Secondary metabolites from higher fungi in China and their biological activity

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ABSTRACT: As a part of our search for naturally occurring bioactive metabolites from higher fungi, we investigated the chemical constituents of basidiomycetes and ascomycetes fungi (*Albatrellus confluens, Albatrellus dispansus, Boletus edulis, Boletopsis grisea, Bondarzewia berkeleyi, Cortinarius tenuipes, Cortinarius vibratilis, Daldinia concentrica, Engleromyces goetzii, Hydnum repandum, Hebeloma versipelle, Hygrophorus eburnesus, Lactarius deliciosus, Lactarius hatsudake, Lactarius hirtipes, Lactarius mitissimus, Lactarius rufus, Paxillus panuoides, Pulveroboletus ravenelii, Russula cyanoxantha, Russula foetens, Russula lepida, Russula nigricans, Sarcodon laevigatum, Sarcodon scabrosus, Shiraia bambusicola, Thelephora aurantiotincta, Thelephora ganbajun, Tricholomopsis rutilans, Tylopilus virens, Tuber indicum, Xylaria euglossa, etc.*), and isolated a number of novel terpenoids, phenolics, and nitrogen-containing compounds. The isolation, structural elucidation, and biologically activity of the new compounds are discussed.

Key Words: Higher fungi, secondary metabolites, biological activities, natural products

Introduction

China is extraordinary rich in higher fungi. To date, about 10,000 species of fungi have been reported from China's vast territories. Of them, nearly 6,000 species, belonging to about 1,200 genera, are higher fungi (excluding lichens). In bio-resources, higher fungi belong to very productive biological sources that produce a large and diverse variety of secondary metabolites. Biologically active substances present in untapped and diverse sources of higher fungi from China are interesting. The isolation, structural elucidation, and biologically activity of new compounds prior to 2002 were previously reviewed (*1*,*2*).

Recently several dozen new natural substances and bioactive compounds were found in selected mushrooms on the basis of using our knowledge on the collection of fruiting bodies, strain preservation, fermentation, biologically screening and chemical investigation of higher fungi. The isolation, structural elucidation and biologically activity of the novel terpenoids, phenolics and nitrogen-containing compound from basidiomycetes and ascomycetes fungi (*Albatrellus confluens*, *Albatrellus dispansus*, *Boletus edulis*, *Boletopsis grisea*, *Bondarzewia berkeleyi*, *Cortinarius tenuipes*, *Cortinarius vibratilis*, *Daldinia concentrica*, *Engleromyces goetzii*, *Hebeloma versipelle*, *Hydnum repandum*, *Hygrophorus eburnesus*, *Lactarius deliciosus*, *Lactarius hatsudake*, *Lactarius hirtipes*, *Lactarius mitissimus*, *Lactarius rufus*, *Paxillus panuoides*, *Pulveroboletus ravenelii*, *Russula cyanoxantha*, *Russula foetens*, *Russula lepida*, *Russula nigricans*, *Sarcodon laevigatum*, *Sarcodon scabrosus*, *Shiraia bambusicola*, *Thelephora aurantiotincta*, *Thelephora ganbajun*, *Tricholomopsis rutilans*, *Tylopilus virens*, *Tuber indicum*, *Xylaria euglossa*, *etc*.) are reviewed.

Concentricolide, an anti-HIV agent, and other compounds from the ascomycete *Daldinia concentrica*

Although anti-HIV-1 drugs now available have improved the quality of the lives of HIV/AIDS patients, the rapid evolution of new HIV clades and drug resistant variants in AIDS patients urged the search for new anti-HIV-1 agents and targets. A large variety of natural substances including alkaloids, flavonoids, coumarines, lignans, phenolics, triterpenoids, saponins, sulfated polysaccharides, phospholipids, quinones and peptides with anti-HIV-1 effect have been described, and for a portion thereof the target of interaction has been identified (*3*). Natural substances provide a large reservoir for screening of anti-HIV-1 agents with novel structure and anti-viral mechanisms.

