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Hericium erinaceus - A Rich Source of Diverse Bioactive Metabolites

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ABSTRACT

Hericium erinaceus (commonly known as lion's mane mushroom) is an edible mushroom used in traditional Chinese medicine. It is a prolific producer of diverse bioactive metabolites with neuroprotective and neuroregenerative properties (e.g. β-glucan polysaccharides, hericenones, erinacine terpenoids, isoindolinones, sterols, and myconutrients). Because of its anti-inflammatory properties and promotion of nerve growth factor (NGF) gene expression and neurite (axon or dendrite) outgrowth, *H. erinaceus* is used for the treatment of Alzheimer's as well as Parkinson's diseases. This review provides a comprehensive account of the bioactive compounds from *H. erinaceus* (both from the fruit bodies and mycelia) and their biological activities such as neuroprotective functions, cytotoxicity, anticarcinogenic, antidiabetic, antimicrobial, and herbicidal activities.

Keywords – Alzheimer's disease – anticancer agents – antidiabetic – anti-inflammatory – antimicrobial – erinacine terpenoids – herbicidal – hericenone – neurite outgrowth – neuroprotection – Parkinson's disease

Introduction

In recent years, research on *H. erinaceus* has been focused on its antidepressant-like effects to treat depressive disorders (Yao et al. 2015, Chiu et al. 2018, Ryu et al. 2018). This review focuses on bioactive compounds of different strains of *H. erinaceus.* Primary emphasis is laid on the pharmacological activities of various metabolites of *H. erinaceus* along with bioactive compounds and their biological properties.

Hericium erinaceus (Bull.) Pers., is a macro fungus belonging to the family *Hericiaceae* (*Russulales, Agaricomycetes, Basidiomycota*). *Hericium erinaceus* is an edible mushroom possesses several medicinal properties. It has many common names: bear's head mushroom, bearded hedgehog mushroom, bearded tooth fungus/mushroom, hog head fungus, Hou Tou Gu (Chinese), lion's mane mushroom, monkey head mushroom, old man's beard mushroom, Pom Pom Mushroom, Satyr's beard fungus, white beard mushroom and Yamabushitake (Japanese). It is reported from China, Japan, Europe, and North America; found on dead oak, walnut, beech, maple, sycamore, and other broadleaf trees. It is most frequently found on logs or stumps and has a long

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history of usage in traditional Chinese medicine (Venturella et al. 2021). Bioactive constituents of *H. erinaceus* include alkaloids, fatty acids, terpenoids, phenolics, steroids, pyranones, and about 80 small compounds are isolated from *H. erinaceus* (Zhang 2016). Purified bioactive metabolites of the fruit body or mycelia of *H. erinaceus* possess a wide range of biological activities viz. anticancer (Wang et al. 2001, Zhang et al. 2020), antidiabetic (Yi et al. 2015), antihyperglycemic (Liang et al. 2013), anti-inflammatory (Mori et al. 2015), antimicrobial (Zhang et al. 2015a), antioxidant (Rahman et al. 2014), and hypolipidemic properties (Yang et al. 2003). In addition, *H. erinaceus* has been investigated as a potential treatment option in cognitive impairments (Mori et al. 2009), Alzheimer's disease (Tsai-Teng et al. 2016), Parkinson's disease (Kuo et al. 2016), ischemic stroke (Lee et al. 2014), and presbycusis (Chan et al. 2019). In recent years, research has been focused on its antidepressant-like effects for treating depressive disorders (Yao et al. 2015, Chiu et al. 2018, Ryu et al. 2018). This review focuses on bioactive compounds of different strains of *H. erinaceus.* This review highlights the pharmacological activities of metabolites derived from *H. erinaceus* and their biological properties.

Box 1 Impact of *Hericium erinaceus* in human health and wellbeing

- Improves brain health
- Fight anxiety and depression
- Supports the immune response
- Anti-inflammatory
- Supports the health and good circulation
- Supports fat burning and healthy metabolism
- Stabilizes blood sugar levels
- Improves digestive health
- Anticancer properties
- Improves energy levels

Stimulation of nerve growth factor

The nerve growth factor (NGF), a polypeptide, is a member of the neurotrophin family. NGF is involved in the progress as well as maintenance of neurons in the peripheral nervous system and is essential for the functions of cholinergic neurons in the central nervous system (CNS). An optimum supply of NGF from the cortex and the hippocampus is required for proper function and morphology of basal forebrain cholinergic neurons (BFCNs). Age-dependent degeneration BFCNs contributes significantly to cognitive decline in AD. The agents that increase the level of NGF showed improvement in cognitive functions and AD (Salehi et al. 2004, Aloe et al. 2012). Several metabolites from *H. erinaceus* have shown significant CNS activity, such as improvement in cognitive function and increase in NGF activity, thus investigated for the treatment of dementia and Alzheimer’s disease (AD).

Hericenones

Hericenones (benzyl alcohol derivatives) are aromatic compounds obtained from the fruit bodies of *H. erinaceus*. The fresh fruit bodies of the mushroom were extracted with acetone followed by recurrent chromatography of chloroform-soluble fractions (chloroform, then ethyl acetate) crude extract subject to HPLC (High-performance liquid chromatography) filled with ODS column to yield hericenones. Hericenones A (**1**) and B (**2**) were isolated during 1990 without their neurite outgrowth activity (Kawagishi et al. 1990). Novel compounds, hericenones C (**3**), D (**4**) and E (**5**) were purified from *H. erinaceus* (Kawagishi et al. 1991). Compounds (**3**–**5**) displayed stimulating activity towards the synthesis of NGF in vitro. In their presence (**3**–**5**) (33 µg/mL), astroglial cells of mouse secreted 10.8, 23.5, and 13.9 pg/mL of NGF into the medium, respectively. The extent of activity for (**4**) was comparable to the epinephrine, a potent stimulator.

However, the activity of (**3**) and (**5**) are lower than (**4**). Interestingly, the variation in the activity of these compounds is rely on the length of chain and the double bond of the fatty acid (Kawagishi et al. 1991).

Hericenone E (**5**) (Fig. 1) was isolated from the fruit bodies of *H. erinaceus*. It has the capability to stimulate in vitro secretion of NGF in rat pheochromocytoma cells with two-fold higher than the positive control. Neuritogenesis was partially blocked by the receptor of tyrosine kinase (Trk) inhibitor (K252a) indicating the neuritogenic activity was not exclusively by the NGF. Hericenone E is known to increase the phosphorylation of extracellular-signal-regulated kinases (ERKs) as well as protein kinase B (Akt). Hericenone E (**5**) potentiated the NGF-induced neuritogenesis in PC12 cells via the MEK/ERK and PI3K/Akt pathways (Phan et al. 2014). Novel chroman, hericenone F (**6**), G (**7**), and H (**8**) were also purified from *H. erinuceum*. In the presence of hericenones H (**8**) at 33 μg/mL, mouse astroglial cells secreted 45.1 pg/mL NGF into the culture medium (Kawagishi et al. 1993, Ma et al. 2010).

Three new compounds, hericenone I (**9**) and hericenone J (**10**) 3-hydroxyhericenone F (**11**), (Fig. 1) were purified from the mushroom *H. erinaceus*. Compounds (**11**) displayed significant dose-dependent protective action against tunicamycin- and thapsigargin-toxicity at concentrations up to 10 μg/mL in the assay against endoplasmic reticulum (ER) stress-dependent apoptosis. The ER stress was elicited by incorporation of thapsigargin or tunicamycin into the culture medium of Neuro-2a cells. Thapsigargin is an inhibitor of ER Ca^{2}+-ATPase that causes depletion of Ca2+ in the ER, while tunicamycin is one of the inhibitors of N-glycosylation to glycoproteins and it is responsible for protein-misfolding in the ER. The results indicate that (**11**) could protect the neuronal cells by attenuating the ER stress by inducing apoptotic pathways on neural cells (Ueda et al. 2008) and may be helpful in the management of Alzheimer's disease.

Diling et al. (2017) purified 3-hydroxyhericenone F (**11**) (Fig. 1), which downregulates the β-site of β-amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) and decreases the serum cytokines (IFN-γ, IL-1β, IL-17α) level, tumor necrosis factor (TNF-α) and production of reactive oxygen species (ROS). Hence, it confirms that the mushrooms enriched either hericenones ameliorate amyloid beta (Aβ) pathology as well as oxidative stress in Alzheimer's disease. Dilinoleoyl-phosphatidylethanolamine (DLPE) (**12**) is a phosphatidylethanolamine bearing two linoleic acids, and was purified from *H. erinuceum.* The DLPE can protect neuronal cells from ER stress-induced cell death, and the PKC pathway is involved in the protective mechanism (Nagai et al. 2006).

Another new compound isohericerinol A (**13**) (Fig. 1) along with previously reported compounds such as hericerin (**14**), N-de-phenylethyl isohericerin (**15**) and corallocin A (**16**) were extracted from the fruit bodies of *H. erinaceus*. The compound isohericerinol A (**13**) increased the production of nerve growth factor (NGF) strongly in C6 glioma cells compared to isohericerinol A (**13**) and corallocin A (**16**). Increase in NGF production by these compounds promote the neurite outgrowth in N2a neuronal cells. According to Ryu et al. (2021), the Western blot analysis confirmed increased expression of protein by NGF, synaptophysin (SYP) and brain-derived neurotrophic factor (BDNF) in C6-N2a cells.

Erinacines

Novel diterpenoids, erinacines A (**17**), B (**18**), and C (**19**) (Fig. 2) were isolated from the cultured mycelia of *H. erinaceus*. In the bioassay of mouse astroglia cells with erinacines A-C (**17–19**) **(**1.0 mM), the quantity of NGF secretion into the medium was 250.1, 129.7, and 299.1 pg/mL, respectively. These activities were much more potent (69.2 pg/mL at 1.0 mM) than known potent stimulator epinephrine (positive control) (Kawagishi et al. 1994). The biologically active compound erinacine A (**17**) has the capacity to decrease the ischemic injury in brain. Studied carried out in vitro showed that erinacine A can decelerate the cerebral ischemic brain injuries via inactivation of pathways: iNOS/RNS and p38 MAPK/CHOP. Erinacine A is also mediating the antioxidative and anti-inflammatory functions during an intermittent ischemic brain injury. Thus, compounds derived from *Hericium* (e.g. erinacine A) are capable to enhance the synthesis of NGF

as well as induce neuroprotection, whereas its polysaccharides are capable to scavenge the ROS (Lee et al. 2014).

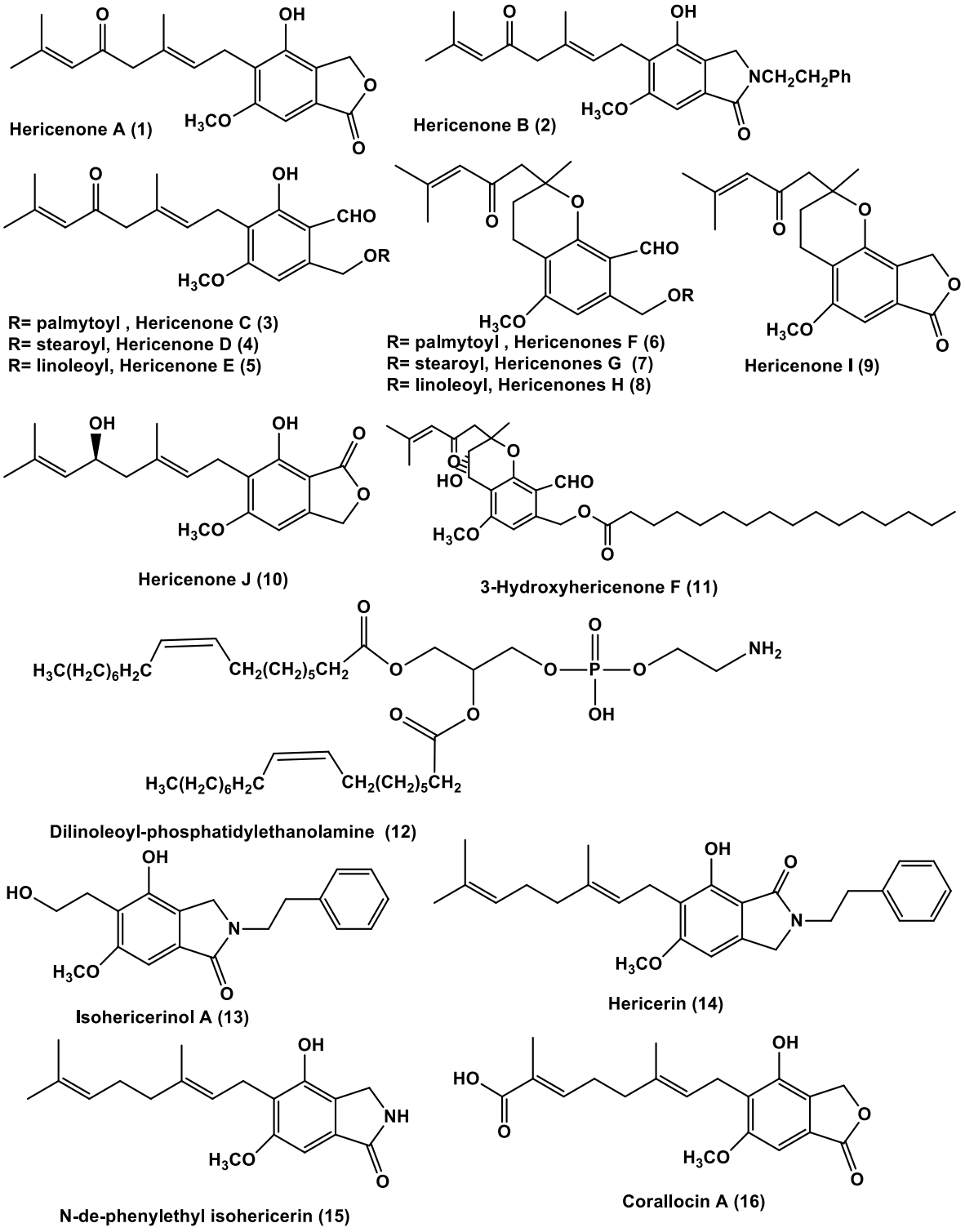

Fig. 1 – Hericenones isolated from *Hericium erinaceus*.

