

Review

Bioactive Phytochemical Constituents of Wild Edible Mushrooms from Southeast Asia

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Abstract: Mushrooms have a long history of uses for their medicinal and nutritional properties. They have been consumed by people for thousands of years. Edible mushrooms are collected in the wild or cultivated worldwide. Recently, mushroom extracts and their secondary metabolites have acquired considerable attention due to their biological effects, which include antioxidant, antimicrobial, anti-cancer, anti-inflammatory, anti-obesity, and immunomodulatory activities. Thus, in addition to phytochemists, nutritionists and consumers are now deeply interested in the phytochemical constituents of mushrooms, which provide beneficial effects to humans in terms of health promotion and reduction of disease-related risks. In recent years, scientific reports on the nutritional, phytochemical and pharmacological properties of mushroom have been overwhelming. However, the bioactive compounds and biological properties of wild edible mushrooms growing in Southeast Asian countries have been rarely described. In this review, the bioactive compounds isolated from 25 selected wild edible mushrooms growing in Southeast Asia have been reviewed, together with their biological activities. Phytoconstituents with antioxidant and antimicrobial activities have been highlighted. Several evidences indicate that mushrooms are good sources for natural antioxidants and antimicrobial agents

Keywords: wild edible mushrooms; Southeast Asia; phytochemical constituents; antioxidant and antimicrobial properties; cytotoxic and immunomodulatory effects

1. Introduction

Popularly, the term mushrooms (or higher fungi) is used to identify fungi producing macroscopic fruiting bodies. This rather inaccurate definition mostly refers to species belonging to the *phyla* Basidiomycota and Ascomycota. The total number of species of the kingdom fungi is far from being exactly known. It was believed to be around 1.5 millions [1], but more recent estimates have increased the number to a range of 2.2–3.8 millions, worldwide [2]. With 120,000 currently accepted

species, it appears that at best just 8% and, in the worst case scenario just 3%, are named so far [2]. The species of fungi described so far are about 120,000. About 35,000 fungal species belong to the phylum Basidiomycota, which comprises the majority of “mushrooms” [3].

Mushrooms have been exploited by humans since prehistoric times, both for food and medicinal purposes. About 1069 mushroom species have been reported to be eaten [4]. Indeed, collection and consumption of wild growing mushrooms as a food is a traditional practice in many human cultures. However, cultivated mushrooms are also marketed, and cultivation of mushrooms is increasing everywhere in the world [5]. However, it has been reported that wild mushrooms contain a higher fiber content and more bioactive compounds than cultivated mushrooms [6].

The importance of mushrooms as a food is due not only to their pleasant organoleptic properties but also to the rich content of substances which must be present in a healthy human diet. In fact, mushrooms contain amino acids, fatty acids (many of them being unsaturated or poly-unsaturated, such as oleic, linoleic and linolenic acids), vitamins, sterols, and some essential minerals [7–13]. As concerns carbohydrates, the most abundant sugar present is trehalose, the $\alpha 1 \rightarrow \alpha 1$ dimer of D-glucose, which is responsible of several alimentary intolerances in people who digest it with difficulty. More elaborate polysaccharides comprise chitin, the fungal *fiber*, which is a homopolymer of N-acetylglucosamine and other sugars occurring in fungal cell walls. Notwithstanding the edible properties, a word of warning must be added, about the possibility that toxic metals such as arsenic, mercury, etc. occur in edible mushrooms collected from polluted soils [14–16].

In addition as a food, there is an increasing interest in developing mushroom bioactive constituents as control agents of several diseases and to delay aging processes [17–20]. Friedman, et al. reviewed mushroom polysaccharides which have shown therapeutic properties such as anti-obesity, anti-diabetes, anticancer and antibiotic properties [21]. Mushrooms endowed with potent antimicrobial and antioxidant properties, among other important bioactivities, have been reported in several studies [6,18,22–26].

Little information exists about the phytochemical constituents of edible mushrooms growing in Southeast Asian countries. This review describes the data reported in Reaxys database until January 2020 for some selected edible mushroom growing in Southeast Asia. One purpose of this work is to foster systematic studies on the region’s rich mycological flora.

2. Wild Edible Mushroom Species in Southeast Asia

Southeast Asia refers geographically to the corner of Asia east of India, south of China, west of New Guinea, and north of Australia (Figure 1). It is a region with an outstanding high biodiversity, encompassing about 20 percent of global plant, animal and marine species [27,28]. Comparing with the rest of the world, Southeast Asia is more rural as 41.8% of the nearly 590 million people live in the countryside in 2010 [27]. The climate, sea level fluctuations and biotas of this region seem to have created a habit favoring the explosive growth of countless new animal and plants species. In the region surrounding the Mekong river, 2077 new animal and plants species have been described since 1997 and 367 new species were added to the new species record in only two years, 2012–2013 [29]. These findings clearly indicate that the Mekong region has a higher rate of species discovery than other parts of the world.

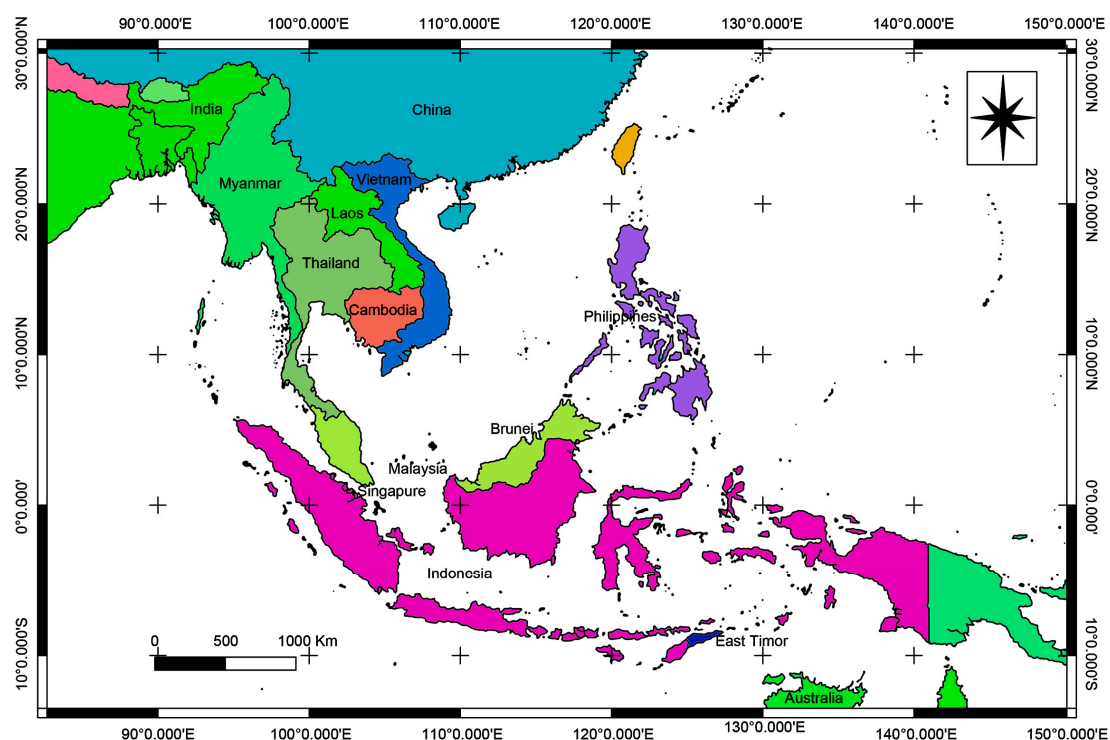


Figure 1. Map showing Southeast Asian countries.

About fungal species, 93% of the fungi growing in northern Thailand appeared to be novel [30]. Therefore, the biodiversity of Southeast Asia is likely to be a vast reservoir for finding new mushroom species, since fungi occurring in Myanmar, Laos, Vietnam, and Cambodia have barely been studied so far [30]. Moreover, it is worth noting that numerous ethnic groups living in Southeast Asian countries resort to several wild mushrooms for obtaining food and medicines; however, very few studies have been carried out on the nutritional value and biological activities of these mushrooms. This review has collected the information available in the literature on the phytochemical constituents of selected wild edible mushrooms occurring in Southeast Asian countries, namely *Agaricus silvaticus*, *Ampulloclitocybe clavipes*, *Butyriboletus roseoflavus*, *Cantharellus cibarius* (Figure 2a), *Craterellus cornucopioides*, *Craterellus odoratus*, *Fistulina hepatica*, *Hydnum repandum* (Figure 2b), *Laccaria amethystea*, *Lactarius hatsudake*, *Lepista sordida* (Figure 2c), *Lycoperdon pyriforme* (Figure 2d), *Neolentinus lepideus* (Figure 2e), *Phlebopus portentosus*, *Polyozellus multiplex*, *Ramaria botrytis*, *Rugiboletus extremiorientalis*, *Russula virescens* (Figure 2f), *Sarcodon imbricatus*, *Termitomyces albuminosus*, *Termitomyces eurhizus*, *Termitomyces heimii*, *Termitomyces microcarpus*, *Thelephora ganbajun*, and *Volvariella bombycina*. These species were selected on the basis of their wide use as a food in Southeast Asia and difficult cultivation. Moreover, they are among the most common mushrooms growing in this part of the world. Likewise all selected macrofungi are a natural resource of economic, ecological, scientific and cultural importance among ethnic groups in Southeast Asia.

The most important biological/pharmacological activities reported for extracts and isolated compounds are also described, with special attention to antioxidant, antimicrobial and cytotoxic properties. They have been summarized in Table 1. The chemical structures of new compounds or compounds that are specific to the collected mushroom species are depicted in Figures 3–20. It is worth noting that a great number of data reported herein have been collected through investigations conducted on mushroom samples collected outside Asia, especially in Europe. Therefore, even if the same species is reported to grow in different continents, varieties or sub-varieties may exist for the same species. Thus, possible differences may exist for the phytochemical contents of mushrooms growing in different ecosystems.



Figure 2. (a) *Cantharellus cibarius*; (b) *Hydnum repandum*; (c) *Lepista sordida*; (d) *Lycoperdon pyriforme*; (e) *Neolentinus lepideus*; (f) *Russula virescens*.

3. Antioxidant Activity

Reactive oxygen (ROS) and nitrogen (RNS) species, which are extremely reactive with most organic compounds, are products of the normal cellular metabolism [31] and may have either harmful or beneficial effects on living systems [32]. Free radicals are atoms or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals [33]. They are formed naturally in the body, especially in mitochondria, as necessary intermediates in a variety of normal biochemical reactions, thus playing a positive role in many normal cellular processes. However, at high concentrations, ROS and RNS are responsible for the oxidative damage to biological macromolecules, including DNA, proteins, and lipids in cell membranes. The damage to cells caused by free radicals, especially the damage to DNA, may contribute to the development of many diseases, including cancer [34,35].

Free-radical scavengers or free-radical quenchers are chemicals that react with free radicals and neutralize them, thus helping stop or limit damages caused by those reactive species. Most cells in our body produce antioxidant and repair systems which protect them against oxidative damage; however, these systems are often insufficient to prevent or repair the damage entirely [36]. Therefore, the introduction in the body of additional antioxidant agents from the diet is believed to be critical for maintaining cell homeostasis and thus a healthy organism [37]. Although synthetic antioxidants such as butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), propyl gallate (PG) and *tert*-butylhydroquinone (TBHQ) have commonly been used as antioxidant additives in foods for years, their safety has long been questioned [38]. This finding has led to an increased interest in natural antioxidants. Antioxidant activities of extracts and isolated compounds from edible mushrooms have been determined by several research groups that used different tests *in vitro* to measure the reducing power ability, the total antioxidant activity, the 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity, the lipid peroxide inhibitory activity, the ferric reducing antioxidant power, the nitric oxide (NO) scavenging activity, and the ABTS radical scavenging, superoxide radical, and hydroxyl radical scavenging properties. Thus, a large number of results in the literature clearly indicates that several edible mushrooms have significant antioxidant properties due to their bioactive compounds, such as polyphenols, polysaccharides, vitamins, carotenoids and minerals [18,39–41].

