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Mushrooms: An Important Source of Natural Bioactive Compounds

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Abstract – Mushrooms are known for their various attributes in the fields of nutrition and therapeutics. With exceptional taste, aroma, and nutritional value, they are considered 'functional food'-improving health and providing nutritional benefits to the body. Mushrooms have also been widely applied therapeutically as they possess diverse bioactive compounds known as secondary metabolites. These secondary metabolites demonstrated diverse biological properties such as anticancer, anti-diabetic, immunomodulatory, antimicrobial, anti-inflammatory, antiviral, anti-allergic, and antioxidative activities. This review presents bioactive compounds from the field of mushroom metabolite research and discusses important findings regarding bioactive compounds identified during the last five years (2015 – 2019).
Keywords – Mushrooms, Secondary metabolites, Biological activities

Introduction

Mushrooms, classified as fungi, are defined as "a macrofungus with a distinctive fruiting body".[1] In other words, they are filamentous fungi with fruiting bodies packed with beneficial nutrients such as carbohydrates, fibers, proteins, vitamins, and minerals.[2] They have been known for centuries to have an essential nutritional as well as medicinal value.[2] Mushrooms with medicinal value are defined as "mushroom nutraceuticals" and are consumed in capsule or tablet form as dietary supplements.[3] Owing to the therapeutic properties conferred by various secondary metabolites, mushrooms have received significant attention, which has intensified in recent years.[2,3] Simultaneously, interest in mushrooms as a potential source of bioactive compounds has increased, and much research on the bioactivity of these compounds has been conducted in the last two decades.[3] The secondary metabolites derived from mushrooms have demonstrated diverse biological properties such as anticancer, anti-diabetic, immunomodulatory, antimicrobial, anti-inflammatory, antiviral, anti-allergic, and antioxidative activities. These bioactive secondary metabolites have been evaluated for potential drug development to treat various diseases. The vast applications of the bioactive compounds obtained from mushrooms have shifted toward a new trend: the development of novel drugs.[2,3] In this review, the biological activities exhibited by the bioactive metabolites derived from various mushrooms investigated during the last five years (2015–2019) are described and important findings regarding these bioactive compounds are emphasized for their potential therapeutic applications.

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Cytotoxicity and Anticancer Activities

Multiple studies demonstrated that certain mushrooms exhibit cytotoxic or anticancer properties. Kim et al.[4] reported that vulpinic acid (**1**), isolated from the extract of *Pulveroboletus ravenelii*, reduces human cancer cells by inducing the apoptosis of these cells, including lung adenocarcinoma cell lines (A549, NCI-H1264, NCI-H1299, and Calu-6), pancreatic ductal adenocarcinoma cell lines (PANC-1 and MIAPaCa-2), and a hepatocellular cell line (Hep G2) with 50% inhibitory concentration (IC_{50}) values ranging from 219.8 to 490.5 μg/mL.[4] In another study, (*E*)-5-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one (isohericerin) (**2**), isolated from *Hericium erinaceus*, an edible and medicinal mushroom known as the lion's mane mushroom, demonstrated a weak antitumor effect on two cell lines (A549 and HeLa) with IC_{50} values of 49.0 and 40.5 μM, respectively.[5] *Albatrellus confluens* contains a secondary metabolite, grifolin (**3**), which prevents cell invasion, inhibits the cell cycle (at the G1 phase), and

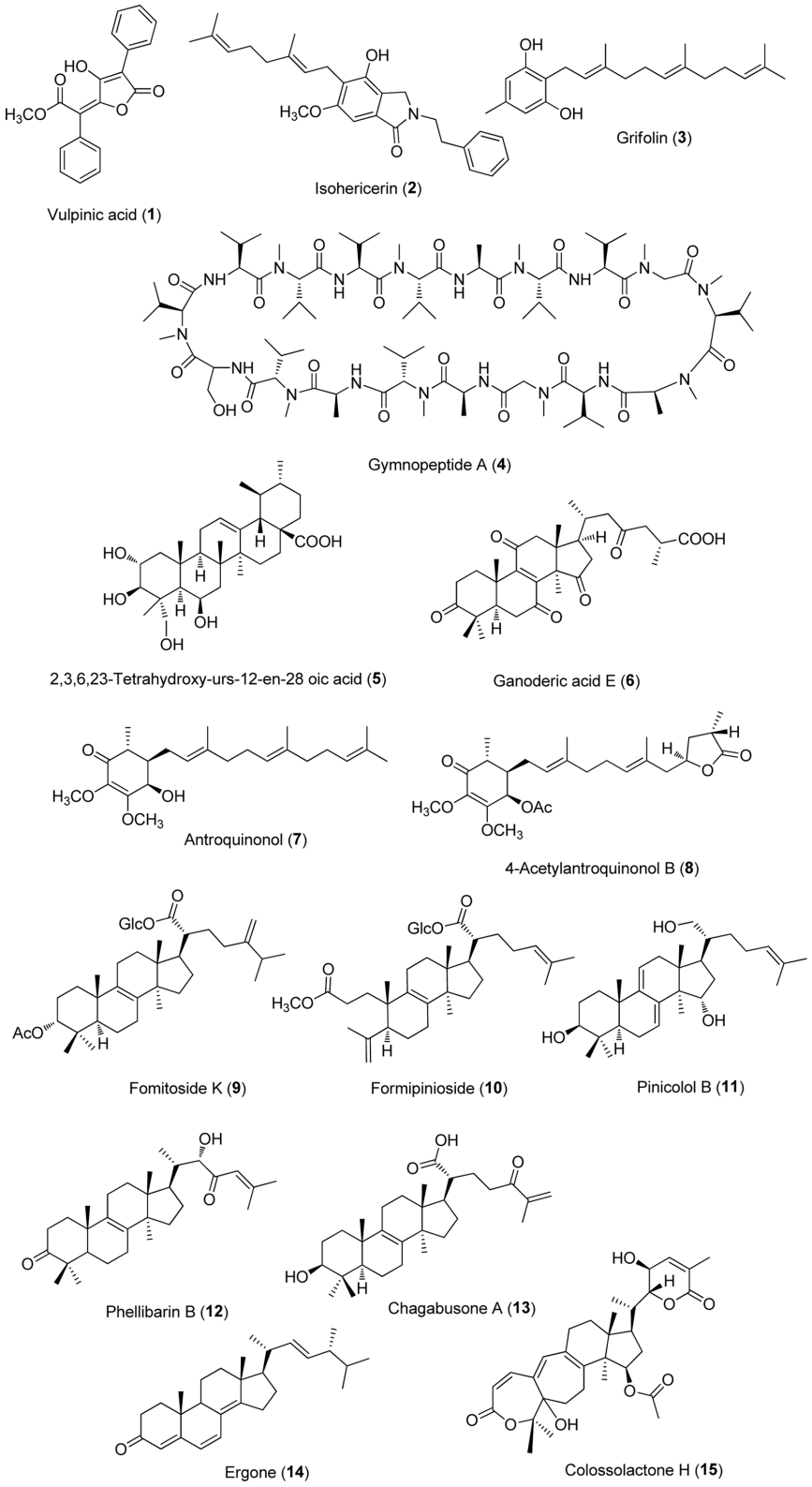


Fig. 1. Chemical structures of important active compounds with cytotoxic and anticancer activities.

increases the apoptosis of cancer cells. In addition, upregulation of the death-associated protein kinase (dapk1) gene by grifolin was observed in the naso-pharyngeal carcinoma cell line CNE1.[6] Gymnopeptides A

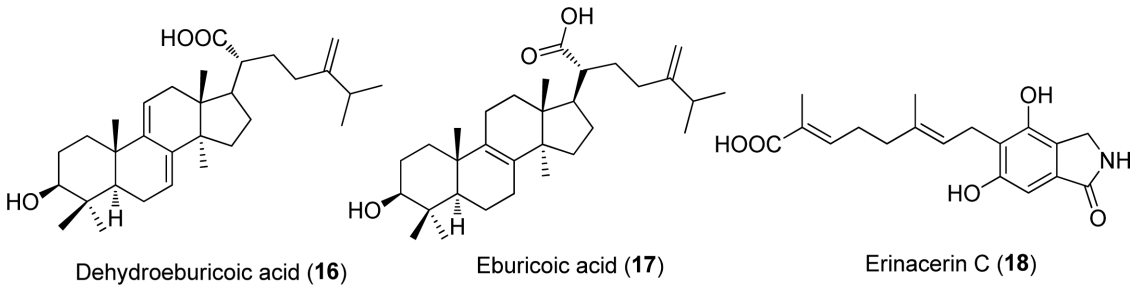


Fig. 2. Chemical structures of important compounds with anti-diabetic activity.