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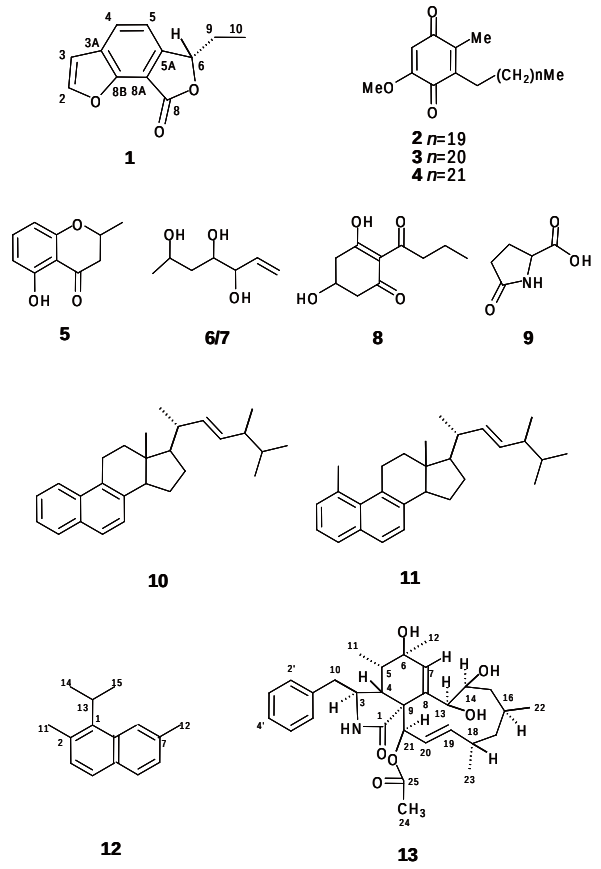


Figure 1. Different compounds of the ascomycete *Daldinia concentrica.*

A novel benzofuran lactone, named concentricolide (**1**), was isolated along with the four known compounds (friedelin, cytochalasin *L*-696,474, armillaramide, russulamide) from the fruiting bodies of the xylariaceous ascomycete *Daldinia concentrica*. The structure of concentricolide was established by spectroscopic methods and X-ray crystallographic analysis. Its anti-HIV-1 activity was tested. Results showed that concentricolide inhibited HIV-1 induced cytopathic effects. The EC_{50} value was 0.31 μg/mL. The therapeutic index (TI) was 247. Concentricolide exhibited the blockage (EC_{50} 0.83 μg/mL) on syncytium formation between HIV-1 infected cells and normal cells (*4*).

Except concentricolide (**1**), a new homologous series of 3-alkyl-5-methoxy-2-methyl-1,4-benzoquinones (**2**-**4**) with chain length C_{21} to C_{23} were isolated from the fruiting bodies of *Daldinia concentrica* (*5*). Two novel heptenetriol stereoisomers, hept-6-ene-2,4,5-triols **6** and **7**, were, along with three known compounds, *i.e.*, 2,3-dihydro-5-hydroxy-2-methyl-4*H*-1-benzo-pyran-4-one (**5**), 3,5-dihydroxy-2-(1-oxobutyl)-cyclohex-2-en-1one (**8**), and pyroglutamic acid (= 5-oxo-*L*-proline) (**9**), isolated from the culture broth of *D. concentrica* (*6*). Compound **5** is reported to be a metabolite from the rice culture solution of the fungus *Phialophora gregata* and has been shown to have biological activity on soybean cells (*7*). Compound **8** has also previously been isolated from the culture broth of the fungus *Nodulisporium* sp. and has been found to have chlorotic activity (with greater activity on monocotyledons than on dicotyledons) (*8*).

The identification of aromatic steroid hydrocarbons bearing a methyl group at positions 1, 2, 3, 4, or 6 in sediments and petroleum is enigmatic since possible steroidal precursors have not yet been reported in living organisms. Two new aromatic steroids (**10** and **11**) were isolated from the fruiting bodies of *D. concentrica*, and one, compound **11,** bears an unusual methyl group at position 1. These compounds presumably originate with the transformation undergone by their precursors due to microbial action. Compounds **10** and **11** could be long-sought, biological precursor steroids for organic matter in the Earth's subsurface (*9*). Two other new compounds, 1-isopropyl-2,7-dimethylnaphthalene (**12**) and 21-acetyloxyl-16,18-dimethyl-10-phenyl-6,13,14-trihydroxyl-[11]-cyto-chalasa-7,19-diene-1-one (**13**), were also isolated from the fruiting bodies of *D. concentrica* (*10*).