4. Antimicrobial Activity

Infectious diseases produced by organisms such as bacteria, viruses, fungi or parasites, are among the most serious causes of morbidity and mortality worldwide [42]. Nowadays many infections are often caused by multi-resistant microorganisms resulting in difficult to treat diseases; as a very well-known example, coronavirus Covid-19 is killing thousands of people worldwide. Consequently, healthcare costs are increasing substantially every year, becoming a serious problem in many countries [43–45]. This situation has led to an increasing search for new antimicrobial agents from different sources. Several researches have been conducted to explore the antimicrobial potential of natural or synthetic compounds [46,47]. Thus, natural sources, including mushrooms, have been investigated for finding novel antimicrobial compounds [48–51].

In food industry, contamination of food products by bacteria and fungi may be the result of exposure to sources of contamination during harvesting, processing and/or packaging process [52]. Therefore, chemical additives have been extensively used in food industries to increase the shelf life of food and to prevent the proliferation of microorganisms. In this regard, natural antimicrobials, including those isolated from mushrooms, are gaining an increasing importance as potential alternatives to synthetic preservatives, whose safety and impact on human health are still questionable [53–55]. Instead, the safety of many natural antimicrobials have been generally recognized in EU and USA [56].

5. Bioactive Phytochemical Constituents of Wild Edible Mushrooms from Southeast Asian Countries

5.1. *Agaricus silvaticus* Schaeff.

Agaricus silvaticus Schaeff. is a common edible mushroom belonging to the family Agaricaceae. It is distributed in China, Thailand and Mongolia [4,57,58]. Boonyanuphap and Hansawasdi studied the beta-glucan content of *A. silvaticus* comparing it with other wild edible mushrooms found in Thailand [59]. β -Nitroaminoalanine, *N*-nitroethylenediamine and glutamic acid were identified as secondary metabolites of *A. silvaticus* [60–62]. Lodonjav et al. [57] investigated the chemical components of *A. silvaticus* and identified $5\alpha,6\alpha$ -epoxy-(2*E*,24*R*)-ergosta-8(14),22-diene-3 β ,7 α -diol (1 in Figure 3), ergosterol, ergosterol peroxide, (2*E*,24*R*)-ergosta-7,22-diene-3 β ,5 α ,6 β ,9 α -tetraol (2), cerevisterol (3), (2*R*,3*S*,4*R*,6*E*)-*N*-[(*R*)-2'-hydroxytetracosanoyl]-1,3,4-trihydroxy-2-amino-octadeca-6-ene, benzoic acid, cinnamic acid and *D*-mannitol. The antimicrobial activity of *A. silvaticus* has not been reported, whereas the antioxidant activity has been determined [63,64].

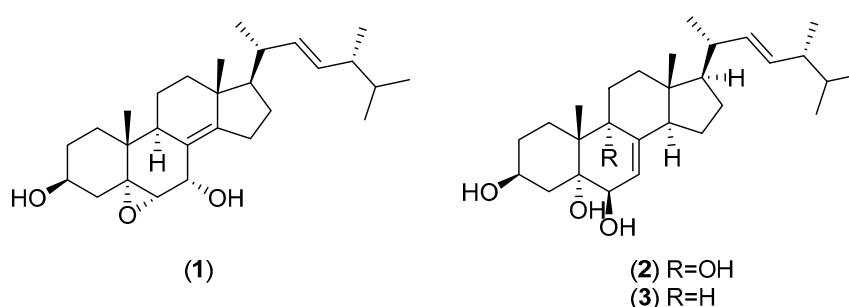


Figure 3. Chemical structures of selected compounds isolated from *Agaricus silvaticus*.

5.2. *Ampulloclitocybe clavipes* (Pers.) Redhead, Lutzoni, Moncalvo and Vilgalys

Ampulloclitocybe clavipes (Pers.) Redhead, Lutzoni, Moncalvo & Vilgalys, formerly known as *Clitocybe clavipes* (Pers.) P. Kumm, belongs to the family Hygrophoraceae. It is a wild mushroom growing in China, Thailand, and Japan [4,58,65]. Clavilactones A–C (4–6, Figure 4) were isolated in an Italian laboratory from a culture of the fungus and exhibited antifungal and antibacterial activities [66]. The structures of clavilactones D and E (7), were initially inferred by 1- and 2-D NMR data [67]. However, the subsequent total synthesis of clavilactones A, B, and D led to a revision of the original structure of clavilactone D which was established to be as formula (8) in Figure 4 [68]. Clavilactone A, B, and D displayed potent inhibitory activity in kinase assays against the Ret/ptc1 and epidermal growth factor receptor (EGFR) tyrosine kinases [67,69]. Subsequently, Sun et al. [70] isolated from a fungal strain of *A. clavipes*, clavilactone F (12) together with three novel meroterpenoids, named clavipines A–C (9–11), which exhibit a benzoquinone ring fused to an azepine ring and a ten-membered carbocycle bearing an α,β -epoxy/unsaturated- γ -lactone. Compound 9 exhibited significant antiproliferative activity against HepG2 and A549 cells with IC_{50} values of 4.28 ± 0.26 and 7.49 ± 0.41 μ M, respectively [70]. Subsequently, clavipols A–B (13–14) containing a 12-membered ether ring and clavilactones G–I (15–17) were isolated from the fruiting bodies of *A. clavipes* collected in China. Compound 16 exhibited moderate cytotoxic activity against Hela and SGC-7901 cancer cell lines, with IC_{50} values of 23.5 and 14.5 μ M, respectively [71]. Five fatty acid derivatives, isolated from *A. clavipes* have been reported to have potent strong inhibitory activity against aldehyde dehydrogenase [65].

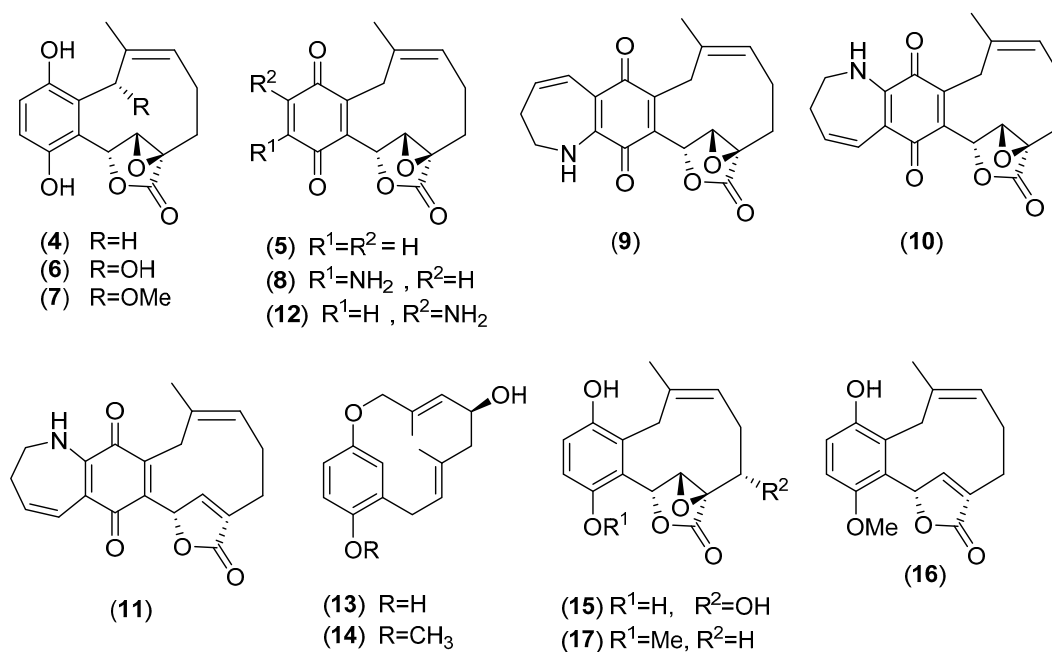


Figure 4. Chemical structures of selected compounds isolated from *Ampulloclitocybe clavipes*.

5.3. *Butyriboletus roseoflavus* (M. Zang and H.B. Li) D. Arora and J.L. Frank

Butyriboletus roseoflavus is an Asian species which was previously named *Boletus speciosus* Frost. It belongs to the family Boletaceae and to the genus *Butyriboletus*, which has recently been created to accommodate the former section *Appendiculati* within the large genus *Boletus*. This edible mushroom grows abundantly in Southern China (Yunnan) and Thailand, and it is commonly sold in street markets [4,58]. A group of Chinese researchers reported the isolation, from the fruiting bodies of a novel heteropolysaccharide, which has a backbone of (1→4)- α -L-mannopyranose residues, which branched at O-6. The branches are mainly composed of one with \rightarrow 1)- α -D-galactopyranose residue [72]. In addition to a strong antioxidant activity [72], this polysaccharide with a unique structure activates the secretion of cytokines from immune cells and inhibits the growth of Hep-2 cells. The concentration of 400 μ g/mL has the highest inhibitory rate [73,74]. A new water-soluble polysaccharide, having a backbone of 1,4-linked β -D-glucose, with branches mainly composed of two 1,6-linked α -D-galactose residues and bearing a 4-linked β -D-glucose unit at the end of the branches, has been reported to exhibit unique antitumor and immunoregulatory properties [75]. Sun et al. [76] reported that hemagglutinin isolated from *B. speciosus*, showed antiproliferative activity towards hepatoma Hep G2 cells and mouse lymphocytic leukemia cells (L1210) in vitro, with an IC₅₀ of 4.7 μ M and 7.0 μ M, respectively. It also exhibited HIV-1 reverse transcriptase inhibitory activity with an IC₅₀ of 7.1 μ M.

5.4. *Cantharellus cibarius* Fr.

Cantharellus cibarius Fr., belonging to the family Cantharellaceae, is an edible mushroom, which grows widely in China, India, Thailand, America and several European countries [4,58,77–79]. The polysaccharides isolated from the fruiting bodies of *C. cibarius* were galactans and glucans, including a novel linear 3-O-methylated galactan and a new heteropolysaccharide. These macromolecules showed a wide range of biological activities, such as antioxidant, antitumor, antiproliferative, immunomodulatory and neuroprotective properties [80–86]. Mittermeier et al. [87] investigated the taste active and taste modulating compounds from this mushroom by LC–MS and 1D/2D-NMR experiments and identified several C18-acetylenic acids: 14,15-dehydrocrepenynic acid methyl ester, 14,15-dehydrocrepenynic acid ethyl ester, 14,15-dehydrocrepenynic acid, (9Z,15E)-14,17,18-trihydroxy-9,15-octadecadien-12-ynoic acid, (9Z,15E)-14-oxo-9,15-octadecadien-12-ynoic acid, (10E,15E)-9-hydroxy-14-oxo-10,15-octadecadien-12-ynoic acid, (10E,15E)-9-hydroperoxy-14-oxo-10,15-octadecadien-12-ynoic acid, (10E,15E)-9,14-dioxo-10,15-octadecadien-12-ynoic acid, (9Z,15E)-14-oxo-9,15-octadecadien-12-ynoic acid methyl ester, (9Z,15E)-17(18)-epoxy-14-oxo-9,15-octadecadien-12-ynoic acid methyl ester, (10E,14Z)-9-hydroperoxy-10,14-octadecadien-12-ynoic acid, (10E,14Z)-12-hydroxy-10,14-octadecadienoic acid, (9Z,11Z)-14,18-dihydroxy-9,11-octadecadienoic acid, (9Z,11Z)-14,17,18-trihydroxy-9,11-octadecadienoic acid, (10E,14Z)-9-hydroxy-10,14-octadecadien-12-ynoic acid and (10E,14Z)-9-oxo-10,14-octadecadien-12-ynoic acid. Further studies showed that *C. cibarius* also contains (9Z,13Z,15E)-14,18-dihydroxy-12-keto-9,13,15-octadecatrienoic acid, 14,15-dehydrocrepenynic acid, (10E,14Z)-9-oxooctadeca-10,14-dien-12-ynoic acid and (10E,14Z)-9-hydroxyoctadeca-10,14-dien-12-ynoic acid and ergocalciferol [88–90]. Crude extracts of *C. cibarius* showed antioxidant [91], antimicrobial activity [92] and cytotoxic activities [93].

