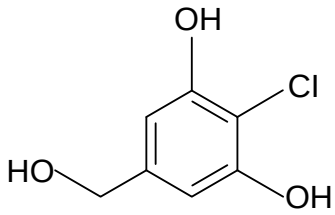


(6) erinapyrone C

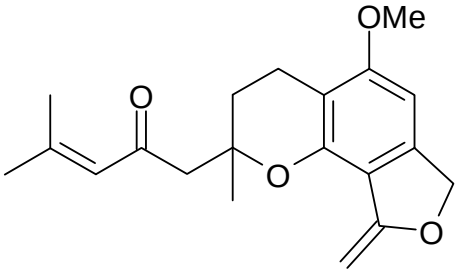
Fig. 2



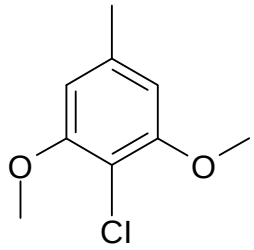
(10) 4-chloro-3,5-dihydroxybenzaldehyde



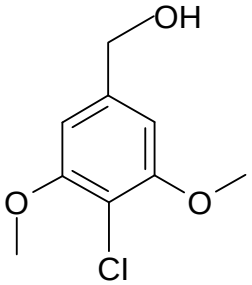
(11) 4-chlro-3,5- dihydroxybenzyl alcohol



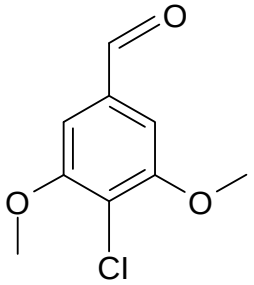
(12) 2,3,4,7-Tetrahydro-5-methoxy-2-methyl-2-(4-methyl-2-oxo-3-pentenyl)-9*H*-furo[3,4-*h*]-1-benzopyran-9-one



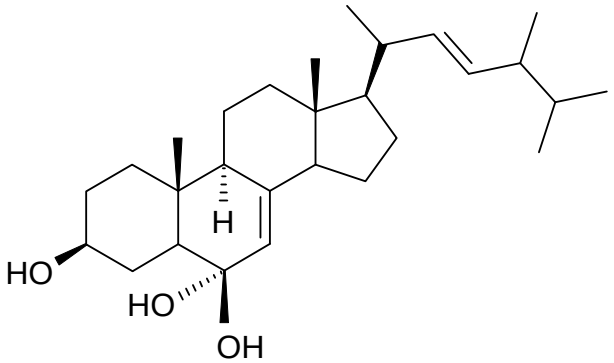
(13) 2,6-dimethoxy-4-methyl-chlorobenzene



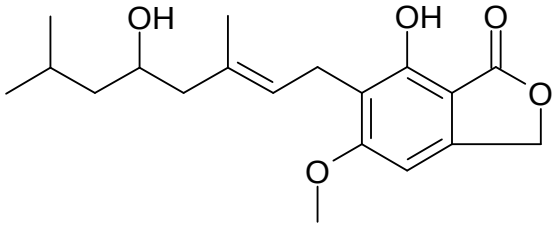
(14) 3,5-dimethoxy-4-chloro-benzyl alcohol



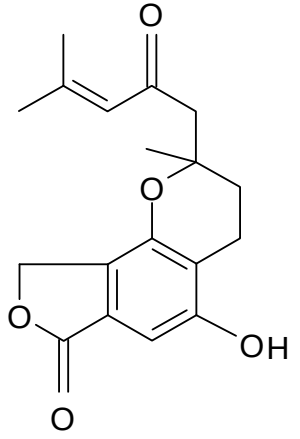
(15) 3,5-dimethoxy-4-chloro-benzaldehyde