(**4**) and B, isolated from *Gymnopus fusipes*, are peptides that showed antiproliferative effects on human adherent cancer cell lines, including cervical (HeLa), skin epidermoid (A431), and breast (T47D, MCF7, and MDA-MB-231) cell lines. It was found that gymnopeptide B had lower IC_{50} values (14.0 – 44.3 nM) than gymnopeptide A (18.0 – 88.4 nM) for the HeLa, A431, MCF7, MDA-MB-231, and T47D cell lines.[7] *Poria cocos* contains a medicinal polysaccharide with a β-glucan structure containing a β-(1->3)-linked glucose backbone and -(1->6)-linked glucose side chains. This polysaccharide and its derivatives showed significant antiproliferative effects on cancer cells; they helped increase the host's immune system and caused apoptosis of the cancer cells.[8] *Pleurotus eryngii* also contains many polysaccharides that have antitumor effects. Its primary monosaccharide components include D-Glu, D-Gal, and D-Man.[9] In addition, *P. eryngii* contains three pentacyclic triterpenoids-2,3,6,23-tetrahydroxy-urs-12-en-28-oic acid (**5**), 2,3,23-trihydroxyurs-12-en-28-oic acid, and lupeol-showing anticancer effects on breast cancer cells (MCF-7) with IC_{50} values of 15.71, 48, and 66.89 μM, respectively.[10] In particular, 2,3,6,23-tetrahydroxy-urs-12-en-28-oic acid is the most effective antitumor agent.[10]

Six triterpenoids isolated from *Ganoderma lucidum* have cytotoxic effects on human carcinoma cells. They include ganoderic acid E (**6**), lucidumol A, ganodermanontriol, 7-oxo-ganoderic acid Z, 15-hydroxy-ganoderic acid S, and ganoderic acid DM; these compounds inhibit the growth of three types of human carcinoma cells (Caco-2, HepG2, and HeLa) and increase the apoptosis of HeLa cells.[11] *Fomitopsis betulina* (formerly *Piptoporus betulinus*) contains an compound, carboxymethylated (1→3)-α-D-glucans, which showed cytotoxicity *in vitro*, though α-glucans are typically believed to be biologically inactive.[12] *Antrodia camphorata* contains antroquinonol (**7**), also known as (4*R*,5*R*,6*R*)-4-hydroxy-2,3-dimethoxy-6-methyl-5-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl]cyclohex-2-en-1-one, which exhibits potential antitumor activity.[13] It is a ubiquinone derivative that has a quinol ring and a polyprenyl side chain. This antitumor compound exhibited significant inhibition of cell proliferation and migration in human breast cancer, lung cancer (H661, H441, and A549 cell lines), pancreatic cancer (PANC-1 and AsPC-1), colon cancer (HCT15 and LoVo), brain cancer, and liver cancer cell lines.[14] *Antrodia camphorata* also contains 4-acetylantroquinonol B (4-AAQB) (**8**), which has a suppressive effect on ovarian cancer cells and colorectal cancer cells. Compared to antroquinonol, 4-AAQB exhibited low IC_{50} values ranging from 11.3 to 39.2 μM.[14] Recently, 35 lanostane-type triterpenoids were isolated from *Fomitopsis pinicola* (Sw. Ex Fr.) Krast; among these, forpinioside, fomiroid A, ganosinoside A, and fomitoside C showed cytotoxic effects on human cancer cell lines, and fomitoside K (**9**) and formipinioside (**10**) selectively inhibited the HL-60, SMMC-7721, and MCF-7 cell lines with IC_{50} values ranging from 3.92 to 28.51 μM.[15] *Phellinus baumii* contains antitumor compounds, ergosterol, ergosta-7,22-dien-3-yl-pentadecanoate, 3,4-dihydroxy benzaldehyde, inoscavin A, and 24-ethylcholesta-5,22-dien-3-ol, which displayed significant inhibitory effects on some cancer cell lines, such as K562, L1210, SW620, HepG2, LNCaP, and MCF-7, with IC_{50} values ranging from 19.52 to 60.22 μg/mL.[16,17] *Antrodia cinnamomea* contains antcin-A, which inhibits the migration and invasion of human breast cancer cells (the MCF-7 and MDA-MB-231 cell lines).[17] Pinicolol B (**11**), identified in the mycelium of *Antrodia cinnamomea*, showed antitumor effects on nasopharyngeal carcinoma cells, TW02 and TW04, by inducing apoptosis with IC_{50} values of 63.3 and 115.0 μM, respectively.[18]

Phellinus rhabarbarinus soaked in wine is used as folk medicine by the residents of the Ailao mountain of Yunnan province, China; they drink it to enhance immunity and treat diseases such as cough, gastritis, and cancer. Chemical investigation of this mushroom revealed several lanostane-type triterpenoids, phellibarins B (**12**) and C, igniarens D and C, and gilvsins A and D, which