5.5. *Craterellus cornucopioides* (L.Fr.) Pers

Craterellus cornucopioides (L.Fr.) Pers. (family-Cantharellaceae) is an edible fungus with a wide distribution in Europe, North America, Korea, Japan, China, and Thailand [4,58,94,95]. A new triple-helix polysaccharide, a heteroglycan with (1→3)-linked- β -D-Manp-(1→6)-linked α -D-Galp backbone distributed by (1→4)-linked- α -D-Xylp-t- α -D-Manp and t- β -D-Glup units at O-6, was isolated from *C. cornucopioides*. This compound activated RAW264.7 macrophages in vitro, and enhanced the immunomodulatory activity in immunosuppressive mice models [94–96].

Yang et al. [97] isolated a novel polysaccharide fraction from the fruiting bodies. The dominant linkage types were $\rightarrow 3,6$ -Manp (1 \rightarrow , T-Araf, $\rightarrow 4,6$ -Manp (1 \rightarrow , $\rightarrow 5$)-Araf (1 \rightarrow and $\rightarrow 3$)-Araf (1 \rightarrow). The polysaccharide possessed strong scavenging abilities on DPPH and ABTS radicals. Three illudin sesquiterpenoids, craterellins A–C (structures 18–20 in Figure 5), and one gymnomitrane sesquiterpenoid, gymnomitr-3-en-10 β ,15-diol (21), together with illudin F, illudin M, illudin T and illudalenol were isolated in China from cultures of this mushroom. Compound 20 exhibited moderate cytotoxicity against A-549 cells with an IC₅₀ value of 21.0 μ M [98]. In addition to a new menthane monoterpene, 4-hydroxy-4-isopropenylcyclohexanemethanol acetate (22), craterellins D (23) and E (24) were later isolated from fungal cultures after minor modifications of the original cultural conditions. The cytotoxic activities of these compounds on five tumor cell lines were also reported [99]. Three new keto esters, 4-oxo-hex-1,6-diyl diacetate, 4-oxo-hex-5-enyl acetate and 6-hydroxy-4-oxo-hexyl acetate were isolated from a tissue culture of fruiting bodies of *C. cornucopioides* collected in China [100]. Magnus's group isolated three tryptophol (indole-3-ethanol) derivatives, namely 2-(indol-3-yl)ethyl octadeca-(9Z)-enoate (structure 25 in Figure 5), 2-(indol-3-yl)ethyl octadeca-(9Z,12Z)-dienoate and 2-(indol-3-yl)ethyl octadeca-(9Z,14Z)-dien-12-ynoate from the fruiting bodies of this mushroom [101]. Glycerol *tri*-dehydrocrepenynate, glycerol trioleate and glycerol linoleate dioleate were also isolated by the same research group [102]. Piceatannol, vitamin B₁₂, ergosterol and ergosteryl derivatives are other chemical constituents isolated from *C. cornucopioides* [93,103,104]. Various extracts of *C. cornucopioides* showed antioxidant, antimicrobial, anti-inflammatory and cytotoxic activities [91,93,105–108].

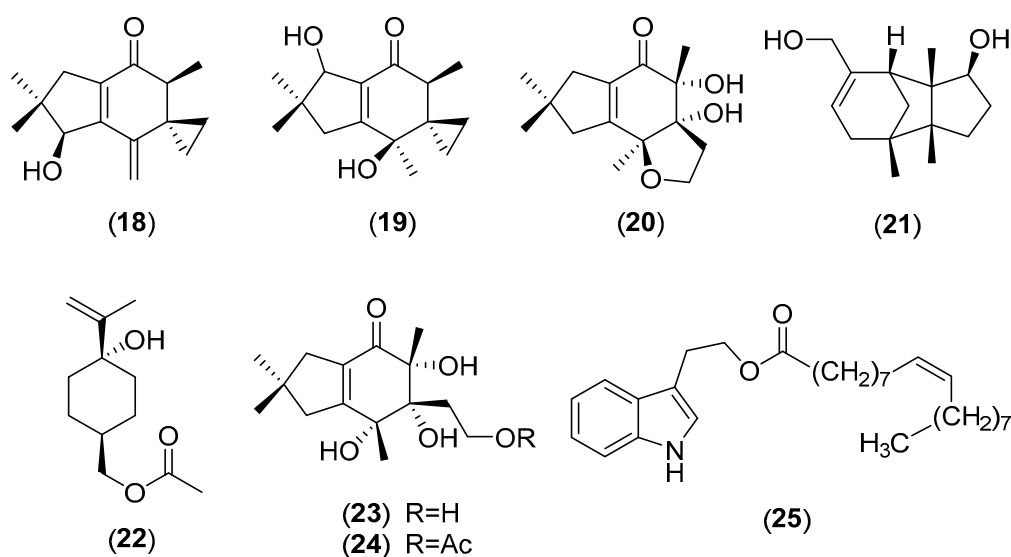


Figure 5. Chemical structures of selected compounds isolated from *Craterellus cornucopioides*.

5.6. *Craterellus odoratus* (Schwein.) Fr.

Craterellus odoratus (Schwein.) Fr. is a tasty mushroom of the family Cantharellaceae, which is widely collected in China and Thailand [58,109,110]. Three rare merosesquiterpenoids, named craterellins A–C (26–28 in Figure 6), were isolated from cultures of *C. odoratus* together with known massarinolin C. They showed inhibitory activities of 11 β -hydroxysteroid dehydrogenases (11 β -HSD1 and 11 β -HSD2) [111]. Craterellin A (26) demonstrated significant inhibitory activity against human 11 β -HSD2 with an IC₅₀ value of 1.5 μ g/mL [111]. Craterellin D (29), 5-hydroxymethyl-2-hydroxy-4-methoxy-phenylethanone, 2-(1,2-dihydroxypropan-2-yl) benzofuran-5-carboxylic acid, 6 α -hydroxy-3-methoxy-4 α -methyl-2-cyclohexen-1-one have been isolated from the cultures of *C. odoratus*. 5-hydroxymethyl-2-hydroxy-4-methoxy-phenylethanone exhibited inhibitory activity against human 11 β -HSD1 with an IC₅₀ value of 16.4 μ g/mL [109]. Guo et al. [112] extensively studied the cultures of *C. odoratus* and identified five new polyketides, named craterellones A–E (structures 30–34 in Figure 6), together with the known compounds

decumbenones A and B, versiol, calbistrin A and calbistrin C. Their cytotoxic activities were reported [112]. Subsequently, the Chinese research group reported the chemical structures of two rare 4,6-dimethyl-3,4-dihydrochromen-2-one derivatives, cralactones A (35) and B (36), which were isolated from the culture broth of *C. odoratus*. The pancreatic lipase inhibitory activity of the compounds were also described [113]. Recently, the origin of these isolated compounds has been discussed. In fact, it has been debated if they are true metabolites of *C. odoratus* or are formed by the associated fungus *Montagnula donacina* [114].

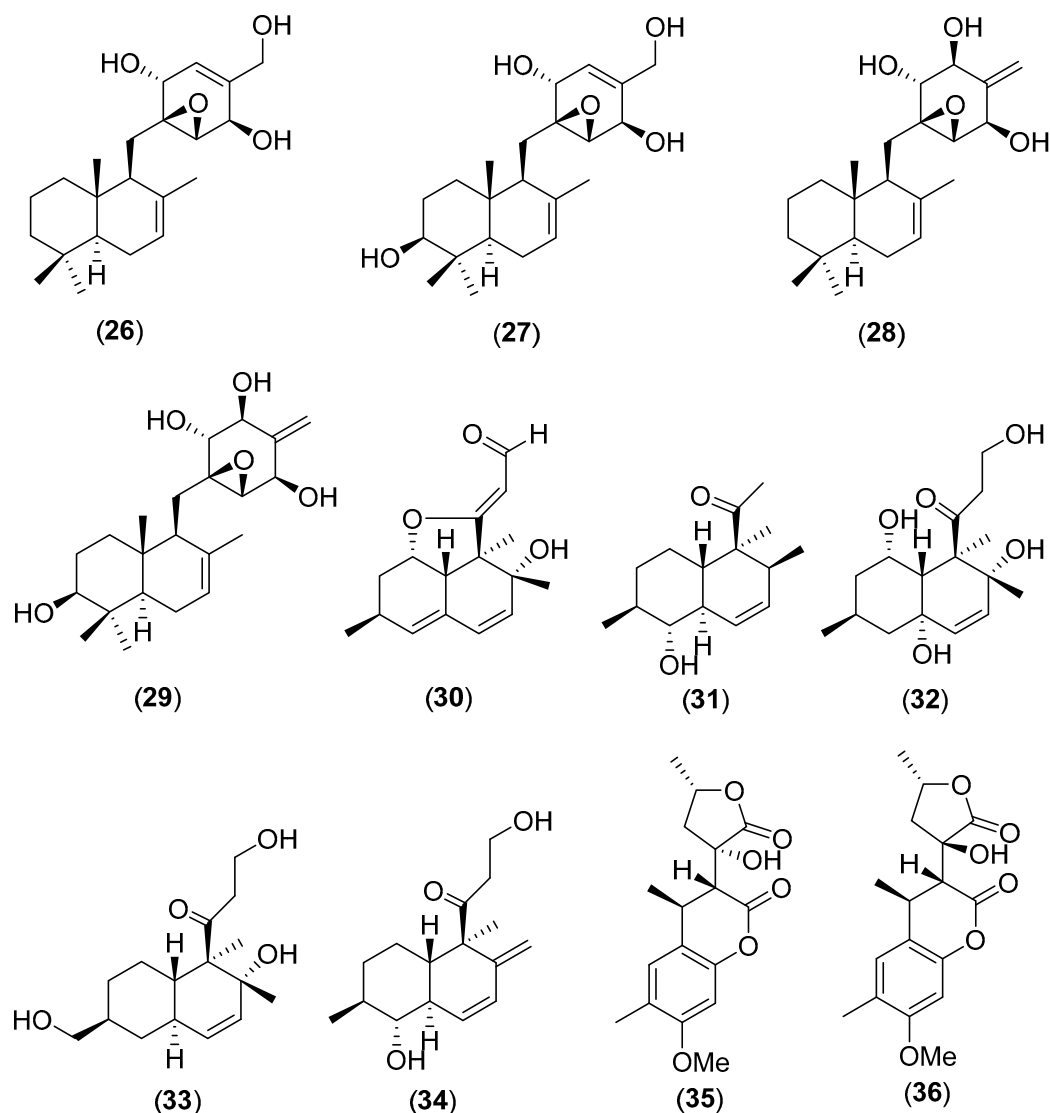


Figure 6. Chemical structures of selected compounds isolated from *Craterellus odoratus*.

5.7. *Fistulina hepatica* (Schaeff.)

Fistulina hepatica (Schaeff.), commonly known as beefsteak fungus, is a wild edible fungus belonging to the family Fistulinaceae [95]. It is distributed in temperate and subtropical hardwood forests of China, Thailand, Hungary, Portugal [4,58,115,116], and other European countries. Two novel triacetylene derivatives have been isolated from the fruiting bodies and named cinnatriacetins A (37) and B (38) [117]. Compounds 37 and 38 (see structures in Figure 7) showed antimicrobial activity against gram-positive bacteria, but no activity towards gram-negative bacteria [117]. Caffeic acid, *p*-coumaric acid, ellagic acid, hyperoside, quercetin, oxalic acid, aconitic acid, citric acid, malic acid, ascorbic acid and fumaric acid were also isolated from *F. hepatica*, and an aqueous extract showed a significant scavenger activity of

DPPH• and superoxide radicals [118]. A sample of *F. hepatica* collected in Portugal contained tocopherols and showed strong antioxidant activity [115,119]. Ribeiro and his co-workers extensively studied the free amino acid and fatty acid composition of *F. hepatica*, comparing their contents with those of other wild edible mushrooms [120,121]. Wu et al. [122] studied the volatile compounds from the fruiting bodies and 11 compounds were identified as responsible for the characteristic odor of the fungus. They were: 1-octen-3-one, 1-octen-3-ol, linalool, phenylacetaldehyde, butanoic acid, (*E*)-2-methyl-2-butenic acid, methyl (*E*)-cinnamate, (*Z*)-9-hexadecenoic acid methyl ester, bisabolol oxide B, phenylacetic acid, and an undetermined mouldy compound. (*E*)-2-Methyl-2-butenic acid and bisabolol oxide B have not been identified as native fungal volatile metabolites. Other studies on the volatiles from *F. hepatica* have been performed in Portugal and German laboratories [123,124]. A methanol/water (80:20) extract of *F. hepatica* collected in Portugal inhibited the growth of gram-negative (*Escherichia coli*, *Morganella morganni* and *Pasteurella multocida*) and gram-positive (*Staphylococcus aureus*, MRSA, *Enterococcus faecalis*, *Listeria monocytogenes*, *Streptococcus agalactiae* and *Streptococcus pyogenes*) bacteria [22]. Moreover, the crude extract showed high synergistic effects in combination with cefuroxime against MRSA [116,125].