Grifolin, a potential natural antitumor substance produced by inducing apoptosis *in vitro* in *Albatrellus confluens*, and other related compounds from the same genus

Grifolin (**14**) is a natural biologically active substance isolated from the fruiting bodies of *Albatrellus confluens*. Here, novel activity of grifolin is described for the first time, namely its ability to inhibit the growth of tumor cells by the induction of apoptosis. Grifolin strongly inhibited tumor cells lines CNE1, HeLa, MCF7, SW480, K562, Raji, and B95-8. Analysis of acridine orange (AO)/ethidium bromide (EB) staining and flow cytometry showed that grifolin possessed apoptosis induction activity with respect to CNE1, HeLa, MCF7, and SW480. Furthermore, cytochrome *c* release from mitochondria was detected by confocal microscopy in CNE1 cells after 12 h of treatment with grifolin. The increase in caspase-8, 9, 3 activity revealed that caspase was a key mediator of the apoptotic pathway induced by grifolin, and the under-expression of Bcl-2 and up-regulation of Bax resulted in the increase in Bax: Bcl-2 ratio, suggesting that the Bcl-2 family is involved in the control of apoptosis. Owing to the combination of its significant antitumor activity by inducing apoptosis and the compound's natural abundance, grifolin represents an interesting antitumor agent that deserves further laboratory and *in vivo* examination (*11*).

In the course of screening for novel naturally occurring fungicides from mushrooms in Yunnan province of China, the ethanol extract of the fruiting bodies of *Albatrellus dispansus* was found to show antifungal activity against plant pathogenic fungi. The active compound was isolated from the fruiting bodies of *A. dispansus* by bioassay-guided fractionation of the

extract and identified as grifolin (**14**) by IR, ^{1}H and ^{13}C NMR, and mass spectral analysis. Its antifungal activity was evaluated *in vitro* against 9 plant pathogenic fungi and *in vivo* against the plant disease *Erysiphe graminis*. *In vitro*, *Sclerotinia sclerotiorum* and *Fusarium graminearum* were the most sensitive to grifolin, and at 0.1 μg/mL their levels of mycelial growth inhibition were 86.43 and 80.90%, respectively. Spore germination of *F. graminearum*, *Gloeosporium fructigenum* and *Pyricularia oryzae* were almost completely inhibited by 12.5 μg/mL of grifolin. The curative effect of grifolin (**14**) on *Erysiphe graminis in vivo* was 65.52% at 100 μg/mL (*12*).

In a previous report, the effects of albaconol (**15**) from *Albatrellus confluens* on vanilloid receptors were studied electrophysiologically in rat ganglion neutrons as well as in recombinant cell lines expressing rat VR1 receptor (*13*). Recently, the effects of albaconol (**15**) on the inhibition of human tumor cell growth, DNA topoisomerase (topo)-mediated DNA cleavage, and direct DNA breakage were investigated. Albaconol (**15**) significantly inhibited the growth of human chronic myelogenous leukemia K562, lung adenocarcinoma A 549, gastric adenocarcinoma BGC-823 and breast carcinoma Bcap-37 cell lines with IC_{50} values of 2.77 ± 0.14, 2.58 ± 0.88, 1.45 ± 0.05, and 1.10 ± 0.31 μg/mL, respectively. Albaconol (**15**) stabilized and increased the topo II-mediated DNA cleavable complex and inhibited the religation activity of topo II in a dose-dependent manner, but it failed to affect the activity of topo I. Albaconol (**15**) acts to break strands of pBR322 DNA at relatively high concentrations but no effect on the macromolecule DNA of K562 cells. These results strongly suggest that albaconol (**15**) specifically targets DNA topo II and that this is one of the mechanisms of albaconol's antitumor action; the direct action of albaconol (**15**) on DNA may contribute to its antitumor activity at high concentrations (*14*).

