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•Review•

The chemical structures, biosynthesis, and biological activities of secondary metabolites from the culinary-medicinal mushrooms of the genus *Hericium*: a review

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[ABSTRACT] Fungal phytochemicals derived from higher fungi, particularly those from the culinary-medicinal genus *Hericium*, have gained significant attention in drug discovery and healthcare. This review aims to provide a comprehensive analysis of the chemical structures, biosynthetic pathways, biological activities, and pharmacological properties of monomeric compounds isolated from *Hericium* species. Over the past 34 years, 253 metabolites have been identified from various *Hericium* species, including cyathane diterpenes, alkaloids, benzofurans, chromenes, phenols, pyrones, steroids, and other miscellaneous compounds. Detailed investigations into the biosynthesis of erinacines, a type of cyathane diterpene, have led to the discovery of novel cyathane diterpenes. Extensive research has highlighted the biological activities and pharmacological properties of *Hericium*-derived compounds, with particular emphasis on their neuroprotective and neurotrophic effects, immunomodulatory capabilities, anti-cancer activity, antioxidant properties, and antimicrobial actions. Erinacine A, in particular, has been extensively studied. Genomic, transcriptomic, and proteomic analyses of *Hericium* species have facilitated the discovery of new compounds and provided insights into enzymatic reactions through genome mining. The diverse chemical structures and biological activities of *Hericium* compounds underpin their potential applications in medicine and as dietary supplements. This review not only advances our understanding of *Hericium* compounds but also encourages further research into *Hericium* species within the realms of medicine, health, functional foods, and agricultural microbiology. The broad spectrum of compound types and their diverse biological activities present promising opportunities for the development of new pharmaceuticals and edible products.

[KEY WORDS] *Hericium*; Secondary metabolites; Biological activity; Biosynthesis
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Introduction

Basidiomycetes, renowned for their secondary metabolites, present promising opportunities for the discovery of novel natural products with significant application potential. Mushrooms, a major group within basidiomycetes, encompass over 30 000 species [1] and are acclaimed for their nutritional, medicinal, and health-promoting properties [2-4]. Among these, *Hericium erinaceus*, *Ganoderma lucidum*, *Phellinus igniarius*, and *Antrodia camphorata* have attracted significant attention due to their rich bioactive secondary metabolites and potential for development into therapeutic agents and health foods.

Hericium, an edible mushroom genus in the family Hericiaceae, is found in Asia, Europe, and North America [5]. The most notable species in this genus is *Hericium erinaceus* (Fig. 1), also known as “Houtou” in China, “yamabushitake” in Ja-

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These authors have no conflict of interest to declare.

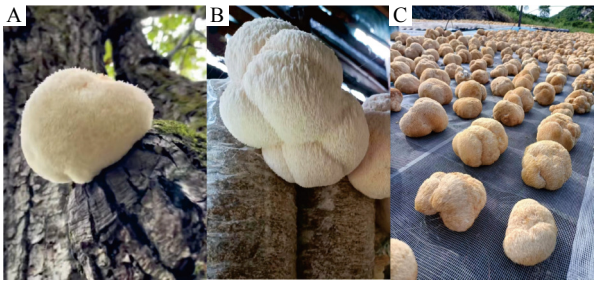

Fig. 1 Morphological photograph of wild (A), cultivated (B), and drying (C) fruiting bodies of *Hericium erinaceus*.

pan, and "Lion's mane mushroom" in Western countries. It has been used in traditional Chinese medicine and is highly regarded for its health benefits. Extensive research on the chemical composition of *Hericium* species has led to the identification of compounds with diverse biological activities. Erinacines, a class of cyathane diterpenes derived from *H. erinaceus* mycelia, have shown potential in treating neurodegenerative diseases [6-9], tumors [10, 11], diabetes [12], inflammation [13], and cardiovascular diseases [14]. Clinical trials have demonstrated the positive effects of orally administering *H. erinaceus* in alleviating cognitive impairment [15], improving symptoms of Alzheimer's disease (AD) [16, 17], and preventing disease progression [18].

Despite previous studies summarizing the compounds and activities of *Hericium* species [5, 19-22], recent advancements in identifying new chemical components and elucidating erinacine biosynthesis necessitate an updated review of *Hericium* metabolites. This review aims to provide a comprehensive summary of 253 secondary metabolites isolated from *Hericium* species, including twenty compounds involved in erinacine biosynthesis. It will detail their chemical structures, isolation sources, biosynthetic pathways, biological activities, and pharmacological mechanisms, as documented in the literature over the past four decades.

Chemical Structures

Cyathane diterpenoids

Diterpenoids derived from macrofungi exhibit extensive chemical diversity, with cyathane diterpenoids being a specific type found predominantly within the *Hericium* genus. These compounds represent the largest group of diterpenoids derived from macrofungi [23, 24] and are characterized by a distinctive angularly fused 5-6-7 tricyclic heterojunction structure [25]. *Hericium* species are major producers of cyathane diterpenes, with 37 such diterpenes reported so far from natural sources. Most cyathane diterpenoids derived from *Hericium* species are part of the erinacine series, named after the earliest identified compounds erinacines A−C [26]. These compounds share a common cyathane diterpene scaffold and often feature D-xylosyl moieties attached to their C-14 hydroxyl groups. The incorporation of D-xylosyl residues enhances their structural complexity and diversity, making them highly distinctive molecules within the *Hericium* genus. The chemical structures of these compounds are illustrated in Fig. 2.

In 1994, Kawagishi *et al.* isolated and identified three cyathane diterpenes, named erinacines A−C (**1**−**3**), from the liquid fermenting mycelium of *H. erinaceum* (now known as *H. erinaceus*) [26]. Research on *Hericium erinaceus* has led to the discovery of additional erinacines, specifically erinacines D−K (**4**−**11**) [27-30] and four unnamed cyathane diterpenes (**12**−**15**) [31, 32]. The stereochemistry of compound **6** was recently elucidated using computational nuclear magnetic resonance (NMR) analysis. Notably, compounds **7** and **10** are unique among *Hericium* mushrooms for possessing an open-ring cyathane skeleton. Further studies by Kenmoku *et al*. [28, 33] identified erinacines P and Q (compounds **16** and **17**), as well as several unmodified components (**18**−**22**) from *H. erinaceus* YB4-6237 [34-36]. Compounds **21** and **22** were originally isolated from *Cyathus earlei* Lloyd [37]. Erinacine R (**23**) was isolated from the mycelium of *H. erinaceus*, with its relative stereochemistry determined using Rotating-frame Overhauser Effect Spectroscopy (ROESY) [38]. A newly discovered diterpene (**24**) with antibacterial activity was isolated from *H. erinaceus* mycelia, and its absolute configuration was confirmed through experimental and computational Vibrational Circular Dichroism (VCD) spectra [39]. Additionally, three erinacines, T−V (**25**−**27**), were isolated from *H. erinaceus*. Two cyathane diterpenoids, erinacines Z1 and Z2 (**28**−**29**), were obtained from mycelial cultures of *H. erinaceus* and the rare species *H. flagellum* [38]. In 2018, three erinacine-type cyathane diterpenoids, hericinoids A−C (**30**−**32**), were isolated from the fermentation broth of *H. erinaceus*. The absolute configurations of hericinoids **30** and **31** were further elucidated using ROESY correlations and $DP4^+$ calculations [40]. Erinacine S (**33**), isolated from ethanol extracts of *H. erinaceus* mycelia, was determined through X-ray experiments [41]. Although **33** was initially classified as a sesterterpene due to its 25-carbon skeleton, it was considered a cyathane-type diterpenoid based on its biosynthetic pathway. Additionally, three cyathane diterpenoids, CJ-15544, CP-412065, and CJ-14258 (**34**−**36**), were derived from *H. ramosum* CL24240, fermented in various media [41]. Lastly, compound **37**, known as erinacine L, was recently discovered in the rice medium of *H. erinaceus* mycelium and contained a rare hemiacetal group. This comprehensive review of cyathane diterpenoids from *Hericium* species highlights the significant chemical diversity and potential biological activities of these compounds, underscoring their importance in natural product research and their potential therapeutic applications [33].

Alkaloids

Isoindoline-1-one compounds form a significant group of secondary metabolites derived from *Hericium*, representing a substantial portion of its metabolic profile. Pyridinone alkaloids, another important class of compounds found in *Hericium*, are categorized separately. Additionally, this category encompasses various structurally distinct nitrogen-containing small molecules and diketopiperazines. The chemical struc-

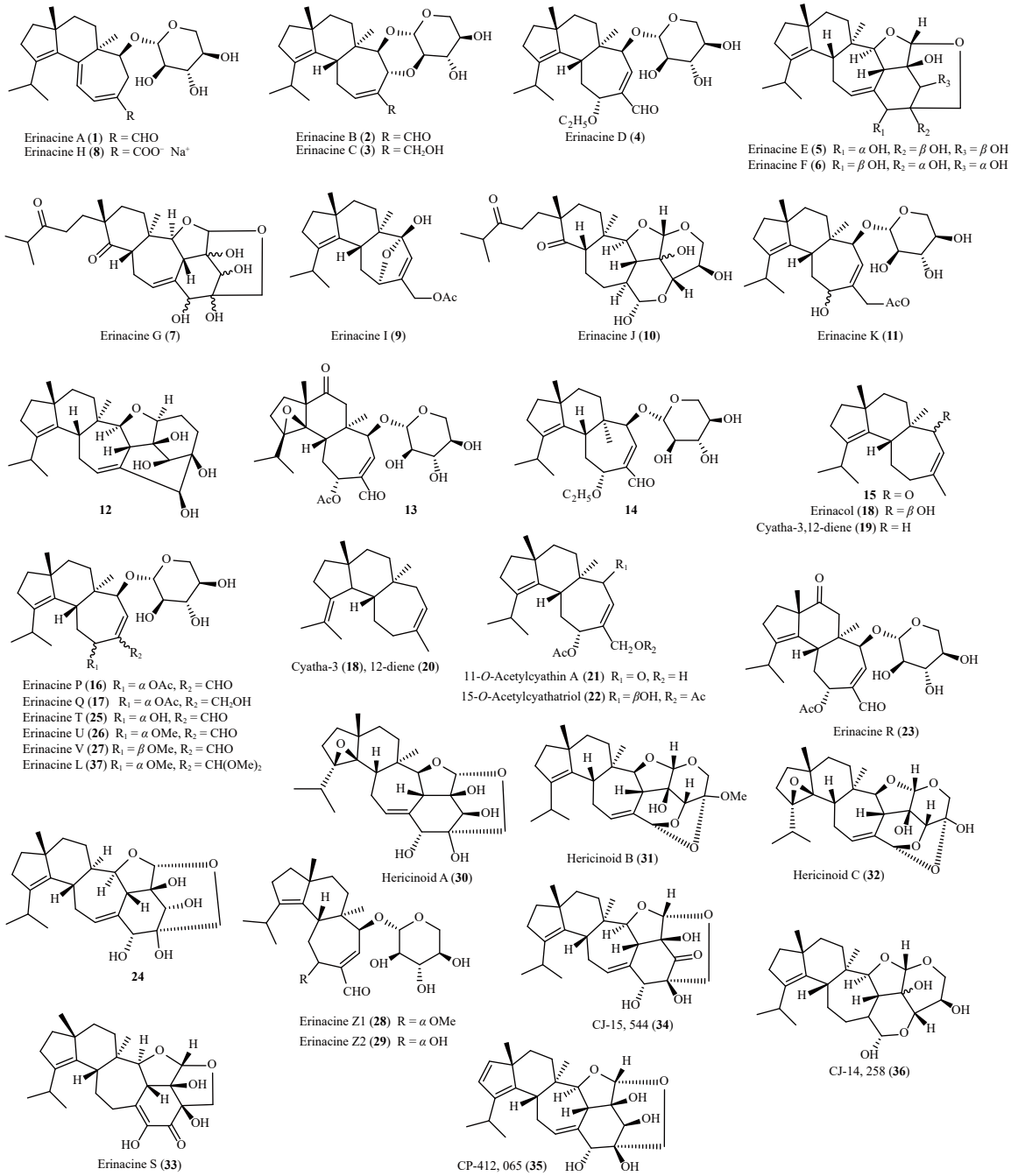

Fig. 2 Chemical structures of cyathane diterpenoids from *Hericium*.

tures of all alkaloids isolated from *Hericium* species are depicted in Fig. 3.