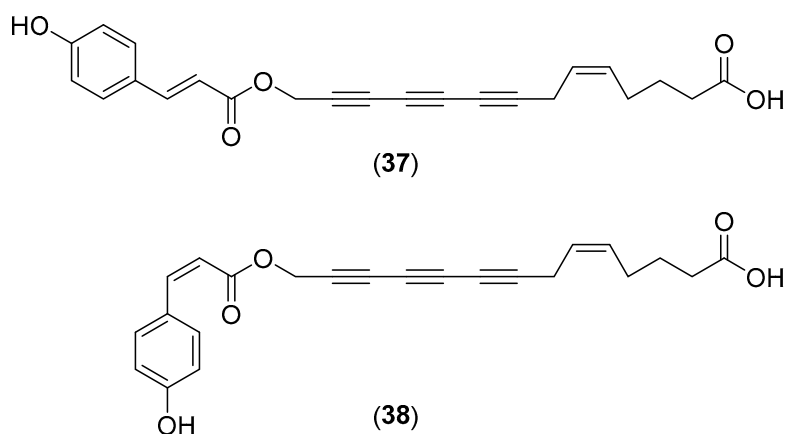


Figure 7. Chemical structures of selected compounds isolated from *Fistulina hepatica*.

5.8. *Hydnum repandum* L.

Hydnum repandum L. is a wild edible mushroom belonging to the family Cantharellaceae [95]. This mushroom is distributed in China, Thailand, India and Portugal [58,126–128]. A new cytotoxic diepoxide, namely repandiol (structure 39 in Figure 8), was isolated from fruiting bodies collected in Japan and displayed potent cytotoxic activity against various tumor cell lines, especially colon adenocarcinoma cells with an IC_{50} value of 0.30 $\mu\text{g}/\text{mL}$ [129]. Sarcodonin A, scabronine B (40), 3 β -hydroxy-5 α ,8 α -epidioxyergosta-6,22-diene, (22*E*,24*R*)-ergosta-7,22-diene-3 β ,5 α ,6 β -triol, (22*E*,24*R*)-ergosta-7,22-diene-3 β -ol, benzoic acid, 4-hydroxybenzaldehyde, 4-monopropanoylbenzenediol, ethyl- β -D-glucopyranoside, thioacetic anhydride, and (2*S*,2'*R*,3*S*,4*R*)-2-(2-hydroxytricosanoylamino) hexadecane-1,3,4-triol have also been isolated [130]. Fatty acids such as pentadecanoic, heptadecanoic, oleic, myristoleic, palmitoleic, linolenic, palmitic and stearic acids were detected in the fruiting bodies of *H. repandum* collected in India [128]. Antioxidant, antiproliferative, cytotoxic, and pro-apoptotic activities of *H. repandum* were investigated by Vasdekis and collaborators. A significant cytotoxicity ($IC_{50} = 1.0 \text{ mg} \cdot \text{mL}^{-1}$) was determined against an A549 cell line, and, piceatannol was identified by LC/MS and MS analysis [93]. The influence of *H. repandum* extract on the growth and sporulation of *Penicillium expansum* was studied in vitro. A significant reduction of the mycelial growth and inhibition of the pathogen sporulation were observed [131]. *In vitro* antimicrobial and antioxidant susceptibility studies were performed by many research groups [92,115,126,127,132,133].

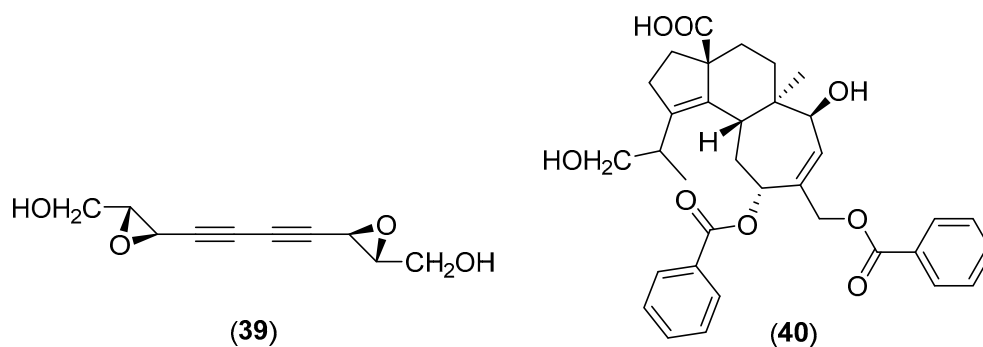


Figure 8. Chemical structures of selected compounds isolated from *Hydnum repandum*.

5.9. *Laccaria amethystea* (Bull.) Murrill

Laccaria amethystea (Bull.) Murrill, belonging to the family Hydnangiaceae, is an edible mushroom with a wide distribution in China, Thailand and Laos [4,58]. Berg et al. [134] reported the isolation from a strain of *L. amethystea*, of new protease inhibitors, called laccaridiones A and B (structures 41 and 42, respectively, in Figure 9), which inhibited a series of proteases such as commercial trypsin, papain, thermolysin, collagenase, and zinc-protease from *Bacillus subtilis*. In addition, compound 42 showed strong antiproliferative effects on the murine fibroblast-cell line L-929 ($IC_{50} = 2.4 \mu\text{g/mL}$) and the human leukemia cell line K-562 ($IC_{50} = 1.8 \mu\text{g/mL}$) [134]. 3-(3-Methylbut-2-enyloxy)-4-O- α -D-ribofuranosyl-benzoic acid methyl ester (43), was also isolate from a culture of this mushroom [135]. *L. amethystea* showed effective anti-hyperglycemia and anti-oxidative properties; the highest α -amylase inhibitory activity (EC_{50} value $4.37 \mu\text{g/mL}$) and metal chelating activity (EC_{50} value 2.13 mg/mL) were observed for an aqueous extract [106].

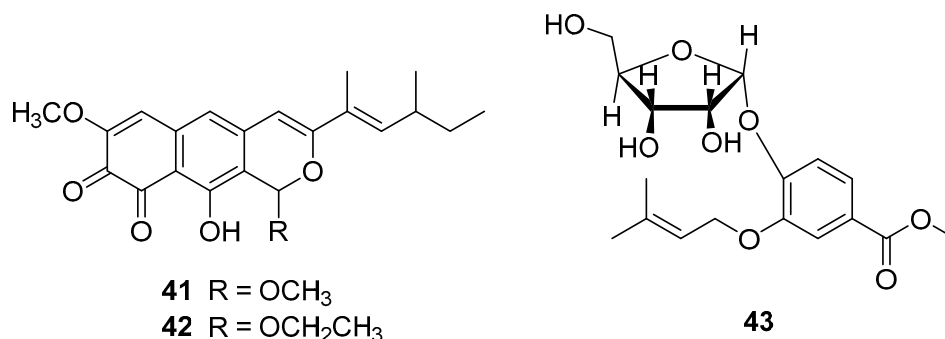


Figure 9. Chemical structures of selected compounds isolated from *Laccaria amethystea*.

5.10. *Lactarius hatsudake* Nobuj. Tanaka

Lactarius hatsudake Nobuj. Tanaka, belonging to the genus *Lactarius* of the family Russulaceae, is an edible, slightly bitter mushroom, which is widely distributed in China, Thailand and Bhutan [4,58]. Artificial cultures are obtained with difficulty [136]. A review on the secondary metabolites isolated from the fruiting bodies of European *Lactarius* species [137] does not include this mushroom, which is a typical Asian species for which a limited number of reports exists. Miyazawa et al. [138] studied the components of the volatile oil from this mushroom. *cis*-Isolongifolanone, α -cedrene epoxide, humulene epoxide III, clovane, linoleic acid and palmitoleic acid were the main components among the 71 identified compounds. Ergosterol, ergosterol peroxide, 5 α ,8 α -epidioxy-(24S)-ergosta-6-en-3 β -ol and (22E,24R)-ergosta-7,22-dien-3 β ,5 α ,6 β -triol were isolated from the fruiting bodies, and their inhibitory activities against *Crotalus adamanteus* venom phospholipase A₂ (PLA₂) enzyme and HIV in vitro were reported [139,140]. Fang et al. [141] isolated 7-(1-hydroxy-1-methylethyl)-4-methylazulene-1-carbaldehyde (structure 44 in Figure 10), 4-methyl-7-(1-methylethyl) azulene-1-carboxylic acid (45) and

4-methyl-7-(1-methylethyl)azulene-1-carbaldehyde from the fruiting bodies. Other new guaiane sesquiterpenes, called lactariolines A and B (structures 46 and 47, respectively, in Figure 10), together with known 4-methyl-7-isopropylazulene-1-carboxylic acid, 1-formyl-4-methyl-7-isopropyl azulene, lactaroviolin and 1-formyl-4-methyl-7-(1-hydroxy-1-methylethyl) azulene, were isolated by a Korean research group [142].

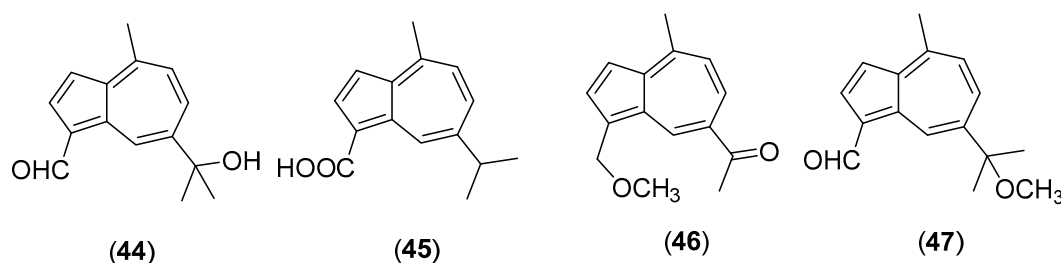


Figure 10. Chemical structures of selected compounds isolated from *Lactarius hatsudake*.

5.11. *Lepista sordida* (Schumach.) Singer

Lepista sordida (Schumach.) Singer, a basidiomycetous fungus of the family Tricholomataceae, is an edible and medicinal agaric species which grows in the wild in China, Thailand, Korea [4,58,143]. Moreover, there is a report on the artificial cultivation of a wild strain of *L. sordida* from Thailand [144]. A water-soluble polysaccharide isolated from the fruiting bodies, which significantly increased the nitric oxide and NF- α release from macrophages, was established to have a backbone consisting of (1 \rightarrow 6)-linked- α -D-glucopyranosyl and (1 \rightarrow 2,6)-linked- α -D-glucopyranosyl residues, terminated with a terminal (1 \rightarrow)- α -D-galactopyranosyl residue at the O-3 position of a (1 \rightarrow 2,6)-linked- α -D-glucopyranosyl residue along the main chain [145]. Miao and co-worker extracted four water-soluble polysaccharides from the fruiting bodies which showed potent antiproliferative effects on human laryngocarcinoma Hep-2 cells in vitro and in vivo [146,147]. Intracellular polysaccharides from mycelium of *L. sordida* have demonstrated to possess a significant free radical-scavenging activity in vitro on hydroxyl, superoxide anion and DPPH radicals [148]. Two new diterpenoids, lepestal and lepestol (structures 48 and 49, respectively in Figure 11), were isolated from fungal fermentations of *L. sordida* collected in France [149]. Aldehyde 48 was more active than alcohol 49 as regards the cytotoxic, antibacterial and antifungal activities [149]. Compounds 50–52 (see structures in Figure 11), named lepepistamides A–C, were also isolated, in conjunction with diatretole, from samples of *L. sordida* collected in China [150]. A group of Japanese researchers isolated plant-growth regulating compounds, 2-azahypoxanthine (53), 2-aza-8-oxohypoxanthine (54), and imidazole-4-carboxamide (55) [151–154], whereas compounds 56–59 (see structures in Figure 11), showing inhibitory activity of the bentgrass root growth, were isolated from a culture broth [155]. The isolation of three new chlorinated sesquiterpenes from a culture broth of *L. sordida*, named lepepistatins A–C (see structures 60–62 in Figure 11), was reported by a Korean research group along with their antibacterial and antiproliferative activities [143]. In conclusion, polysaccharides from *L. sordida* were determined to possess immunoregulatory [145], antiproliferative [146], anticancer [146,147], and antiradical activities [148], while different secondary metabolites showed antimicrobial [149], cytotoxic [149], and plant growth regulatory activities [151–154].