(**16**) 5-dihydroxy-6-β-methoxyergosta-7,22-diene

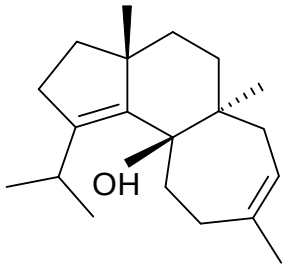


(17) isobenzofuranone

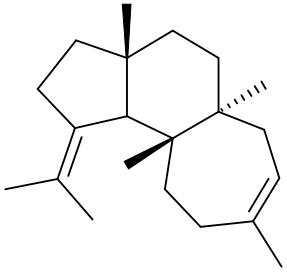


(18) Benzopyran

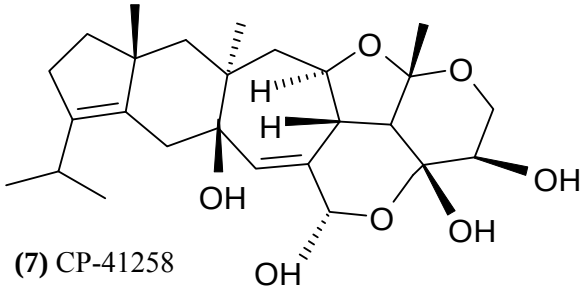
Fig. 3



(8) cyatha-3, 12-diene

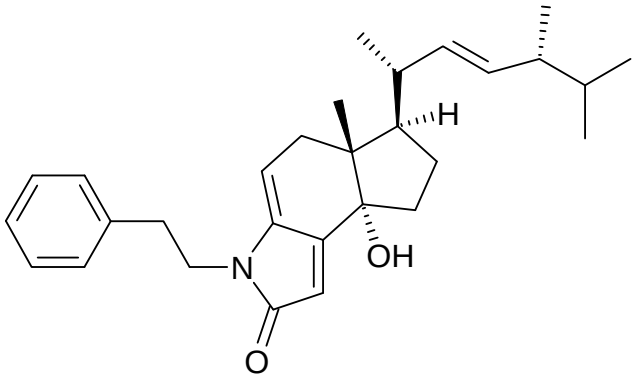


(9) cyatha-3, 12-diene derivative

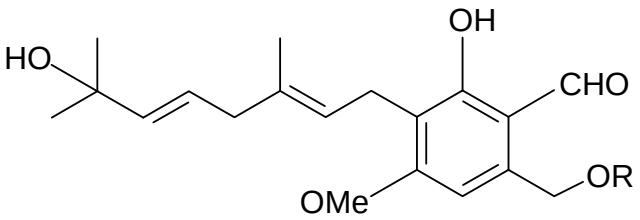


(7) CP-41258

Fig. 4

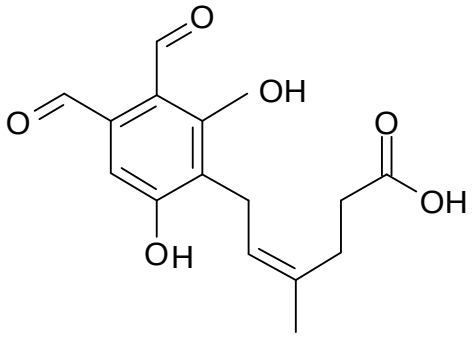


(**19**) hericirine

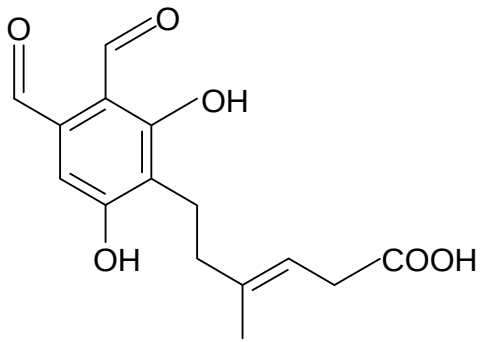


(**20**) Erinacene D

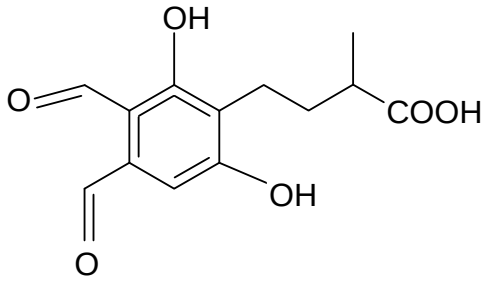
Fig. 5



(**21)** hericenal A

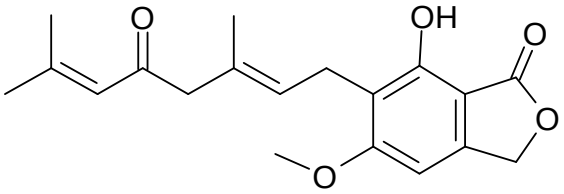