Isoindoline-1-one alkaloids

Hericenone B (**38**), the first isoindoline-1-one alkaloid isolated from the fruiting body of *H. erinaceus* in 1990, exhibited cytotoxic properties [42]. However, its structure was later corrected to its carbonyl regioisomer (**38a**) through the total synthesis of eight compounds [43]. Erinacerin A (**39**), a tricyclic compound exhibiting properties of both isoindolinone and chromone, was also isolated from the fruiting bodies of *H. erinaceus* [44]. Hericerin (**40**) was identified as (*E*)-6-(3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-5-methoxy-2-phenethylisoindolin-1-one [45]. Isohericerin (**41**), a carbonyl regioisomer of hericerin, and *N*-de-phenylethyl isohericerin (**42**) were also isolated [46]. The structure of hericerin (**40**) was later revised to (*E*)-5-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one [47], which is actually compound **41**, which corresponds to isohericerin (**41**). Additionally, compound **42** was identified as 5-[(2′*E*)-3′,7′-dimethyl-2′,6′-octadienyl]-4-hydroxy-6-methoxy-1-isoindolinone [48]. Both isohericerin (**41**) and isohericenone (**43**) were obtained from methanol extracts of partially dried *H. erinaceus* fruiting bodies [49]. Ten isoindoline-1-one alkaloids, termed erinacerins C−L (**44**−**53**), were isolated from the

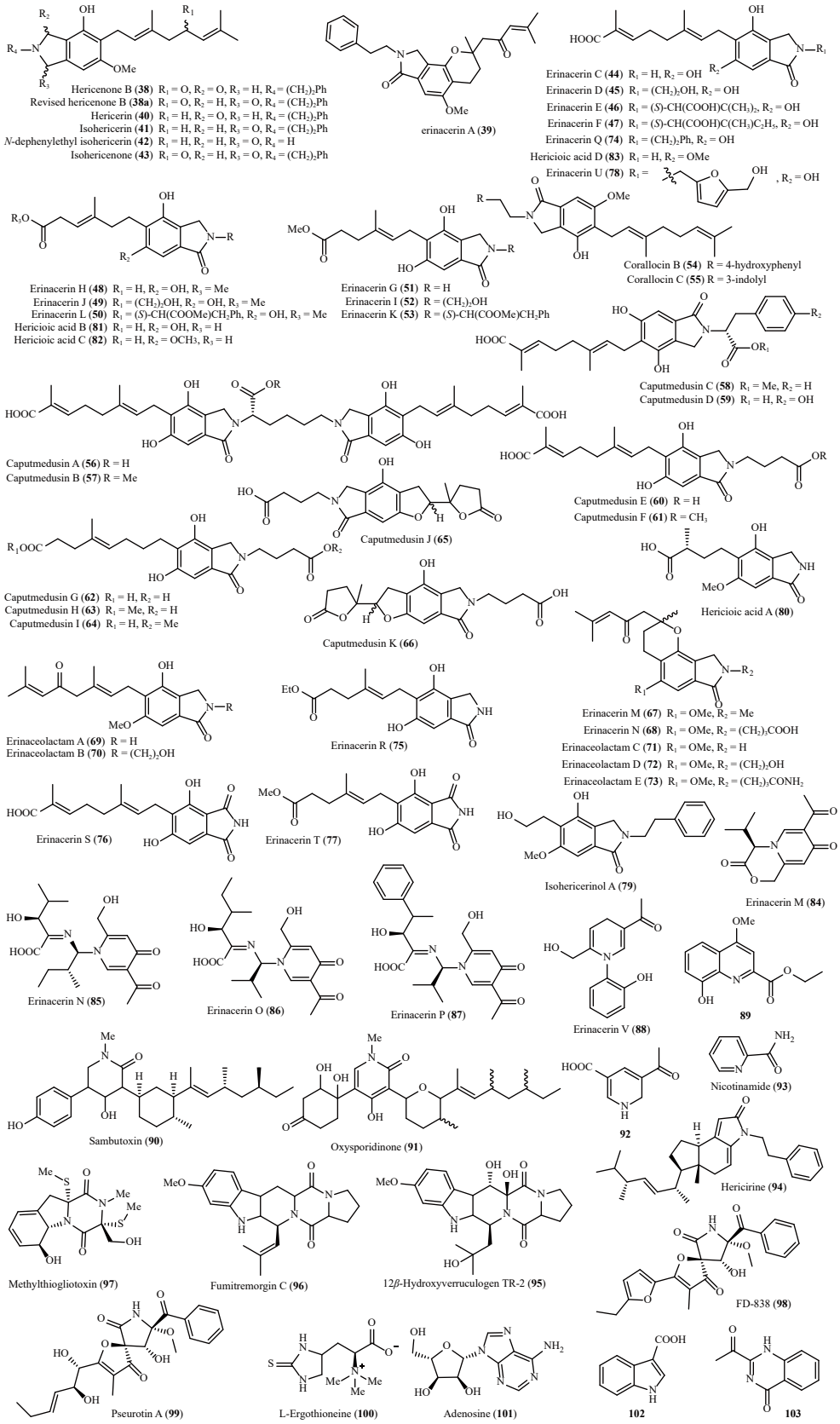

Fig. 3 Chemical structures of alkaloids from *Hericium*.

solid fermentation of *H. erinaceus*. Their structures were determined through spectroscopic analysis, with some absolute configurations established by comparing specific rotations with their derivatives [50].

Corallocins B (**54**) and C (**55**), which feature an isoindoline-1-one scaffold, were isolated from *H. coralloides* [51]. Additionally, eleven isoindoline-1-one derivatives, named caputmedusins A−K (**56**−**66**), were identified in the fermentation broth of *H. caputmedusae* [52]. It is speculated that caputmedusins A (**56**) and B (**57**) are dimers composed of two congeners of compound **52** and L-lysine [52]. Two isoindolin-1-ones, erinacerins M (**67**) and N (**68**), were isolated from the fruiting bodies of *H. erinaceus*. Their structures were elucidated through spectroscopic studies and comparisons with known analogs [53], but their absolute configurations have not yet been determined. Five isoindolinones, erinaceolactams A−E (**69**−**73**), were isolated from the fruiting bodies of *H. erinaceus*. Their structures have been verified by spectroscopic analysis, but the absolute configurations of erinaceolactams C−E (**71**−**73**) remain uncertain [54].

Eight additional alkaloids (**74**−**77** and **80**−**83**) were discovered during a study investigating trace alkaloids in a culture solution of *H. erinaceus* [55]. Four of these compounds, erinacerins Q−T (**74**−**77**), contained an isoindoline core and exhibited inhibitory activities against both *α*-glucosidase and protein tyrosine phosphatase-1B [55]. Erinacerins S (**76**) and T (**77**) feature an unusual isoindoline-1,3-dione core, making them unique among natural products in the *Hericium* genus. Erinacerin U (**78**), a 5-(hydroxymethyl) furan substituent of erinacerin C, was isolated and structurally elucidated [56]. Isohericerinol A (**79**), with an isoindoline-1-one framework, was isolated from the fruiting bodies of *H. erinaceus* [57]. Lastly, hericioic acids A−D (**80**−**83**), four isoindolinone derivatives, were isolated from a solid rice culture of the rare European edible fungus *H. flagellum* [58].

Pyridine alkaloids

Erinacerins M−P (**84**−**87**), compounds featuring a 2-acetyl-5-(hydroxymethyl)pyridin-4(1H)-one moiety, were isolated from *H. erinaceus* [55]. The absolute configurations of these compounds were determined through comparisons of experimental circular dichroism (CD) spectra with calculated electronic CD (ECD) spectra [55]. Notably, a naming error resulted in the duplication of compound names between erinacerins M (**84**) and N (**85**) with different structures compared to previously identified compounds **67** and **68**. Erinacerin V (**88**), also containing a 2-acetyl-5-(hydroxymethyl)pyridin-4(1H)-one moiety, was obtained from a mycelial culture of *Hericium* sp. WBSP8 using the One Strain Many Compounds (OSMAC) strategy [59]. Ethyl 8-hydroxy-4-methoxyquinoline-2-carboxylate (**89**), although a known patented immunosuppressant [60], was reported for the first time as a natural product along with erinacerin U (**78**) [56]. Sambutoxin (**90**), initially isolated from *Fusarium sambucinum* [61], was identified in *H. alpestre*, highlighting this species' significance among specialty mushrooms [62]. The biosynthetic pathway and chemical logic of sambutoxin (**90**) were recently elucidated by reconstituting its biosynthetic cluster from *F. commune* in the engineered strain *Aspergillus nidulans* ΔSTΔEM [63]. Oxysporidinone (**91**), a 3,5-disubstituted *N*-methyl-4-hydroxy-2-pyridone originally isolated from *F. oxysporum* [64], was found in cultures of *H. alpestre* [65]. A dihydropyridine compound (**92**) was isolated from methanol extracts of *H. erinaceus* mycelium along with **1** [66]. Nicotinamide (**93**), first isolated in 1989 from Mallotus leaves [67], was also obtained from cultures of *H. erinaceus* fruiting bodies, along with **84**−**85** [53].

Other alkaloids

Hericirine (**94**), an ergosterol-conjugated alkaloid, was isolated from dried fruiting bodies of *H. erinaceus* [68]. Three diketopiperazine alkaloids—12*β*-hydroxyverruculogen TR-2 (**95**), fumitremorgin C (**96**), and methylthiogliotoxin (**97**)—were identified, along with two azaspirobicyclic alkaloids, FD-838 (**98**) and pseurotin A (**99**), in the mycelia of *H. erinaceus* through spectroscopic analyses [69]. L-Ergothioneine (**100**) was found in both the fruiting body and mycelium of *H. erinaceus* [70]. Adenosine (**101**), a pyrimidine alkaloid, was isolated along with erinacerins M−T [55]. Additionally, 3-indoleacetic acid (**102**) and 2-acetylquinazolin-4(1*H*)-one (103) were isolated from cultures of *H. alpestre* [65]. The structure of methylthiogliotoxin (**97**) was determined by 1D NMR data and further confirmed by X-ray crystallographic analysis [65].

Benzofurans

Benzofuran ring compounds are an important class of aromatic constituents found in *Hericium* species, known for their remarkable biological activities. Within this class, only a few molecules have an isobenzofuranone skeleton. The structures of these compounds are shown in Benzofuran ring compounds are an important class of aromatic constituents found in *Hericium* species, known for their remarkable biological activities. Within this class, a subset of molecules features an isobenzofuranone skeleton. The structures of these compounds are shown in Fig. 4A.