The effects of erinacine A-enriched *H. erinaceus* mycelia (HE-My) on the pathological changes in APPswe/PS1dE9 transgenic mouse model of Alzheimer's disease were studied. After 30 days of oral administration (300 mg/kg/day) to 5-months-old female transgenic mice (APPswe/PS1dE9), it was established that HE-My and its ethanol extracts (HE-Et) has the capacity to attenuate the burden of cerebral Aβ plaque (Tsai-Teng et al. 2016). It is interesting to note that

the portion of attenuated plaque is a non-compact structure. The HE-My as well as HE-Et have increased the level of insulin-degrading enzyme in the cerebral cortex, while in the cerebral cortex and hippocampus, the number of astrocytes and plaque-activated microglia decreased. Administration of HE-My and HE-Et promoted hippocampal neurogenesis and increased the ratio of NHF-NGF precursor (pro-NGF). According to Tsai-Teng et al. (2016), such administration in APPswe/PS1dE9 transgenic mice improved the activity of daily living skills.

A novel diterpenoid, erinacine D (**20**) (Fig. 2), along with the previously known compounds (erinacines A, B, and C) were isolated from the mycelia of *H. erinaceus*. The compound erinacine D (**20**) showed stimulating activity to NGF-synthesis by rat astroglial cells; the amount of NGF secreted into the culture medium in the presence of 4 (1.67 mM) was 141.5 pg/mL. This activity was stronger (69.2 pg/mL at 1.0 mM) than a positive control epinephrine (Kawagishi et al. 1996a). Compounds erinacines E (**21**), F (**22**), and G (**23**) were purified from the mycelia of *H. erinaceus*. The compounds (**21** and **22**) showed powerful stimulating activity against the NGF synthesis by astroglial cells. In the bioassay using rat astroglial cells, the amounts of NGF secreted into the medium in the presence of (**21**) and (**22**) at 5.0 mM were 105 and 175 pg/mL, respectively. These activities were stronger (70.2 pg/mL at 1.0 mM) than the known potent stimulator epinephrine used as a positive control (Kawagishi et al. 1996b).

Two erinacine derivatives (**24, 25**) (Fig. 2) purified from the mycelia of *H. erinaceus* were reported to induce the biosynthesis of NGF, which is useful to treat dementia (Shimada et al. 1996). Similarly, the other two erinacine diterpenoids (**26, 27**) from the mycelia of *H. erinaceus* were also reported to induce the production of NGF (Kawagishi et al. 1995). Bioactive cyatha-3, 12-diene (**28**) along with its isomer (**29**) was purified from the mycelia of *H. erinaceus* serves as an intermediate of cyathane diterpenoids (Kenmoku et al. 2001). Biotransformation capability of erinacine E (**21**) was evaluated using 81 microbes. Among the tested microbes, *Caladariomyces fumago* (ATCC 16373) was capable to transform erinacine E (**21**) into a new analog CP-412,065 (**30**) and the conversion rate was 29% (Saito et al. 1998).

Two new diterpenoids, erinacines H (**31**), and I (**32**) (Fig. 2), were purified from the mycelia of *H. erinaceus*. The compound erinacines H (**31**), showed stimulating activity to synthesize NGF using astroglial cells. The amounts of NGF (31.5 pg/mL) secreted into the medium in the presence of 33.3 µg/mL of (**31**), was five times greater than those in the absence of the compound (Lee et al. 2000). According to Mori et al. (2008), the ethanol extract of *H. erinaceus* stimulated NGF mRNA as well as protein levels in human astrocytoma cells (1321-N1) and stimulated neurite outgrowth in pheochromocytoma cells (PC12) by promoting c-Jun N-terminal kinase activity. The aqueous extract of *H. erinaceus* contained neuroactive compounds, which induced NGF-synthesis and promoted neurite outgrowth in NG108-15 cells. The extract also enhanced the neurite outgrowth stimulation activity of NGF when applied in combination. The aqueous preparation of *H. erinaceus* showed neurotrophic but not neuroprotective activity (Lai et al. 2013).

A known compound 3,4-dihydro-5-methoxy-2-methyl-2-(4'-methyl-2'-oxo-3'-pentenyl)-9(7H)-oxo-2H-furo[3,4-h]benzopyran (**33**) (Fig. 2), was extracted from the fruit bodies of *H. erinaceus*. This compound (**33**) displayed activity of high neurite outgrowth-promoting in NGF-induced cells (PC12) (Zhang et al. 2015b). Compounds such as 4-chloro-3,5-dimethoxybenzoic methyl ester (**34**) (Fig. 2), and erinacine A (**17**) were purified from the methhanolic extract of *H. erinaceus* mycelia. The compounds (**17** and **34**) efficient in protection of neuronally-differentiated pheochromocytoma cells (PC12) against deprival of NGF. The compound (**17**) capable to mimic the neuritogenic activity of NTs in the neurons of primary rat cortex. Similarly, the compounds (**17** and **34**) were also capable to potentiate the NGF-induced outgrowth of neurite devoid of the stimulation of NGF synthesis in PC12 cells. The cellular signaling pathways disclosed that NGF-induced neurite outgrowth is stimulated by compounds (**17** and **34**) fully by TrkA, while partially Erk1/2 (Zhang et al. 2017).

Previously unknown erinacine Z1 (**35**) (Fig. 3), along with known compounds erinacine A (**17**), erinacine B (**18**), erinacine C (**19**) were retrieved from the mycelium of *H. erinaceus*, while a known compound CJ14.258 (**36**) was retrieved from mycelium of *Hericium flagellum* (Rupcic et al.

2018). None of the tested compounds showed intrinsic neurothrophic activity, stimulating neurite outgrowth directly from cultured PC12 cells; compounds (**17–19, 35, 36**) enhanced the neurotrophin production in astrocytic cells. Promoting the effect of cyathane diterpenoid derivatives on BDNF expression was also observed. Since erinacines can stimulate the transcription of both investigated neurothrophins, it suggests an upstream target, which is common to upstream events of NGF as well as BDNF induction (Rupcic et al. 2018).

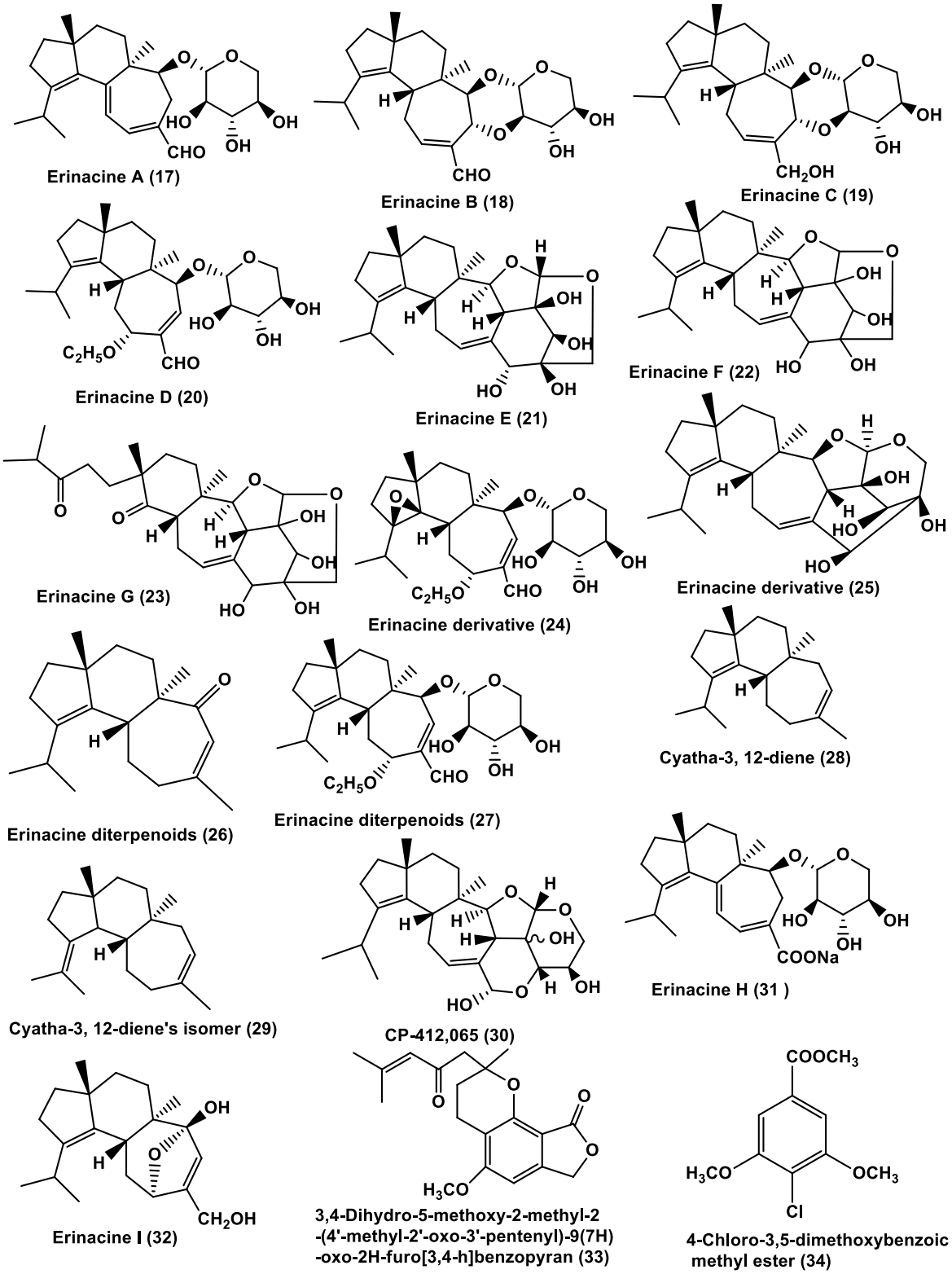

Fig. 2 – Erinacines isolated from *Hericium erinaceus.*

Three new cyathane diterpenes erinacines T-V (**37–39**) (Fig. 3), and two previously reported cyathane diterpenes erinacine P (**40**) were extracted from the liquid cultures of *H. erinaceus*. The compounds (**37–40**) showed significant neurotrophic effects in the range of 2.5-10 μM as compared with a control group. The percentage of neurite-bearing cells for cells treated with compounds (**37–40**) at 10 μM reached 43.7, 76.31, 65.3, and 48.3%, respectively. The NGF is used as a positive control with neurite-bearing cells of 40.3% at the concentration of 40 ng/mL (Zhang et al. 2018).