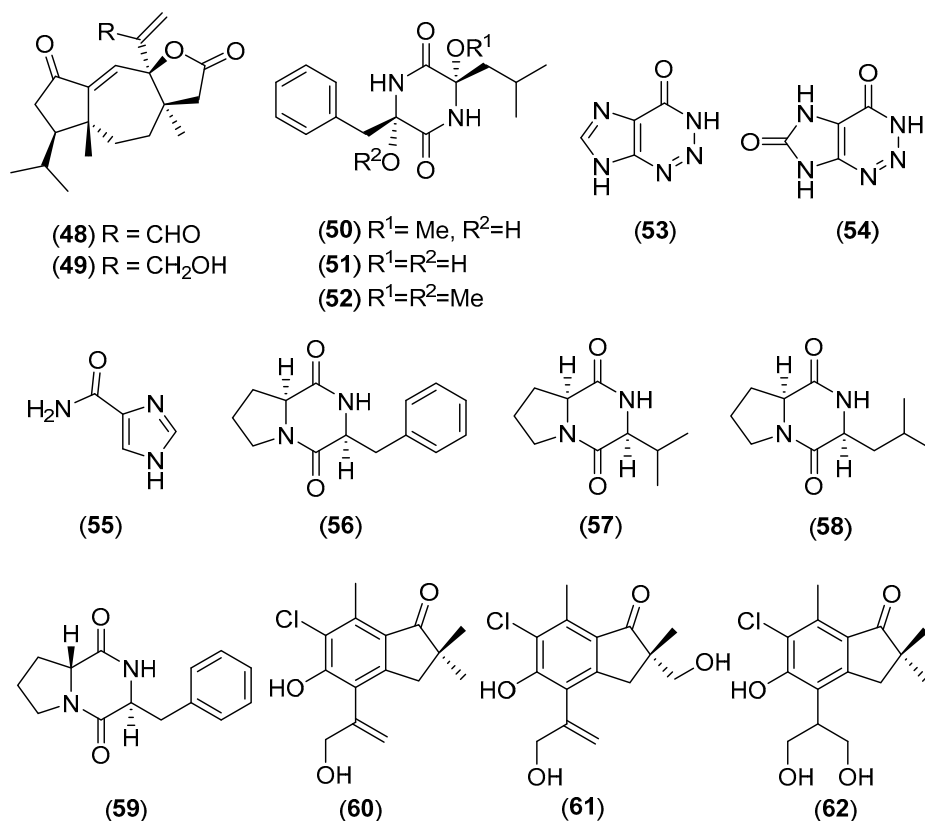


Figure 11. Chemical structures of selected compounds isolated from *Lepista sordida*.

5.12. *Lycoperdon pyriforme* Schaeff.

Lycoperdon pyriforme Schaeff., belonging to the family Agaricaceae, is a wild edible mushroom which grows in China, Thailand, Turkey and Bulgaria [4,58,156,157]. Akatin reported the isolation and characterization of a new β -glucosidase [157]. Another research group isolated 4-methoxy-benzene-1-azoformamide (63), 4-methoxybenzene-1-ONN-azoxyformamide (64) and 3,5-dichloro-4-methoxybenzene-1-ONN-azoxyformamide (65) [158]. Compounds 63 and 64 (see structures in Figure 12) were active against the plant parasitic nematode *Meloidogyne incognita*, and showed weak antimicrobial effects against *Nadsonia fulvescens* and *Penicillium notatum*. Compound 65 (see structure in Figure 12) exhibited weak cytotoxicity against L1210, HL-60, and HeLa S3 cells [158]. *L. pyriforme* has also been reported to contain linoleic, oleic, palmitic, stearic, 9-eicosenoic, 9,12-eicosadienoic, tricosanoic, pentacosanoic, hexacosanoic, and 11-hexacosanoic acids [156]. Biological studies were conducted on the antioxidant and antimicrobial activities of *L. pyriforme* [159–161].

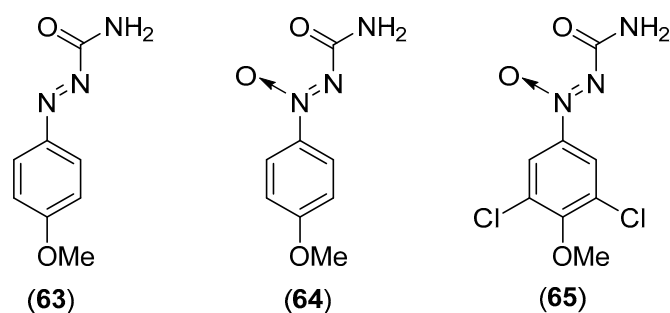


Figure 12. Chemical structures of selected compounds isolated from *Lycoperdon pyriforme*.

5.13. *Neolentinus lepideus* (Fr.) Redhead and Ginns

Neolentinus lepideus (Fr.) Redhead & Ginns, belonging to the family Polyporaceae, was previously named *Lentinus lepideus*. It grows in China, Thailand, Japan and Korea [4,58,162,163]. It is worth noting that while some authors qualify this mushroom as edible, others describe it as inedible. Hanssen extensively studied the liquid cultures and reported the presence of (–)-torreyol, (–)-T-muurolol, (+)-T-cadinol, (–)- α -cadinol, cubenol, epicubenol, *trans,trans*-farnesol, drimenol, α -copaene, α -elemene, *trans*- β -farnesene, γ -muurolene, α -muurolene, δ -cadinene, cadina-1,4-diene and calacorene [164,165]. A new γ -pyrone derivative, named lepidepyrone (see structure 66 in Figure 13), together with methyl 3-hydroxy-4-methoxycinnamate and ergosterol were isolated from the cultured mycelium of the mushroom. Compound 66 showed high inhibitory activity on mammalian HAase with an $IC_{50} = 3.3$ mM [162]. Phytochemical investigations of *N. lepideus* established the presence in the fruiting bodies of two new secondary metabolites, 5-methoxyisobenzofuran-4,7(1*H*,3*H*)-dione (67) and 1,3-dihydroisobenzofuran-4,6-diol (68), together with the known compounds 5-methoxy-2,3-dimethylcyclohexa-2,5-diene-1,4-dione, (*E*)-3-(3-methoxyphenyl)acrylic acid, 3-(4-methoxyphenyl)propan-1-ol, (*E*)-3-(4-methoxyphenyl)acrylic acid, methyl (*E*)-3-(2-methoxyphenyl)acrylate, methyl (*E*)-3-(3-hydroxy-4-methoxyphenyl)acrylate, and methyl (*E*)-3-(4-methoxyphenyl)acrylate [166]. Compounds 67 and 68 (see structures in Figure 13) showed nitric oxide inhibitory activity with IC_{50} values of 6.2 μ M and 88.8 μ M, respectively. In addition, compound 68 displayed antioxidant activity with an IC_{50} value of 68.6 μ M [166]. 1,3-Dihydroisobenzofuran-4,5,7-triol (69) and 5-methoxy-1,3-dihydroisobenzofuran-4,7-diol (70) were isolated from an EtOAc extract of a culture filtrate and showed tyrosinase inhibitory activity with IC_{50} values of 173 and 263 μ g/mL, respectively [167]. Extracts from the fruiting bodies of *N. lepideus* have been reported to possess antioxidant [168], antityrosinase [168], antihyperlipidemic [163], and immunomodulating activities [169,170].

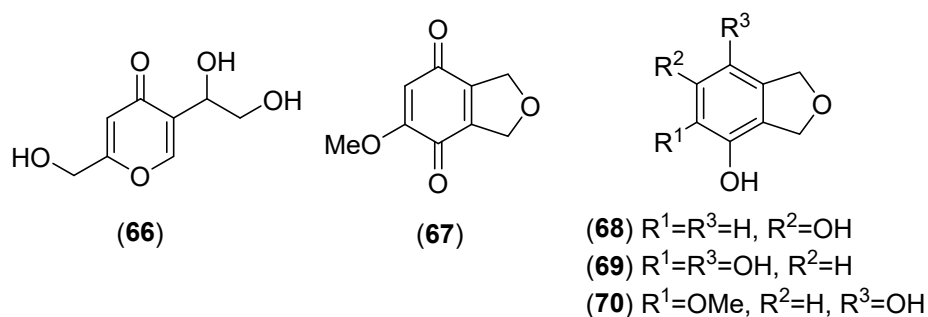


Figure 13. Chemical structures of selected compounds isolated from *Neolentinus lepideus*.

5.14. *Phlebopus portentosus* (Berk. & Broome) Boedijn

Phlebopus portentosus (Berk. & Broome) Boedijn, belonging to the family Boletiniaceae, is a popular edible mushroom in China and Thailand [171]. Although this mushroom grows wild in association with hosts in mixed forests and orchards, nowadays it can be grown in artificial cultures [171,172]. Kaewnarin et al. [173] evaluated the antioxidant, anti-tyrosinase, and antihyperglycaemic activities of *P. portentosus* as well as the phenolic content, comparing it with other three wild edible mushrooms. Three novel pyrrole alkaloids, named phlebopines A–C (structures 71–73 in Figure 14), together with four known ones, 2-[2-formyl-5-(methoxymethyl)-1*H*-pyrrole-1-yl]propanoate, inotopyrrole, 1-isopentyl-2-formyl-5-hydroxy-methylpyrrole and inotopyrrole B (74), were isolated from fruiting bodies collected in China. Among these isolated compounds, inotopyrrole B (74) displayed remarkable neuroprotective effects against hydrogen peroxide-induced neuronal-cell damage in human neuroblastoma SH-SY5Y cells [174].

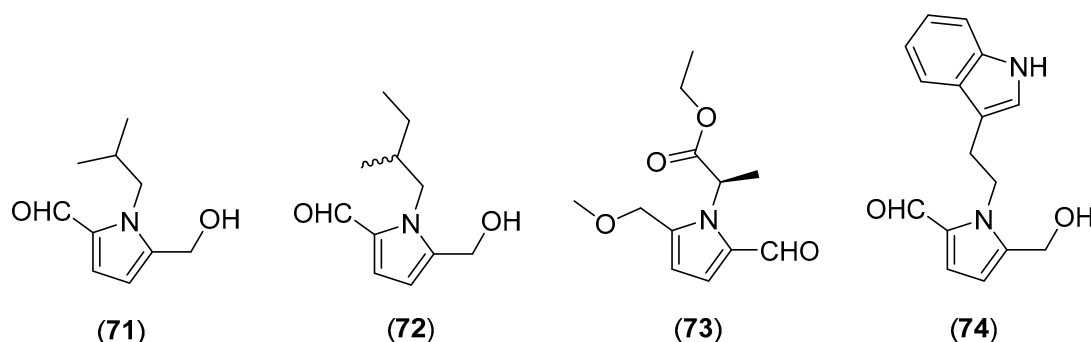


Figure 14. Chemical structures of selected compounds isolated from *Phlebopus portentosus*.