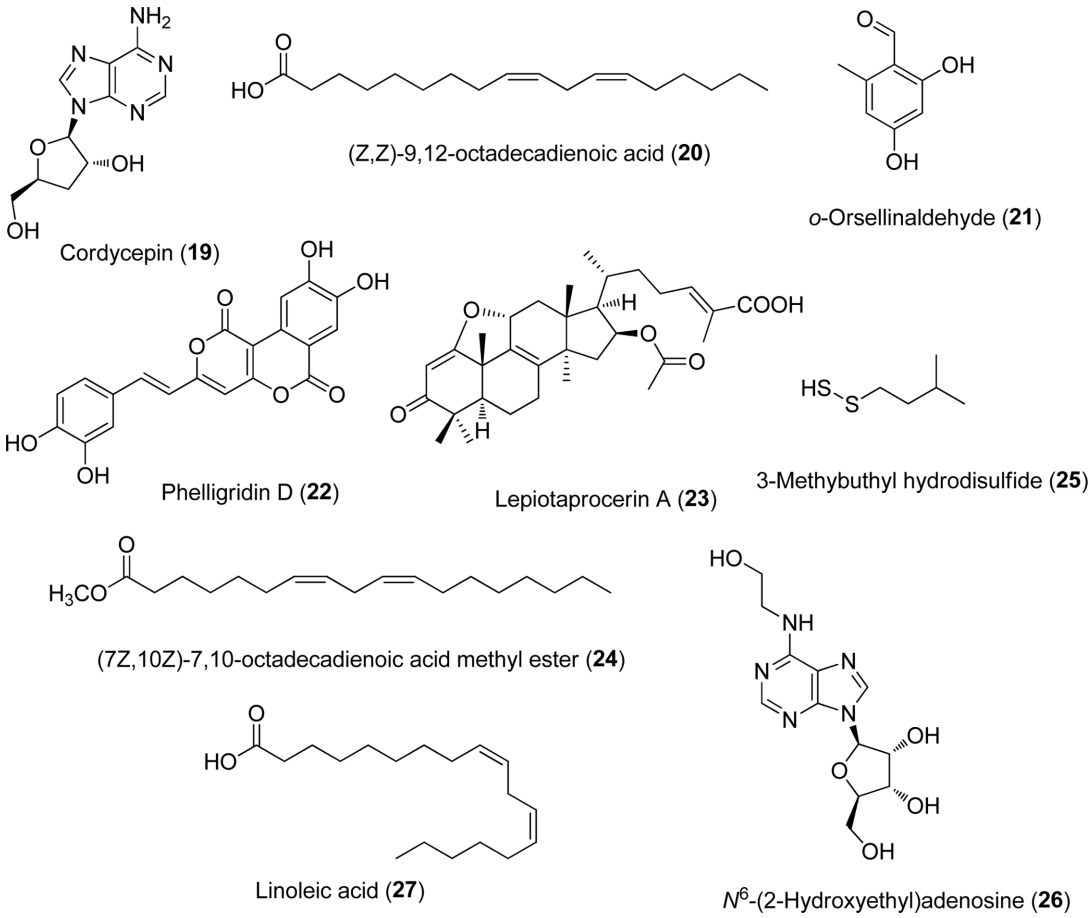


Fig. 3. Chemical structures of important compounds with anti-inflammatory activity.

are cytotoxic to human cancer cells.[19] The obtained results suggest that the lanostane-type triterpenoids in the fruiting bodies of *P. rhabarbarinus* play key roles in its folk usage. *Inonotus obliquus*, also known as the Chaga mushroom, contains an antitumor agent inotodiol; it induces apoptosis and inhibits the migration and invasion of HeLa cells.[20] Bioactivity-guided fractionation and preparative/semi-preparative HPLC purification with LC/MS analysis of *I. obliquus* resulted in the isolation of three triterpenoids 3*β*-hydroxylanosta-8,24-dien-21-al, trametenolic acid, and chagabusone A (**13**), which are cytotoxic to human lung cancer cell lines, with IC_{50} values ranging from 75.1 to 227.4 μM; their cytotoxicity is mediated by apoptosis accompanied by caspase 3 activation.[21] Bioactivity-guided isolation of active principles from the MeOH extract of *Fulvifomes fastuosus* led to the identification of ergone (**14**), which exhibits promising cytotoxic effects against muscle rhabdomyosarcoma cells; a modest cytotoxic effect was observed against CC-1 cells, the normal liver cells of Wistar rats. In addition, ergone exerts a strong cytotoxic effect against HepG-2 cells and a weak cytotoxic effect against CC-1 cells. Apoptotic features in cells treated with ergone were detected via morphological characterization and ethidium bromide/acridine orange staining.[22] Three pentacyclic triterpene dilactones were isolated from the fruiting bodies of *Ganoderma colossum*, a medicinal mushroom.[23] Colossolactone H (**15**), isolated as a new compound, was the most cytotoxic compound; it was found to exhibit cytotoxicity against lung cancer, breast cancer, colon cancer, and hepatoma cells, suggesting its potential application as a useful adjunct in the treatment of a wide range of cancers. Colossolactone H was also found to halt cell growth and induce cell apoptosis via the elevation of cellular reactive oxygen species to cause DNA damage and an increase in tumor suppressor p53 protein.[24] Furthermore, the combination of colossolactone H and gefitinib effectively inhibits the growth of tumor xenografts in athymic mice.[23]

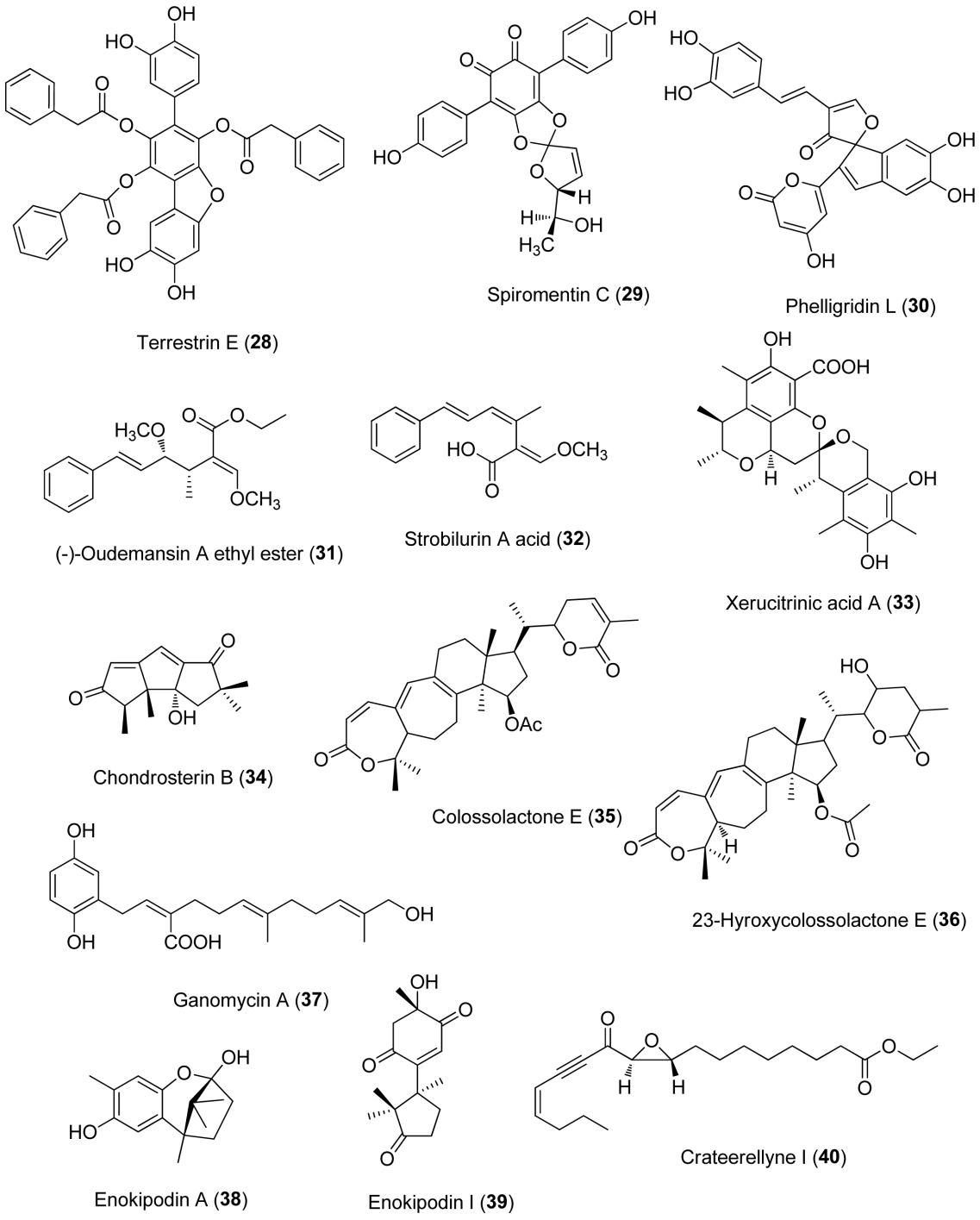


Fig. 4. Chemical structures of important compounds with antimicrobial activity.