The peripheral nerve injury (PNI) is one of the significant health concerns. The NGF is known to play pivotal role in the growth, survival and maintenance of different neurons in the nervous system. The study of neuroprotective effects (NPE) of *H. erinaceus* and NGF against the mouse PNI model revealed that *H. erinaceus* shows a higher NPE than the NGF. The bioactive comounds of *H. erinaceus* avoid the death of neurons by regeneration of their axons leading to neuroprotection and neuro-regeneration help treating PNI. Further evaluation of bioactive compounds of *H. erinaceus* as a prospective source to cure PNI are necessary (Üstün & Ayhan 2019). Trovato et al. (2016) showed evidence of the neuroprotective potential of *H. erinaceus* on oral administration to the rats. In the brain of those rats treated with fungus, induction of LXA4 was maximum in cortex and hippocampus, striatum and cerebellum.

A recent clinical trial has been performed to assess the capability of *H. erinaceus* various neurological disorder (e.g. anxiety, binge eating, depression and sleep disorders) (Vigna et al. 2019). A total of 77 subjects affected by obesity with one or more mood disorders was evaluated to receive three capsules of an *H. erinaceus* as dietary supplement daily up to two months with a low-calorie diet regime. The administered fungal extract was with 80% mycelia and 20% fruit body. Prior to treatment, after the one and two months, the above-referred ailments were assessed (Symptom Checklist-90, Zung's Self-Rating Depression Scale, Zung's Self-Assessment Anxiety Scale, and Binge Eating Scale or BES). All the studies revealed significant improvements disorders (depression, anxiety, and sleep quality) in the *H. erinaceus* treated group. Further, concerning the serum balance in brain-derived neurotrophic factor (BDNF) and its precursor pro-BDNF, increased circulating pro-BDNF levels was evident. Still, clarifications are needed to understand whether these neurotrophins could be used as biomarkers in mood disorders (Vigna et al. 2019).

Effects on dementia and Alzheimer's disease

Dementia is a CNS disorder characterized by severely decline in mental ability which affect normal daily life of patients. Alzheimer's disease (AD) is the most common cause of dementia. AD is the fifth-leading cause of death among adults aged 65 years and older and is also a leading cause of disability and morbidity (Alzheimer's Association, 2019). Some of the bioactive isolated from *Hericium* were found active against Alzheimer's disease and are illustrated below.

A new sesterterpene, erinacine S (**41**) (Fig. 3), and, erinacine A (**17**) (Fig. 2), were purified from the ethanol extract obtained from the mycelia of *H. erinaceus*. A 30-day oral trial of erinacines A (**17**) and S (**41**) has attenuated the Aβ plaque burden in the brains of 5-month-old female transgenic mice APP/PS1. In addition, erinacines A and S increased significantly the level of insulin-degrading enzymes in the cerebral cortex (Chen et al. 2016). Compounds (**17** and **41**) reduced the cortical and hippocampal amyloid plaque growth, promoted hippocampal neurogenesis putatively by inhibition of glial cells and increased insulin-degrading enzyme (IDE) expression in the APP/PS1 mice. However, only compound (**17**) was capable to decrease Aβ production as well as the initiation of plaque formation. In addition, erinacine A recovers the behavioral deficits in the APP/PS1 mice. These suggest that the compound (**17**) may possesses therapeutic potential to treat Alzheimer's disease (Tzeng et al. 2018). Pharmacokinetics of compound (**41**), on oral dosing at 2.395 g/kg BW (*H. erinaceus* mycelial extract equivalent to 50 mg/kg body weight) of compound (**41**) in the male Sprague-Dawley rats was 15.13%. The leading site of compound (**41**) absorption was stomach, while the primary route of elimination of the compound (**41**) is the fecal excretion. This was the first study to demonstrate that compound (**41**) could enter the blood-brain barrier of rats as well as support the development of *H. erinaceus* mycelia to treat the neurological disorders (Hu et al. 2019).

A new cyathane-xyloside derivative named erinacine R (**42**) (Fig. 3), was isolated from the mycelia of *H. erinaceus* (Ma et al. 2008). Occurrence of extract of *H. erinaceus* in culture media supported the development of cerebellar neural cells (in vitro) by stimulating regulatory processes of myelinogenesis (Kolotushkina et al. 2003), which may be helpful in degenerative neuronal disorders such as Alzheimer's disease and peripheral nerve regeneration.

The *H. erinaceus* being a medicinal mushroom, which improves the recognition memory in mice. Using the HPLC-UV-ESI/MS analyses, the quantities of erinacine A (**17**) and hericenones C (**3**) and D (**4**) in the extracts of *H. erinaceus* were standardized to test against the animal model towards physiological aging. Oral administration up to two-months with *H. erinaceus*, the age decline of recognition memory reversed. The doublecortin (DCX) immunohistochemistry and proliferation of cell nuclear antigen (PCNA) in the hippocampus and cerebellum in experimental mice resulted in a positive effect of *H. erinaceus* of neurogenesis (Ratto et al. 2019).

Li et al. (2020) conducted a clinical trial to study the safety and efficacy of mycelia of the *H. erinaceus* enriched with 5 mg/g erinacine A++. The patients with mild Alzheimer's disease consumed three capsules daily (lyophilized mycelia of 350 mg/capsule containing 5 mg/g erinacine A). This study involved a 3-weeks-no-drug screening period, followed by a 49-weeks double-blind treatment with two parallel groups where the patients were randomized either three mycelial capsules per day or identically appearing placebo capsules. The score showed intellectual health performance such as Cognitive Abilities Screening Instrument (CASI), Mini-Mental State Examination (MMSE), and Instrumental Activities of Daily Living (IADL) of the patients significantly increased by consumption of the capsules then the placebo group. This trial was performed based on various in vivo and in vitro studies that erinacine A (**17**) has positive impacts on the dementia (Li et al. 2020).

The beneficial effects of *H. erinaceus* have been confirmed in numerous clinical trials. For example, Mori et al. (2009) carried out a placebo-control, parallel-group and double-blind clinical trial on 30 patients with middle cognitive impairment by providing four 250 mg tablets consist of 96% mushroom powder or placebo thrice a day up to 16 weeks, continued the trial up to four weeks and assessed using a cognitive function scale by Revised Hasegawa Dementia Scale (HDS-R). On comparison to the placebo group (weeks 8, 12, and 16) treatment and four weeks of follow-up, the yamabushitake group revealed significantly increased scores. However, in the fourth week, at the end of ingestion the values significantly decreased. However, *H. erinaceus* has proved to be valuable in the improvement of average cognitive impairment.

Hericium erinaceus stopped the impairments of visual recognition and spatial short-term memory because of induction by Aβ25-35 peptide administered in mice intracerebroventricularly (Mori et al. 2011). Owing to the effect of *H. erinaceus* on the brain function as well as autonomic nervous, Nagano et al. (2010) studied the impacts on menopause, depression, sleep quality, and undefined disorders (randomized, double-blind, placebo-controlled trials). Assessments were carried out based on the Kupperman Menopausal Index (KMI), the Pittsburgh Sleep Quality Index (PSQI), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Indefinite Complaints Index (ICI). A group of 30 females was randomly allotted to consume either cookies four *H. erinaceus* (0.5 g powder carpophore/cookie) or four placebo cookies once a day up to one month. In the treated group, after the HE intake, the CES-D and ICI scores significantly lowered than before, on comparison with the placebo group, the "insensitive" and "palpitation" terms of the ICI were substantially lower, and the terms "concentration", "irritating", and "anxious" tended to be lower. This study showed that *H. erinaceus* is capable to alleviate the anxiety and depression (Nagano et al. 2010).

Supplementation with erinacine A-enriched *H. erinaceus* mycelia extended the lifespan in both *Drosophila melanogaster* and SAMP8 mice by a maximum of 32% and 23%, respectively, compared to the untreated controls. Moreover, erinacine A-enriched *H. erinaceus* mycelia decreased TBARS levels and induced the antioxidative enzyme activities of superoxide dismutase, catalase, and glutathione peroxidase (Li et al. 2019).

Anticancer/antitumor activities

Cancer is the second most significant cause of human mortality across the globe, which was the reason for almost 10 million cancer deaths during 2020 (Sung et al. 2021). Extended protocols of treatment and the severe side effects of the current anticancer drugs demand an urgent need to explore safe and effective drugs. Mushrooms are important source of novel metabolites with unique structural and functional traits with potent cytotoxicity. Recently, various structurally of bioactive metabolites have been identified from *Hericium* and assessed for their anticancer potential. Bioactive metabolites of *Hericiumm* also serve as lead molecules for the pharmacological industry to develop new drugs. Here we summarize the anticancer impacts of natural products derived from *H. erinaceus*.

The extract obtained from *H. erinaceus* displayed various biological activities including anticancer one (Li et al. 2014a). Erinacine A-enriched *H. erinaceus* mycelia was found to be active against the ischemic stroke, as it reduces the neuronal apoptosis plus the size of the stroke cavity in brain by aiming iNOS/reactive nitrogen species (RNS) and p38 mitogen-activated protein kinase (MAPK)/CCAAT enhancer-binding protein homologous protein (CHOP) pathways (Li et al. 2018).

Novel cytotoxic phenols are known as hericenone A (**1**) and B (**2**) (Fig. 1) were obtained from the mushroom *H. erinaceus*. The minimum concentrations lead to complete inhibition of growth of HeLa cells for hericenone A (**1**) was 100 µg/mL, for hericenone B (**2**) was 6.3 µg/mL, the potent cytotoxicity of (**2**) may be due to γ-1actam and its N-substituent (Kawagishi et al. 1990). Novel γ-pyrones, erinapyrones A (**43**), and B (**44**) (Fig. 3) have been isolated from the culture-broth of *H. erinaceus* mycelia. The compound (**43**) and (**44**) exhibited cytotoxicity against HeLa cells minimum concentration giving complete death of the cells for (**43**) was 0.88 and for (**44**) was 1.76 mM (Kawagishi et al. 1992).

Aromatic compound hericenone L (**45**) (Fig. 3), isolated from the fruit bodies of *H. rinaceum* and displayed cytotoxic activity against the EC109 cell line with an IC_{50} of 46 µg/mL (Ma et al. 2012). A new isoindolinone alkaloid named isohericenone (**46**), together with compounds, namely isohericerin (**47**), erinacerin A (**48**), 3,4-dihydro-5-methoxy-2-methyl-2-(4'-methyl-2'-oxo-3'-pentenyl)-9(7H)-oxo-2H-furo[3,4-h]benzopyran (**33**), were extracted from the semi dried fruit bodies of *H. erinaceus*. The compound **(46**) displayed the potent cytotoxic activity with IC_{50} values of 2.6, 3.1, 1.9, and 2.9 µM against A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines, respectively. The compound (**47**) showed cytotoxic activity against A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines (IC_{50} values of 21, 8.9, 3.1, and 19 µM, respectively). The compound (**33**) was found to be active against A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines (IC_{50} values of 17, 11, 13, and 16 µM, respectively). The compound (**48**) showed toxicity against A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines (IC_{50} values of 11, 11, 7.7, and 14 µM, respectively). Doxorubicin a positive control displayed cytotoxicity against A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines (IC_{50} values of 0.001, 0.003, 0.002, and 0.081 µM, respectively) (Kim et al. 2012).

A new diterpene (**49**) (Fig. 3), was isolated from the fungal mycelia of *H. erinaceus* and displayed good cytotoxicity against K562, LANCAP, HEP2 cancer cell lines with I IC_{50} values of 124.5, 362.3 and 198.6 µM, respectively. Positive control fluorouracil displayed cytotoxicity against K562, LANCAP, HEP2 cell lines with IC_{50} values of 76.9, 61.5, and 38.5 µM, respectively (Zhang et al. 2015a). Compounds (E)-5-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one (**50**), was purified from the solid culture of *H. erinaceus*. The compound (**50**) also showed poor cytotoxic activity against A549 and HeLa, cells (IC_{50} values of 49.0 and 40.5 µM, respectively) (Wang et al. 2015a).

New alkaloids, erinacerin M (**51**), erinacerin N (**52**) (Fig. 3), erinacerin O (**53**), erinacerin P (**54**) (Fig. 4), were extracted from the solid cultures of *H. erinaceus*. The compounds (**51**–**54**) showed moderate cytotoxicity against wild K562 cells with the IC_{50} values of 16.3, 18.2, 15.9, and 11.4 µM, respectively (adriamycin as positive control, IC_{50} = 0.6 µM) (Wang et al. 2015b). Later erinacerin O (**53**) and erinacerin P (**54**), were also isolated from *H. erinaceus*. The compound erinacerin P (**54**) displayed good cytotoxic activity against human glioma cell line U87 with an IC_{50}

value of 19.32 μg/mL. It was observed that the apoptosis of U87 cells treated with (**54**) increased, and the morphology of U87 cells altered significantly. Erinacerin P (**54**) increases the rate of apoptosis rate of U87 cells through Bax/capase-3 pathway and reduces DNA replication. (Zhang et al. 2020).