5.15. *Polyozellus multiplex* (Underw.) Murrill

Polyozellus multiplex (Underw.) Murrill, belonging to the family Thelephoraceae, grows in the wild in Japan, Korea, China, and Thailand [4,58,175]. A new inhibitor of prolyl endopeptidase (PEP) with an IC_{50} value of 2.72 μ M, named polyozellin, was identified from a methanolic extract of fresh fruiting bodies collected in Korea [176]. The total synthesis of polyozellin by Takahashi and his collaborators led to a revision of the structure which was determined to be **75** [177]. A Korean research group investigated the EtOAc soluble fraction of the mushroom and reported the chemical structure of two active compounds, thelephoric acid (**76**) and kynapcin-9 (**77**) with their PEP activities [178]. Another *p*-terphenyl derivative, named kynapcin-12, having PEP inhibitory activity with an IC_{50} value of 1.25 μ M, was isolated by Lee and collaborators from a methanolic extract [179]. The correct chemical structure of kynapcin-12 (**78**) was later assigned by total synthesis [180]. Polyozellic acid (**79**), and the acetone adduct (**80**), together with thelephoric acid, were isolated from *P. multiplex* collected in Japan and showed inhibitory effects on the proliferation, tubule formation, and invasion of human umbilical vein endothelial cells [181]. Compounds **75**, **76**, **78**, and **79** (see structures in Figure 15) inhibited BACE1 activity with IC_{50} values of 3.08, 3.50, 4.78, and 15.79 μ M, respectively, and neuroprotective activities in glutamate-induced HT22 cell death [175]. Kim et al. [182] reported the isolation of two new benzofurans, named kynapcin-13 (**81**) and kynapcin-28 (**82**), from *P. multiplex*, which inhibited prolyl endopeptidase with IC_{50} values of 76.80 and 0.98 μ M, respectively. Another new benzofuran dimer, kynapcin-24 (**83**), was later isolated from *P. multiplex*. It inhibited PEP with an IC_{50} value of 1.14 μ M [183]. Separation of a methanol extract of fruiting bodies of *P. multiplex* collected in Korea afforded linoleic acid and oleic acid together with thelephoric acid [184]. Extracts of this mushroom were reported to have inhibitory effects on the proliferation of cancer cell lines [185], inhibitory activities (IC_{50} 10 μ g/mL) against α -glucosidase [186] and DPPH radical scavenging activity [187]. Finally, it is worthy of note that polyozellin exhibits high important bioactivities, such as antioxidant [187], anti-carcinogenic [188] and inflammatory activities [189–195].

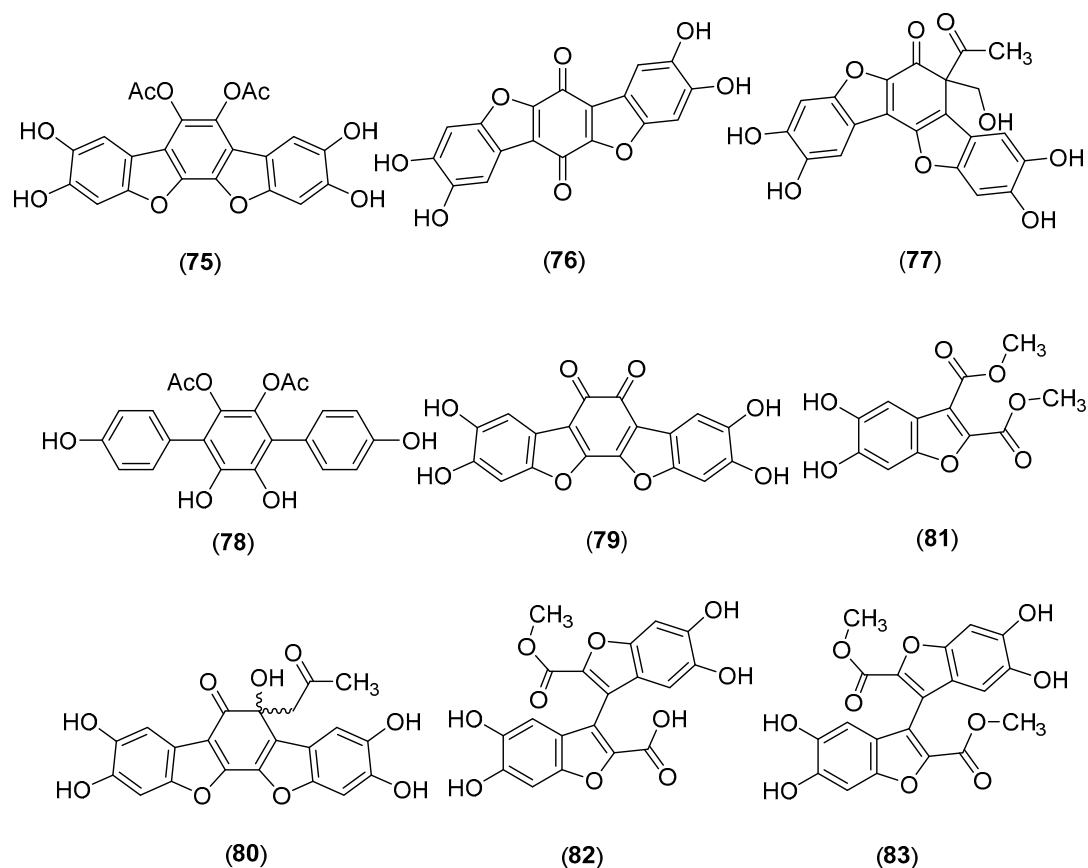


Figure 15. Chemical structures of selected compounds isolated from *Polyozellus multiplex*.

5.16. *Ramaria botrytis* (Pers.) Bourdot

Ramaria botrytis (Pers.) Bourdot, belonging to the family Ramariaceae, is a wild edible mushroom which grows in mountains of eastern Asia, China, Thailand, Europe, and North America [4,58,196]. Zhou et al. reported the isolation of a novel ubiquitin-like antitumour protein which significantly inhibited the growth and induced apoptosis in A549 cells [196]. Bhanja and his collaborators isolated two water-insoluble glucans from the fruiting bodies of *R. botrytis* collected in India. One glucan was composed of (1→3)-linked α -D-glucopyranosyl residues and the other one was a β -D-glucan with a backbone of four (1→3)-linked β -D-glucopyranosyl units, with one single unit β -D-glucopyranosyl branch substituted at O-6 position [197]. A glucan consisting of (1→6)-linked- β -D-glucopyranosyl residues as backbone, branched at O-3 position with a (1→3)-linked- β -D-glucopyranosyl unit and a non-reducing end β -D-glucopyranosyl residue has been purified by the same research group. This glucan showed immunostimulating activity on RAW 264.7, a murine macrophage cell line, by nitric oxide production [198]. Moreover, polysaccharides from *R. botrytis* showed potent antioxidant activities [199]. Fresh fruiting bodies of the mushroom collected in Japan have been reported to contain (2*S*,2'*R*,3*R*,4*E*,8*E*)-*N*-2'-hydroxyoctadecanoyl-2-amino-9-methyl-4,8-heptadecadiene-1,3-diol, 5 α ,6 α -epoxy-3 β -hydroxy-(2*E*)-ergosta-8(14),22-dien-7-one, ergosterol peroxide, cerevisterol and 9 α -hydroxycerevisterol [200]. The in vitro antioxidant and antimicrobial potentials of extracts of *R. botrytis* were investigated by several research groups [26,201–204].

5.17. *Rugiboletus extremiorientalis* (Lj.N. Vassiljeva) G. Wu and Zhu L. Yang

Rugiboletus extremiorientalis (Lj.N. Vassiljeva) G. Wu & Zhu L. Yang [family Boletaceae, formerly named *Leccinum extremiorientale* (Lj.N. Vassiljeva) Singer] is an edible mushroom growing in northern temperate regions, especially in China, Laos and Thailand [4,58,205]. Leccinine A (84) and pyrrolezanthine (85) (see structures in Figure 16), were initially isolated from the mature

fruiting bodies collected in Japan and showed protective activity against endoplasmic reticulum stress-dependent cell death [205]. Ito et al. isolated (8*E*,12*Z*)-10,11-dihydroxyoctadeca-8,12-dienoic acid and leccinine A, reporting their growth regulatory activity against lettuce [206]. Subsequently, the new pyrrole alkaloid 2-[2-formyl-5-(methoxymethyl)-1*H*-pyrrol-1-yl]acetic acid (**86**), together with 4-[2-formyl-5-(methoxymethyl)-1*H*-pyrrol-1-yl]butanoic acid and 4-[2-formyl-5-(hydroxymethyl)-1*H*-pyrrol-1-yl]butanoic acid were isolated from an ethyl acetate extract and exhibited poor cytotoxicity against K562, BEL7702, and SGC7901 cell lines with IC₅₀ values higher than 40 μM [207]. The possible antioxidant and antimicrobial activities of secondary metabolites from *R. extremiorientalis* have not been examined so far.

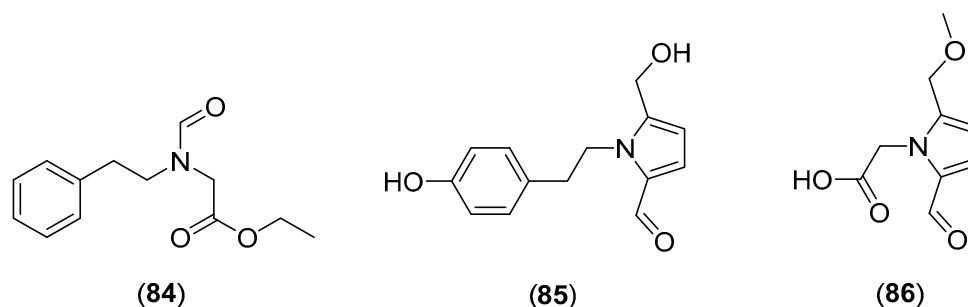


Figure 16. Chemical structures of selected compounds isolated from *Rugiboletus extremiorientalis*.

5.18. *Russula virescens* (Schaeff.) Fr.

Russula virescens (Schaeff.) Fr., is a wild mushroom with a delicious taste, belonging to the family Russulaceae. It grows in nature on the roots of pine trees throughout China, Thailand, Lao, Nepal, and Europe [4,58]. The mushroom has long been used as a folk remedy in the traditional Chinese medicine [208]. Zhu et al. purified a novel laccase from *R. virescens* and then studied its dye decolorizing properties [209]. A water-insoluble linear (1→3)-β-D-glucan from the fresh fruiting bodies was isolated by the Sun's group and did not exhibit antitumor activity, however, the sulfation of the native (1→3)-β-D-glucan improved the antitumor activity [210]. The extraction and purification of two novel water-soluble polysaccharides from fresh fruiting bodies of *R. virescens* were reported by the same research group. They revealed an interesting antioxidant properties [208]. Sun et al. [211] also isolated a water-soluble polysaccharide from the fruiting bodies of *R. virescens*, which had a backbone consisting of (1→6)-linked-α-D-galactopyranosyl and (1→2,6)-linked-α-D-galactopyranosyl residues that terminated in a single non-reducing terminal (1→)-α-D-mannopyranosyl residue at the O-2 position of each (1→2,6)-linked-α-D-galactopyranosyl residues along the main chain in the ratio of 1:1:1. The polysaccharide exhibited a significant scavenging effects of hydroxyl radicals in vitro. Canthin-6-one, 5α,8α-epidioxy-(2*E*,24*R*)-ergosta-6,22-dien-3β-ol, (2*E*,24*R*)-ergosta-5,7,22-trien-3β-ol, (2*E*,24*R*)-ergosta-7,22-dien-3β,5α,6β-triol, thioacetic anhydride, maleic acid, D-allitol and ribosidoadenine are secondary metabolites isolated from *R. virescens* [212]. Studies on the antioxidant activity of *R. virescens* revealed that this mushroom can be considered as an accessible source of natural antioxidants [204,206,213,214].

5.19. *Sarcodon imbricatus* (L.) P. Karst

Sarcodon imbricatus (L.) P. Karst, belonging to the family Bankeraceae, is an edible fungus occurring in China, Thailand, and Turkey [4,58,215]. It is widely used in Asian medicine [216]. An investigation on a polysaccharide-enriched extract of *S. imbricatus* revealed that it stimulates the immune response in CTX-induced immunosuppressed mice via modulation of oxidative pathways [216]. An extract of *S. imbricatus* exhibited the growth of gram-negative and gram-positive bacteria [22,217]. A Portugal research group reported that methanolic extracts of the mushroom showed potent antioxidant activity and antimicrobial activity against *Bacillus cereus* and *Cryptococcus*

A (**104**) were isolated by from a fermentation broth of *T. albuminosus* [243]; *epi*-guaidiol A (**104**) showed potent anti-acetylcholinesterase activity in a dose-dependent manner [243].