(22) hericenal B

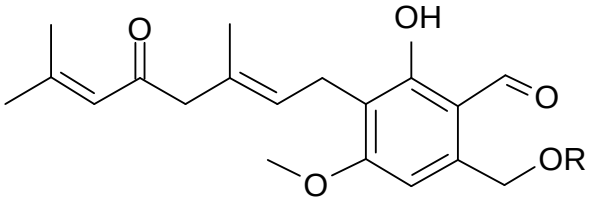


(23) hericenal C

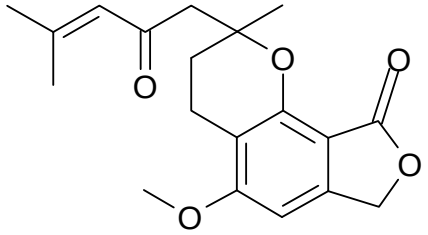
Fig. 6



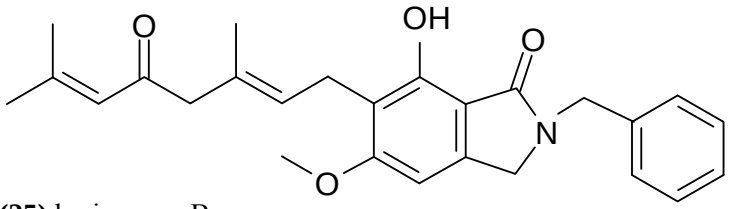
(24) hericenone A



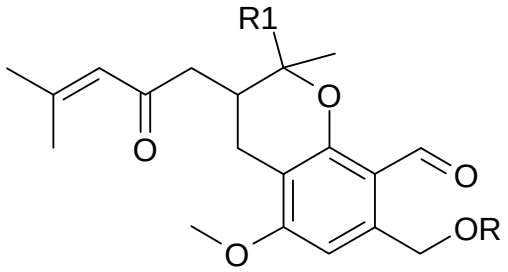
(26) hericenone C (R = palmitoyl)
(27) hericenone D (R = stearoyl)
(28) hericenone E (R = linoleoyl)



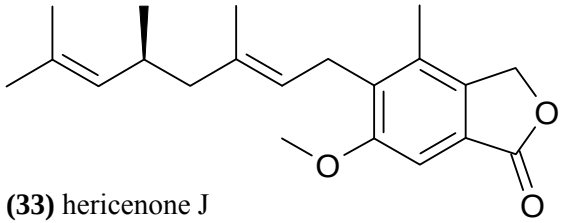
(32) hericenone I



(25) hericenone B

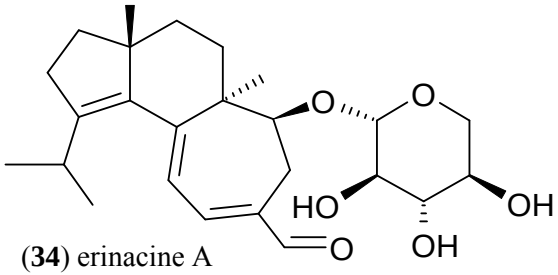


(29) hericenone F (R = palmitoyl, R1 = H)
(**29a**) 3-hydroxyhericenone F (R = palmitoyl, R1=OH)
(30) hericenone G (R = stearoyl, R1 = H)
(31) hericenone H (R = linoleoyl, R1 = H)