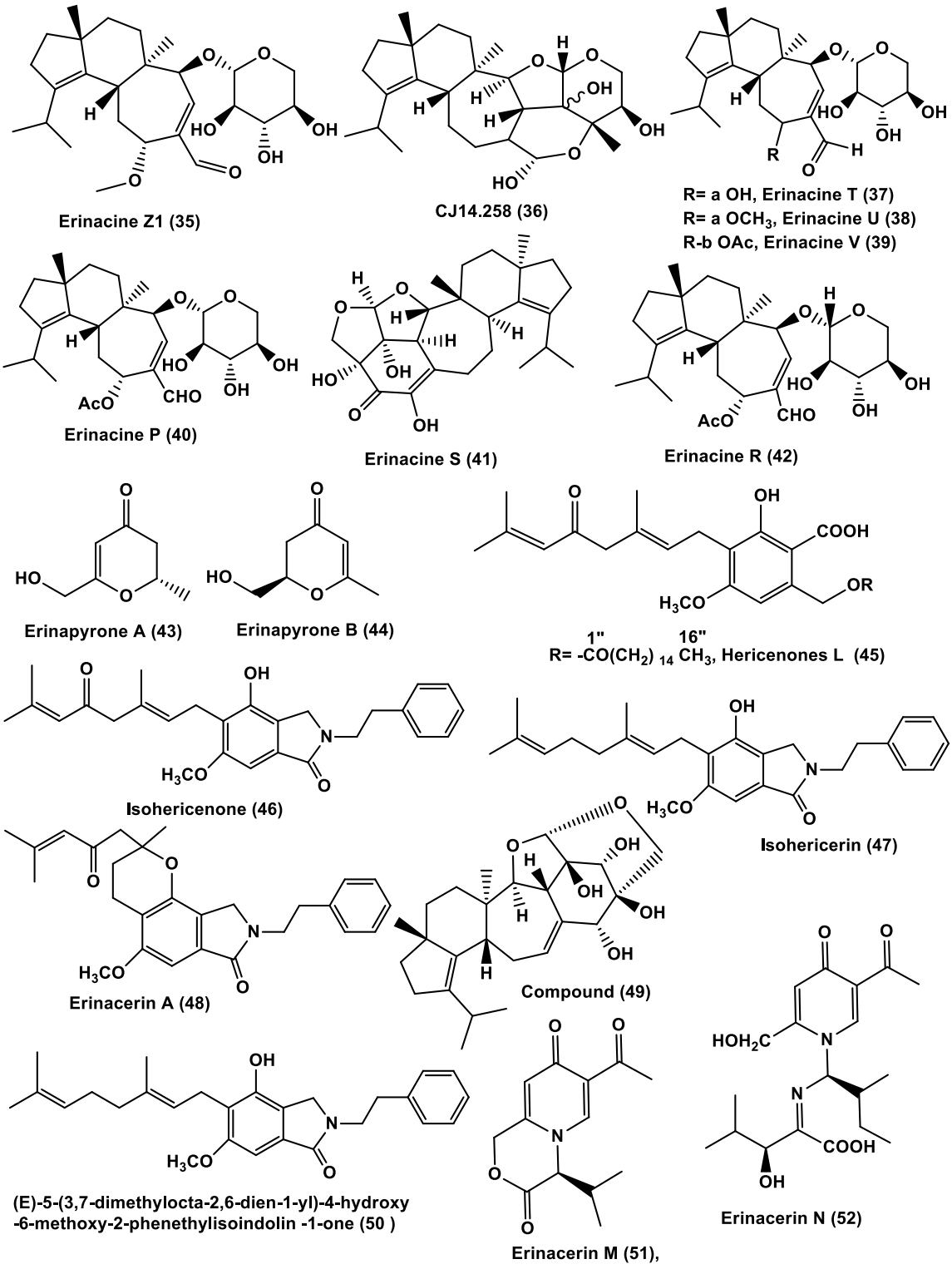

Fig. 3 – Cytotoxic compounds isolated from *Hericium erinaceus.*

Two new aromatic compounds, hericerin A (**55**) and isohericenone J (**56**), along with five known compounds, isoericerin (**57**), hericerin (**58**), N-De phenylethyl isohericerin (**59**), hericenone J **(10)**, and 4-[3',7'-dimethyl-2',6'-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol (**60**),

were obtained from a methanol extract of the fruiting bodies of *H. erinaceus*. The compounds (**10, 55–60**) displayed cytotoxicity against HL-60 cell lines with IC_{50} of 4.13, 3.06, 59.74, 5.47, 62.24, 4.10, and 4.28 μM, respectively (positive control Mitoxantrone IC_{50} 0.075 μM). The compound (**10, 55, 56, 60**) displayed cytotoxicity against HEL-299 cell lines with IC_{50} of 5.07, 64.61, 5.79, and 8.46 μM, respectively. The compounds (**55**) and (**58**) also induced apoptosis of HL-60 cells along with time-dependent downregulation of c-myc and p-AKT levels (Li et al. 2015a). Two purified compounds, 1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone (**61**) and 2,5-bis(methoxycarbonyl)terephthalic acid (**62**), were obtained from the ethanoic extract of fruit bodies of *H. erinaceus* and displayed weak cytotoxicity against K562 with IC_{50} <200mM (Liu et al. 2016).

Five new isoindolinones named erinaceolactams A-E (**63–67**) (Fig. 4), together with five known compounds hericenone A (**1**), hericenone J (**10**), erinacerin A (**48**), hericerin (**58**), and N-De phenylethyl isohericerin (**59**) were purified from the fruit bodies of *H. erinaceus* extracted in 70% ethanol. These compounds (**1, 10, 59, 48, 58, 63–67**) exhibited significant cytotoxicity against SMMC-7221 comparable to or more potent than 5-FU. Some compounds (**1, 10, 48, 63, 65–67**) serve as growth inhibitors of SMMC-7221 in a dose-dependent manner. In MHCC-97H, compounds (**1, 59, 67**), inhibited the cell growth dose-dependently. Among these compounds (**1, 10, 59, 48, 58, 63–67**), compound (**1**) (20 μg/mL) showed the most potent activity against the growth of SMMC-7221 and MHCC-97H (Wang et al. 2016).

A new cyathane-type diterpenoids, hericinoid B (**68**) and known analogues erinacine Z2 (**69**) (Fig. 4), erinacine Z1 (**35**), were isolated from fermentation broth of *H. erinaceus*. The compounds (**68, 35,** and **69**) displayed potent cytotoxicity against HL-60 cell lines with the IC_{50} values of 18.3, 8.9, and 0.5 μM, respectively. The compounds (**35**) and (**69**) showed moderate cytotoxicity against MCF-7 cell lines with the IC_{50} values from 13.4 to 15.8 μM. Cisplatin as positive control showed cytotoxic activity towards HL-60 MCF-7 cells (with IC_{50} value of 2.8 and 27.7 μM, respectively), while paclitaxel as another positive control showed cytotoxic activity towards HL-60 MCF-7 cells (IC_{50} of <0.008 μM each) (Chen et al. 2018).

A known cyathane diterpene erinacine A (**17**) was isolated from the liquid cultures of *H. erinaceus* and displayed weak cytotoxicity against PC12 cells (IC_{50} of 73.7 μM) (Zhang et al. 2018). Known compounds ergosteryl stearate (**70**), ergosterol peroxide (**71**) **(**Fig. 5**)**, and hericenone I (**9**) were isolated from the fruiting bodies of the medicinal mushroom *H. erinaceus*. The compound (**9**) displayed potent cytotoxic activity against SH-SY5Y, 1321N1, HCT-116, Caco-2, OVK18, and HeLa cell lines with IC_{50} values of 36.69, 41.66, 7.66, 49.53, 0.99, and 25.94 μM, respectively. The compound (**71**) displayed potent cytotoxic activity against SH-SY5Y, 1321N1, HCT-116, Caco-2, OVK18, and HeLa cell lines with IC_{50} values of 10 8.84, 21.68, 52.73, 6.35, 8.07, and 33.04 μM, respectively. The compound (**70**) displayed selective cytotoxic activity against SH-SY5Y, HCT-116, and OVK18 cell lines (IC_{50} values of 35.52, 2.77, and 8.1 μM, respectively) (Ashour et al. 2019).

The peptide Lys-Ser-Pro-Leu-Tyr (KSPLY) was derived from *H. erinaceus*, its synthetic peptide showed potential immunomodulatory activity at 100 μmol/l and also promoted NO, IL-1β, IL-6 and TNF-α secretion of by the macrophages. The KSPLY also inhibited secretion of nitric oxide (NO) as well as IL-6 by the M1 macrophages with a tendency of transformation of macrophages M2 macrophages into M1. This peptide is an effective immunomodulation seems to be beneficial to combat human cancer (Yu et al. 2021).

A study by Tung et al. (2021) indicated that erinacine S (**41**) specifically induces cell apoptosis and increased ROS production in gastric cancer cells only. The normal cells are not affected. Erinacine S (**41**) also suppressed tumor growth in a xenograft mouse model. Furthermore, erinacine S (**41**) treatment significantly increases the FasL and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) protein. In contrast, it also decreased the levels of PCNA as well as cyclin D1 in the gastric cancer xenograft in mice. In human gastric epithelial cell line (AGS) the erinacine S (**41**) triggers the apoptosis pathways (TRAIL, Fas-L and caspase-8, -9, -3) as well as suppresses the expression of the antiapoptotic molecules like Bcl-2 and Bcl-XL. Besides, erinacine S (**41**) causes arrest of cell cycle phase G1 via inactivation of CDKs/cyclins. The data

also revealed that activation of AKT/FAK/PAK1 and ROS-derived pathways involved in the erinacine S-mediated transcriptional activation of Fas-L and TRAIL by H3K4 trimethylation on their promoters (Tung et al. 2021).

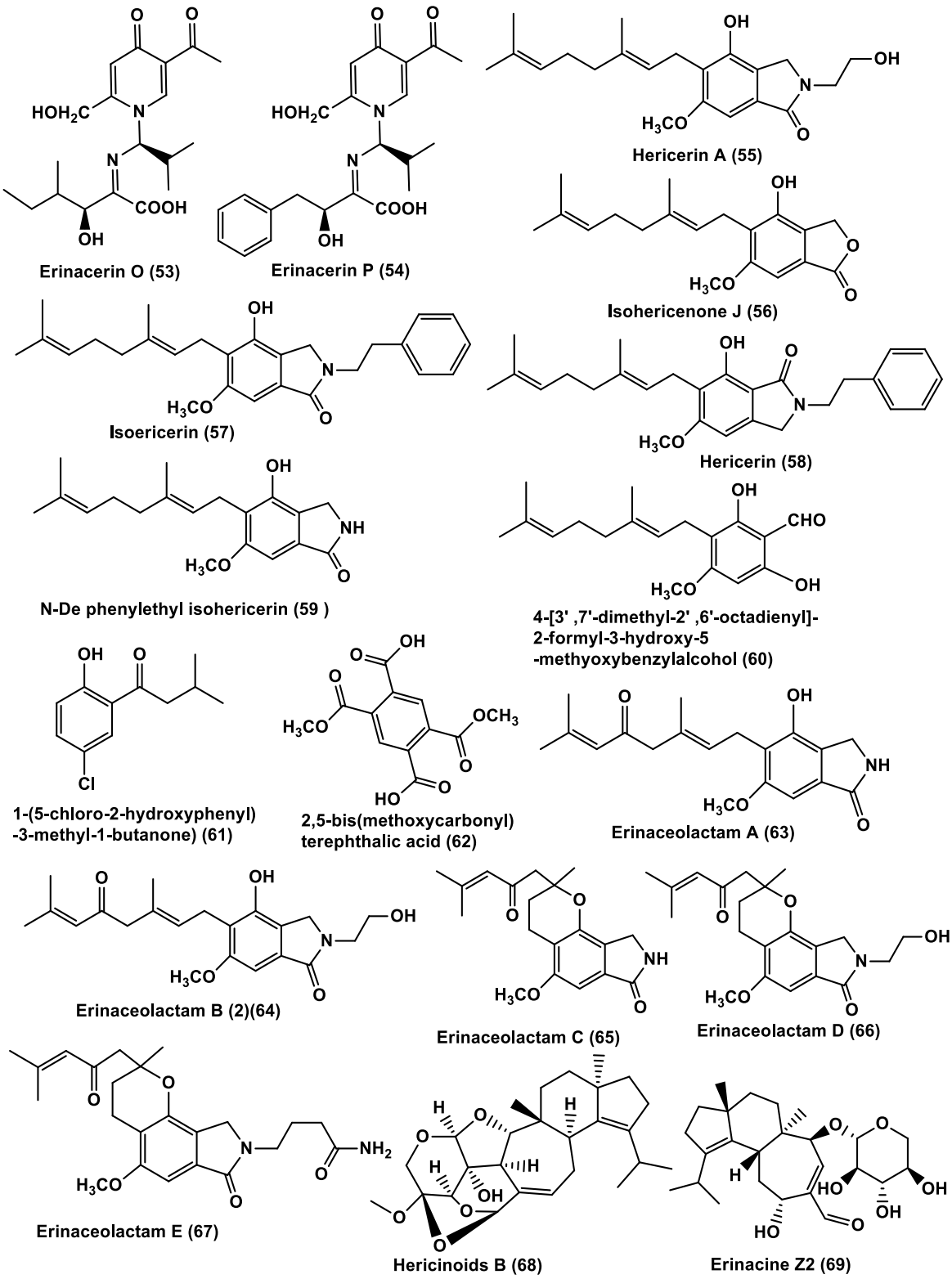

Fig. 4 – Cytotoxic compounds isolated from *Hericium erinaceus* (cont.).