Anti-diabetic Activity

Dehydroeburicoic acid (**16**), isolated from the MeOH extract of *Antrodia camphorata*, an edible Taiwanese mushroom, was examined for its effects on membrane glucose transporter 4 and lipid homeostasis using high fat diet (HFD)-fed mouse models.[24] The results demonstrated that it increases the membrane levels of glucose transporter 4. Its structure is similar to that of antcin K, which is effective in the treatment of type 2 diabetes and hypertriglyceridemia.[24] The MeOH extract of *Antrodia cinnamomea* demonstrated potent α-glucosidase inhibitory

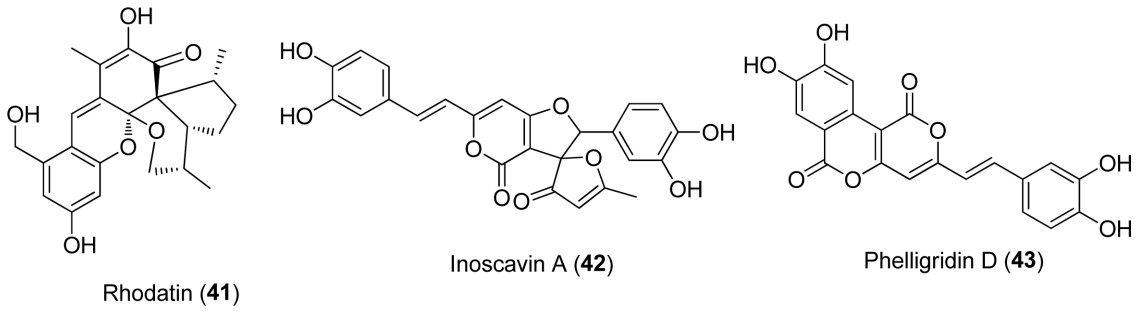


Fig. 5. Chemical structures of important compounds with antiviral activity.

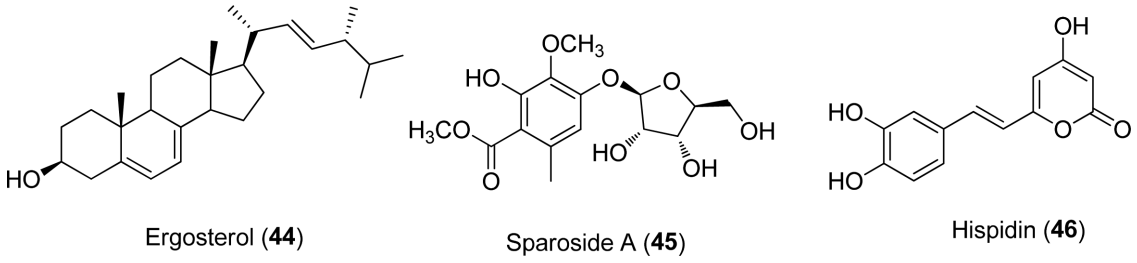
activity.[24] Chemical analysis of the extract led to the isolation of the active compounds 25*R*-antcin K, dehydrosulphurenic acid, 25*S*-antcin B, dehydroeburicoic acid, and eburicoic acid (**17**), which demonstrated a greater α-glucosidase inhibitory effect (EC_{50} = 0.025 – 0.21 mg/mL) than acarbose (EC_{50} = 0.278 mg/mL).[25] Erinacerin C (**18**) and its analogues, which were isolated as new isoindolin-1-ones from *H. erinaceus*, demonstrated α-glucosidase inhibitory effects with IC_{50} values ranging from 5.3 to 145.1 μM.[25] Structure-activity analysis indicated that the terpenoid side chain and the phenolic hydroxy groups in the structures of the active compounds contributed greatly to the α-glucosidase inhibitory activity.

Immunomodulatory Activity

Dictyophora indusiata (Vent ex. Pers.) Fischer, also known as bridal veil fungus, contains polysaccharides as major bioactive components, primarily *β*-(1 → 3)-D-glucan with side branches of β-(1 → 6)-glucosyl units, which has the effect of immune control.[26] It exerts both immunostimulatory and immunosuppressive effects; the immunostimulatory property may be applicable in cancer, whereas the immunosuppressive property may be applicable in chronic inflammation.[27]

Anti-inflammatory Activity

Natural cyathane diterpenes, sarcodonin A, neosarcodonin O, allocyathin B2, and neosarcodonin A, from the mushroom *Sarcodon scabrosus*, which is rich in cyathane diterpenes, show anti-inflammatory activity as assessed by the mouse ear inflammatory test.[28] Cordycepin (**19**) isolated from *Cordyceps militaris*, a well-known medicinal mushroom with anti-inflammatory effects, shows inhibitory effects on NO formation in lipopolysaccharide (LPS)-activated RAW 264.7 cells. The anti-inflammatory activity is demonstrated by the suppression of the kinase activity of AKT, an essential signaling enzyme in LPS-induced NO production, by interacting with its ATP binding.[29] The MeOH extract of the fruiting bodies of *Armillariella tabescens* shows concentration-dependent anti-gastritis activity against ethanol-induced gastric damage in rats and a notably lower gastric damage index value than the control. Chemical investigation of the MeOH extract led to the isolation of five active compounds, 11-dehydroergosterol peroxide, ergosterol peroxide, (17*R*)-17-methylincisterol, (3β,5α,22*E*)-ergost-22-en-3-ol, and (*Z*,*Z*)-9,12-octadecadienoic acid (**20**), with inhibitory effects on NO production with IC_{50} values of 22.46 ± 1.59, 38.12 ± 0.50, 36.48 ± 0.42, 40.75 ± 1.28, and 24.71 ± 1.66 μM, respectively. The most active compound (*Z*,*Z*)-9,12-octadecadienoic acid inhibits the expression of iNOS, COX-2, phospho-IKKα, IKKα, phospho-IκBα, IκBα, and NF-κβ in LPS-stimulated RAW 264.7 cells.[29] *o*-Orsellinaldehyde (**21**), from the mushroom *Grifola frondosa*, exerts anti-inflammatory and pro-apoptotic effects by acting as an IKK-2 inhibitor. Specifically, IKK-2 is the main component responsible for activating the nuclear-factor κβ transcription factor (NF-κβ).[30] Phelligridin D was isolated as a hispidin analog from *P. baumii*, which is widely used as a food source in East Asia. Phelligridin D (**22**) exerts anti-inflammatory effects on LPS-induced human periodontal ligament cells (HPDLCs).[31] It decreases the levels of inflammatory molecules and increases those of osteogenic molecules via downregulation of the extracellular signal-regulated kinase and c-Jun *N*-terminal kinase pathways among the mitogen-activated protein kinases, followed by the blocking of NF-κβ translocation from the cytosol to the nucleus.[32] Lanostane-type triterpenoids, lepiotaprocerin A (**23**) and its analogues, were isolated from the fruiting bodies of the edible mushroom *Macrolepiota procera* collected from Poland. Biologically, lepiotaprocerins A–F displayed significantly greater inhibition of NO production than the positive control L-N^G-monomethyl arginine (L-NMMA).[33] Structure-



Ergosterol (**44**) Sparoside A (**45**) Hispidin (**46**)

Fig. 6. Chemical structures of important compounds with anti-allergic activity.

activity relationship analysis suggested that structures with 26,23-lactone functionality were less potent than those with the free carboxylic acid group; moreover, the 23*R* or 23*S* configuration of the γ-lactone group caused no differences in the inhibitory activities on NO production.[33]

Bioassay-guided fractionation based on the anti-inflammatory effects of the fruiting bodies of *Calvatia nipponica*, one of the rarest mushroom species, led to the isolation of the anti-inflammatory compound (7*Z*,10*Z*)-7,10-octadecadienoic acid methyl ester (**24**).[34] The active compound was further investigated with regard to its mechanism of action, which was mediated through the inhibition of iNOS and COX-2 expression.[34] Repeated column chromatographic separation of the *n*-BuOH-soluble fraction of the MeOH extract of *Boletus pseudocalopus*, an inedible mushroom that mainly causes gastrointestinal irritation, resulted in the isolation of three anti-inflammatory compounds: 3-methylbutyl hydrodisulfide (**25**), phenylethyl hydrodisulfide, and uracil. These active compounds exert anti-inflammatory effects in LPS-activated microglia BV-2 cells by inhibiting NO levels with IC_{50} values of 40.98, 60.94, and 34.55 μM, respectively.[35]