Isobenzofuranones

Hericenone A (**104**), the first isobenzofuranone compound derived from *H. erinaceus*, was isolated in 1990 together with **38a** [42]. Initially postulated as (*E*)-6-(3,7-dimethyl-5-oxoocta-2,6-dien-1-yl)-7-hydroxy-5-methoxyisobenzofuran-1(3*H*)-one, its structure was later revised through chemical synthesis to (*E*)-5-(3,7-dimethyl-5-oxoocta-2,6-dien-1-yl)-4-hydroxy-6-methoxyisobenzofuran-1(3*H*)-one (104a) [71]. Erinacerin B (**105**), isolated from the fruiting bodies of *H. erinaceus*, has similar 1D NMR spectra to **104**, except for the replacement of the C-5' carbonyl group with a hydroxyl group, which was confirmed by ^{1}H–^{1}H Correlated Spectroscopy (COSY) experiment [44]. An unnamed compound (**106**) with an unusual isobenzofuranone backbone was also isolated from the fruiting bodies of *H. erinaceus* [72]. Hericenone K (**107**), a hydroxylated product of compound **106**, was obtained from the fruiting bodies of *H. erinaceus* [73]. Hericenones I (**108**) and J (**109**) were isolated from the ethanol

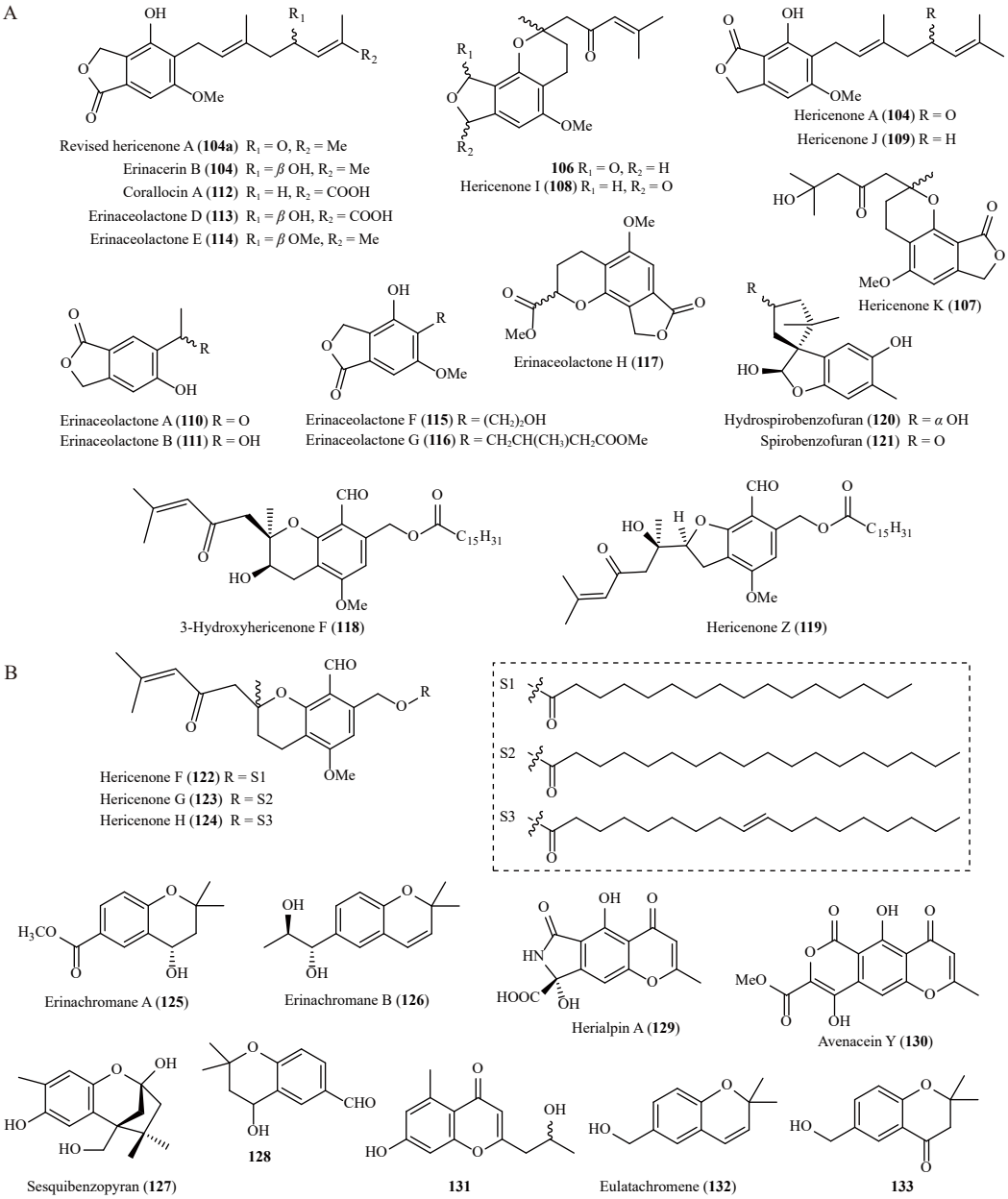

Fig. 4 Chemical structures of benzofurans (A) and chromenes (B) from *Hericium*.

and acetone extracts of fresh fruiting bodies of *H. erinaceus*, with compound **109** exhibiting racemic nature based on its CD spectrum [74]. Detailed separation of extracts with *n*-hexane and ethyl acetate from the fermentation broth of *H. erinaceus* led to the discovery of two isobenzofuranone derivatives, erinaceolactones A (**110**) and B (**111**), both of which exhibited allelopathic activity [75]. However, due to the structural specificity of **111**, its absolute configuration remains undetermined. Corallocin A (**112**), sharing the same 4-hydroxy-6-methoxy-1(3*H*)-isobenzofuranone fragment with **104a** and **105**, was isolated from *H. coralloides*. Three derivatives of isobenzofuranone, erinaceolactones D−F (**113**−**115**), were isolated from a 70% ethanol extract of the fruiting bodies of *H. erinaceus* [76]. Simultaneously, two erinaceolactone derivatives, G (**116**) and H (**117**), were isolated from the ethanolic extract of the fruiting bodies of *H. erinaceus*, and the C-2′ absolute configuration of **116** was determined by comparing its specific rotation value with that of its analogs [77]. Compound **118**, 3-hydroxyhericenone F, was originally characterized as (2*S**,3*S**)-8-formyl-3-hydroxy-5-methoxy-2-methyl-2-(4-methyl-2-oxopent-3-enyl) chroman-7-ylmethyl palmitate [78]. However, subsequent total synthesis revised its structure to [(*S*)-7-formyl-2-((*R*)-2-hydroxy-6-methyl-4-oxohept-5-en-2-yl)-4-methoxy-2,3-dihydrobenzofuran-6-yl]methyl palmitate, a benzofuran-type compound, named hericenone Z (**119**) [78].

Spiro-benzofurans

Two spiro-benzofuran compounds, hydrospirobenzofuran (**120**) and spirobenzofuran (**121**), were isolated from the culture broth of *H. coralloides* using a bioassay-guided fractionation method [79]. Initially, the limited quantity of hydros-

pirobenzofuran (**120**) hindered the determination of its absolute stereochemistry. Although this compound was first isolated from *Acremonium* sp. KI 0230 [80] and its absolute configuration were eventually determined by total chemical synthesis, the absolute stereochemistry of **120** derived from *H. coralloides* was conclusively established using the modified Mosher's method [79].

Chromenes

Kawagishi *et al.* identified three chromone compounds, hericenones F−H (**122**−**124**), in the fruiting bodies of *H. erinaceus*. These compounds feature modified chromone frameworks attached to long-chain fatty acids [81]. During a search for plant growth-regulating compounds in a culture broth, erinachromanes A (**125**) and B (**126**) were also isolated from *H. erinaceus* [82]. The absolute configuration of erinachromane A was confirmed by comparing its specific rotation with a reference compound, while that of erinachromane B was determined based on its derived *p*-bromobenzoate [82]. Sesquibenzopyran (**127**), a sesquiterpene containing a dihydrobenzopyran moiety, was isolated from the culture broth of *H. coralloides* [79]. Additionally, compound **128**, an aldehyde derivative of 4-hydroxy chroman, was isolated from a mycelial culture of a unique North American edible mushroom, *Hericium* sp., collected from a marina in St. Croix, Minnesota, USA [59]. Herialpin A (**129**), avenacein Y (**130**), and 2-(2′-hydroxypropyl)-5-methyl-7-hydroxychromone (**131**) were obtained from a culture of *H. alpestre* [65]. Herialpin A (**129**) and avenacein Y (**130**) are atypical chromone molecules with a tricyclic ring system. Herialpin A exhibited weak anti-cancer activity, while avenacein Y, originally isolated as a mycotoxin [83], demonstrated significant anti-cancer activity [65]. Structural analysis suggests that the pyrano[3,4-*g*] chromene-4,6-dione moiety in avenacein Y is the key pharmacophore responsible for its cytotoxicity [65]. Compound **131**, initially isolated from the medicinal plant Rhei Rhizoma [84], awaited confirmation of its absolute configuration. Eulatachromene (**132**) and 6-hydroxymethyl-2,2-dimethyl-chromanone (**133**), two chromanones previously reported in other fungi, were also first isolated from the culture broth of *H. erinaceus* [82]. Their structures are displayed in Fig. 4B.

Phenols

Phenolic compounds in this section refer to monophenylene ring aromatic compounds with hydroxyl groups, distinct from chromones, chromenes, and benzofurans.

Compounds **134**−**138** are chlorinated orcinol derivatives frequently isolated from the mycelial cultures [75, 82, 85, 86] and mycelium [39, 87] of *H. erinaceus*, as well as from mycelial cultures of *Hericium sp*. WBSP8 [59]. Compounds **139** and **140** are unmethylated forms of compounds **135** and **136**, respectively, obtained from *H. erinaceus* mycelium [85], providing insights into their biosynthesis. Erinaceolactone C (**141**), a chlorinated orcinol derivative with a *γ*-lactone attached to the C-5 of phenyl chloride, was isolated from the culture broth of *H. erinaceus*, with its planar structure and absolute configuration determined through X-ray crystallographic analysis [75]. Another chlorine-containing phenol compound, 1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone (**142**), was isolated from the mycelium [39] and fruiting bodies [88] of *H. erinaceus*. Compound **143** was purified as red crystals from *H. erinaceus* waste culture beds [86]. Compounds **144**−**146** are other phenolic compounds derived from organic solvent extracts of the culture broth of *H. erinaceus*, with compound **146** being a newly discovered compound named erinaphenol A [82]. Compound **147**, 3-acetyl-4-methoylbenzoic acid, was isolated from the fungal mycelia of *H. erinaceus* [39]. Coralcuparene (**148**), featuring a cyclopentenone moiety, was isolated from the culture broth of *H. coralloides* [79]. Hericenals A−C (**149**−**151**), three phenolic compounds with significant hypoglycemic activity, were found in the mycelium of *H. erinaceus* and have been patented in Europe [89]. Hericenes A−C (**152**−**154**) are the palmitic, oleic, and stearic esters, respectively, of 4-(3',7'-dimethyl-2',6'-octadienyl)-2-formyl-3-hydroxy-5-methoxybenzyl alcohol (**155**), isolated from culture extracts of *H. erinaceus* CBS 233.87 [90]. Hericene (**155**), initially obtained through methanolysis of compounds **152**−**154**, was first isolated from *H. erinaceus* fruiting bodies in 2012 [48]. Compound **153** was also discovered in *H. novae-zealandiae* [46], a native edible mushroom from New Zealand [91]. Hericene D (**156**), a linoleic ester of **155**, was isolated from the dried fruiting bodies of *H. erinaceus* in 2010 [92]. The methanolysis of **156** yielded the methyl ester of linoleic acid and another product containing a phenol backbone named hericene, which was the previously mentioned compound **155** [92]. Erinacene D (**157**), a palmitic acid ester molecule linked to hydroxylated modified hericene, was isolated from *H. erinaceus* fruiting bodies along with compounds **152**−**154** and hericenones C−E (**158**−**160**) [93]. The fatty acid groups of **158**−**160** corresponded to those of **152**−**154**, with the difference lying in the phenol skeleton. The phenol skeleton in the latter is called hericenone (**161**) [93]. Hericenone I (**162**) is identical in structure to hericenone D (**159**), while the name was given by MA *et al*. [92], and it refers to the isobenzofuranone compound **108** [74]. Hericenone L (**163**), a new derivative of **158**, was isolated from *H. erinaceus* fruiting bodies alongside **152** and **158** [94]. Hericenes E−H (**164**−**167**), four meroterpenoids containing an orsellinic aldehyde core, have recently been reported as conventional *H. erinaceus* derivatives. The modification of the C-5' on the skeleton sets **164**−**167** apart from the previously reported hericenes [95]. Hricioic acids E−G (**168**−**170**) were isolated from a solid rice culture of the rare European edible fungi *H. flagellum*. Two chlorinated orsellinic esters (**171** and **172**) and an isopentenyl *p*-hydroxybenzoate (**173**) were found in the fruiting liquid (FL) of *H. erinaceus*, suggesting that the FL plays an important role in the formation of fungal fruiting bodies [58]. Their structures are displayed in Fig. 5A.