The microwave-assisted extraction in 50% ethanol, hot water extract (HWE), acidic as well as alkaline extracts of the fruit body of *H. erinaceus* showed the apoptotic ability against the U937 human monocytic leukemia cells. Assays like cell viability, cytotoxicity, chromosomal DNA

integrity, and expression of pro- and anti-apoptotic proteins, mitochondrial membrane potential and activation and inhibition of caspase assays were performed to define the mechanism of apoptosis. The aqueous as well as aqueous/ethanolic extracts were active these assays, whereas the acidic and alkaline extracts were inactive. The results of the bioassays showed activation of mitochondria-mediated the caspase-3 and caspase-9 but not the caspase-8 (Kim et al. 2011). Erinacine A (**17**) also exhibited significant antitumor activity against TSGH 9201 cancer cell lines. It induced apoptosis in association with increased phosphorylation of focal adhesion kinase/protein kinase FAK/Akt/p70S6K as well as serine/threonine kinase PAK-1 pathways. It also involved in increase of cytotoxicity, increase of ROS generation, reduction of invasiveness, activation of caspases, and expression of tumor necrosis receptor (TRAIL) (Kuo et al. 2017).

Erinacine A is one of the major bioactive diterpenoids extracted from cultured mycelia of *H. erinaceus*, which displays pronounced antitumorigenic activities. An *in vitro* study on two human colon cancer cell lines: DLD-1 and HCT-116 showed that erinacine A stimulates the extrinsic apoptosis activation pathways (TNFR, Fas, FasL and caspases) and decreases the levels of antiapoptotic molecules Bcl-2 and Bcl-XL, suppresses of phosphorylation of Jun N-terminal kinase JNK1/2 and responsive to stress stimuli (NF-κB p50 and p330). The in vivo assay showed that Erinacine A increases the levels of histone H3K9K14ac, histone acetylation on Fas and FasL including TNFR promoters (Lee et al. 2019).

Anticancer effect of extracts (HTJ5 and HTJ5A) obtained from the broth of *H. erinaceus* was evaluated against many cancers by in vitro cancer cell lines and in vivo tumor xenografts (e.g. gastrointestinal cancers: liver, colorectal and gastric). The *H. erinaceus* extracts HTJ5 and HTJ5A displayed cytotoxic activity against the liver (HepG2 and Huh-7), colon (HT-29), and gastric (NCI-87) cancer cells. In in vivo tumor xenograft studies, the HTJ5 and HTJ5A exhibited significant antitumor activity against the four xenograft models (HepG2, Huh-7, HT-29, and NCI-87) without the host toxicity. In addition, the HTJ5 and HTJ5A showed higher effect compared to the 5-FU against the above-mentioned tumors with less toxicity. A total of 22 compounds were fetchd from the fractions of HTJ5/HTJ5A with seven cyclic dipeptides, six small aromatic compounds, five indole, three flavones, one anthraquinone, pyrimidines and amino acids derivatives. These compounds include seven cyclic dipeptides: cyclo(Val-Tyr), cyclo(Leu-Tyr), cyclo(Phe-Tyr), cyclo(Phe-Phe), cyclo(Leu-Leu), cyclo(Leu-Ala), and cyclo(Val-Ala); five indole, pyrimidines, amino acids and derivative: 5-hydroxy-2-pyridinecarboxylic acid, 3-formylindole, uracil, 2,3,4,9-tetrahydro-1Hpyrido[3,4-b]indole-3-carboxylic acid, and tryptophan; three flavones (flavonoid glycoside): neoliquirtin, liquiritigenin, and calycosin; one anthraquinone: emodin; and six small aromatic compounds: 4-hydroxy-3-methoxybenzoic acid, 4-hydroxy-3-methoxycinnamic acid, hydroxy-benzaldehyde, 4-hydroxybenzoic acid, 3,4-dihydroxybenzaldehyde and syringic acid (Li et al. 2014a).

Anticarcinogenic effects

An anticarcinogen is a carcinopreventive agent that counteracts the effects of a carcinogen on normal cells and inhibits the development of cancer. Extract from *H. erinaceus* or bioactive from *H. erinaceus* possess anticarcinogenic effects, and some of them are illustrated below.

The mutagenicity and genotoxicity effects of erinacine A-enriched *H. erinaceus* (EAHE) mycelium were evaluated by in three standard tests (chromosomal aberration, micronuclei tests and reverse mutation). The results showed that the EAHE mycelium has not increased the number of revertant colonies in bacterial reverse mutation and not induced higher frequency of aberrations. In addition, there was no significant EAHE mycelium-induced increase was seen in the incidence of reticulocytes per 1000 RBC as well as micronucleus per 1000 reticulocytes. All these three standard tests suggested lack of mutagenicity and genotoxicity of EAHE mycelium at test doses under standard experimental conditions (Li et al. 2014b). Glycosphingolipid (monoglycosylceramides cerebroside E) (**72**), is a new cerebroside isolated from the fruit bodies of *H. erinaceus* (Fig. 5). This has alleviated cisplatin-induced nephrotoxicity (in LLC-PK1 cells) as well as inhibited the angiogenesis in HUVECs (Lee et al. 2015).

The *H. erinaceus* has been showed a protective effect on cell death of ischemia-injury-induced neurons in rats. It has been demonstrated that pretreatment with *H. erinaceus* attenuated the DEHP-induced cell death significantly. Such protective effect may be owing to its ability to reduce the intracellular levels of ROC species, which preserves the activity of respiratory complexes to stabilize the potential of mitochondrial membrane. In addition, *H. erinaceus* pre-treatment has modulated Nrf2 and Nrf2-dependent vitagenes expression significantly, thus prevents rise of pro-apoptotic and the fall of antiapoptotic markers. Overall, the present study provided evidence towards new preventive nutritional strategy by *H. erinaceus* over DEHP-induced apoptosis (PC12 cells) (Amara et al. 2020).

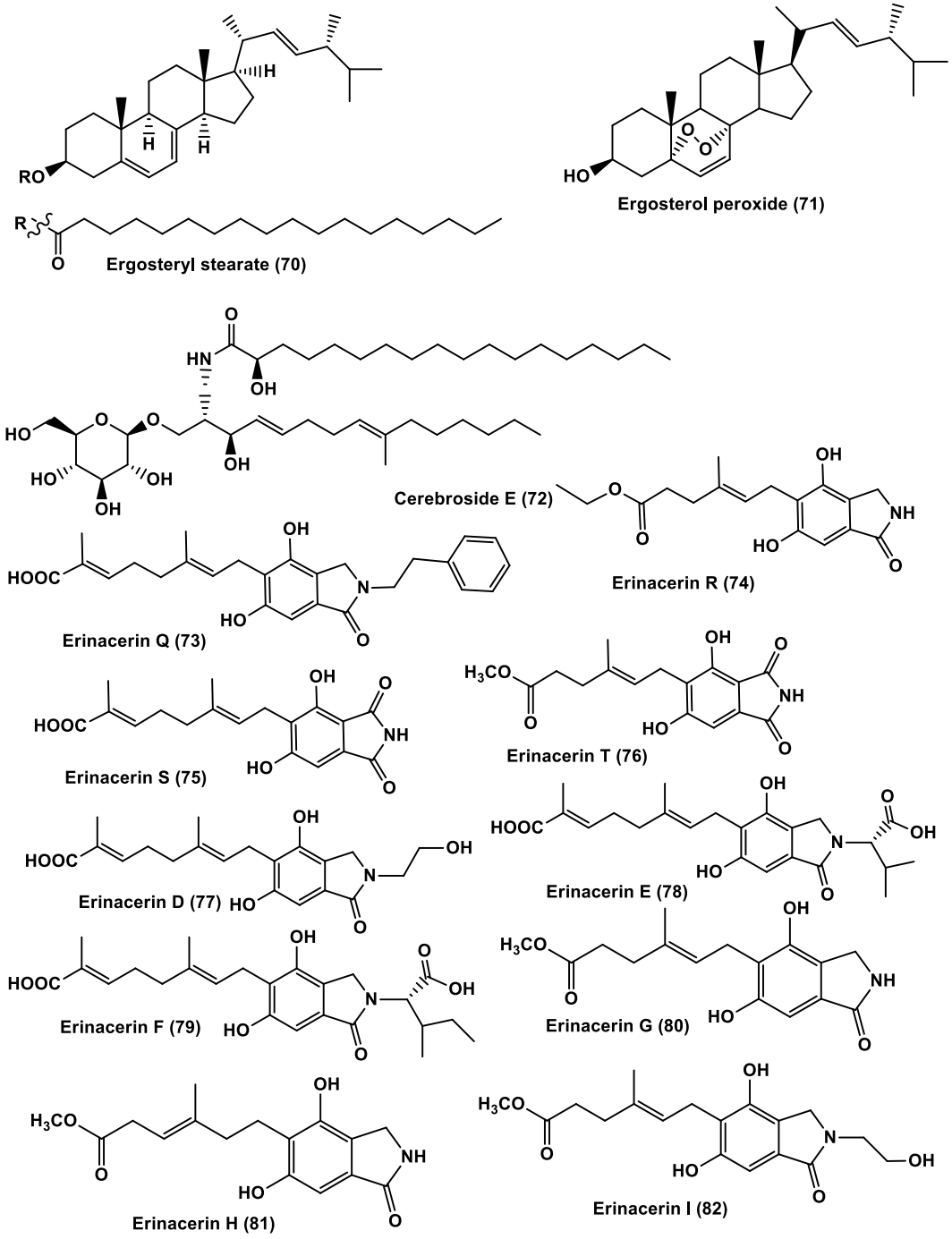

Fig. **5 –** Cytotoxic compounds isolated from *Hericium erinaceus* (cont.).

The *H. erinaceus* mycelium-enriched erinacine A (5 mg/g) toxicity by a 28-day oral administration using Sprague-Dawley rats at three doses (low, 1 g; medium, 2 g; high 3 g/kg body

weight/day) were selected with distilled water as control showed survival of all the animals till end of the study. No abnormality in clinical signs were observed without adverse differences were found in haematology, serum biochemical parameters and urinalysis among the control and treated groups. Similarly, pathologically and histopathological manner, no gross changes were evident. Thus, the EAHE at 3g/kg body weight/day has no adverse effects on test Sprague-Dawley rats (Li et al. 2014c).

Antidiabetic Activity (Alpha-glucosidase inhibitors)

Diabetes mellitus (DM) is one of the rapidly growing lifestyle disorders of 21st century, affecting the health of significant population worldwide. According to recent statistical studies, it is estimated that about 415 million people across the world are presently suffering from diabetes (Ogurtsova et al. 2017). Some of the compounds isolated from *H. erinaceus* possess antidiabetic propert*ies* and are illustrated below.

New alkaloids, erinacerins Q (**73**), R (**74**), S (**75**), and T (**76**), were purified from the cultures of *H. erinaceus* (Fig. 5). These compounds (**73–76**) showed inhibitory activities against PTP1B with IC_{50} values of 29.1, 42.1, 28.5, and 24.9 μM, respectively (positive control, sodium vanadate IC_{50} = 1.2 μM). The compounds (**73–76**) showed inhibitory activities against a-glucosidase inhibition with IC_{50} values of 12.7, 23.3, 19.5, and 20.1 μM, respectively (positive control, acarbose IC_{50} = 273.1 μM) (Wang et al. 2015b).