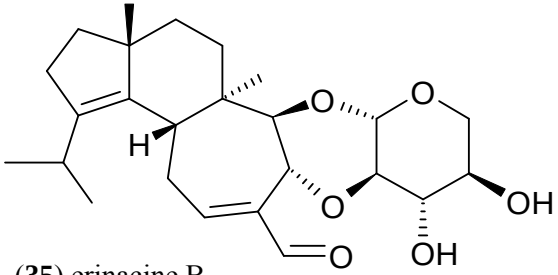


(33) hericenone J

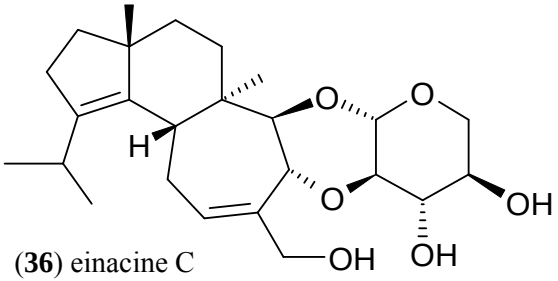
Fig. 7



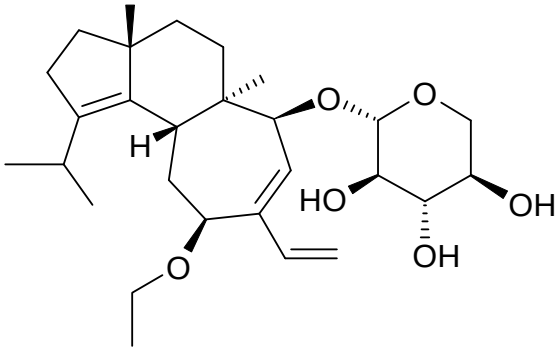
(**34**) erinacine A



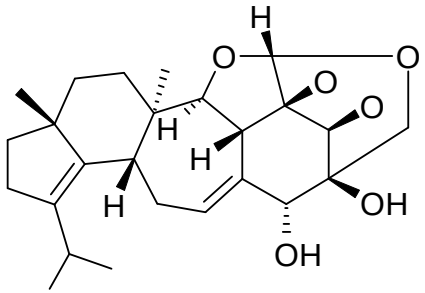
(**35**) erinacine B



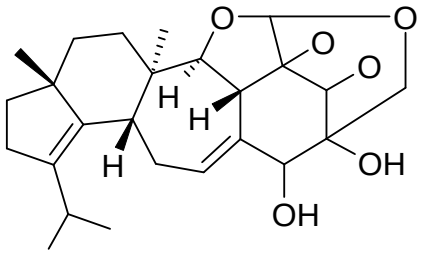
(**36**) einacine C



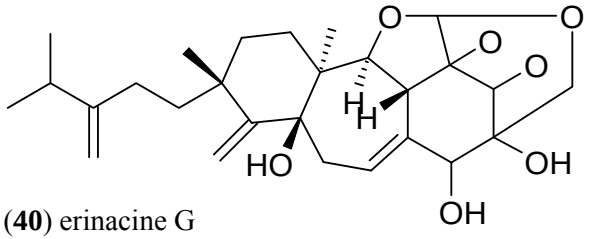
(**37**) erinacine D



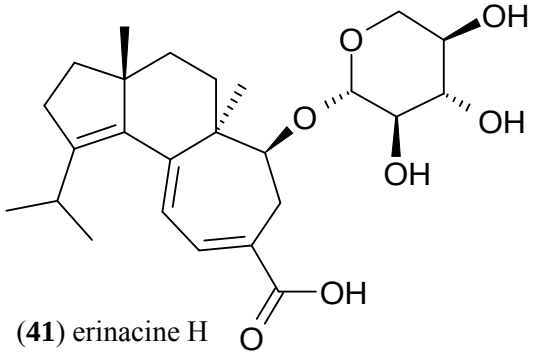
(**38**) erinacine E



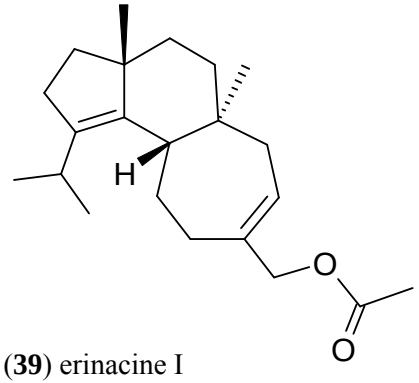
(**39**) erinacine F



(**40**) erinacine G

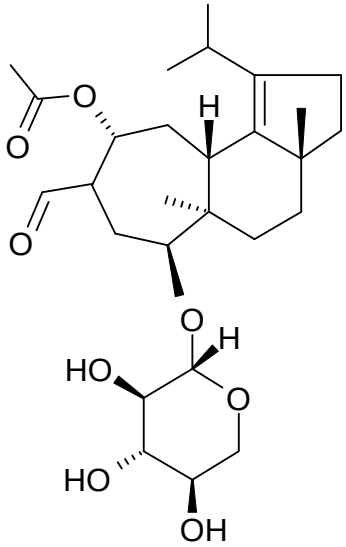


(**41**) erinacine H

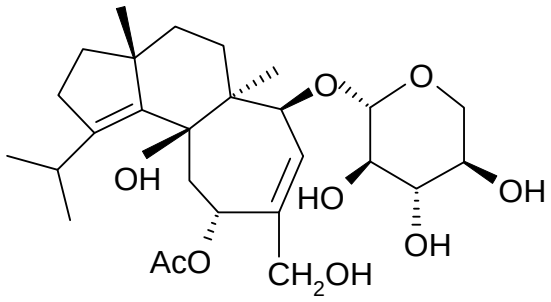


(**39**) erinacine I

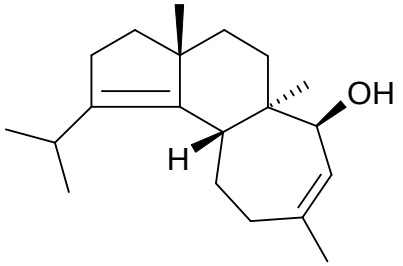
Fig. 8



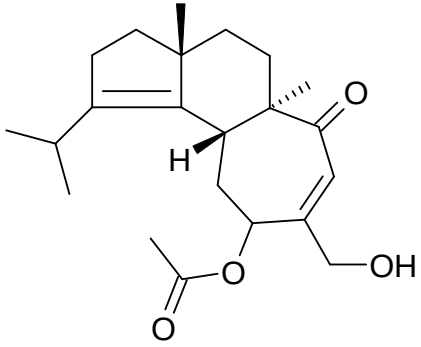