Pyrones

Herierins III (**174**) and IV (**175**) were the first pyrone compounds reported from a culture of *Hericium* species [85]. Two *γ*-pyrones, erinapyrones A (**176**) and B (**177**), were later isolated from the culture broth of *H. erinaceus* [96]. Erin-

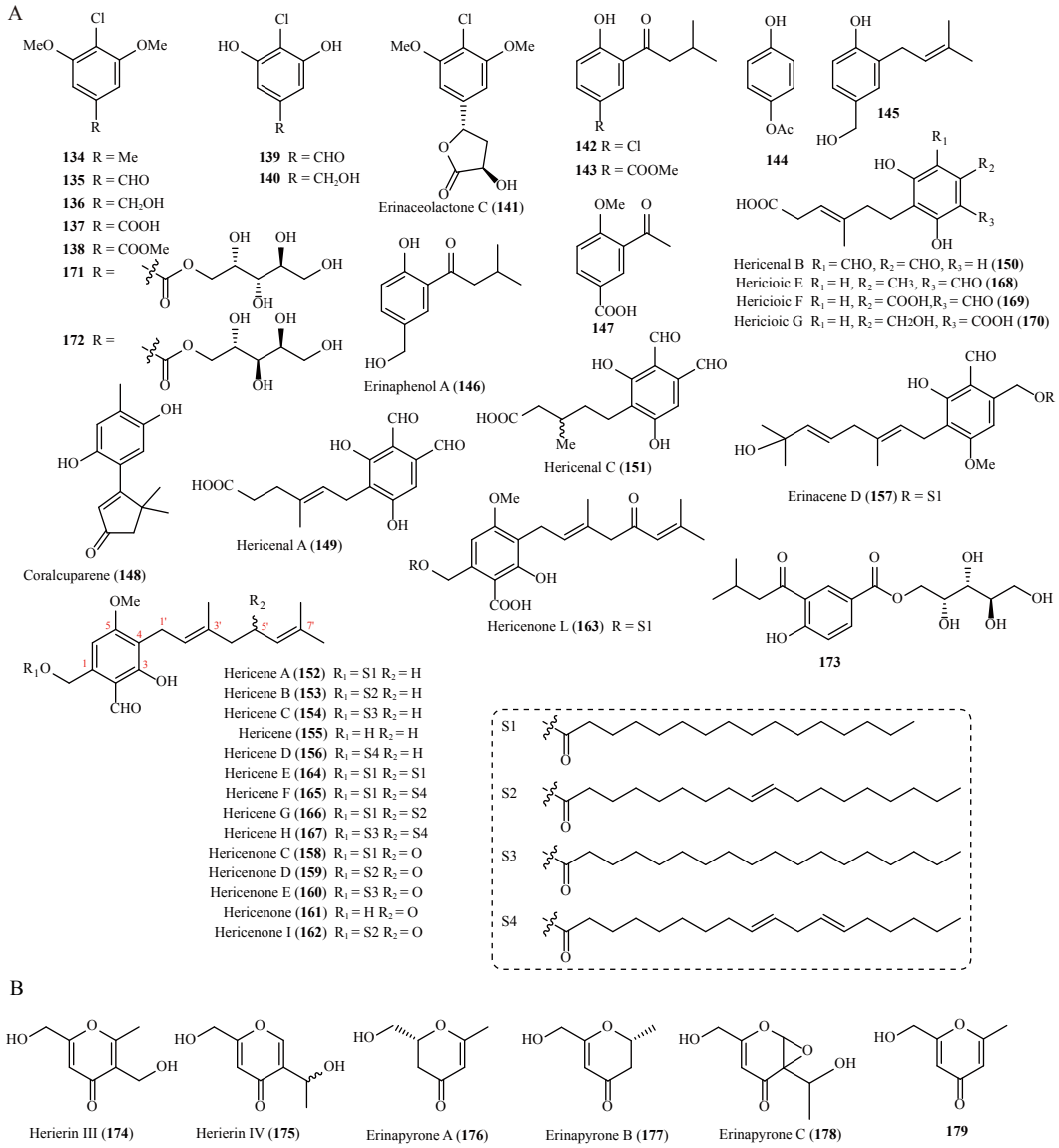

Fig. 5 Chemical structures of phenols (A) and pyrones (B) from *Hericium*.

apyrone C (**178**), a *γ*-dihydropyrone with certain activity against Gram-positive bacteria, was isolated from a culture of *H. erinaceus* CBS 233.87 [90]. Although compound **179** had been previously synthesized, it was reported for the first time as a natural product isolated from the culture broth of *H. erinaceus* [75]. The structures of these compounds are displayed in Fig. 5B.

Steroids and terpenoids

Steroids are a common component of most macrofungi [97], and studies on chemical components derived from higher fungi have often focused on steroids and triterpenoids. However, in the genus *Hericium*, cyathane diterpenes and alkaloids have garnered more attention due to their significant anti-neurodegenerative disease activity [25, 98].

According to the available literature, compounds **180**−**186** were the earliest reported steroids isolated from the genus *Hericium*. Among them, 3*β*-glucopyranosyl-5*α*, 6*β*-dihydroxyergosta-7, 22-diene (**183**) was identified as a new compound [99]. Compound **182** was also isolated from the mycelia of *H. erinaceus* [69]. Three known steroids (**187**−**189**) were isolated from the fruiting bodies of *H. erinaceus* for the first time [48]. Compounds **180** and **185** were also discovered from *H. novae-zealandiae* [91]. Eleven ergostane-type sterol fatty acid esters (**190**−**200**) were isolated from the methanol extract of the dried fruiting bodies of *H. erinaceus*, with the first six named erinarols A−F (**190**−**195**) [100]. Four sterol fatty acid esters, erinarols G−J (**201**–**204**), and ten known ergostane-type steroids (**205**−**214**) were isolated from the methanol extract of dried fruiting bodies of *H. erinaceus*. Compound **200** features an unusual dioxolane B ring, a unique structure among steroids from *Hericium* species [101]. In the search for biologically active secondary metabolites from higher basidiomycetes, three ergostane-type steroids (**182**, **193**, **194**) and five triterpenoids (**215**–**219**) were isolated from the fruiting bodies of *H. erinaceus*, with compounds **215**−**219** being isolated from *Hericium* species for the first

time [73]. Cerevisterol 6-cinnamate (**220**) and five known steroids (**182**, **221**−**224**) were isolated from the fruiting bodies of *H. erinaceus* [102].

A systematic investigation of the chemical composition of the fruiting bodies of *H. erinaceus* led to the isolation and identification of thirty-five steroids (**180**−**182**, **185**, **190**−**203**, **205**−**214**, and **221**−**227**) [103]. Compounds **225** and **226** possess rare structural units of 1(10-6)abeo-5,7,9-triene-3*R*,11*R*-diol, which are uncommon among steroids from the genus *Hericium* [103]. Additionally, three steroids (**180**, **228**, and **229**) were isolated from a culture of *H. alpestre*, with the latter two not previously reported in *Hericium* species [65]. Recently, a fatty acid ester of ergosterol was isolated from the fruiting body and named erinarol K (**230**) [104]. The structures of these compounds are displayed in Fig. 6A.

Miscellaneous compounds

Herialpin B (**231**), a tricyclic compound with weak activity against certain tumor cell lines, was isolated from the culture of *H. alpestre*, along with three known compounds (**232**−**234**) [65]. Dibutyl phthalate (**232**), commonly found in various consumables, may not be a natural product of *H. alpestre.* 3-(Hydroxymethyl)-2-furaldehyde (**235**), a natural product, was isolated from the methanolic extract of cultured mycelium of *H. erinaceus* [66]. An aromatic compound (**236**) was obtained from raw ethanol extracts of *H. erinaceus* [88]. KSPLY (**237**), a naturally immunologically active peptide, was isolated and purified from *H. erinaceus* [105]. Compounds **238**−**242**, consisting of four fatty acid esters and one fatty acid, were isolated from the fruiting bodies of *H. erinaceus* [46, 103, 106-108]. Compound **238** is a D-arabinitol ester [46]. Compounds **239**−**241**, cerebrosides B, D, and E, are widely used as functional health foods and dietary supplements [106]. Other compounds, including (*S*)-(+)-ipsdienol (**243**) and (*R*)-(−)-ipsdienol (**244**) [44], lovastatin (**245**) [70], limonene (**246**), *α*-terpineol (**247**), linalool (**248**) [109], 7*α*,8*β*,11-trihydroxydrimane (**249**) [39], and compound **250** and **251** [82], are nine known compounds derived from *Hericium* species with diverse structures. The most recently discovered active compounds from the genus *Hericium* include 16-carboxy-13-epi-neoverrucosane (**252**) [33] and hericiofuranoic acid (**253**) [58]. Their structures are displayed in Fig. 6B.

An interesting phenomenon observed in *Hericium* species is the specific distribution of metabolites in different tissues (fruiting bodies and mycelium). All cyathane diterpenoids are present in the mycelium (including the mycelial fermentation broth), whereas almost all steroids are derived from the fruiting bodies. A recent investigation into the distribution of secondary metabolites in the mycelium, primordium, and sporophores of *H. erinaceus* reflected similar results [110]. The mycelium and fruiting bodies of fungi occupy different environments and perform different functions during their life cycle. This supports the view that the production of secondary metabolites is closely related to the organism's ecological niche [111]. This knowledge is valuable for the targeted production and isolation of specific components, such as steroids or diterpenes, in the genus *Hericium*.

Since 1990, our research group has been working on the discovery of compounds from *Hericium* mushrooms that can treat AD. Of the 253 secondary metabolites (Table S1) of *Hericium* mushrooms reported so far, the number of those first reported as new compounds by our research group is no less than 60 [9, 82, 98, 112]. These compounds mainly include cyathane diterpenoid erinacines A−K (**1**−**11**) [26, 28-30], benzyl alcohol derivatives hericenones A−J (**104**, **38**, **158**−**160**, **122**−**124**, and **107**−**109**) [42, 74, 81, 113], erinaceolactones A−C (**110**, **111**, and **141**) [75], erinaphenol A (**146**) [82], and **170**−**172** [114], and chromanone derivatives erinachromanes A and B (**125** and **126**) [82]. These compounds were named based on their structural characteristics, and subsequent researchers have followed these designations.

Biosynthesis

Species diversity

Hericium is a genus of edible-medicinal mushrooms in the family *Hericiaceae*, order *Russulales*, within *Basidiomycota*. The classification of *Hericium* species has evolved from traditional morphological methods to molecular phylogenetic techniques based on internal transcribed spacer (ITS) and 28S rDNA sequences. A recent study revealed the evolutionary relationships among ten *Hericium* species (including subspecies) [115], accounting for nine *Hericium* species and seven subspecies, with *H. erinaceus* previously spelled "erinaceum" [5] considered as one species. *Hericium* sp. WBSP8, a new species recently reported from St. Croix, Minnesota (USA) [59], has morphological characteristics closest to those of *H. americanum*, though molecular analysis suggests they are distinct species [59]. *H. novae-zealandiae*, another new *Hericium* species recently identified in New Zealand [116], is notable for its high yield of compound **153** (28.53 mg·g^{-1} dry weight) [91].