New compounds isoindolin-1-ones designated as erinacerins D-L (**77–85**) along with (E)-5-(3,7-dimethylocta-2,6-dien-1-yl) -4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one (**50**) were obtained from the cultures of *H. erinaceus*. These compounds (**50, 77–85**) showed inhibitory effect at IC_{50} ranging from 5.3–145.1 μM in α-glucosidase inhibition assay (Fig. 6). The structure-activity relationship indicated that the presence of terpenoid side chain and phenolic hydroxy groups are conducive for the α-glucosidase inhibitory activity of **50** and **77–85)** (Wang et al. 2015a).

Four new compounds, erinacenol D (**86**), together with known compounds 4-[3',7'-dimethyl-2',6'-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol (**87**), hericene A (**88**), hericene D (**89**), and known compound hericenone D (**4**) retrieved from the fruit bodies of *H. erinaceus*. These compounds (**86–89** and **4**) displayed potent α-glucosidase inhibitory activity with IC_{50} 19.6, 7.5, 6.7, 3.9, and 15.5 μM, respectively (positive control acarbose, IC_{50}, 71.2 μM). The molecular docking showed the interaction of α-glucosidase as well as isolated compounds supporting the inhibitory activity against α-glucosidase (Lee et al. 2020).

Meroterpenoids hericenes B (**90**) and hericenones C(**3**), E(**5**), F(**6**), G(**7**) were purified from the fruit body of *H. erinaceus*. The most potent inhibitory activities on PNPG (4-Nitrophenyl beta-D-galactopyranoside) showed by the compound (**7**) and sucrose (IC_{50} of 15.2 and 12.6 μM, respectively). The compound (**3**) possesses the strongest inhibitory activities on maltose (IC_{50} of 15.3 μM), while the positive control acarbose showed IC_{50} of 38.1, 20.5, and 17.1 μM against PNPG, sucrose, and maltose, respectively. The compound (**90**) led the most potent inhibitory activities on PNPG sucrose maltose (IC_{50} of 29.6, 29.1, and 65.5 μM, respectively). The compound (**3**) showed the most potent inhibitory activities agaonst PNPG, sucrose and maltose with the IC_{50} of 21.9, 13.5, and 15.3 μM, respectively. The compound (**5**) possesses the strongest inhibitory activities against PNPG, sucrose and maltose with the IC_{50} of 23.3, 42.5, 25.5, μM, respectively. The compound (**6**) was the most potent inhibitory potential against PNPG sucrose maltose with the IC_{50} of 45.3, 67.1, >100 μM, respectively. The compound (**7**) also showed the most potent inhibitory potential against PNPG, sucrose and maltose with the IC_{50} of 15.2, 12.6 and 33.1 μM, respectively. The positive control acarbose showed the most robust inhibition against PNPG, sucrose, and maltose with IC_{50} of 45.3, 67.1, >100, 38.1, 20.5, and 17.1 μM, respectively (Chen et al. 2020).

Antioxidant potential

Antioxidants are the substances that protects the cell organelles by reacting with highly reactive free radicals which are produced during metabolism. Among various natural alternative

sources, mushrooms are identified as a major source of potent antioxidant compounds (Mishra et al. 2020). Bioactive metabolites from *Hericium* with antioxidant properties are illustrated below.

Lew et al. (2020) investigated the antioxidant activities of a standardized aqueous extract of *H. erinaceus* in an in vitro model of FRDA (Friedreich Ataxia) involving L-Buthionine sulfoximine (L-BSO)-induced human dermal fibroblast expressing abnormal expansion of GAA triplet repeat. L-buthionine sulfoximine is an inhibitor of γ-glutamylcysteine synthetase, which plays a role in GSH biogenesis (Lew et al. 2020).

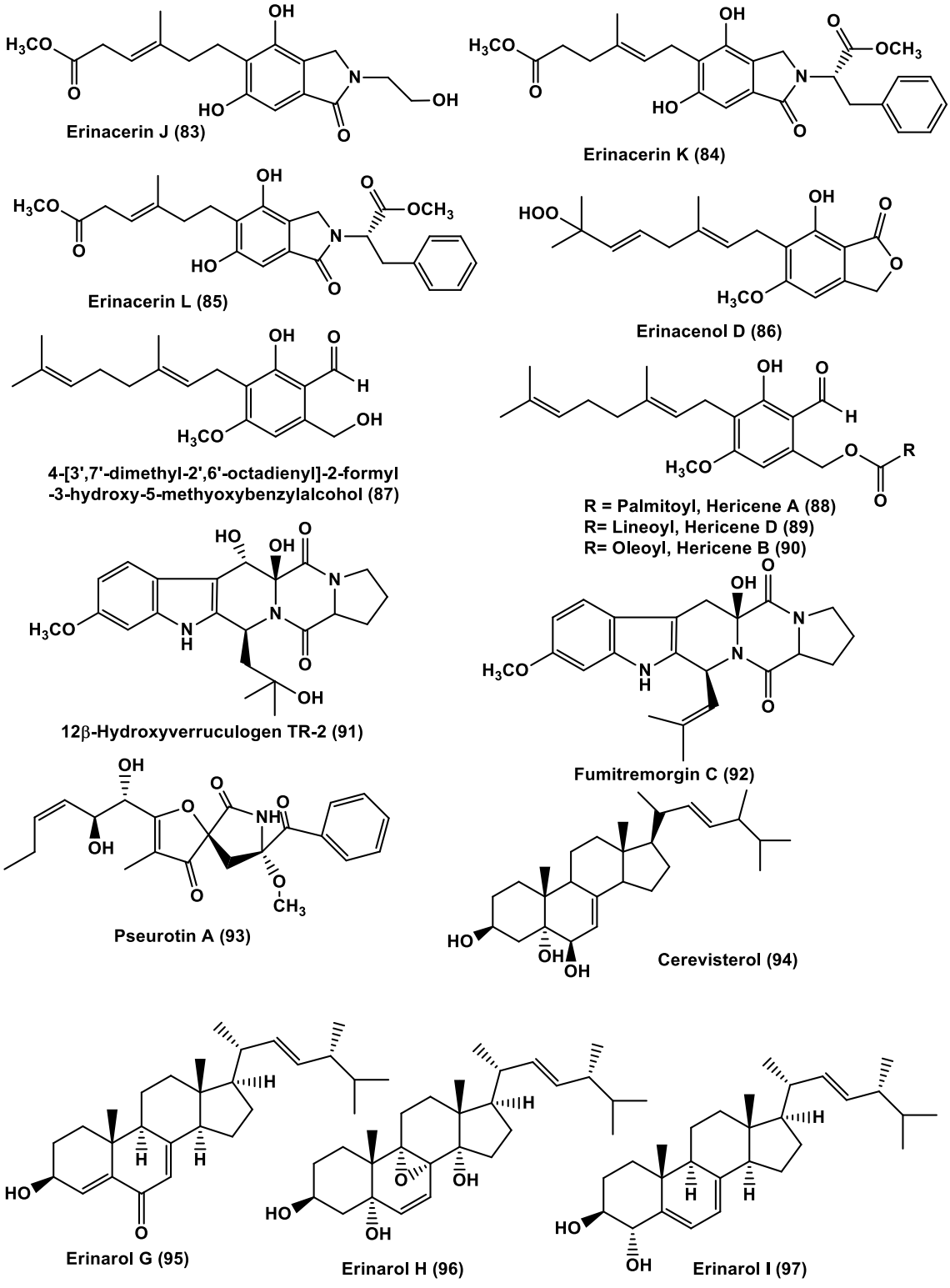

Fig. **6 –** Anti-diabetic compounds isolated from *Hericium erinaceus.*

Previously reported diketopiperazine alkaloids, 12b-hydroxyverruculogen TR-2 (**91**), fumitremorgin C (**92**), and hetero-spirocyclic γ-lactam alkaloids, pseurotin A (**93**), and cerevisterol (**94**) were purified from the mycelium of the *H. erinaceus*. These compounds (**91–94**) displayed scavenging activity in DPPH assay with IC_{50} values of 12.56, 50.00, 12.56, and 11.38 μM, respectively (positive control TBHQ IC_{50}, 5.75 μM, while the ascorbic acid showed IC50, 1.95 μM) (Fig. 6). The results indicate that compounds (**91, 93,** and **94**) exhibited better antioxidant activity against in DPPH assay with IC_{50} of ca. 12 μM, compared with the tertiary butylhydroquinone as a positive control (Lu et al. 2014).

Anti-inflammatory activity

Inflammation is one of the protective processes that can become disrupted under pathological conditions. It can lead to many ailments such as multiple sclerosis, rheumatoid arthritis, psoriasis and inflammatory bowel diseases. It also plays a crucial role in many complex disorders like cancer, cardiovascular disease and AD. Many therapies could be followed to treat inflammation-driven ailments such as antihistamines, steroids and non-steroidal anti-inflammatory drugs. In spite of some success, still there is a gap to treat the inflammatory diseases. Various structurally diverse bioactive metabolites are reported from *Hericium* with the capability to serve as a lead molecule to develop as an anti-inflammatory drug in the future. Here we summarize the anti-inflammatory property of bio-actives from *H. erinaceus*.

Erinacine C (**19**) is well known for antineuro-inflammatory and neuroprotective functions, which could be accomplished by mechanisms such as inducible nitric oxide synthase (iNOS) protein expression, activation of Nrf2/HO-1 stress-protective pathway and inhibition of IκB, p-IκBα (involve in the upstream NF-κB signal transduction cascade) (Wang et al. 2019a). Treating human BV2 microglial cells with lipopolysaccharide (LPS)-induced inflammation caused reduction in levels of many constituents such as: IL-6, TNF-α, nitric oxide (NO) and iNOS; expression of the heme oxygenase-1 (HO-1) protein; increased nuclear transcription factor erythroid 2-related factor (Nrf2); inhibition of phosphorylation of IκBα (p-IκBα) proteins; inhibition of NF-κB expression; inhibition of Kelch-like ECH-associated protein 1 (Keap1). Considering these data, the mechanism of action of EC includes: expression of iNOS, activation of the Nrf2/HO-1 pathway and inhibition of IκB, p-IκBα (Wang et al. 2019a).

Four new sterols namely erinarol G (**95**), erinarol H (**96**) (Fig**.** 6**)**, erinarol I (**97**), erinarol J (**98**), along with known sterols namely (3b,5a,22E)-ergosta-6,8(14),22-triene-3,5-diol (**99**), fomentarol A (**100**), (3b,7a,22E)-ergosta-8(14),22-diene-3,7-diol (**101**), 7-ketobrassicasterol (**102**), (3b,22E) ergosta-5,8(14),22-triene-7-one (**103**), 5a,6a-epoxy-3b-hydroxy-ergosta-22-ene-7-one (**104**), 5a,6a-epoxy-(22E,24R)-ergosta-8(14),22-diene-3b,7b-diol (**105**), 5a,6a-epoxy-(22E,24R)-ergosta-7,22-diene-3b-ol (**106**), 5a,6a;8a,9a-diepoxy-(22E,24R)-ergosta-22-ene-3b-7a-diol (**107**), and 5a,6a;8a,9a-diepoxy-(22E,24R)-ergosta-22-ene-3b-7b-diol (**108**) were isolated from a methanol extract of the dried fruiting bodies of *H. erinaceus* (Fig. 7). Anti-inflammatory functions of these compounds were evaluated towards NO production in LPS-stimulated murine RAW264.7 macrophage cells and inhibition of TNF-α. The compounds (**96**, **98–100**) exhibited inhibitory activity against TNF-α secretion, with inhibition values of 37.5%, 43.3%, 36.7%, and 33.7%, respectively, at 10 μM (positive control Celecoxib, 52.5% at 1 μM). The compounds (**95**, **97, 101**, and **103**) exhibited moderate inhibitory activity of TNF-α secretion with inhibition ranging from 24.6–26.3% at the same concentration. Compounds (**98**, **102–104**), exhibited significant inhibitory effects against NO production, with inhibition values of 38.4%, 50.5%, 71.5%, and 51.6%, respectively, while at 10 μM (positive control Celecoxib, 55.9% at 1 μM), compounds (**99**) and (**106–109**) exhibited moderate inhibitory activities. Only compound (**98**), which possesses a 6,8-dioxabicyclo[3.2.1]oct-2-ene moiety, showed strong inhibition in both the nitric oxide and TNF-a secretion assay (Li et al. 2015b).