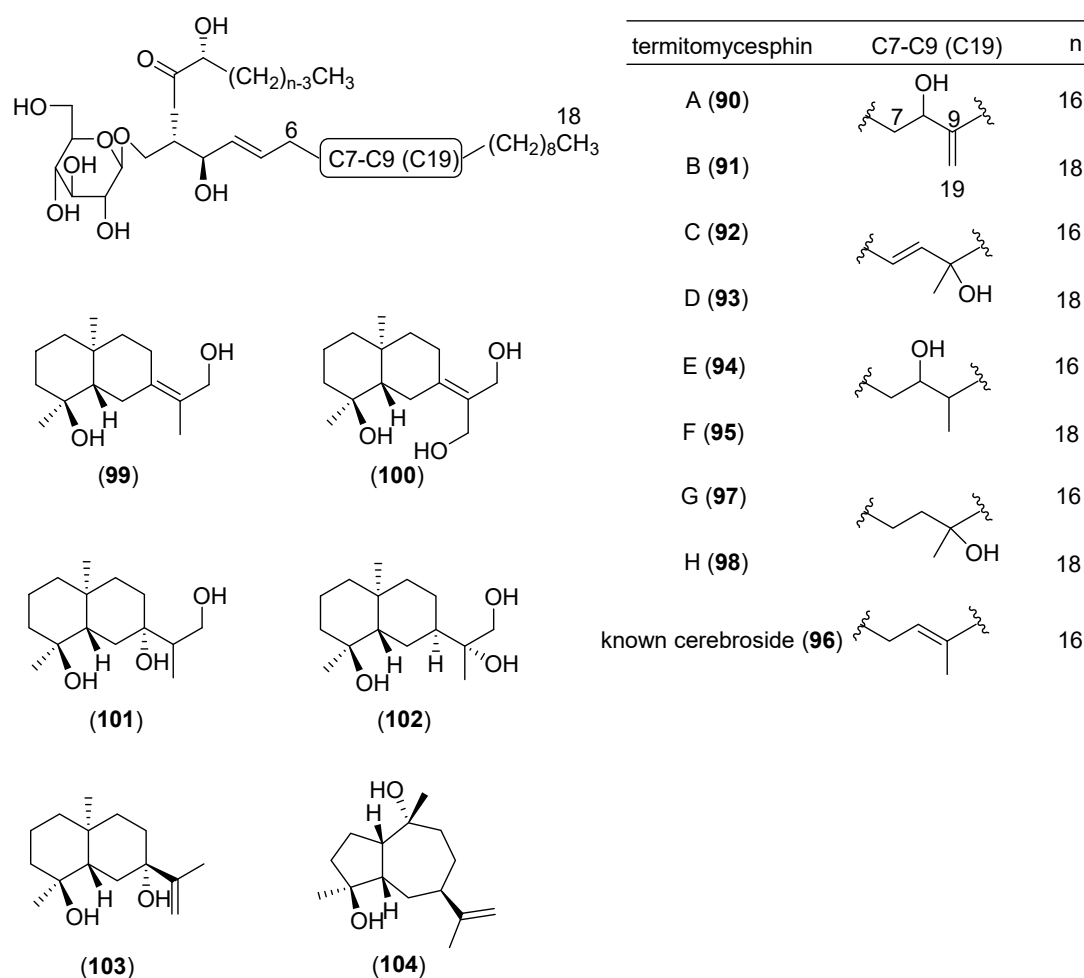


Figure 18. Chemical structures of selected compounds isolated from *Termitomyces albuminosus*.

5.21. *Termitomyces eurhizus* (Berk.) R. Heim

Termitomyces eurhizus (Berk.) R. Heim, belonging to the family Lyophyllaceae, is a wild edible mushroom, which grows in association with termites in China, India, Myanmar, Malaysia, Nepal and Thailand [4,58,228,244]. Two water-soluble polysaccharides, whose structures were established to be (1→3)-D-Glcp and (1→6)-D-Glcp, and (1→6)-D-Glcp were isolated from a hot aqueous extract of fruiting bodies [244]. On the other hand, a water-insoluble (1→3)-β-D-glucan was isolated from a hot alkaline extract of the mushroom collected in India [245]. The biological activity of a water-soluble polysaccharide-rich fraction of *T. eurhizus* was investigated by an Indian research group. The fraction revealed healing properties against indomethacin-induced stomach ulceration in mice [246]. Pharmacological studies on mushroom polysaccharides have highlighted other biological properties such as anticarcinogenic, antimicrobial, antioxidant and anti-inflammatory activities etc. [21]; therefore, *T. eurhizus* deserves further in-depth pharmacological investigations.

5.22. *Termitomyces heimii* Natarajan

Termitomyces heimii Natarajan, (family-Lyophyllaceae) is a wild edible mushroom which grows in nature in symbiosis with termites in China, Malaysia, Thailand, and India [4,58,228,247]. Manna et al. reported the structure of a water-soluble β-glucan from this mushroom, together with its antioxidant activity [248]. The polysaccharide consisted of a backbone chain of two (1→6)-β-D-glucopyranosyl

residues, one of which was branched at the O-3 position with a side chain consisting of two (1→3)-β-D-glucopyranosyl units and one terminal β-D-glucopyranosyl residue. The lipid content of *T. heimii* was analyzed by Abd Malek's group who identified ergosterol and linoleic acid as the major components, and tetracosane, methyl palmitate, ethyl palmitate, methyl linoleate, ethyl linoleate, ethyl oleate, ethyl eicosanoate, ethyl tetracosanoate, ebericol, lanosterol, palmitic acid, oleic acid, stearic acid, neoergosterol, ergosta-5,8-dien-3-ol, ergosta-5,8(14)-dien-3-ol, 7-ergostenol, brassicasterol, γ-ergostenol, myristic acid, linoleic acid, benzaldehyde, 4-hydroxybenzaldehyde, benzeneacetamide, cinnamic acid and nicotinamide as the minor components [249]. A polyphenol-rich fraction of *T. heimii*, collected in West Bengal, showed potent antioxidant activity [247].

5.23. *Termitomyces microcarpus* (Berk. and Broome) R. Heim

Termitomyces microcarpus (Berk. & Broome) R. Heim (family Lyophyllaceae) is an edible mushroom which generally grows on termite material in China, Malaysia, Philippines, Thailand, India, and Nigeria [4,58,228,250,251]. Different α- and β-glucans were isolated from *T. microcarpus* and the repeating units of the new polysaccharides were identified by means of NMR studies and chemical investigations [252–254]. Dimethylcisterol, 5α,8α-epidioxy-(22E,24R)-ergosta-6,9(11),22-trien-3β-ol, 5α,8α-epidioxy-(22E,24R)-ergosta-6,22-dien-3β-ol, 5α,6α-epoxy-(22E,24R)-ergosta-8(14),22-diene-3β,7α-diol, (22E,24R)-ergosta-7,22-diene-3β,5α,6β-triol, and betulinic acid were isolated by Njue et al., who also reported their cytotoxic activities [255]. Nakalembe and Kabasa studied the antimicrobial activity and the bioactive compounds from *T. microcarpus* collected in Uganda, using GC-MS [256]; an interesting antimicrobial activity, especially against *S. aureus* and *P. aeruginosa*, was determined. In other studies, a mushroom extract displayed significant antioxidant and free radical scavenging activities [37,257–259].

5.24. *Thelephora ganbajun* M. Zang

Thelephora ganbajun M. Zang, belonging to the family Thelephoraceae, is one of the most favorite edible mushrooms. It widely grows in symbiosis with pine trees in China and the Greater Mekong region [260], where it is highly prized for its unique taste and flavor [260,261]. A novel ribonuclease, showing potent inhibitory activity toward HIV-1 reverse transcriptase, was isolated from dried fruiting bodies of the mushroom by Wang and Ng [262]. Two new polysaccharide fractions isolated from the fruiting bodies were characterized by Gong's group [263]. They exhibited strong inhibitory effects on HeLa cells and moderate inhibitory effect on α-amylase and α-glucosidase. Separation of an EtOAc-partitioned MeOH extract of *T. ganbajun* fruiting bodies collected in China afforded, in addition to 3-O-methylatromentin, five new poly(phenylacetyloxy)-substituted 1,1':4',1''-terphenyl derivatives, called ganbajunins A–E (see structures 105–109 in Figure 19) [264]. Subsequently, ganbajunin F and G (see structures 110–111 in Figure 19), together with cycloleucomelone were isolated from fresh fruiting bodies by the same research group [265]. The extracts obtained under optimized conditions by an ultrasonic-assisted extraction procedure, possessed significant antiproliferative activities towards human lung and liver cancer cells [266]. Moreover, ganbajunins A–C (105–107) and 3-O-methylatromentin possessed potent lipid peroxidation inhibitory activity, SOD activity in rat liver homogenate, and DPPH radical scavenging activity [261,267,268].

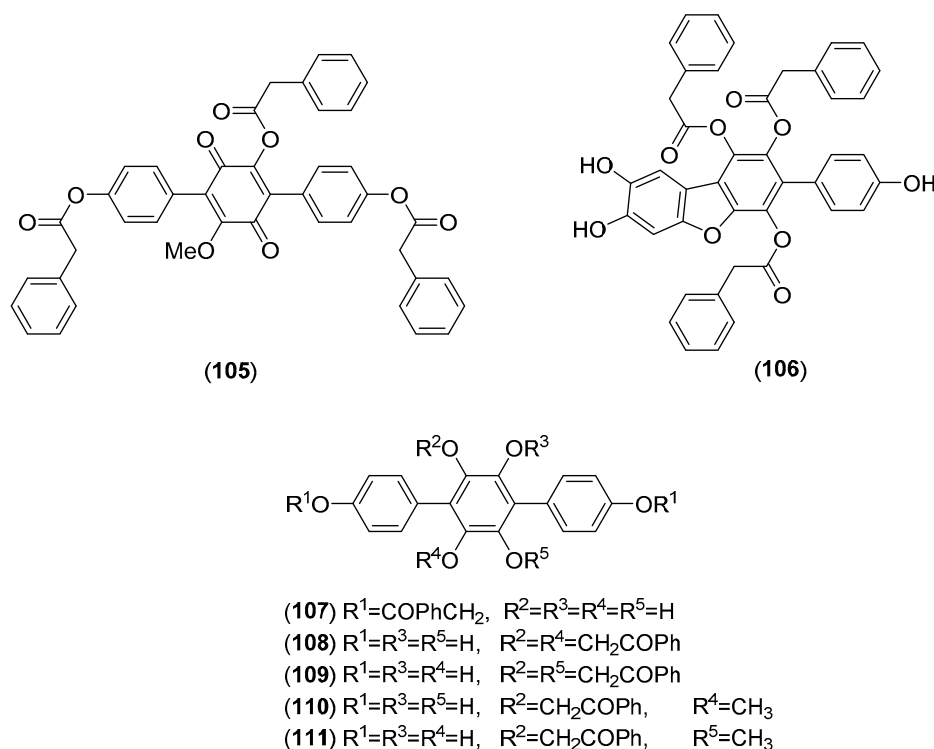


Figure 19. Chemical structures of selected compounds isolated from *Thelephora gambajun*.

5.25. *Volvariella Bombycina* (Schaeff.) Singer

Volvariella bombycina (Schaeff.) Singer is a wild edible mushroom belonging to the family Pluteaceae which grows in Asia in China and Thailand [4,58,269]. Das et al. [270] isolated a water-soluble polysaccharide from the hot aqueous extract of the mushroom collected in India. The repeating unit was identified as a $\rightarrow 6$ - β -D-Glcp-(1 \rightarrow 6)- α -D-Manp-(1 \rightarrow 6)- α -D-Glcp-(1 \rightarrow backbone to which an α -D-galactosyl unit was attached. A novel compound, named isodeoxyhelicobasidin (structure 112 in Figure 20), was isolated by a Korean research group from a culture broth of *V. bombycine*. Compound 112 was reported to possess human neutrophil elastase (HNE) activity with an IC_{50} value of 9.0 μ M and antibacterial activity against several gram-positive bacteria, including *S. aureus* 503, methicillin-resistant *S. aureus* CCARM 3167 (MRSA), quinolone-resistant *S. aureus* CCARM 3505 (QRSA), *Bacillus subtilis* 1021, *Staphylococcus epidermidis* 3958 and *Streptococcus mutans* 3065, with MIC values in the range of 3.1–12.4 μ g/mL [271]. Ergosta-4,6,8(14),22-tetraene-3-one (113), ergosterol peroxide, indole-3-carboxaldehyde (114), and indazole (115) were later isolated from a culture broth of *V. bombycine*. Compound 113 showed inhibitory activity on melanogenesis with an IC_{50} = 80.9 μ M and cytotoxic activity with an LD_{50} value of 50.6 μ M [272]. Moreover, a *V. bombycina* extract showed a moderate antioxidant activity [269,273].