(**43**) erinacine P



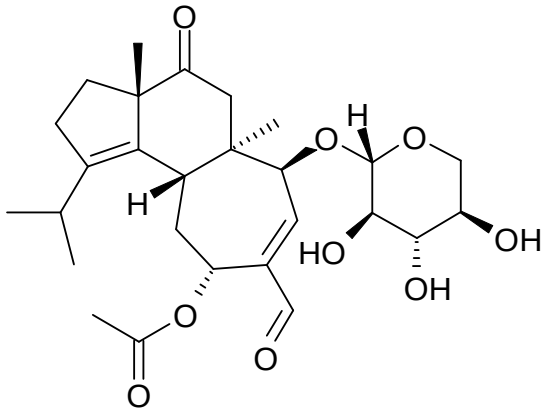
(**44**) erinacine Q



(**45**) erinacol

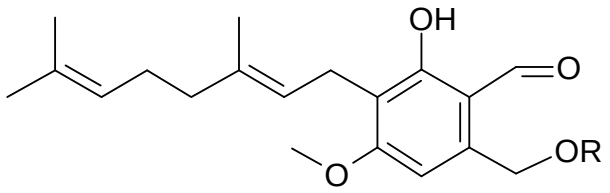


(**46**) 11-O-acetylcyathin A3

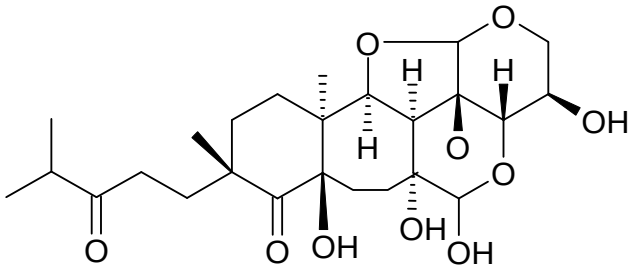


(**47**) erinacine R

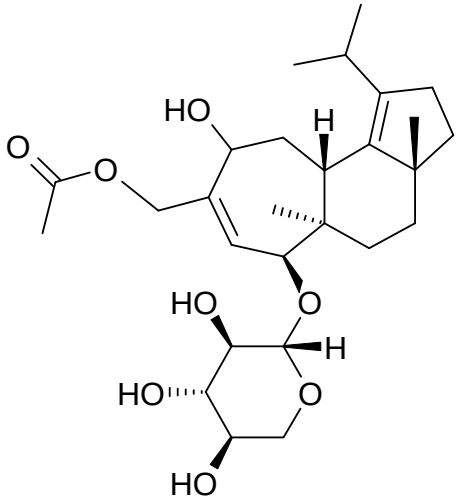
Fig. 9



(**48**) hericene A R = palmytoyl
(49) hericene B R = oleoyl
(50) hericene C R = stearoyl

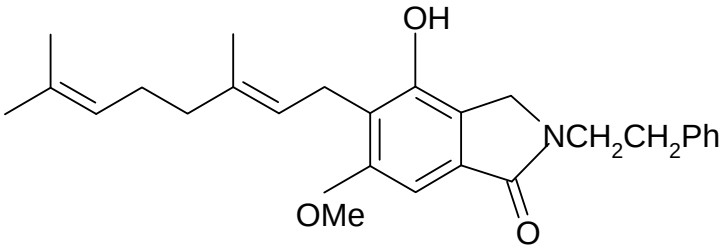


(51) erinacine J

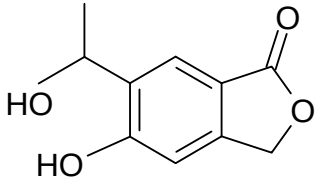


(52) erinacine K

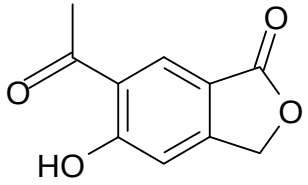
Fig. 10



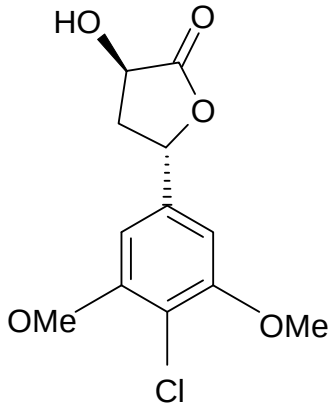
(**53**) Hericerin



(55) erinaceolactone B



(54) erinaceolactone A



(56) erinaceolactone C

Fig. 11