Oral *H. erinaceus* treatment showed promising efficacy in the experimental colitis model. Biochemical indexes and microscopic and macroscopic colitis scores were analyzed. The TNF-α, MPO, NO, MDA, and IL6 cytokines, which affect TBNS-induced colitis models, were examined,

and TNF-α, MPO, NO, MDA, and IL6 levels were lower in the *H. erinaceus* treatment group than in the colitis groups. The less mucosal injury was detected in the *H. erinaceus* treatment group than in the colitis group. The results indicate that the improvement of inflammatory bowel disease (IBD) is due to the anti-inflammatory properties of *H. erinaceus*. The main disadvantage of oral therapy with HE is the unknown dose required for the anti-inflammation effect (Durmus et al. 2021).

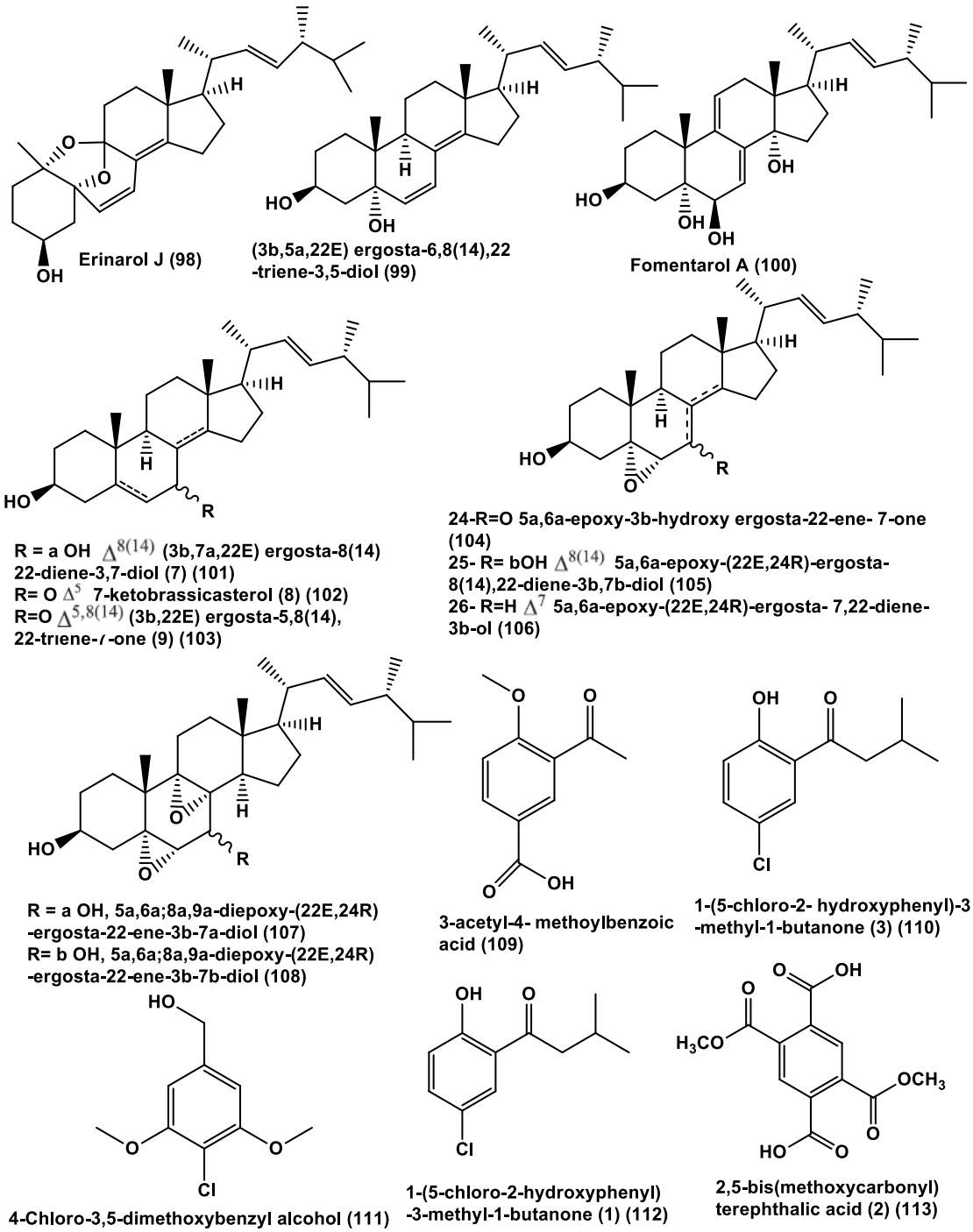

Fig. 7 – Antimicrobial compounds isolated from *Hericium erinaceus.*

Hot water (HE-HWA) and ethanolic (HE-ETH) extracts of *H. erinaceus* were investigated for anti-inflammatory and neuroprotective activities: neurotoxicity of hydrogen peroxide (H_2O_2)-induced in HT22 mouse hippocampal neurons and lipopolysaccharide (LPS)-induced BV2 microglial activation. The HE-ETH revealed a potent neuroprotective action through significant

increase in the viability of H_2O_2-treated neurons. In addition, significant reduction in ROS and improvement in the antioxidant enzyme catalase (CAT) and glutathione (GSH). The HE-ETH showed the capacity to significantly improve the mitochondrial membrane potential (MMP) as well as ATP production, whereas reduction in mitochondrial toxicity, nuclear apoptosis and Bcl-2-associated X (Bax) gene expression. However, some of the functions are not affected: heme oxygenase 1 (HO-1), gene expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and NAD(P)H quinone dehydrogenase 1 (NQO1). The HE-ETH also showed significant reduction in nitric oxide (NO) level in LPS-treated BV2, showed an anti-inflammatory activity in the microglia. Thus, the HE-ETH has the potential towards neuroprotective and anti-inflammatory functions in the neuroglia environment (Kushairi et al. 2019)

Platelet aggregation inhibitor

Platelet aggregation inhibitors prevent platelet adhesion and subsequently clot formation by interfering different steps on clotting cascade**.** Platelet aggregation inhibitors are indicated in myocardial infarction, atrial fibrillation, following coronary bypass, angioplasty, and stenting**.** They are also used prophylactically to prevent myocardial infarction and stroke**.** The reported compounds isolated from *H. erinaceus* with platelet aggregation inhibitor activity are illustrated below.

Hericenone B (**2**) was isolated from the ethanolic extract of *H. erinaceus*. Hericenone B (**2**) selectively inhibited collagen-induced platelet aggregation however, did not affect the aggregation induced by U46619 (TXA_2 analogue), ADP, thrombin, or adrenaline. Furthermore, hericenone B (**2**) did not inhibit arachidonic acid- or convulxin (GPVI agonist)-induced platelet aggregation. Therefore, it was suggested that the hericenone B blocks collagen signaling from integrin α2/β1 to release arachidonic acid (Mori et al. 2010).

Antimicrobial activity

In the last two decades there is steady rise in the discovery of multidrug resistant bacteria (Penicillin resistant *Streptococcus pneumonia*, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*) (Nannini et al. 2010). Due to acquired resistance, it is cumbersome to diagnose and treat many diseases caused by multidrug resistant bacteria (Dheda et al. 2018). Owing to a few alternatives against the fungal diseases, there is necessity to develop compatible antifungal drugs to facilitate therapies like cancer, bone marrow/organ transplants (Lockhart & Guarner. 2019*).* The natural products obtained from *Hericium* are important sources to tune novel metabolites to facilitate the modern medicine. Following sections deal with some developments of using *Hericium*-derived antimicrobials.

One new diterpene (**49**) and new compound 3-acetyl-4-methoylbenzoic acid (**109**), along with four known compounds 1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone (**110**) 4-chloro-3,5-dimethoxybenzyl alcohol (**111**) (Fig. 7) isolated from the mycelium of *H. erinaceus.* The compound (**110**) showed potent antibacterial activity with MIC values 32.5–65 µg/mL, while compound (**49**) and (**109**) showed moderate antibacterial activity against the growth of *Helicobacter pylori* (ATCC43504) (MIC values 50-100 mg/mL), and compound (**111**) showed poor antibacterial activity with MIC values 62.5–125 µg/mL (Zhang et al. 2015a).

Two compounds, 1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone (**112**) and 2,5-bis(methoxycarbonyl)terephthalic acid (**113**) isolated from the ethanoic extract of fruit bodies of *H. erinaceus* (Fig. 8). The fruiting bodies of *H. erinaceus* were obtained at Fengxian District, Shanghai, China. The compound (**112**) displayed anti-*Helicobacter pylori* activity against *H. pylori* ATCC 43504, *H. pylori* SS1, *H. pylori* 9, *H. pylori* 64, *H. pylori* 78, *H. pylori* 83, *H. pylori* W2504, and *H. pylori* DXF with MIC values in the range of 12.5–50 µg/mL. In contrast, the compound (**113**) was found active against the same set of *H. pylori* strains with minimum inhibitory concentration (MIC) values in the range of 6.25–25 µg/mL. Positive control metronidazole displayed anti-*Helicobacter pylori* activity (range, 0.78–1.5625 µg/mL), while the other positive control tetracycline displays anti-*Helicobacter pylori* activity in the range of 0.78–3.125 µg/mL

against the same set of test strains. Both compounds showed weak cytotoxicity against K562 with IC_{50} <200 mM (Liu et al. 2016).

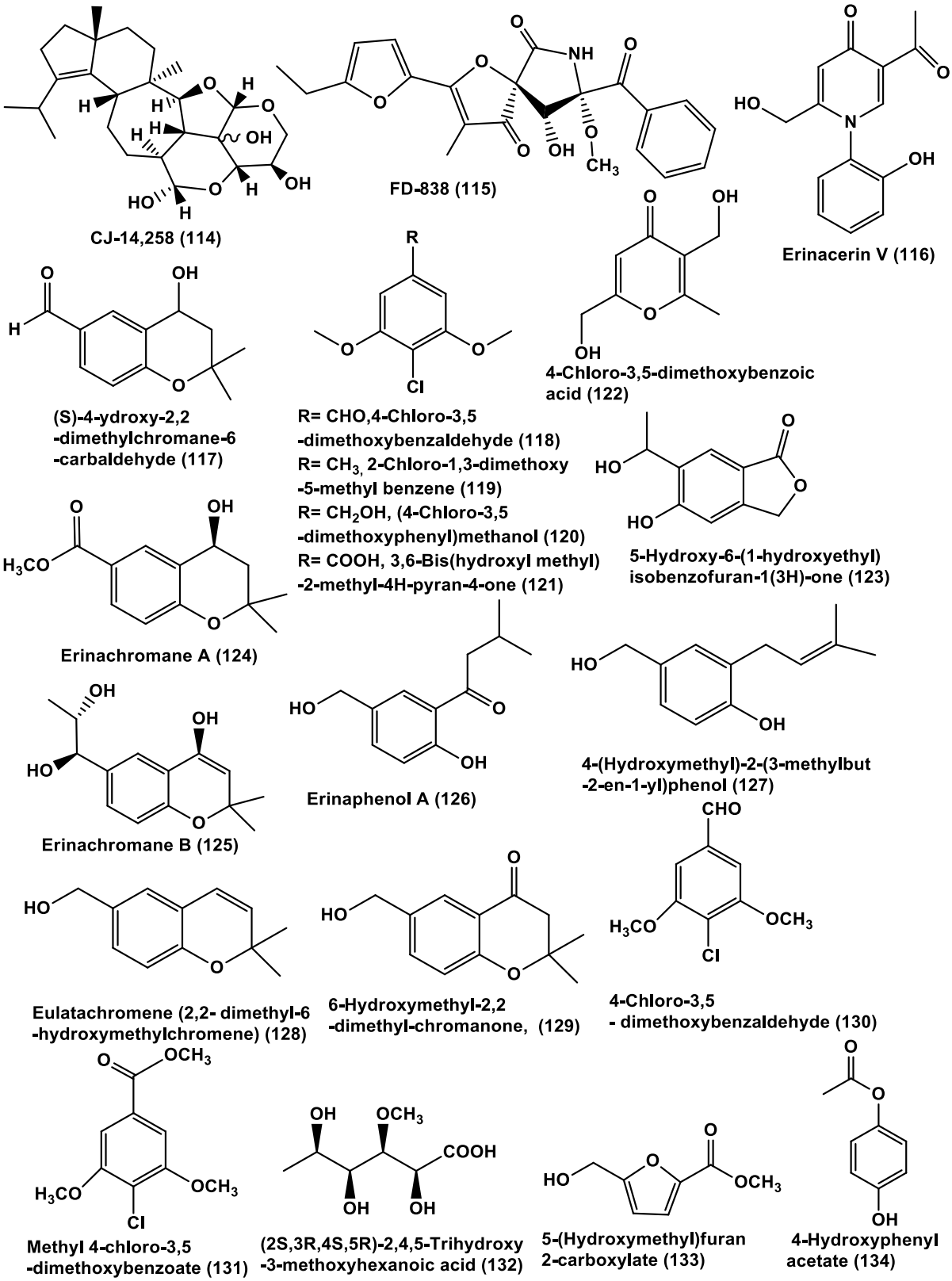

Fig. **8 –** Antimicrobial compounds isolated from *Hericium erinaceus.*

Known compounds CJ-14,258 (**114**) and erinacine C (**19**) isolated from cultured mycelia of *H. erinaceus*. The compounds (**114**) and (**19**) displayed antimicrobial activity against Methicillin-

resistant *Staphylococcus aureus* (MRSA) with MIC of 62.5 μM each (Kawagishi et al. 2006). A hetero-spirocyclic γ-lactam alkaloid called FD-838 (**115**) was isolated from the mycelia of the *H. erinaceus*. Compound (**115**) inhibited the growth of two phytopathogens (*Botrytis cinerea* and *Glomerella cingulate*), with MIC of 6.25 μM for each, similar to that of the positive fungicide carbendazim (Lu et al. 2014).