Genome, transcriptome, and proteome

Currently, seven genomes of four *Hericium* species are publicly available in the NCBI database and the Joint Genome Institute (Table 1). Among the three sequenced subspecies (HerI [117], CS-4 [118], and 0605 [119]) of *H. erinaceus*, CS-4 was sequenced with mononuclear material, resulting in a high-quality assembled genome [118]. *H. coralloides* coralloides tvtc0002, collected from the Qinghai-Tibet Plateau, had its genome sequenced using PacBio RS II, Illumina MiSeq, and Illumina NextSeq500 platforms [120]. *H. coralloides* FP-101451 was sequenced as part of the 1000 Fungal Genomes Project, and its genome was released by the Joint Genome Institute. The genome of *H. rajendrae*, a rare *Hericium* species found in the Qinling Mountains, was recently reported for the first time [121]. These genomic sequences provide valuable insights into the biosynthesis of active compounds in *Hericium*.

Transcriptome analysis of *H. erinaceus* HerI revealed that genes involved in terpene biosynthesis were generally upregulated in the mycelium, while polyketide synthase (PKS) genes were upregulated in substrates [117]. This finding

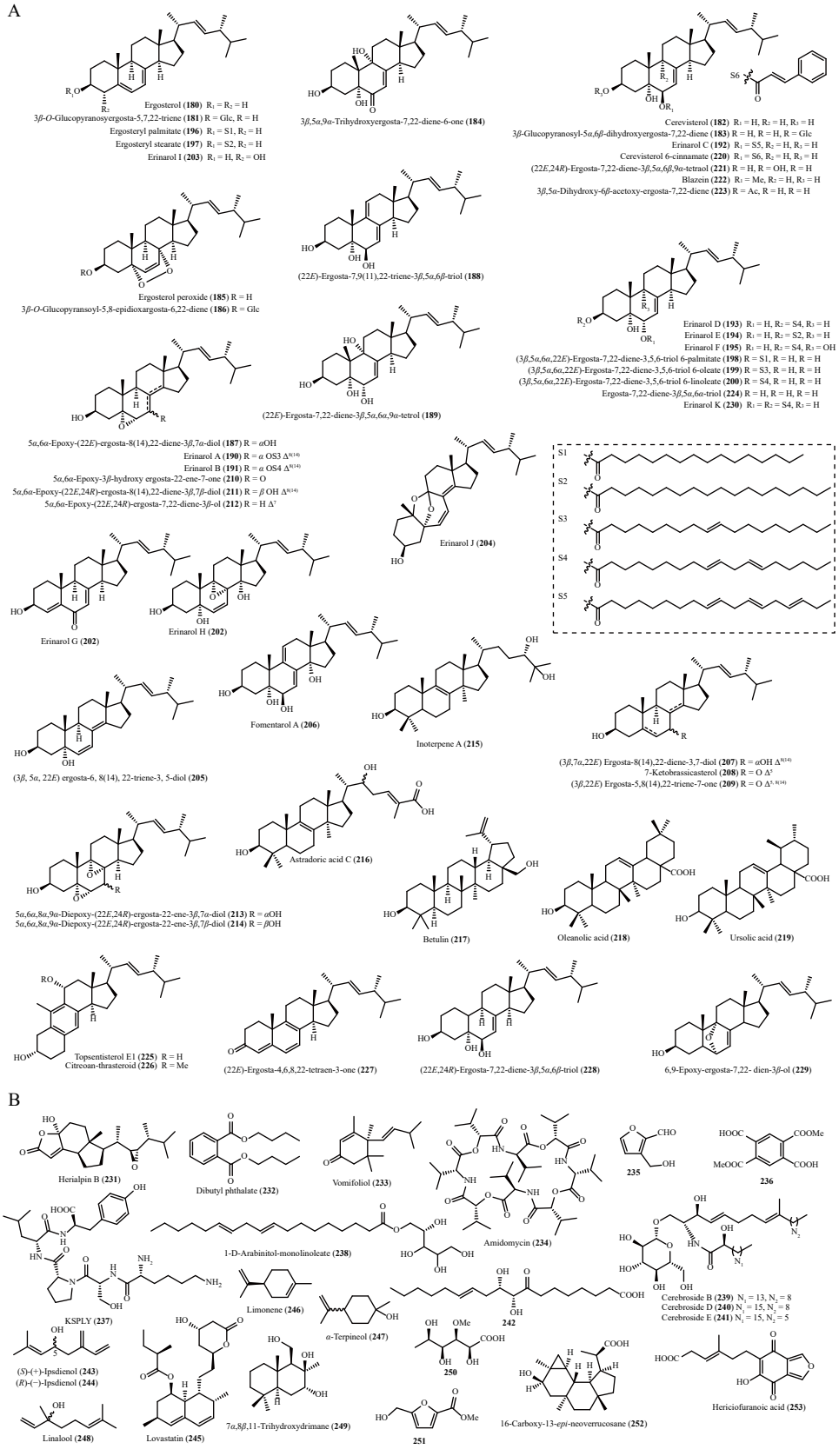

Fig. 6 Chemical structures of sterols and triterpenoids (A) and compounds 231–253 (B) from *Hericium*.

Table 1 Genomic characterization of various species of the genus *Hericium*

Species	*H. erinaceus*			*H. coralloides*		*H. alpestre*	*H. rajendrae*
	Herl	CS-4	0605	TVTC0002	FP101451	DSM 108284	NPCB A08
Genomic size (Mb)	39.4	41.2	38.2	55.8	35.3	37.5	46.8
Sequencing depth	about 200	about 750	70	220	122	31.4	118
Scaffolds	519	45	NA	307	125	3534	15
Contigs	1118	52	20	306	125	3635	19
N50 (kb)	538	3208	2587	441	711	16	3238
GC (%)	53.1	52.3	53.2	53.8	NA	52.4	52.6
Protein-coding genes	9895	10 620	NA	NA	NA	11 007	13 418
Sequencing method	Illumina	PacBio Illumina	PacBio	PacBio Illumina	PacBio	IonTorrent	PacBio Illumina

NA indicates not available.

is crucial for understanding the biosynthesis of specific compounds. Comparative transcriptome analysis of six *H. erinaceus* strains provided insights into polysaccharide biosynthesis [122]. Additionally, single-cell real-time sequencing of the genome helped uncover the main mechanism behind the increase in polysaccharide synthesis induced by atmospheric and room temperature plasma (ARTP) [119]. Proteomic studies have identified differentially regulated proteins involved in the biosynthesis of biologically active metabolites [123], offering valuable guidance for exploring active metabolite biosynthesis.

Biosynthesis of erinacines

Hericium-derived metabolites are renowned for their diverse structures and significant biological activities. However, the biogenic pathways of these metabolites are not yet fully understood. Although the biosynthetic pathways of several compounds have been speculated upon [50, 52, 55], the biosynthesis of cyathane diterpenoids has been the most extensively investigated and elucidated. A plausible biosynthetic pathway, where cyatha-3,12-diene (**19**) is formed by the cyclization of geranylgeranyl diphosphate (GGPP, 254), was initially proposed by Ayer *et al.* during their analysis of diterpenoid metabolites derived from *Cyathus earlei* Lloyd [37]. This pathway was later confirmed through enzymatic transformation using deuterated GGPP as a substrate in cell-free extracts of *H. erinaceus* YB4-6237 [124]. Additionally, cyatha-3(18),12-diene (**20**) was identified as a by-product [124]. Erinacol (**18**) was subsequently discovered and presumed to be an intermediate in the biosynthesis of erinacine Q (**17**). Based on NMR data, ^{13}C-labeling experiments demonstrated that erinacine Q (**17**) could be converted into erinacine C (**3**) *via* erinacine P (**16**) [35], indicating that erinacines Q and P are biosynthetic intermediates of erinacine C. Erinacine P was proposed as an early metabolite of erinacines A (**1**) and B (**2**) [34], supported by data showing a decrease in erinacine P concentration while erinacine C concentration steadily increased in the broth of *H. erinaceus* over time [125]. The *eri* gene cluster (Fig. 7A, Table S3) from *H. erinaceus*, identified as responsible for erinacine biosynthesis, was the first biosynthetic gene cluster (BGC) determined for cyathane diterpenoids. In this pathway, EriG, a UbiA-type diterpenoid cyclase, catalyzes the cyclization of GGPP (**254**) to form the cyathane skeleton, resulting in the production of cyatha-3,12-diene (**19**) [126]. LIU *et al.* developed a Cas9-based method for the targeted insertion of exogenous BGC into the heterologous expression host *Aspergillus oryzae*, successfully achieving efficient production of basidiomycete metabolites, including erinacine Q (**17**, 4.7 mg·L^{-1}) [127]. During this research, the functions of eight genes (*eriA*, *eriC*, *eriE*, *eriG*, *eriH*, *eriI*, *eriJ*, and *eriL*) within the BGC were elucidated. The co-expression of *eriE*, annotated as a GGPP synthase, and *eriG*, identified as a GGPP cyclase, resulted in the production of compound **19**. EriI, EriC, and EriA were found to perform sequential hydroxylation modifications on compound **19** at the C-14 and C-15 methyl groups and at C-11, with EriA's hydroxylation function requiring assistance from a cytochrome P450 reductase or EriH, a short-chain dehydrogenase reductase. The membrane-bound *O*-acyl transferase gene *eriL* was responsible for acetylating the backbone C-11 hydroxyl group to produce compound **267**. EriJ was identified as a UDP-xylosyltransferase through *in vivo* heterologous expression and *in vitro* biochemical characterization (Fig. 7B) [127].

In their extensive genomic analysis of *H. erinaceum*, MA *et al*. identified three critical genes outside the primary biosynthetic gene cluster (BGC): *eriM* (FAD-dependent oxidase) and *eriO/P* (NAD(P)/NAD(P)H oxidoreductases). EriM catalyzes the conversion of erinacine Q (**17**) to form the allyl aldehyde intermediate erinacine P (**16**). This intermediate undergoes a non-enzymatic tandem Michael addition, forming the pivotal intermediate erinacine B (**2**). Erinacine B (**2**) then undergoes non-enzymatic Michael elimination and a double bond shift to produce the final product, erinacine A (**1**). The aldehyde group of erinacine B (**2**) is reduced by EriB to yield erinacine C (**3**). Additionally, erinacine B (**2**) can form erinacine T (**25**), erinacine ZB (**271**), and erinacine ZC (**270**) through different non-enzymatic catalytic processes (Fig. 7B).