N^6-(2-Hydroxyethyl) adenosine (**26**), a physiologically active compound, was identified in the medicinal mushroom *Cordyceps cicadae*, the fruiting body of which has been widely applied in Chinese medicine. The active compound was found to suppress the LPS-stimulated release of pro-inflammatory cytokines by RAW 264.7 macrophages and attenuate the LPS-induced pro-inflammatory response by suppressing the toll-like receptor 4-mediated NF-κB signaling pathway.[36] An active compound was identified from *Agaricus brasiliensis*, a medicinal mushroom that shows NO inhibitory activity-related inflammatory activity.[37] The active compound, linoleic acid (**27**), suppressed the expression of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and NOS2, in RAW 264.7 cells. Linoleic acid also suppressed the expression of the NF-κB subunit p50 and restored PPARα, suggesting that *Agaricus brasiliensis* could play a significant role in the prevention of inflammatory diseases.[37]

Antimicrobial Activity

Terrestrin E (**28**), vialinin B, and ganbajunin E were isolated from the fresh fruiting bodies of *Thelephora palmata*, and they show antimicrobial activity against *Staphylococcus aureus* with minimum inhibitory concentration (MIC) values of 21.7 – 70.4 μM.[38] In addition, terrestrin E and ganbajunin E show antimicrobial activity against *Bacillus subtilis* with MIC values of 70.4 and 44.5 μM, respectively.[38] Bioassay-guided fractionation of the chloroform extract of *Tapinella atrotomentosa* led to the isolation of three secondary metabolites, osmundalactone, 5-hydroxy-hex-2-en-4-olide, and spiromentin C (**29**), which show significant antibacterial activity against multiresistant *Acinetobacter baumannii* and extended-spectrum β-lactamase-producing *Escherichia coli*.[39] Bioassay-guided fractionation of the extracts derived from submerged cultures of a *Sanghuangporus* sp. (i.e., the genus that was, until recently, referred to as the "*Inonotus linteus* complex" of medicinal mushrooms) originating from Kenya led to the isolation of phelligridin L (**30**) and hispidin, which show antimicrobial activities against *Micrococcus luteus* with MIC values of 25 μg/mL and 100 μg/mL, respectively.[39] In addition, ionylideneacetic acid and 1*S*-(2*E*)-5-[(1*R*)-2,2-di-methyl-6-methylidenecyclohexyl]-3-methylpent-2-enoic acid, isolated from *Sanghuangporus* sp., show non-selective antimicrobial and antifungal activities.[40] Recently, 2,4-dihydroxybenzoic and protocatechuic acids, isolated from the wild mushroom *Agaricus bisporus*, showed antimicrobial activities against gram-negative bacteria such as *E. coli*, *Pasteurella multocida*, and *Neisseria gonorrhoeae*.[41] Several antimicrobial compounds, (−)-oudemansin A ethyl ester (**31**), (−)-oudemansin X ethyl ester, strobilurin A acid (**32**),

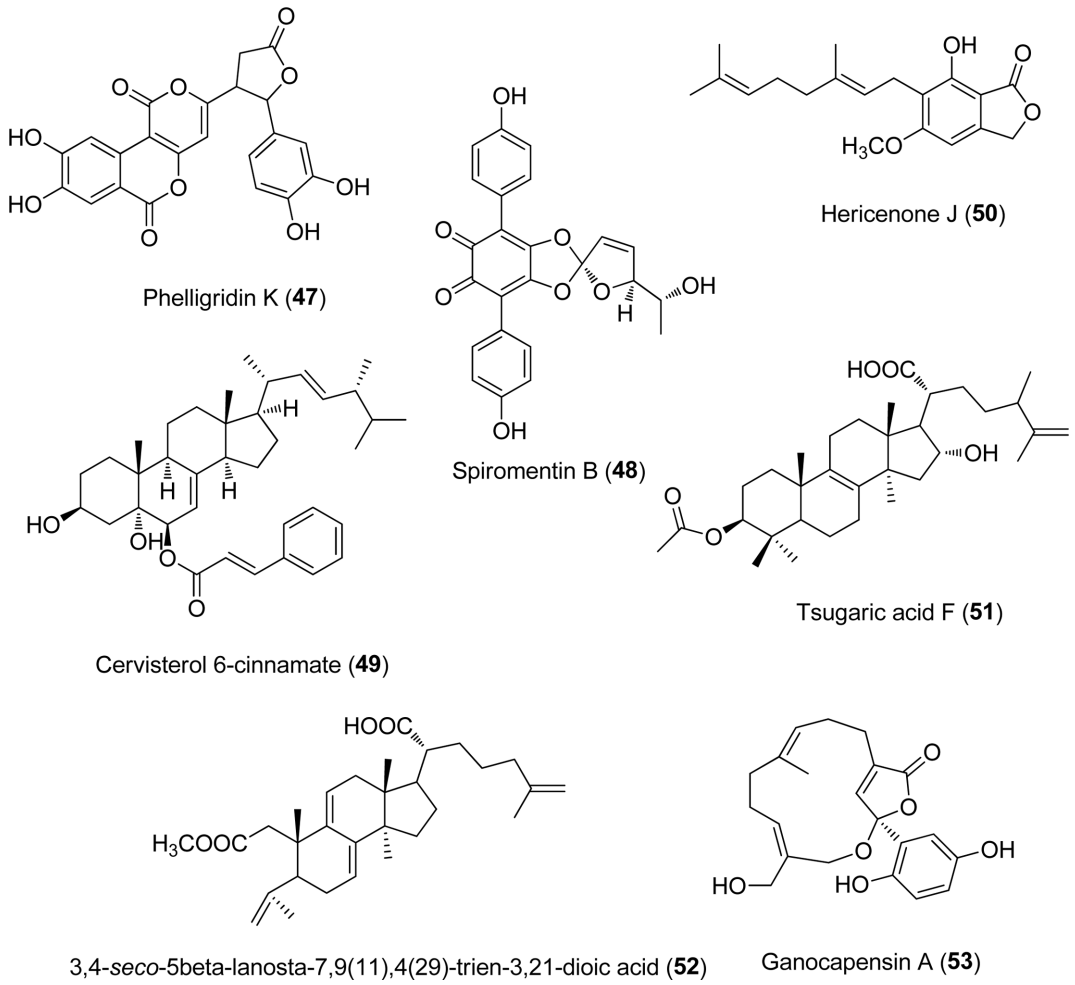


Fig. 7. Chemical structures of important compounds with antioxidative activity.

xerucitrinic acid A (**33**), and 2-(*E*-hept-5-en-1-yl)-3-methyl-6,7,8,8*a*-tetrahydro-4*H*-pyrrolo[2,1-*b*][1,3]oxazin-4-one, were reported from the mushroom *Xerula* sp. BCC56836, and they were found to exhibit anti-*Bacillus cereus* activity with MIC values ranging from 12.5 to 25.0 μg/mL.[42] Antimicrobial sesquiterpenes were isolated from the mushroom *Gloeostereum incarnatum* BCC41461.[43] Incarnatin B and chondrosterin B (**34**) exhibit antimalarial (IC_{50} 3.93 and 3.10 μg/mL, respectively) and anti-*Mycobacterium tuberculosis* (MIC 50.0 and 12.5 μg/mL, respectively) activities; chondrosterin B also shows anti-*B. cereus* activity with an MIC value of 25.0 μg/mL.[43] Dictyochromenol, derived from *G. incarnatum*, also displays antimicrobial activity against *M. tuberculosis* and *B. cereus* with MIC values of 12.50 and 1.56 μg/mL, respectively.[43]