Contraction and desensitization induced by albaconol (**15**) and the influence of capsazepine, capsaicin, and extracellular Ca^{2+} were investigated to see whether action was mediated *via* a specific VR receptor in guinea pig trachea spiral strips *in vitro*. Both albaconol (**15**) and capsaicin were contractors of tracheal smooth muscle, but albaconol (**15**) was not as potent as capsaicin, with -log (M) EC_{50} values of 4.23 ± 0.18 (n = 10) and 7.33 ± 0.21 (n = 10), respectively. Two-point five and 5.0 μM capsazepine competitively antagonized the contractile response to albaconol (**15**), with -log (M) pK_B values of 6.60 ± 0.39 (n = 10) and 7.36 ± 0.45 (n = 10), respectively. Albaconol (**15**) increased the contraction induced by a low dose of capsaicin (10^{-10}-10^{-9} M) but non-competitively antagonized the contraction induced by a high dose of capsaicin (10^{-8}-10^{-3} M). Either albaconol (1,100 mM) or capsaicin (3.0, 10 μM) was able to desensitize the isolated guinea pig bronchi to subsequent addition of albaconol.

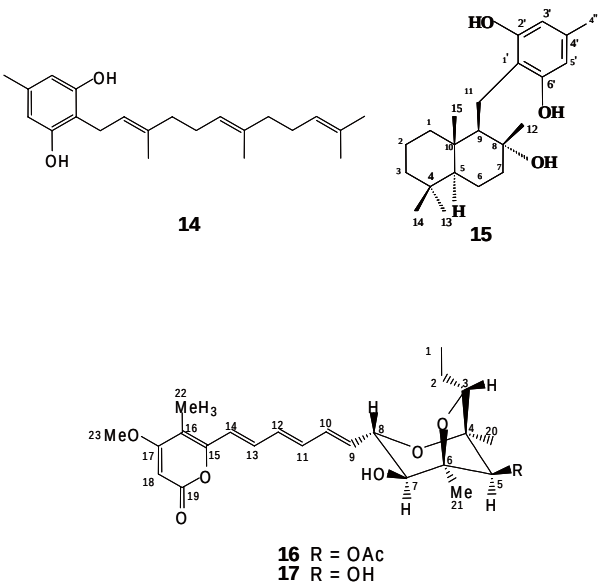


Figure 2. Potential antitumor natural products.

Capsazepine (5.0 μM) significantly prevented the desensitization induced by either albaconol (1, 100 mM) or capsaicin (3, 10 μM). Extracellular Ca^{2+} was essential for albaconol to induce excitation, but it did not affect albaconol- or capsaicin-induced desensitization. These results suggest that albaconol (**15**) induces contraction and desensitization of guinea pig trachea *in vitro* as a partial agonist for VR (*15*).

Albaconol (**15**) inhibited lipid peroxidation in rat liver homogenate with an IC_{50} value of 104.2 μg/mL in comparison to butylated hydroxyanisole (BHA, IC_{50} 40.4 μg/mL) and vitamin E (IC_{50} 127.2 μg/mL). Albaconol increased the activity of SOD (EC_{50} value of 106.3 μg/mL) and BHA (EC_{50} 19.9 μg/mL) (*16*).

When grown in culture, the basidiomycete *Albatrellus confluens* produces a polyene pyrone mycotoxin, aurovertin E (**17**), along with aurovertin B (**16**). This was the first example of the occurrence of aurovertins in macromycetes (*17*). The aurovertins, metabolites from the fungus (anamorphic ascomycetes) *Calcarisporium arbuscula*, are a group of acute neurotoxic substances that act as potent inhibitors of ATP synthesis and ATP hydrolysis catalyzed by mitochondrial enzyme systems (*18-21*).

Radical scavenging activity of natural *p*-terphenyls obtained from three edible mushrooms indigenous to China and other natural *p*-terphenyls

Ten natural *p*-terphenyl derivatives (**18-27**) obtained from the fruiting bodies of three edible mushrooms (*Thelephora ganbajun*, *Thelephora aurantiotincta*, and *Boletopsis grisea*) indigenous to China were assessed in terms of DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity. The compounds **18-20** showed potent DPPH radical scavenging activity in comparison