In a growth inhibition assay on six strains *H. pylori*, the ethanolic extracts of *H. erinaceus* showed growth inhibition of all strains with a MIC value of 2 mg/mL. Extract of *H. erinaceus* inhibited adhesion capacity of (AGS) *H. pylori* (ATCC CRL-1739). Extract of *H. erinaceus* inhibited adhesion capacity of (AGS) *H. pylori* (ATCC CRL-1739). Interleukin-8 (IL-8, an immune response factor) in supernatants from AGS and 8-oxo-guanine (8-oxoG, marker for oxidative DNA damage of the total host cell DNA) exposed to *H. erinaceus* extract were monitored prior to addition of *H. pylori*. The result was *H. pylori*-mediated immune response (IL-8 production) significantly decreased by the *H. erinaceus* extract, while at concentration 1.0 mg/mL, the IL-8 expression reversed to almost the background level (when no *H. pylori* added). Infection of AGS by *H. pylori* resulted in a 3-fold increase of host's 8-oxoG, however such increase was turndown by addition of 2 mg/mL *H. erinaceus* extract. Assays were carried out on colonization of C57BL mice on homogenized stomachs three weeks later inoculating *H. pylori*. The mice receiving the *H. erinaceus* extract had a mean *H. pylorus* at 6×10^4 CFU/g in the stomach, which was one log lower than the control (without extract) (Wang et al. 2019b).

The ethyl-acetate extract obtained from culture filtrate and mycelium of *H. erinaceus* displayed potent anti-*H. pylori* activities with MIC (MBC) of 1.25–1.5 (5–7.5) mg/mL and potential urease inhibitory activity with IC_{50} of 0.34-0.35 mg/mL. The culture filtrate extract also displayed good antioxidant activity (IC_{50}, 11.83 mg/mL), which was marginally better than that of mycelium extract (IC_{50}, 14.75 mg/mL). It was also found that the water fractions from the culture filtrate and the mycelium exhibited noticeable inhibitory activities against bacterial urease (IC_{50}, 1.26–1.40 mg/mL). However, they had poor or no anti-*H. pylori* activities with poor antioxidant activities (Ngan et al. 2021).

Using OSMAC (One Strain, Many Active Compounds approach a new erinacerin alkaloid erinacerin V (**116**), and a new aldehyde derivative of 4-hydroxy chroman, (S)-4-hydroxy-2,2-dimethylchromane-6-carbaldehyde (**117**), along with four known compounds 4-chloro-3,5-dimethoxybenzaldehyde (**118**), 2-chloro-1,3-dimethoxy-5-methyl benzene (**119**), (4-chloro-3,5-dimethoxyphenyl)methanol (**120**), 3,6-bis(hydroxyl methyl)-2-methyl-4*H*-pyran-4-one (**121**), 4-chloro-3,5-dimethoxybenzoic acid (**122**), 5-hydroxy-6-(1-hydroxyethyl)isobenzofuran-1(3*H*)-one (**123**), and erinacine *E* (**21**) were isolated from a mycelial culture of *Hericium* sp. (Fig. 8). Compound (**119**), exhibited antifungal activity against *Candida* such as *C. albicans* and *C. neoformans* (MIC, 31.3–62.5 μg/mL, respectively) and also inhibited biofilm formation of *C. albicans* and *C. neoformans* at 7.8 μg/mL (Song et al. 2020).

The related Basidiomycota *Agaricus blazei* Murill (AbM), *H. erinaceus* (HE), and *Grifola frondosa* (GF) have been shown to exert antimicrobial activity against viral agents, Gram-positive and Gram-negative bacteria, and parasites in vitro and in vivo. Since these basidiomycetes also have anti-inflammatory potential, they may be suitable to treat lung inflammation that often caused by COVID-19 infection.

Herbicidal activity

Herbicides are agents that are destructive to weeds or cause an alteration in their normal growth. The global herbicide market size is expected to reach overall market revenue of $7,998.9 million by 2025 by growing at a CAGR of 4.8% during the said period. There are some reports of herbicidal properties of bioactive metabolites. Three new compounds such as erinachromanes A and B (**124, 125**) and erinaphenol A (**126**) with ten previously reported compounds [4-(hydroxymethyl)-2-(3-methylbut-2-en-1-yl)phenol (**127**), eulatachromene (2,2-dimethyl-6-hydroxymethylchromene) (**128**) (Fig. 8)**,** 6-hydroxymethyl-2,2-dimethyl-chromanone, (**129**), 4-chloro-3,5-dimethoxybenzaldehyde (**130**), methyl 4-chloro-3,5-dimethoxybenzoate (**131**) and

(2S,3R,4S,5R)-2,4,5-trihydroxy-3-methoxyhexanoic acid (**132**), 5-(hydroxymethyl)furan 2-carboxylate (**133**), and 4-hydroxyphenyl acetate (**134**), compound (**135**), compound (**136**) were purified from the culture broth of *H. erinaceus* (Fig. 9). All of these compounds significantly halted the growth of lettuce. Some of the compounds such as (**134**) and (**135**) inhibited the growth of hypocotyl at low doses (1 and 10 nmol/paper) and exhibited poor activity at higher doses (100 nmol and 1 μmol/paper). Among the chromans (**124, 125, 128, 129**), (**128**) showed the potent inhibitory activity against hypocotyl (at 1 μmol/paper). Comparison of structures among (**125**) and (**128**) showed that the hydroxymethyl group at C-6 plays vital role in such activity. The compound (**129**) significantly ceased the growth of root (at 1 μmol/paper). It suggests that the chromanone skeleton (**129**) has mail role in root growth inhibition. The compound (**126**) also showed similar activity like the compound (**127**), indicates the side chain at C-1′ did not influence the growth regulation of plant. Among the dimethoxychlorobenzenes (**130, 131,** and **136**), (**136**) exhibited the strongest inhibition of root growth (at 1 μmol/paper). This suggests that the hydroxymethyl group is responsible for strengthening the inhibitory activity (Wu et al. 2019).

Two unique compounds, erinaceolactones A to B (**137**, **138**), and previously reported compounds 2-(hydroxymethyl)-6- methyl-4H-pyran-4-one (**139**), erinapyrones A (**140**) and B (**141**) and compound **(142)** were retrieved from the cultures of *H. erinaceus* (Fig. 9). Compounds such as (**139** and **142**) weakly inhibited the lettuce root growth (1 μmol/paper), while the compounds like (**138, 140,** and **141**) showed inhibition at lower dose (100 nmol/paper). The lettuce hypocotyl growth was inhibited by the compounds (**140** and **141**) 1 μmol/paper and 100 nmol/paper, respectively. The compound (**139**) inhibited the growth of root as well as hypocotyl at lower doses (1 and 10 nmol/paper, respectively), but no activity showed at the higher doses (100 nmol and 1 μmol/paper, respectively) (Wu et al. 2015).

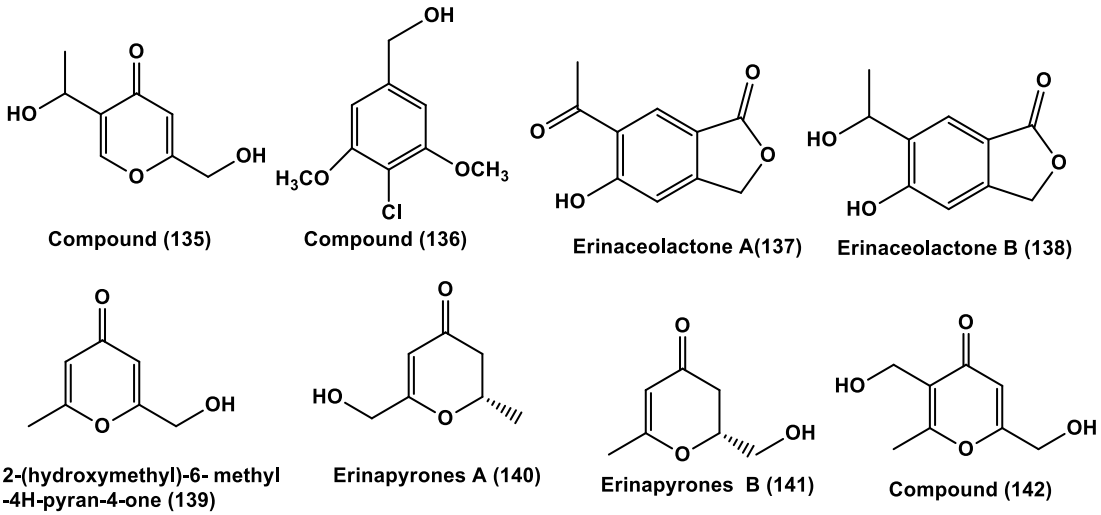

Fig. **9 –** Herbicidal compounds isolated from *Hericium erinaceus*

Conclusion

Hericium erinaceus is an edible mushroom with a long history of use in traditional Chinese medicine. It has the capacity to prevent or alleviate or cure major diseases such as cancers, diabetes, lipidemia and depression including the neurodegenerative diseases. Many bioactive metabolites from *H. erinaceus* have been isolated as well as characterized by advanced techniques. Important metabolites characterized include hericenones, erinacine terpenoids, isoindolinones, and sterols. They possess diverse pharmacological properties such as antibiotic, anticarcinogenic, antidiabetic, hepatoprotective, nephroprotective and neuroprotective properties such as improvement of anxiety, cognitive function, and depression. Some of the compounds isolated from *H. erinaceus* possess herbicidal activity. Erinacines have potential neuroprotective properties, hericerins possess potent cytotoxic activity; sterols have anti-inflammatory and antiproliferative

properties, while erinaceolactones inhibit hypocotyl as well as root growth of lettuce at very low concentrations. Although a large number of compounds were obtained from *Hericium* with moderate to potent biological activities, rational derivatization and high-throughput screening are warranted. Such attempts help to follow NGF, anticancer and anti-inflammatory activities, and the molecules with superior activity profiles could be employed for various pharmaceutical applications. It is warranted to understand their individual as well as synergistic actions, with specific attention towards in vivo dynamics as well as in vivo and clinical experiments.

There is a great demand to use different strategies to isolate the new compounds because conventionally used methods results in production of known compounds. Highly diverse secondary-metabolite production could be achieved by simple approach as one strain many compounds (OSMAC). Such approach needs varied media composition (metal ion concentration salinity and C/N ratio) and fermentation conditions (solid/liquid, static/dynamic, pH, temperature and oxygen level). The other methods can be co-cultivation/mixed fermentation and addition of enzyme inhibitors including precursor/s. The approach of co-cultivation of fungi mimics the ecological conditions, where the two or more interacting partners involve in fermentation process, which leads to production of new metabolites (Moussa et al. 2020, Sari et al. 2020). Similarly, another approach could be followed include incorporate of different biosynthetic precursors in to the fermentation media, which alters the biosynthetic pathways of secondary metabolites (Ramm et al. 2017). With the implementation of approaches like genetic engineering, metabolic engineering, and fermentation technology help producing value added compounds from fungi. The diverse metabolites of *H. erinaceus* with potential biological activities provide ample opportunities to develop versatile compounds. Such novel compounds could be assessed for pharmacological potential to treat dreadful diseases like Alzheimer's and cancer. In addition, a combination of existing drugs with *H. erinaceus* metabolites may also provide new insights towards efficient solutions to combat the lifestyle diseases.

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