Ganoderma sp. has been reported to be an important source of antimicrobial bioactive compounds.[44] Colossolactone E (**35**) and 23-hydroxycolossolactone E (**36**), two colossolactone-triterpenes from *Ganoderma* sp., were found to be active against *B. subtilis* and *Pseudomonas syringae*.[44] Moreover, two hydroquinones ganomycins A (**37**) and B, isolated from *Ganoderma* sp., were reported to be the most effective in the inhibition of *S. aureus* and *Micrococcus flavus*, with MIC values of 25 and 2.5 μg/mL, respectively.[44] Steroidal compounds ergosta-5,7,22-trien-3*β*-yl acetate, ergosta-5,7,22-dien-3*β*-yl acetate, ergosta-7,22-dien-3-one, ergosta-7,22-dien-3*β*-ol, ergosta-5,7,22-trien-3*β*-ol, and ganodermadiol from *Ganoderma* sp. were found to be effective against *S. aureus* and *B. subtilis* with an MIC value of 2.5 – 5 mg/mL; 12*β*-acetoxy-3*β*,7*β*-dihydroxy-11,15,23-trioxolanost-8-en-26-oic acid butyl ester from the fruiting bodies of *G. lucidum* shows significant inhibition of *S. aureus* and *B. subtilis* with MIC values of 68.5 μM and 123.8 μM, respectively.[44] Interestingly, composites produced using the extracellular

metabolites of *G. cattienensis* SIE1302 with 4-hydroxy-3-(3-oxo-1,3-diphenyl propyl)-chromen-2-one and those of *G. lucidum* SIE1303 with 4-hydroxy-3-(3-oxo-1-(3-nitrophenyl)-3-phenylpropyl)-chromen-2-one exert strong antibacterial activity against plant pathogenic bacteria *Clavibacter michiganensis* subsp. *sepedonicus*.[45] It was reported that enokipodin A (**38**) and its analogues, a group of α-cuparene-type sesquiterpenoids isolated from *Flammulina velutipes* (golden needle mushroom or winter mushroom), exhibit antibacterial activity mainly against gram-positive bacteria such as *B. subtilis* and *S. aureus*.[46] Enokipodins I (**39**) and J from *F. velutipes* also show antimicrobial activity against *B. subtilis* with MIC values of 164.3 ± 6.2 and 151.2 ± 4.5 μM, respectively.[46] Several new acetylenic acids and their derivatives, including craterellynes G–Q, 9-epi-craterellyne H, and 14-*O*-ethyl-craterellyne O, were isolated from the fruiting bodies of edible mushrooms *Craterellus lutescens*; craterellyne I (**40**) was found to show antimicrobial activity against *Candida albicans* with an MIC_{50} value of 53.5 μg/mL.[47]

Antiviral Activity

Rhodatin (**41**), a novel meroterpene with an underlying acorane-type substructure, featuring a unique pentacyclic scaffold with both spiro and spiroketal centers, was isolated from the wrinkled peach mushroom, *Rhodotus palmatus*.[48] Rhodatin shows strong antiviral effects against the hepatitis C virus in a dose-dependent manner with an IC_{50} value of 9.5 μM and strong inhibitory effects at 40 μM without any effect on cell viability. The study suggests that rhodatin could be a highly innovative source of drugs for the treatment of hepatitis C infection in the future.[48] The mushroom *Lentinus edodes* is a popularly consumed health food in China, Japan, and other Asian countries; it is known to contain various bioactive compounds in its fruiting bodies and liquid-cultured mycelia. Letinan is a heteroglucan comprising a β-(1→3)-glucan backbone and (1→6)-glucosyl side chain terminated by mannosyl and galactosyl residues.[49] Letinan shows significant antiviral activity against infectious hematopoietic necrosis virus (IHNV) at multiplicity of infection (MOI) values of 0.05 and 0.1, respectively. The anti-IHNV mechanism mainly focuses on the direct inactivation and inhibition of viral replication. This mechanism is attributed to the regulation of the innate immune response and specific immunity according to the observation that letinan significantly downregulates the expression of TNF-α, IL-2, and IL-11 and upregulates the expression of IFN-1 and IFN-γ after confronting IHNV.[49]

Five polyphenol bioactive compounds, hispidin, hypholomine B, inoscavin A (**42**), davallialactone, and phelligridin D (**43**), were isolated from the ethanolic extract of the fruiting bodies of *P. baumii*.[50] All five compounds noncompetitively inhibit the activity of HINI, H5N1, and H3N2 neuraminidase and reduce the virus-induced cytopathic effect in a dose-dependent manner. In particular, inoscavin A shows the most potent antiviral activity, with an IC_{50} value of 22.6 μM. Phelligridin D also exhibits potent antiviral activity in MDCK cells, with an IC_{50} value of 24.6 μM.[50]

Anti-allergic Activity

Ergosterol (**44**), 6β-methoxyergosta-7,22-dien-3β, 5α-diol, and 6-oxoergosta-7,22-dien-3β-ol were identified as active anti-allergic compounds from the extract of *Grifola frondosa*.[51] *G. frondosa*, containing ergosterol and its derivatives as bioactive components, provides insights into the prevention of type 1 allergies by inhibiting the antigen-induced release of β-hexosaminidase and histamine. The release of β-hexosamide was significantly suppressed by *G. frondosa* extract at concentrations of 20 and 50 μg/mL, in a dose-dependent manner. Interestingly, ergosterol inhibits the aggregation of the high-affinity IgE receptor (FcεRI), which is the first step in the activation of mast cells and antigen-induced tyrosine phosphorylation. Furthermore, it suppresses antigen-increased IL-4 and TNF-α mRNA, suggesting that ergosterol exerts inhibitory actions on both anaphylactic responses and the progression of allergic disorders.[51] The extracts of an edible mushroom *Sparassis crispa*, also known as cauliflower mushroom, show potential inhibitory effects on allergic rhinitis by demonstrating obvious inhibitory effects on the degranulation of mast cells and allergen-induced IgE. Sparoside A (**45**) derived from *S. crispa* was confirmed to have strong anti-inflammatory activity with an IC_{50} value of 5.06 ± 0.60 μM via a decrease in intracellular Ca^{2+} mobilization in a dose-dependent manner.[52] Sparoside A shows obvious inhibitory effects not only on the degranulation of mast cell- and allergen-induced IgE but also on pro-inflammatory mediators such as NO, PGE_2, and cytokines (including TNF-α, IL-6, and IL-1β) without cytotoxicity.[52]

Recently, the ethanol extracts of 90 wild mushrooms from Nepal and the pure compound hispidin were screened for their ability to inhibit allergic activities. Samples belonging to Hymenochaetales and Polyporales show promising anti-allergic activity. Moreover, the IC_{50} value of allergic activity for *Inonotus clemensiae* was determined to be 51.24 μg/mL, whereas hispidin (**46**), the

major bioactive compound in *I. clemensiae* showed an IC_{50} value of 82.47 ± 8.8 μg/mL, which indicates that *I. clemensiae* contains additional active compounds, or compounds synergistic to hispidin.[53]