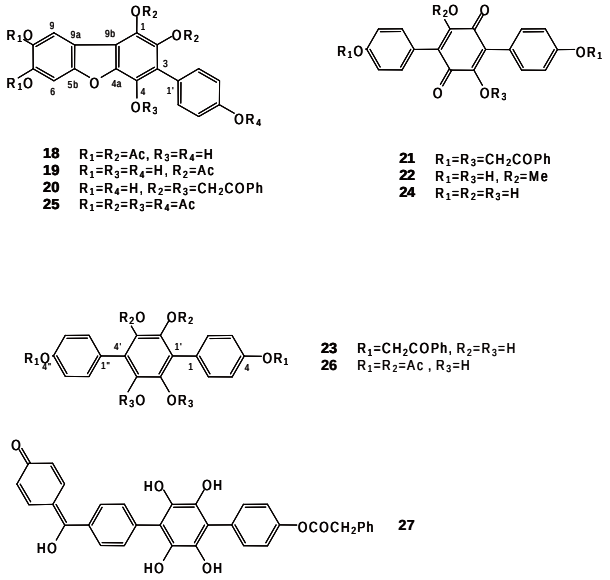


Figure 3. Ten natural *p*-terphenyl derivatives.

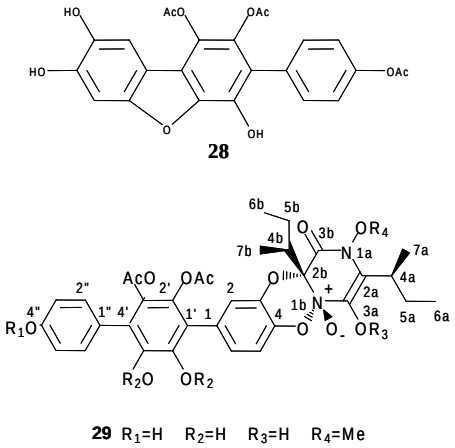


Figure 4. Sarcodan (**28**) and sarcodonin δ (**29**).

to BHA (butylated hydroxyanisol) and α-tocopherol, which are known to be strong activators. The free radical scavenging activity of **19** (EC_{50} = 0.07) was found to be stronger than that of BHA (EC_{50} = 0.09) and α-tocopherol (EC_{50} = 0.25), while that of **18** (EC_{50} = 0.12) and **20** (EC_{50} = 0.13) was similar to that of BHA and stronger than that of α-tocopherol. The formation of furan rings and the numbers and position of hydroxy groups in the molecular structure of *p*-terphenyls have been found to be crucial for modulation of free radical scavenging activity (*22*).

A metabolite with a *p*-terphenyl core, named sarcodon (**28**), was isolated from the fruiting bodies of the basidiomycete *Sarcodon laevigatum* (*23*). Another nitrogenous metabolite with a *p*-terphenyl core, sarcodonin δ (**29**), was isolated from the fruiting bodies of the basidiomycete *Sarcodon scabrosus* (*24*).

Terphenyls are aromatic hydrocarbons consisting of a chain of three benzene rings. There are three isomers, in which the terminal rings are *ortho*-, *meta*-, or *para*-substituents of the central ring. Most of the natural terphenyls are *p*-terphenyl derivatives. The chemical investigation of *p*-terphenyls as one class of the pigments of mushrooms began in 1877 (*25*). In recent years, some terphenyls have been reported to exhibit significant biological activity, *e.g.*, potent immunosuppressant, neuroprotective, antithrombotic, anticoagulant, specific 5-lipoxygenase inhibitory, and cytotoxic activity (see section 5). In addition, terphenyls are, in comparison to other types of complex natural substances, easily synthesized since they contain fewer (or no) chiral centers. Another interesting point is that some popular edible mushrooms are rich in *p*-terphenyls; this is a sign that at least some *p*-terphenyls have a low level of toxicity. Because of their promising biological activity and important properties, terphenyls have generated increasing research interest (*25*).

Antifungal sesquiterpenoid and other compounds from the genera *Lactarius* and *Russula*

The mushrooms belonging to the genus *Lactarius* (family Russulaceae, Basidiomycotina) form a milky juice when the fruiting bodies are injured. In the great majority of *Lactarius* species, different kinds of sesquiterpenes play an important biological role, being responsible for the pungency and bitterness of the milky juice, the change in the color of the latex in air, and constituting a chemical defense system against various predators such as bacteria, fungi, animals, and insects (*26*). Most *Lactarius* sesquiterpenes belonging to the classes of lactaranes, secolactaranes, marasmanes, isolactaranes, norlactaranes, and caryophyllanes are believed to be biosynthesized from humulene (*27-30*).