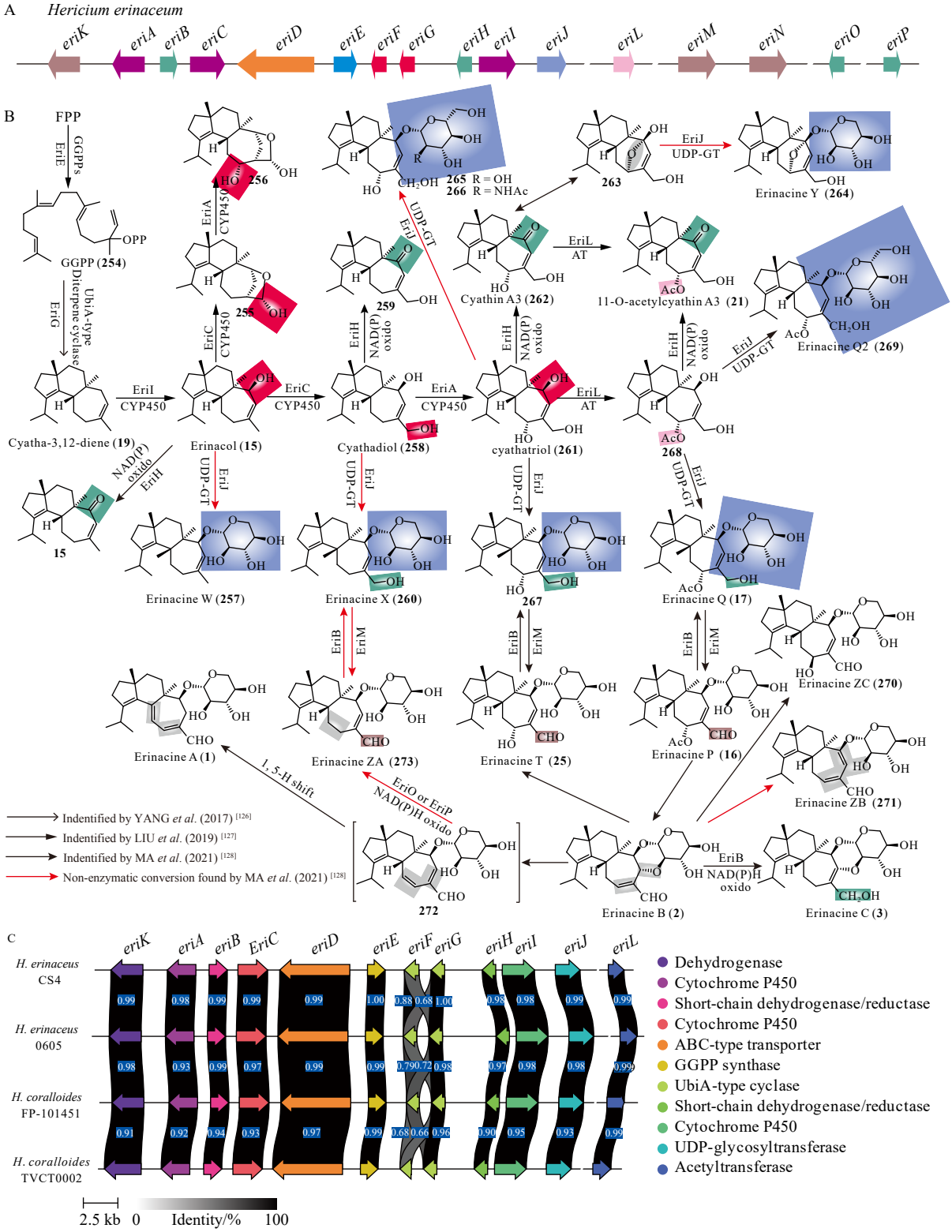

Fig. 7 Biosynthesis of erinacines. The organization of the *Eri* gene cluster from *H. erinaceus* (A). Proposed biosynthetic pathway of erinacines (B). Synteny analysis of erinacines BGCs identified or predicted in different species of the *Hericium* (C).

Research on substrate heterogeneity involving EriJ and EriH has led to the creation of several new, unnatural products, including compounds **257**, **259**, **260**, and **263**−**267**. EriB and EriM demonstrated reciprocal effects in the conversion processes between compounds **260** and **273**, **267** and **25**, and **16** and **17**. Engineered yeast strains, based on these insights, achieved high yields of several cyathane xylosides. Both natural and unnatural cyathane xylosides exhibited significant

neurotrophic effects on PC12 cells [128].

In addition to *H. erinaceus*, other *Hericium* species such as *H. flagellum* [10] and *H. ramosum* [129] also produce erinacines, suggesting that erinacine BGCs may be widespread within the *Hericium* genus. Four erinacine BGCs (Fig. 7C) were identified based on the available genomes of various *Hericium* species. A comparison of BGC similarities using the clinker software [130] package showed high identity among the corresponding genes (Fig. 7C). Furthermore, an examination of the genome of *H. alpestre* DSM 108284 revealed genes homologous to the erinacine BGC. However, due to the poor quality of this genome, related genes were scattered across different contigs or had incomplete coding regions, making comprehensive comparison difficult.

Biosynthesis of orsellinic acid

Although no monomeric compounds of orsellinic acid (OA) have been reported in *Hericium* mushroom metabolites, OA serves as the backbone for many of these metabolites, including compounds **38**−**83** and **149**−**170**. Genome mining revealed a polyketide glycoside synthase named HerA in the genome of *H. erinaceus* [131]. HerA shares 60% amino acid sequence homology with ArmB, an OA synthase found in honey mushrooms (*Armillaria mellea*). The ability of HerA to synthesize OA was confirmed through heterologous expression in *Aspergillus oryzae* [131].

Biological Activities, and Medicinal Potential

Hericium erinaceus has a long history of use as both food and medicine in China. Ancient medical texts, including the Ming Dynasty's Compendium of Materia Medica, have documented its medicinal and edible properties. These texts state that *H. erinaceus* benefits the five viscera and can be used to treat various conditions such as indigestion, neurasthenia, and physical weakness. Currently, the Chinese Food and Drug Administration (CFDA) has approved over twenty patented health products and drugs containing *Hericium* mushroom ingredients [132]. Similar products are also available in the United States, Japan, and Korea [5]. Numerous studies have explored the pharmacological activities and mechanisms of the crude extracts and chemical constituents of *Hericium* species. These studies can be broadly classified into six groups based on their biological and pharmacological activities (Fig. 8A), with erinacine A (**1**) standing out for its diverse range of activities (Fig. 8B). Additionally, the toxicity and nutritional properties of specific *Hericium* mushroom foods are well-documented in the literature. The biological activities of all compounds are summarized in Tables S1 and S2.

Neuroprotective and neurotrophic activities

Nerve growth factor (NGF) is crucial for promoting neuronal growth and preventing neuronal death, thereby maintaining neuronal function [133]. NGF dysfunction has been implicated in the pathogenesis of AD and dementia, highlighting its potential as a therapeutic target in these neurodegenerative diseases [134]. The stimulation of NGF synthesis has traditionally been the primary method to assess the neurotrophic and protective efficacy of compounds. Our research group pioneered the use of NGF synthesis stimulation to evaluate the neurotrophic properties of erinacines A−C (**1**−**3**) and hericenones C−E (**158**−**160**) [26, 113]. This foundational work has significantly contributed to the exploration of *Hericium* metabolites for potential therapeutic applications in neurodegenerative diseases. Currently, stimulating NGF growth remains the predominant approach in neurotrophic studies [98]. Among the compounds studied, over 50 have been reported to stimulate NGF biosynthesis *in vitro* in cell lines such as 1321N1 and PC12, with erinacine and hericenone compounds being the primary contributors [19, 26, 28, 30, 40, 58, 81, 113, 114]. *In vivo* experiments in rats have further confirmed that compound **1** promotes NGF growth [135]. Notably, compounds **1** and **33** have been shown to penetrate the blood-brain barrier in rats [136, 137]. This ability to cross the blood-brain barrier allows these compounds to promote NGF biosynthesis in the brain, overcoming the limitations of NGF, which cannot efficiently cross the blood-brain barrier [138] and is easily degraded as a polypeptide. This finding provides a significant foundation for erinacine compounds in promoting NGF in the brain to protect neurons. Compounds **118** (**119** actually) [74], **134**, **135**, **138**, and **143** [86] have been investigated for their ability to inhibit endoplasmic reticulum (ER) stress, suggesting they also exert neuroprotective effects.

The molecular pharmacological mechanisms of *H. erinaceus* mycelium and its isolated compounds with neurotrophic and neuroprotective activities have been extensively investigated through signaling pathway validation experiments and *in vivo* experiments using animal disease models. Among these compounds, erinacine A (**1**) has been reported to exert its neuroprotective and neurotrophic activities through multiple signaling pathways. In PC12 cells, compound **1** activates the TrkA/Erk1/2 pathway, promoting cell survival and differentiation (Fig. 9A) [66]. In APP/PS1 transgenic mice with AD, it influences the APP/CTF-β/Aβ/oAβ/ThS-P pathway, which is involved in amyloid precursor protein processing and amyloid-beta plaque formation (Fig. 9B) [7, 139, 140]. In a mouse model of depression, it activates the BDNF/TrkB/PI3K/Akt/GSK-3β pathway, crucial for brain-derived neurotrophic factor signaling and neuronal survival (Fig. 9C) [141]. Additionally, in neurotoxic animal models induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), it either induces the p-PAK1/cdc42/PI3K/AKT/LIMK2 cell survival pathway or suppresses the IRE1α/TRAF2/ASK1/GADD45/p21 pathway, which is involved in cell survival and stress responses (Fig. 9D) [6]. Recent studies on cognitive performance have indicated that erinacine A-enriched *H. erinaceus* mycelia not only inhibited early susceptibility in AD mice [16] but also delayed the aging process and slowed cognitive decline in aged mice [142]. Dietary supplementation with compounds **1**, **100**, **158**, and **159** for two months alleviated reduced locomotor activity in weakened mice [143]. Further research demonstrated that compound **1** reduced symptoms of

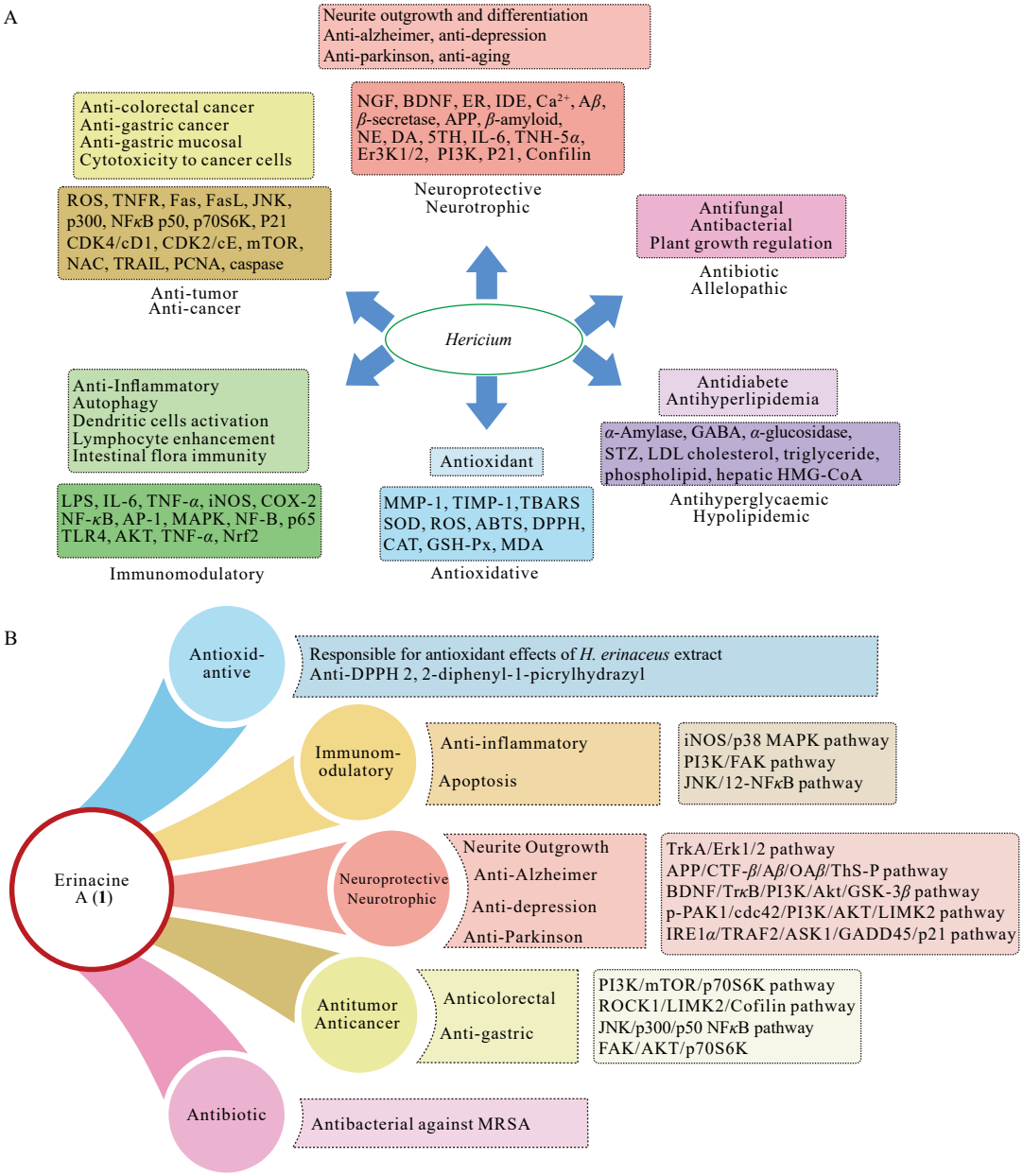

Fig. 8 The bioactivities and proposed mechanisms of *Hericium* compounds (A) and erinacine A (1) (B).

neurological decline and weakness in aging mice, partially restoring function [143]. Moreover, a recent study found that compound **1** was able to repair scopolamine-induced AD patterns in damaged zebrafish brains [144].