Antioxidative Activity

Phelligridin K (**47**) is a novel pyrano[4,3-c][2]benzopyran-1,6-dione derivative, isolated from the methanol extract of the fruiting bodies of *Fomitiporia ellipsoidea*, a giant polypore found on Hainan Island in southern China.[54] Phelligridin K demonstrated the highest ABTS radical cation scavenging activity at the level of 3.56 mM Trolox, showing great potential for development as a natural food antioxidant; inoscavin C and inonoblin B from *F. ellipsoidea* exhibit significant scavenging activity against the ABTS radical cation.[54] Effect-directed isolation of free radical scavengers from the MeOH extract of the freeze-dried fruiting bodies of the cultivated basidiomycetous mushroom black poplar (*Cyclocybe cylindracea*) yielded a β-carboline alkaloid, identified as (-)-(1*S*,3*S*)-7-hydroxy-1-methyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid, which exhibits antioxidant activity (EC_{50} 119.1 ± 1.2 μg/mL).[55] Four secondary metabolites were isolated from the chloroform extract of *Tapinella atrotomentosa*. Among the isolates, osmundalactone and 5-hydroxyl-hex-2-en-4-olide were identified as lactones, whereas spiromentins B (**48**) and C were identified as terphenyl quinones.[39] The investigation of the antioxidant effect of the isolated compounds using the ORAC assay revealed that spiromentins B and C have remarkable antioxidant activity of 16.21 ± 0.38 and 11.23 ± 0.58 mmol TE/g, respectively, which is higher than the activity of ascorbic acid used as the standard compound (6.97 ± 0.01 mmol TE/g).[39]

A novel sterol, cerevisterol 6-cinnamate (**49**), was isolated from the fruiting bodies of *Hericium erinaceus*, together with five aromatic compounds and five sterols. Most of the compounds exhibited peroxyl radical-scavenging capacity, suggesting that *H. erinaceus* could be utilized in the development of natural antioxidants.[56] The results show that hericenone J (**50**), 4-[3′,7′-dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxy-benzylalcohol, and cerevisterol 6-cinnamate have potent peroxyl radical-scavenging activities at 10 μM with oxygen radical absorbance capacity (ORAC) values of 6.05, 4.98, and 8.01, respectively. Cerevisterol 6-cinnamate exhibits the strongest activity among the isolated sterols. Based on structural analysis, the cinnamic acid residue at C-6 appears to be an essential element for peroxyl radical-scavenging activity.[56] A water-soluble heteroglycan (PS-1) was isolated from the aqueous extract of a wild edible mushroom *Lentinus sajor-caju*. PS-1 comprises a repeating unit of a backbone chain of three (1→6)-α-D-galactopyranosyl residues, two (1→6)-β-D-glucopyranosyl residues, one (1→4)-α-D-mannopyranosyl residue, and two (1→3)-β-D-glucopyranosyl residues, where one (1→4)-α-D-galactopyranosyl residue is branched at the O-2 position with terminal α-D-galactopyranosyl residues. PS-1 was found to be a moderate antioxidant compound that shows 2,2,1-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging, hydroxyl radical-scavenging, and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ABTS radical-scavenging activites.[57] A water-soluble heteroglycan (PCPS) was isolated from the extract of an edible mushroom *Pleurotus cystidiosus*, commonly known as the brown oyster mushroom. Its structure contains a repeating unit with a backbone comprising one unit of (1→6)-β-D-glucopyranosyl, two (1→3)-β-D-glucopyranosyl, one (1→3)-α-D-glucopyranosyl, one (1→6)-α-D-glucopyranosyl, and two (1→6)-α-D-galactopyranosyl moieties; of these, one (1→3)-β-D-glucopyranosyl residue is branched at O-6 with a terminal β-D-glucopyranosyl moiety and another (1→6)-α-D-galactopyranosyl residue is branched at O-2 with a terminal β-D-mannopyranosyl moiety. The polysaccharide was found to exhibit cytotoxicity activities at different cell concentrations (10, 25, 50, 100, 200, and 400 μg/mL) and maintain a redox balance while also reducing lipid peroxidation, which protects against cell destruction. The study suggests that PCPS exhibits antioxidant activity, demonstrating a beneficial effect on the cellular system.[58]

A new lanostanoid, 3β-acetoxy-16α-hydroxy-24ξ-methyl-5α-lanosta-8,25-dien-21-oic acid, named tsugaric acid F (**51**), was isolated and characterized from the fruiting bodies of a medicinal mushroom, *Ganoderma tsugae*. Tsugaric acid F (**51**) and a known compound, 3-oxo-5α-lanosta-8-en-21-oic acid, from *G. tsugae* show inhibitory effects on xanthine oxidase with IC_{50} values of 313.3 ± 80.0 and 43.9 ± 29.9 μM, respectively. Another known compound, 3,4-*seco*-5β-lanosta-7,9(11),4(29)-trien-3,21-dioic acid (**52**), which is a 3,4-*seco*-compound obtained from the cleavage of ring A of the active compound, 3-oxo-5α-lanosta-8-en-21-oic acid, exhibits potent inhibitory effects against superoxide generation in rat neutrophils stimulated with formyl-Met-Leu-Phe (fMLP)/cytochalasin B with an IC_{50} value of 1.3 ± 0.2 μM.[59] Phytochemical investigation of the fruiting bodies of *Ganoderma capense* led to the isolation of eight aromatic meroterpenoids, including ganocapensins A and B, which are macrocyclic

aromatic terpenoids possessing a thirteen-membered ether ring and a fourteen-membered ether ring, respectively. All isolated aromatic meroterpenoids, including ganocapensins A (**53**) and B, show significant DPPH radical scavenging activities with IC_{50} values ranging from 6.00 ± 0.11 to 8.20 ± 0.3 μg/mL in the DPPH radical scavenging assay.[60]

Conclusion

This review demonstrates that mushrooms have immense potential to produce useful bioactive metabolites and that they are a prolific source of drugs. Many mushroom-derived secondary metabolites have shown diverse biological properties including anticancer, antidiabetic, immunomodulatory, antimicrobial, anti-inflammatory, antiviral, anti-allergic, and antioxidative activities. This review presents mushroom-derived bioactive metabolites investigated during the last five years (2015 – 2019) (Table 1). Based on the increasing knowledge of the chemistry, biotechnology, and molecular biology of mushroom-derived metabolites, a rapid increase in the application of mushrooms for medicinal purposes can be expected. Further in-depth biological studies on metabolites obtained from different mushrooms, as an important source of natural bioactive compounds, are required to discover potential drug candidates.

Table 1. Summary of mushroom-derived bioactive metabolites investigated during the last five years (2015 – 2019).

Biological property	Scientific name	Bioactive compound	Effects	Reference
Cytotoxicity and anticancer activities	*Pulveroboletus ravenelii*	vulpinic acid	inducing the apoptosis	[4]
	Hericium erinaceus	isohericerin	antitumor effect	[5]
	Albatrellus confluens	grifolin	upregulation of the death-associated protein kinase (dapk1) gene	[6]
	Gymnopus fusipes	gymnopeptides A and B	antiproliferative effects	[7]
	Pleurotus eryngii	2,3,6,23-tetrahydroxy-urs-12-en-28-oic acid, 2,3,23-trihydroxyurs-12-en-28-oic acid, and lupeol	anticancer effects on breast cancer cells	[10]
	Ganoderma lucidum	ganoderic acid E, lucidumol A, ganodermanontriol, 7-oxo-ganoderic acid Z, 15-hydroxy-ganoderic acid S, and ganoderic acid DM	inhibition of the growth of human carcinoma cells	[11]
	Antrodia camphorata	antroquinonol	inhibition of cell proliferation and migration in human cancer	[13]
	Fomitopsis pinicola	forpinioside, fomiroid A, ganosinoside A, and fomitoside C, fomitoside K and formipinioside	cytotoxicity	[15]
	Phellinus baumii	ergosterol, ergosta-7,22-dien-3-yl-pentadecanoate, 3,4-dihydroxy benzaldehyde, inoscavin A, and 24-ethylcholesta-5,22-dien-3-ol	inhibitory effects on cancer cell lines	[16, 17]
	Antrodia cinnamomea	antcin-A, pinicolol B	inhibition of the migration and invasion of human breast cancer cells; inducing apoptosis	[17, 18]
	Phellinus rhabarbarinus	phellibarins B and C, igniarens D and C, and gilvsins A and D	cytotoxicity	[19]
	Inonotus obliquusa	inotodiol, 3β-hydroxylanosta-8,24-dien-21-al, trametenolic acid, and chagabusone A	inducing apoptosis and inhibits the migration and invasion of HeLa cells; cytotoxicity	[20, 21]
	Fulvifomes fastuosus	ergone	cytotoxicity	[22]
	Ganoderma colossum	colossolactone H	cytotoxicity; halts cell growth and induces cell apoptosis; inhibits tumor growth	[23]