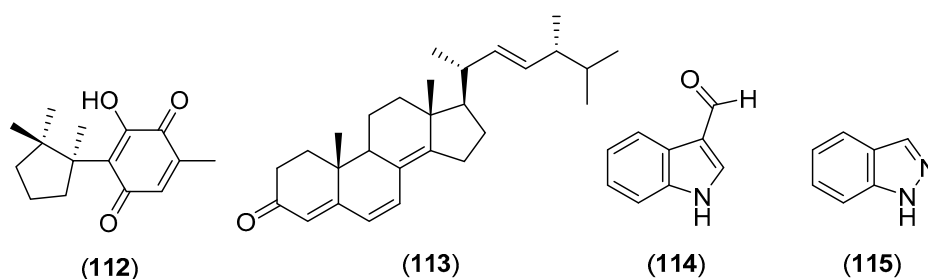


Figure 20. Chemical structures of selected compounds isolated from *Volvariella bombycina*.

Table 1. Biological/pharmacological activities of extracts/compounds isolated from selected wild edible mushrooms growing in Southeast Asia countries.

Mushroom Species	Metabolites with Antioxidant Activity	Metabolites with Antimicrobial Activity	Metabolites with Cytotoxic and/or Antiproliferative Activity	Metabolites with Other Biological Activities
<i>Agaricus silvaticus</i> Schaeff. (Agaricaceae)	Extract [64,65]	-	-	-
<i>Ampulloclitocybe clavipes</i> (Pers.) Redhead, Lutzoni, Moncalvo & Vilgalys (Hygrophoraceae)	-	Clavilactone A-C (4–6) [66]	Clavipines A (9) [70], Clavilactone H (16) [71]	Clavilactone B (5) (inhibitory activity of the growth of <i>Lepidium sativum</i>) [66]. Clavilactones A, B, D (4,5,8) (tyrosine kinases inhibitory activity [67,69]). Fatty acid derivatives (aldehyde dehydrogenase inhibitory activity [65])
<i>Butyriboletus roseoflavus</i> (M. Zang & H.B. Li) D. Arora & J.L. Frank (Boletaceae)	Polysaccharide [72]	-	Polysaccharide [73–75], Hemagglutinin [76]	Polysaccharide (immunoregulatory activity [73–75]). Hemagglutinin (HIV-1 reverse transcriptase inhibitory activity [76])
<i>Cantharellus cibarius</i> Fr. (Cantharellaceae)	Polysaccharide [85,86]	Extract [92]	Polysaccharide [80,82]	Polysaccharide (immunomodulatory [81,86] and neuroprotective activities [85])
<i>Craterellus cornucopioides</i> (L.Fr.) Pers. (Cantharellaceae)	Polysaccharide [97], Extract [91,93,105,106,108]	Extract [105]	Craterellin C (20) [98], Extract [93,105]	Polysaccharide [94,96]. Extract (antimutagenic effects [105], antihyperglycemic [106] and anti-inflammatory activities [107,108])
<i>Craterellus odoratus</i> (Schwein.) Fr. (Cantharellaceae)	-	-	Calbistrin C [112]	Craterellin A (26) (inhibitory activities against human 11 β -HSD2 [111]). 5-Hydroxymethyl-2-hydroxy-4-methoxy-phenylethanone (inhibitory activity against human 11 β -HSD1 [109])
<i>Fistulina hepatica</i> (Schaeff.) (Fistulinaceae)	Extract [115,118,119]	Cinnatriacetins A (37) and B (38) [117]. Extract [22,116,125]	-	-
<i>Hydnum repandum</i> L. (Cantharellaceae)	Extract [92,115,127,133]	Extract [92,126,131,132]	Repandioliol (39) [129], Extract [93]	-
<i>Laccaria amethystea</i> (Bull.) Murrill (Hydnangiaceae)	Extract [106]	Laccaridiones A (41) and B (42) [134]	Laccaridiones B (42) [134]	Extract (antihyperglycemic activity [106])
<i>Lactarius hatsudake</i> Nobuj. Tanaka (Russulaceae)	-	-	-	Ergosterol peroxide, 5 α ,8 α -epidioxy-(24S)-ergosta-6-en-3 β -ol (antiphospholipase A ₂ activity [139] and anti-HIV activity [140])
<i>Lepista sordida</i> (Schumach.) Singer (Tricholomataceae)	Polysaccharides [148]	Lepistal (48), lepestol (49) [149]	Polysaccharides [146,147], lepestol (48), lepestol (49) [149]	Polysaccharide (immunoregulatory activity [145]). Compounds 56–59 (plant growth inhibitory activity [155])
<i>Lycoperdon pyriforme</i> Schaeff. (Agaricaceae)	Extract [161]	Compounds 63 and 64 [158]. Extract [160]	Compound 65 [158]	Compounds 63 and 64 (nematicidal activity [158])

Table 1. Cont.

Mushroom Species	Metabolites with Antioxidant Activity	Metabolites with Antimicrobial Activity	Metabolites with Cytotoxic and/or Antiproliferative Activity	Metabolites with Other Biological Activities
<i>Neolentinus lepideus</i> (Fr.) Redhead & Ginns (Polyporaceae)	Compound 68 [166], Extract [168]	-	-	Lepidepyrone (66) (inhibitory effects on hyaluronidase [162]. Compounds 67 and 68 (NO inhibitory activity [166]) Compounds 69 and 70 (tyrosinase inhibitory activity [167]). Polysaccharide (immunomodulating activity [169]). Extract (antityrosinase [168], antihyperlipidemic [163] and immunomodulatory activities [170])
<i>Phlebopus portentosus</i> (Berk. & Broome) Boedijn (Boletiniaceae)	Extract [173]	-	-	Extract (tyrosinase and hyperglycaemic moderate inhibitory activities [173]). Compound 74 (neuroprotective activity [174])
<i>Polyozellus multiplex</i> (Underw.) Murrill (Thelephoraceae)	Polyozellin (75) and extract [189]	Extract [188]	Polyozellin (75) [179,190]. Extract [187,190]	Polyozellin (75) (prolyl endopeptidase (PEP) inhibitory activity [176,177], β -secretase (BACE1) inhibitory activities [175], neuroprotective effect [187] and anti-inflammatory activities [189–195]). Thelephoric acid (76) (PEP inhibitory activity [178], β -secretase (BACE1) inhibitory activity [175] and neuroprotective effect [175]). Kynapcin-9 (77) (PEP inhibitory activity) [178]. Kynapcin-12 (78) (PEP inhibitory [179], prolyl oligopeptidase (POP) inhibitory [180] and β -secretase (BACE1) inhibitory activities [175]). Polyozellic acid (79) (antiangiogenesis [181], β -secretase (BACE1) inhibitory activities [175] and neuroprotective effects [175]), compound 80 (antiangiogenesis activity [181]). Kynapcin-13 (81) and -28 (82) (PEP inhibitory activity [182]), Kynapcin-24 (83) (PEP inhibitory activity [183]).
<i>Ramaria botrytis</i> (Pers.) Bourdot (Ramariaceae)	Polysaccharide [199], Extract [202–204]	-	A novel ubiquitin-like protein [196]	Glucan (immunostimulating activity) [198]
<i>Rugiboletus extremiorientalis</i> (Lj.N. Vassiljeva) G. Wu & Zhu L. Yang	-	-	-	Leccinine A (84) (protective activity against endoplasmic reticulum stress-dependent cell death [205] and plant growth regulatory activity [206]). (8E,12Z)-10,11-dihydroxyoctadeca-8,12-dienoic acid (plant growth regulatory activity [206]).
<i>Russula virescens</i> (Schaeff.) Fr. (Russulaceae)	Polysaccharide [208,211], Extract [203,213,214]	-	-	-
<i>Sarcodon imbricatus</i> (L.) P. Karst (Bankeraceae)	Extract [203,219,221]	Extract [22,132,217,218], Polysaccharide [223]	-	Extract (immunomodulatory [216] and antifatigue activities [227]). Polysaccharide (immunoenhancement [225,226] and anti-myelosuppressive activities [224]).

Table 1. Cont.

Mushroom Species	Metabolites with Antioxidant Activity	Metabolites with Antimicrobial Activity	Metabolites with Cytotoxic and/or Antiproliferative Activity	Metabolites with Other Biological Activities
<i>Termitomyces albuminosus</i> (Berk.) R. Heim (Lyophyllaceae)	Polysaccharide [230,232–234], Extract [239]	-	-	Polysaccharide (anti-inflammatory [234] and hepatoprotective effects [232,234]). Extract (analgesic and anti-inflammatory activities [236]). Termitomycesphins A-F (90-95) (neuritogenic activity [240,241]). Termitomycesphins G (97) and H (98) (neuritogenic activity [242]). <i>epi</i> -Guidiol A (104) (anti-acetylcholinesterase activity [243]).
<i>Termitomyces eurhizus</i> (Berk.) R. Heim (Lyophyllaceae)	-	-	-	Extract (anti-ulcerogenic activity) [245]
<i>Termitomyces heimii</i> Natarajan (Lyophyllaceae)	Extract [247] Polysaccharide [248]	-	-	-
<i>Termitomyces microcarpus</i> (Berk. & Broome) R. Hein (Lyophyllaceae)	Extract [36,257–259]	Extract [257]	Dimethylincisterol; 5 α ,8 α -epidioxy-(22E,24R)-ergosta-6,22-dien-3 β -ol [255]	-
<i>Thelephora ganbajun</i> M. Zang (Thelephoraceae)	Ganbajunins A-B (105–106) [261,267,268]. Ganbajunin C (107); 3-O-methylatromentin [267,268]	-	Polysaccharide [263], Extract [266]	Ribonuclease (inhibitory activity toward HIV-1 reverse transcriptase) [262]. Polysaccharides (antidiabetic activity) [263]
<i>Volvariella bombycina</i> (Schaeff.) Singer (Pluteaceae)	Extract [269,273]	Isodeoxyhelicobasidin [271]	Compound 113 [272]	Isodeoxyhelicobasidin (human neutrophil elastase (NHE) activity [271]). Compound 113 (inhibitory effects on melanogenesis [272]).

6. Conclusions

Southeast Asia is one of the biodiversity hot-spots in the world and has an outstanding rate of species discovery. In fact, hundreds of new species are described annually. However, regional biological resources are currently threatened by climatic changes and human activity-related factors such as the high rate of mining in the tropics, the construction of a great number of hydropower dams, and an indiscriminate consumption of plants in traditional medicines [274–276]. Therefore, access to biodiversity resources of Southeast Asia must be done paying great attention to their conservation or renovation. In this context, mushrooms play important roles in different ecosystems; however, they are often obtained in artificial cultures, thus avoiding the collection in the wild.

Although the variety of higher mushroom (Basidiomycetes) growing in Southeast Asia is calculated to be very high, only few scientific mycological investigations have been conducted, and most species growing in countries such as Myanmar, Laos, and Cambodia, have not been identified so far.

We believe that this review clearly demonstrates that edible mushrooms are a rich source of various bioactive substances having antimicrobial, antioxidant, anti-inflammatory, anti-proliferative, cytotoxic, anti-HIV, anti-diabetic properties, among other ones. Therefore, edible mushrooms must be considered not only culinary delicacies but also functional foods and, in some cases, even therapeutic agents. Of course, mushroom edibility is a proof of their non-acute toxicity. Therefore, edible mushrooms containing bioactive compounds can have high potential as sources of medicinal remedies.

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