The deposition of amyloid β (Aβ) peptide, produced by amyloid precursor protein (APP), is a hallmark pathological feature of AD. The internalization of APP facilitates its processing by *β*-secretase, leading to the formation of Aβ [145, 146]. In a mouse model of AD, administration of compounds **1** and **33** inhibited the formation of Aβ and reduced the accumulation of Aβ plaques in the brain [41]. Moreover, *in vivo* experimental results showed that compounds **1** and **33** reduced cortical size, inhibited the growth of hippocampal amyloid plaques, and promoted hippocampal neurogenesis. These effects are believed to be due to the inhibition of glial cells and increased expression of insulin-degrading enzyme (IDE) in APP/PS1 mice [7, 139] (Fig. 9B). Another study demonstrated that compounds **1** and **33** promoted the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes (OLs), a type of central nervous system cell crucial for action potential propagation through myelin generation [147]. Further research using a rat model of AD indicated that administration of *H. erinaceus* reduced hippocampal neuronal damage caused by aluminum chloride (AlCl3) accumulation and decreased the activation of the NLRP3 inflammasome component [148].

The mechanism by which erinacine C (**3**) induces PC12 cell differentiation with neurotrophic properties has been in-

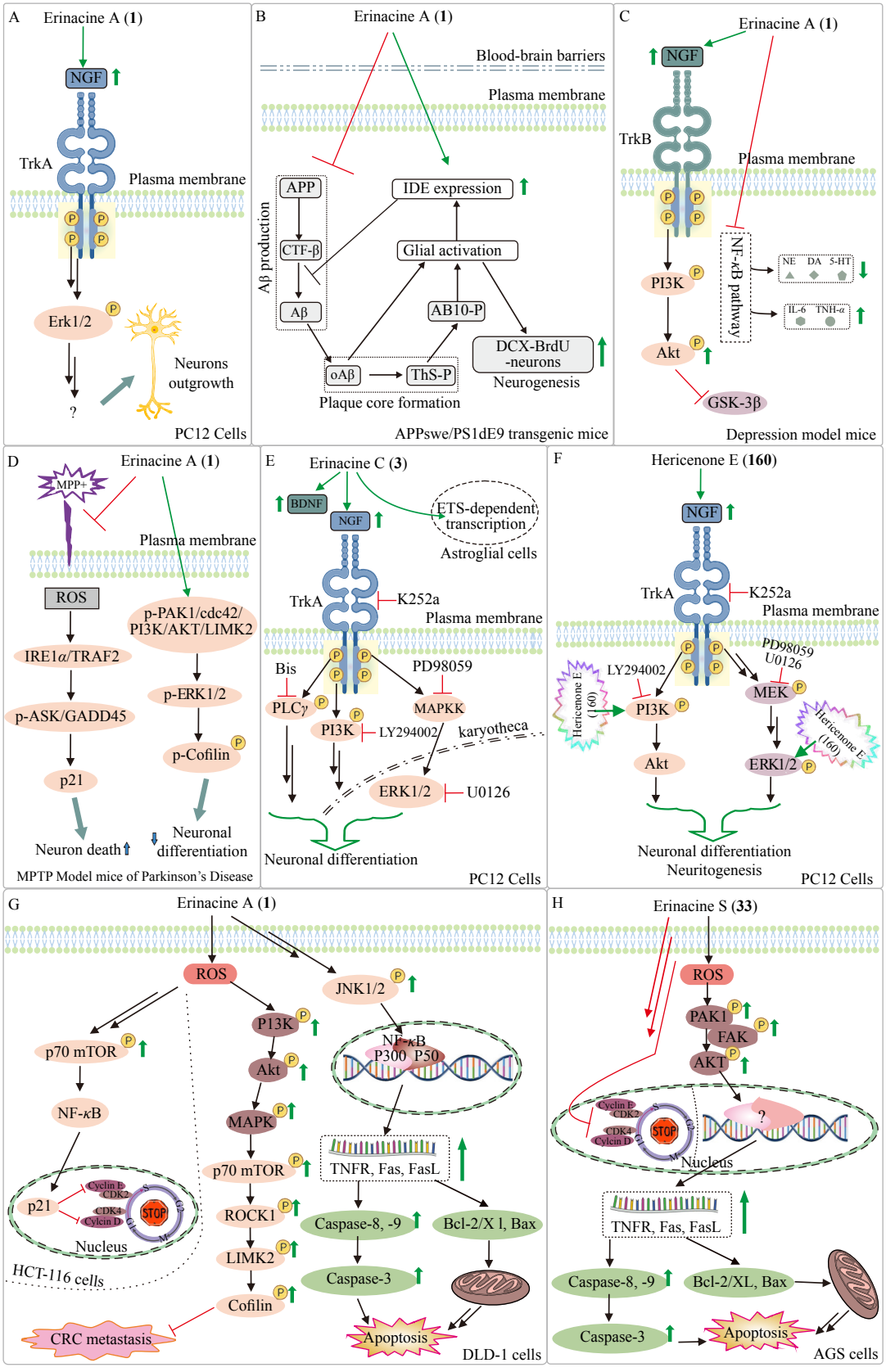

Fig. 9 Schematic diagram of the possible mechanism of erinacine A (1, A−D) erinacine C (3, E) and hericenone E (160, F) exerting neuroprotective and neurotrophic effects through different signal pathways, the possible mechanisms of immunomodulatory effects of erinacine A (1) on colorectal cancer cells (G), and erinacine S (33) on AGS cells (H).

vestigated using a combination of genetic and pharmacological approaches. Results showed that compound **3** induces the expression of neurotrophic factors NGF and BDNF in glial cells, with the potential signal cascade downstream of NGF mediating the differentiation of PC12 cells [10, 149] (Fig. 9E). Additionally, this study found that compound **3** promotes E26 transformation-specific (ETS)-dependent transcription in astrocytes, independent of the process by which it induces PC12 cell differentiation (Fig. 9E). This suggests that erinacine C plays a vital role in the regulation of proliferation and regeneration in the central nervous system [149]. Another investigation demonstrated that compound **160** exhibits neurotrophic activity in PC12 cells, potentially through two simultaneous mechanisms. Firstly, compound **160** increases the expression of NGF, thereby enhancing NGF-mediated phosphorylation of TrKA, which triggers subsequent reactions, ultimately promoting differentiation and regeneration of PC12 cells (Fig. 9F) [150]. Secondly, compound **160** directly activates the ERK1/2 and PI3K/Akt signaling cascades to achieve the same effect (Fig. 9F) [150]. This study represents the first comprehensive investigation into the neurotrophic activity of a non-erinacine compound. Additionally, oral administration of *H. erinaceus* extracts enriched with compounds **1**, **158**, and **159** for two months in physiologically senescent mice not only reversed cognitive decline but also had beneficial effects on the hippocampus and cerebellum. These findings underscore the significant therapeutic potential of *H. erinaceus* compounds in promoting neuronal health and combating neurodegenerative diseases [151].

Immunomodulatory activities

Hericium mushrooms and their chemical components exert immunomodulatory effects by activating immune cells, encouraging cytokine release, and affecting intestinal flora. The presence of inducible nitric oxide synthase (iNOS) can indicate the level of inflammation. Therefore, inhibition of the ability of iNOS to produce NO is an important approach to evaluate anti-inflammatory activity. Compounds **89** [56], **201**–**214** [101], and **237** [105] have been shown to inhibit lipopolysaccharide (LPS)-induced nitric oxide (NO) production, exhibiting significant immunomodulatory activity. The anti-inflammatory properties of *H. erinaceus* crude extracts have been extensively reported in RAW 264.7 mouse macrophages and BV2 microglial cells [152-155]. Studies have found that erinacine C (**3**) not only reduces LPS-induced production of NO, interleukin-6 (IL-6), TNF-α, and iNOS but also inhibits the expression of NF-*κ*B and the phosphorylation of I*κ*Bα. Additionally, compound **3** inhibits the Keap1-Nrf2-HO-1 signaling pathway, suggesting it has a broad inhibitory effect on iNOS-associated inflammation in BV2 cells, thereby reducing the inflammatory response [13]. Furthermore, compounds **105** and **160** have been found to disrupt the phosphorylation of NF-*κ*B and AP-1 induced by LPS. These compounds also downregulate the production of NO and prostaglandin E2 (PGE_2) by inhibiting the activation of NF-*κ*B and AP-1 in macrophage cells [156, 157].

Anti-tumor and anti-cancer activities

As dietary materials, mushrooms prevent malignant cell proliferation and induce apoptosis of abnormal cells through various mechanisms, thereby exhibiting anti-tumor and anti-cancer activities. These mechanisms include the destruction of reactive oxygen species (ROS) that can damage DNA and essential proteins; inhibition of molecules involved in signaling pathways and the expression of proteins associated with carcinogenesis; inhibition of cancer cell metastasis; and stimulation of immune responses that contribute to the elimination of carcinogens [157-159]. Sambutoxin (**90**) is considered an effective anti-cancer candidate against breast cancer cells, inducing cell apoptosis by causing DNA damage and ROS production [62]. Screening experiments to inhibit the growth and survival of cancer cells have led to the discovery of numerous compounds with specific anti-cancer activities, detailed records of which are provided in Table S1.

The anti-colorectal cancer activity of erinacine A (**1**) has been demonstrated both *in vivo* and *in vitro* through multiple investigations [160, 161]. The molecular mechanisms of its inhibition of colorectal cancer cell proliferation are summarized in Fig. 9G. An investigation using proteomic methods to identify target proteins of erinacine A for inhibiting the invasiveness of colorectal cancer cells also yielded similar results [11]. Erinacine S (**33**) was found to significantly induce apoptosis in gastric cancer cells CRL-1739 *in vitro* and inhibit tumor growth in a gastric cancer xenograft mouse model [11]. A series of immunohistochemical and molecular pharmacological experiments showed that compound **33** induced cell cycle G_1 arrest through the inactivation of CDK4/cyclin D1 and CDK2/cyclin E. Additionally, compound **33** stimulated histone H3K4me3 *via* ROS derivation and the AKT/FAK/PAK1 pathway, binding to FasL and TRAIL promoters, and was involved in the apoptosis of gastric cancer AGS cells [162] (Fig. 9H). Erinacine A (**1**) also inhibited invasiveness and induced apoptosis in TSGH 9201 cells, exhibiting significant anti-gastric cancer potential [163].