Table 1. continued

Biological property	Scientific name	Bioactive compound	Effects	Reference
Anti-diabetic Activity	*Antrodia camphorata,*	dehydroeburicoic acid	increasing the membrane levels of glucose transporter 4	[24]
	Antrodia cinnamomea	25*R*-antcin K, dehydrosulphurenic acid, 25*S*-antcin B, dehydroeburicoic acid, and eburicoic acid	potent α-glucosidase inhibitory activity	[24]
	Hericium erinaceus	erinacerin C	α-glucosidase inhibitory activity	[25]
Anti-inflammatory activity	*Sarcodon scabrosus*	sarcodonin A, neosarcodonin O, allocyathin B2, and neosarcodonin A	anti-inflammatory activity	[27]
	Cordyceps militaris	cordycepin	inhibitory effects on NO formation	[28]
	Armillariella tabescens	11-dehydroergosterol peroxide, ergosterol peroxide, (17*R*)-17-methylincisterol, (3β,5α,22*E*)-ergost-22-en-3-ol, and (*Z*,*Z*)-9,12-octadecadienoic acid	inhibitory effects on NO production	[29]
	Grifola frondosa	*o*-orsellinaldehyde	anti-inflammatory and pro-apoptotic effects acting as a IKK-2 inhibitor	[30]
	Phellinus baumii	phelligridin D	decreasing the levels of inflammatory molecules and increases those of osteogenic molecules	[32]
	Macrolepiota procera	lepiotaprocerin A-F	inhibition of NO production	[33]
	Calvatia nipponica	(7Z,10Z)-7,10-octadecadienoic acid methyl ester	inhibition of iNOS and COX-2 expression	[34]
	Boletus pseudocalopus	3-methylbutyl hydrodisulfide, phenylethyl hydrodisulfide,and uracil	inhibitory effects on NO production	[35]
	Cordyceps cicadae	N^6-(2-Hydroxyethyl) adenosine	suppresing the LPS-stimulated release of pro-inflammatory cytokines	[36]
	Agaricus brasiliensis	linoleic acid	inhibitory effects on NO production; suppression the expression of pro-inflammatory cytokines; suppression of the expression of the NF-κB subunit p50 and restored PPARα	[37]
Anti-microbial activity	*Thelephora palmata*	terrestrin E, vialinin B, and ganbajunin E	antimicrobial activity against *Bacillus subtilis*	[38]
	Tapinella atrotomentosa	osmundalactone, 5-hydroxy-hex-2-en-4-olide, and spiromentin C	antibacterial activity against multiresistant *Acinetobacter baumannii* and extended-spectrum β-lactamase-producing *Escherichia coli*	[39]
	Sanghuangporus sp.	phelligridin L and hispidin; ionylideneacetic acid and 1*S*-(2*E*)-5-[(1*R*)-2,2-di-methyl-6-methylidenecyclohexyl]-3-methylpent-2-enoic acid	antimicrobial activities against *Micrococcus luteus;* non-selective antimicrobial and antifungal activities	[39, 40]
	Agaricus bisporus	2,4-dihydroxybenzoic and protocatechuic acid	antimicrobial activities against gram-negative bacteria such as *E. coli*, *Pasteurella multocida*, and *Neisseria gonorrhoeae*	[41]
	Xerula sp. BCC56836	(−)-oudemansin A ethyl ester (31), (−)-oudemansin X ethyl ester, strobilurin A acid, xerucitrinic acid A, and 2-(*E*-hept-5-en-1-yl)-3-methyl-6,7,8,8a-tetrahydro-4*H*-pyrrolo[2,1-b][1,3]oxazin-4-one	antimicrobial activities against Bacillus cereus	[42]
	Gloeostereum incarnatum	incarnatin B and chondrosterin B; dictyochromenol	antimalarial and anti-microbial activity against *Mycobacterium tuberculosis* and *B. cereus*	[43]

Table 1. continued

Biological property	Scientific name	Bioactive compound	Effects	Reference
Anti-microbial activity	*Ganoderma sp.*	colossolactone E and 23-hydroxycolossolactone E; ganomycins A and B; ergosta-5,7,22-trien-3β-yl acetate, ergosta-5,7,22-dien-3β-yl acetate, ergosta-7,22-dien-3-one, ergosta-7,22-dien-3β-ol, ergosta-5,7,22-trien-3β-ol, and ganodermadiol	anti-microbial activity against *B. subtilis and Pseudomonas syringae;* inhibition of S. aureus and *Micrococcus flavus*; effective against *S. aureus* and *B. subtilis*	[44]
	Ganoderma cattienensis	4-hydroxy-3-(3-oxo-1,3-diphenyl propyl)-chromen-2-one	antibacterial activity against plant pathogenic bacteria *Clavibacter michiganensis* subsp. *sepedonicus*	[45]
	Ganoderma lucidum	12β-acetoxy-3β,7β-dihydroxy-11,15,23-trioxolanost-8-en-26-oic acid butyl ester; 4-hydroxy-3-(3-oxo-1-(3-nitrophenyl)-3-phenylpropyl)-chromen-2-one	significant inhibition of *S. aureus* and *B. subtilis*; antibacterial activity against plant pathogenic bacteria *Clavibacter michiganensis* subsp. *sepedonicus*	[45]
	Flammulina velutipes	enokipodins A, I, J	antimicrobial activity against *B. subtilis* and *S. aureus*	[46]
	Craterellus lutescens	craterellyne I	antimicrobial activity against *Candida albicans*	[47]
Antiviral activity	*Rhodotus palmatus*	rhodatin	strong antiviral effects against the hepatitis C virus	[48]
	Lentinus edodes	letinan	antiviral activity against infectious hematopoietic necrosis virus (IHNV)	[49]
	Phellinus baumii	hispidin, hypholomine B, inoscavin A, davallialactone, and phelligridin D	inhibition of the activity of HINI, H5N1, and H3N2 neuraminidase	[50]
Anti-allergic activity	*Grifola frondosa*	ergosterol, 6β-methoxyergosta-7,22-dien-3β, 5α-diol, and 6-oxoergosta-7,22-dien-3β-ol	prevention of type 1 allergies	[51]
	Sparassis crispa	sparoside A	degranulation of mast cells and allergen-induced IgE	[52]
	Inonotus clemensiae	hispidin	inhibition of allergic activities	[53]
Antioxidative activity	*Fomitiporia ellipsoidea*	phelligridin K, inoscavin C and inonoblin B	ABTS radical cation scavenging activity	[54]
	Cyclocybe cylindracea	(-)-(1*S*,3*S*)-7-hydroxy-1-methyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid	antioxidant activity	[55]
	Tapinella atrotomentosa	osmundalactone and 5-hydroxyl-hex-2-en-4-olide, spiromentins B and C	antioxidant activity	[39]
	Hericium erinaceus	cerevisterol 6-cinnamate, hericenone J, 4-[3′,7′-dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxy-benzylalcohol	peroxyl radical-scavenging capacity	[56]
	Ganoderma tsugae	tsugaric acid F and 3-oxo-5α-lanosta-8-en-21-oic acid; 3,4-seco-5β-lanosta-7,9(11),4(29)-trien-3,21-dioic acid	inhibitory effects on xanthine oxidase; inhibitory effects against superoxide generation in neutrophils	[59]
	Ganoderma capense	ganocapensins A and B	DPPH radical scavenging activities	[60]

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