Antioxidant activities

In vitro activity assays show that compounds **96**, **98**, **100**, **120**, **121**, **127**, **148**, and **182** possess significant antioxidant activity [70, 79, 143]. Among them, **120**, **121**, **127**, and **148** exhibited potential antioxidant activities against the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical with IC_{50} values exceeding 80 μmol·L^{-1}. They also demonstrated antioxidant activity against 2,2'-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) (ABTS) with IC_{50} values ranging from 29 to 66 μmol·L^{-1} [79]. Compound **100**, an antioxidant widely found in bacteria and fungi, including *Hericium* species [70], has been noted for its contribution to the recovery of frail mice when administered as part of *H. erinaceus* extracts [143]. Additionally, extracts from the fresh fruiting body of *H. erinaceus* have displayed promising DPPH radical scavenging activity [164]. Erinacine A (**1**)-enriched *H. erinaceus* mycelia have shown potential antioxidant effects under various oxidative stress conditions. In experiments with *Drosophila melanogaster* and aging mice,

the administration of **1**-enriched *H. erinaceus* mycelium acted as an antioxidant, thereby prolonging the lifespans of these organisms. These findings highlight the substantial antioxidant potential of *H. erinaceus* and its compounds, suggesting their possible application in combating oxidative stress and related conditions [165].

Antibiotic and allelopathic activities

Hericium species exhibit a broad spectrum of antimicrobial activities, including significant effects against *Helicobacter pylori*, a highly prevalent pathogen responsible for gastrointestinal diseases such as peptic ulcers, gastric marginal zone lymphoma, and gastric cancer [166]. The chemical components of *Hericium* have demonstrated important antibiotic properties, including anti-*H. pylori* activity. Specifically, compounds **142** and **236** showed inhibitory effects against *H. pylori*, with minimum inhibitory concentration (MIC) values not exceeding 50 μg·mL^{-1} [88]. Additionally, several compounds, including **1**, **3**, **5**, **10**, and **11**, exhibited antibacterial activities against methicillin-resistant Staphylococcus aureus (MRSA), with MIC values ranging from 62.5 to 500 μmol·L^{-1} [28, 30]. Compound **98** demonstrated significant growth inhibition against the plant fungal pathogens *Botrytis cinerea* and *Glomerella cingulata*, with MIC values of 6.25 mmol·L^{-1} for each pathogen [69]. *Hericium erinaceus* extracts have also shown inhibitory activity against *Salmonella typhimurium* [157]. The extracts of the fresh fruiting body of *H. erinaceus* exhibited inhibitory effects against various pathogenic bacteria [164]. Compounds **134**–**136** exhibited antibacterial activity against *Bacillus subtilis*, with compound **136** also inhibiting *Saccharomyces cerevisiae*, *Verticillium dahliae*, and *Aspergillus niger* [87]. Another study found that compound **134** inhibited the fungi *Candida albicans* with an MIC of 31.3 μg·mL^{-1} and *Cryptococcus neoformans* with an MIC of 62.5 μg·mL^{-1} [59]. In addition to their antimicrobial properties, *Hericium* compounds have been evaluated for allelopathic activity, acting as plant growth regulators. Compounds **40**, **110**, **111**, **125**, **126**, **132**, **133**, **135**, **136**, **138**, **144**–**146**, **179**, **250**, and **251** were found to possess allelopathic activity. Compound **40**, in particular, inhibited pine pollen germination and tea pollen growth, while others inhibited lettuce growth [45]. However, the others, derived from cultures of the same *H. erinaceus* species, were able to inhibit lettuce growth [75, 82]. These findings suggest that *Hericium*-derived small molecules with allelopathic activity could serve as effective plant growth regulators [112].

Other biological activities

The inhibition of *α*-amylase and *α*-glucosidase activity has emerged as a primary method for assessing antihyperglycemic activity *in vitro*. Several *Hericium* compounds, commonly known as erinacerins, have shown inhibitory activity against *α*-glucosidase [46, 50, 52, 55]. Hericenals A–C (**149**–**151**) have been identified as useful in the treatment of diabetes, particularly in managing glucose intolerance and other metabolic disorders in humans [167]. Additionally, Hericenone B (**38**, actually **38a**) has been found to stimulate the release of arachidonic acid, which inhibits platelet aggregation, demonstrating its function as a platelet aggregation inhibitor [168]. The aqueous extract of *H. erinaceus* applied to the wounds of injured mice increased collagen content, decreased macrophages, accelerated wound healing, and exhibited no hepatotoxicity or nephrotoxicity [169]. Ergosterol peroxide (**185**) has been found to reduce the side effects of doxorubicin, a chemotherapeutic agent, suggesting a potential role in supportive cancer care [170].

Toxicity

H. erinaceus, a medicinal and edible fungus, has a long history of use, and its safety has been well-established through its extensive use as both an ingredient and medication. The fruiting bodies of *H. erinaceus* have been confirmed to be non-toxic through long-term usage. However, the mycelium, which has different characteristics from the fruiting body, requires separate evaluation. Hericenones and erinacines are two specific types of compounds derived exclusively from the fruiting body and mycelium, respectively. In a toxicity study, mice were orally administered various doses of *H. erinaceus* mycelium enriched with erinacine A (**1**) for 28 days. The results showed no significant differences in the main physiological and biochemical parameters between the treated mice and the control group. Additionally, no histopathological differences were observed, indicating the non-toxic nature of the mycelium [171]. Further toxicity tests confirmed that *H. erinaceus* mycelium is non-mutagenic and non-genotoxic, meeting all international regulatory requirements [172].

The accumulation of heavy metals in edible mushrooms is a serious problem facing the edible mushroom cultivation industry. Excessive accumulation of heavy metals leads to heavy metal contamination and destroys the edible properties of edible mushrooms. Heavy metal accumulation has been reported in wild mushrooms [173] and common cultivated edible mushrooms [174]. To date, no research has been reported on the accumulation of heavy metals in *Hericium* species. Considering the great edible value and medicinal potential of *Hericium* and the increasing number of artificially cultivated *H. erinaceus*, there may be hidden risks of heavy metals, and this is an extremely serious problem that needs to be addressed urgently. Putrescine (PUT) and spermidine (SPD) are high levels of biogenic amines found in mushrooms, including *Hericium*. Blanching, boiling, and grilling may not completely eliminate biogenic amines, increasing the risk of harm [175]. Although *H. erinaceus* has always been a safe food material and dietary supplement, no cases of poisoning have been reported to date, and the above-mentioned professional tests [171] have also confirmed its safety. Moreover, seventeen monomeric compounds (**24**, **27**, **38**, **43**, **79**–**82**, **84**–**87**, **105**, **158**–**160**, **176**, **177**, **236**, **242**, and **249**) derived from *Hericium* have been reported to induce *in vitro* cancer death [39, 42, 49, 55, 88, 93, 96, 107, 176], although the mechanism of toxicity of these compounds has not yet been investigated.

The bioactivity and pharmacological studies of the chem-

ical constituents of *Hericium* were summarized on based of seven categories, and the suitable pharmacological activities of erinacines A (**1**), B (**2**), C (**3**), S (**33**), hericenone E (**160**) highlighted the strong medicinal value of the chemical constituents of *Hericium*. Furthermore, toxicity studies have shown that the non-toxicity of the chemical constituents of *Hericium* enhances the advantages of their medicinal value.

Conclusions and Perspectives

Since the first *Hericium*-derived compound was reported in 1990, a total of 273 compounds (including twenty compounds associated with erinacine biosynthesis) have been discovered and characterized over the past 34 years. These compounds are classified into nine main groups based on their structural characteristics. The identification of these monomeric compounds has greatly enriched the structural diversity of secondary metabolites in medicinal mushrooms, especially with the discovery of polycyclic compounds such as erinacines. Natural products with complex structures usually contain a variety of functional groups, making classification based on structural features cumbersome and challenging. Similar to the classification of diterpenes and triterpenes, some isopentenyl-, farnesyl-, and geranyl-modified heteroterpenes classified into the alkaloid group or the benzopyrone group that are currently classified into the alkaloid or benzopyrone groups could also be placed into an independent heteroterpene group. However, the current classification system appears more logical and reasonable given the existing arrangement of all compounds. As more natural product biosynthetic pathways are elucidated, the classification of compounds based on biogenic pathways may become a popular and practical approach.

The structural identification and activity evaluation of trace natural products are considered a challenging task. Fortunately, chemical synthesis can provide the necessary complementary and ancillary pathways to address the quantitative deficit. The structures of hericenone B (**38**), hericerin (**40**), hericenone A (**104a**), and 3-hydroxyhericenone F (**118**) have been revised and corrected with the aid of total synthesis [43, 47, 78]. The total syntheses of hericenones C−H (**122**−**124** and **158**−**160**) made it possible to evaluate their structure-activity relationship [78]. The chemical synthesis of hericerin (**40**) has enabled the exploration of its comprehensive effects on HepG2 cells [177]. Biosynthetic studies have elucidated the processes involved in synthesizing the hericenone backbone and erinacines. Synthetic biology based on biosynthetic research findings may solve the dilemma of the origin of remarkably active molecules derived from non-renewable higher fungi. Currently, the efficient heterologous production of erinacine Q (**17**) and several of its derivatives has been achieved [127, 128], providing material support for further pharmacological studies of related active molecules. It is believed that the continuous advancement of metabolic engineering and synthetic biology technologies will produce more and more high-value bioactive molecules in the near future.

A variety of edible macrofungi, such as *Hericium*, have become an important part of people's daily diets and health products. While the fruiting bodies of edible fungi are a safe source of isolated active substances, they present limitations, including the cumbersome culture process required for artificial cultivation and reliance on natural sources for those that cannot be cultured. Submerged culture of macrofungi mycelia offers a more controlled process, with higher yields and shorter production cycles compared to the extraction of secondary metabolites from fruiting bodies. All erinacines with anti-neurodegenerative disease activity summarized in this review were derived from the submerged culture of *Hericium* mycelium [125]. It has been shown that the yield of erinacine C (**3**) can be increased by optimizing the submerged culture conditions for *Hericium* mycelium. The fruiting bodies of *Hericium* are themselves valuable edible mushrooms with high nutritional value and have been highly regarded since ancient times. With the development of biotechnology, the mycelium of *Hericium* mushrooms obtained from fermentation culture has also become an important raw material for the food industry. These dietary materials, rich in bioactive molecules, are absorbed by the human body through consumption, thus achieving the effectiveness of "dietary therapy" as described in Traditional Chinese Medicine. As people continue to pursue health, this edible-medicinal mushroom will be even more in demand in the future. In addition, advances in synthetic biotechnology have enabled the efficient production of bioactive compounds. The efficient production of ergometrine in *Aspergillus oryzae* [127] and yeast [128] has been achieved, and similar progress has been made with OA, the backbone of hericenones, in an *A. oryzae* chassis. These advancements suggest that the green production of hericenones, another class of compounds with anti-neurodegenerative disease activity derived from *Hericium* mushrooms, will soon be realized [131]. This progress in synthetic biotechnology will likely increase the availability and efficacy of these valuable compounds, further enhancing their medicinal value.

In conclusion, mushrooms of the genus *Hericium* can be considered excellent natural sources of active secondary metabolites due to their extensive historical use. The wide range of biological activities and pharmacological properties exhibited by these compounds underscores their great promise for medicinal applications while highlighting the natural advantages of *Hericium* mushrooms as a source for the development and production of functional foods. Therefore, it is crucial to elucidate the biosynthetic pathways of these high-value *Hericium* compounds. Furthermore, efficient production of target compounds in natural or heterologous chassis can be achieved through directed evolution of key genetic elements and optimization of biosynthetic pathways. Convenient access to these bioactive molecules is of paramount importance for in-depth pharmacological research as well as for the development and use of functional foods. Consequently, both the development of *Hericium* mushrooms as functional food and the large-scale production of their active ingredients using synthetic biology strategies will be import-

ant directions for the future development of the *Hericium* mushroom industry. In addition, several urgent issues need to be addressed in the chemical and biological studies of *Hericium* mushrooms, such as clinical confirmation of active compounds, understanding the synergistic effects of these compounds, and ensuring fermentation stability during the synthetic biology production of active compounds

Supplementary Information

Supplementary data to this article can be requested by sending E-mails to the corresponding authors.

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