Rufuslactone (**30**) is an isomer of a previously described lactarane 3,8-oxa-13-hydroxylactar-6-en-5-oic acid γ-lactone (**31**) from *Lactarius rufus*. Its structure was elucidated by spectroscopic means. Rufuslactone (**30**) displayed antifungal properties against plant pathogenic fungi (*31*). *Alternaria brassicae* was the most sensitive to Rufuslactone (**30**), and its mycelial growth inhibition was 68.3 at 100 μg/mL.

A humulene sesquiterpene, named 2β,3α-epoxy-6*Z*,9*Z*-humuladien-8α-ol (**32**), was, together with the known compound lactarinic acid, isolated from the fruiting bodies of *Lactarius hirtipes*. For the subdivision Basidiomycotina, fungal sesquiterpenes formed *via* the humulane-protoilludane biosynthetic pathway are also characteristic. However, no representative of humulene sesquiterpenes has been isolated from higher fungi thus far. Compound **32** was the first humulene-type sesquiterpene found in higher fungi (*32*). Five new humulane-type sesquiterpenes, mitissimols A (**33**), B (**34**), and C (**35**), and a mixture of mitissimyl A oleate (**36**) and mitissimyl B oleate (**37**), were isolated from the fruiting bodies of *Lactarius mitissimus* (*33*).

Their structures were elucidated by comprehensive spectroscopic techniques and necessary chemical methods. The relative stereochemistry of **33** was determined by single crystal X-ray diffraction analysis.

Two new red azulene pigments (**38**, **39**) were isolated from the fruiting bodies of the basidiomycete *Lactarius deliciosus* together with one known pigment (**40**) (*34*). Two other new azulene pigments, 1-formyl-4-methyl-7-(11-hydroxyl) isopropylazulene (**41)** and 4-methyl-7-isopropylazulene-1-carboxylic acid (**42**), were isolated from the fruiting bodies of the basidiomycete *Lactarius hatsudake* (*35*).

A new marasmane sesquiterpene, named lactapiperanol E (**43**), was isolated from the fruiting bodies of *Russula foetens* together with a known sesquiterpene, lactapiperanol A (**44**) (*36*). Sesquiterpenes possessing the marasmane skeleton have been known for more than 50 years (*37*). Marasmic acid was found to be an antibacterial substance in *Marasmius conigenus* (*38*), and its 9-hydroxy derivative, detected in another basidiomycete, displayed antifungal, cytotoxic, and phytotoxic activity (*39*). Velutinal and its fatty acid esters represent interesting examples of prodrugs (*40,41*). In most fungi, only the esters, which are cleaved to velutinal in the event of injury to the fruiting bodies, are present (*42*). Pilatin is an antibiotically active marasmane derivative from the culture of *Flagelloscypha pilatii*. It is a higher oxidized derivative of marasmic acid, causes frameshift mutations in *Salmonella typhimurium*, inhibits the growth of bacteria and fungi, and is highly cytotoxic (*43*). The Russulaceae family is one of the largest in the subdivision Basidiomycotina in Whittaker's kingdom of Fungi and consists of hundreds of species (*44*). While secondary metabolites occurring in the fruiting bodies of European *Lactarius* species have been extensively investigated, the *Russula* mushrooms have received less attention, notwithstanding the larger number of existing species (*45*). Recent investigation of the chemical constituents of *Russula lepida* by the current authors led to the identification of some new terpenoids (*46-48*). The minor constituents of *Russula lepida* were further investigated. A novel nitrogen-containing aristolane sesquiterpenoid compound, lepidamine **45**, was isolated from the fruiting bodies of Basidiomycete *Russula lepida*. It is the first aristolane-type sesquiterpene alkaloid isolated from nature (*49*). It is also interesting that nigricanin (**46**), the first ellagic acid related derivative from higher fungi, has been isolated from the fruiting bodies of the basidiomycete *Russula nigricans* (*50*). Ellagic acid and its derivatives are widely distributed in plants but are rare in fungi. Ellagic acid and its derivatives are known to display multiple forms of biological activity such as DNA damage (*51*) or act as antioxidants (*52*). In the case of actinomycete, *e.g.*, *Streptomyces chartreuses*, only the antibiotics D 329C, chartreusin, and elsamicin have been isolated; and these

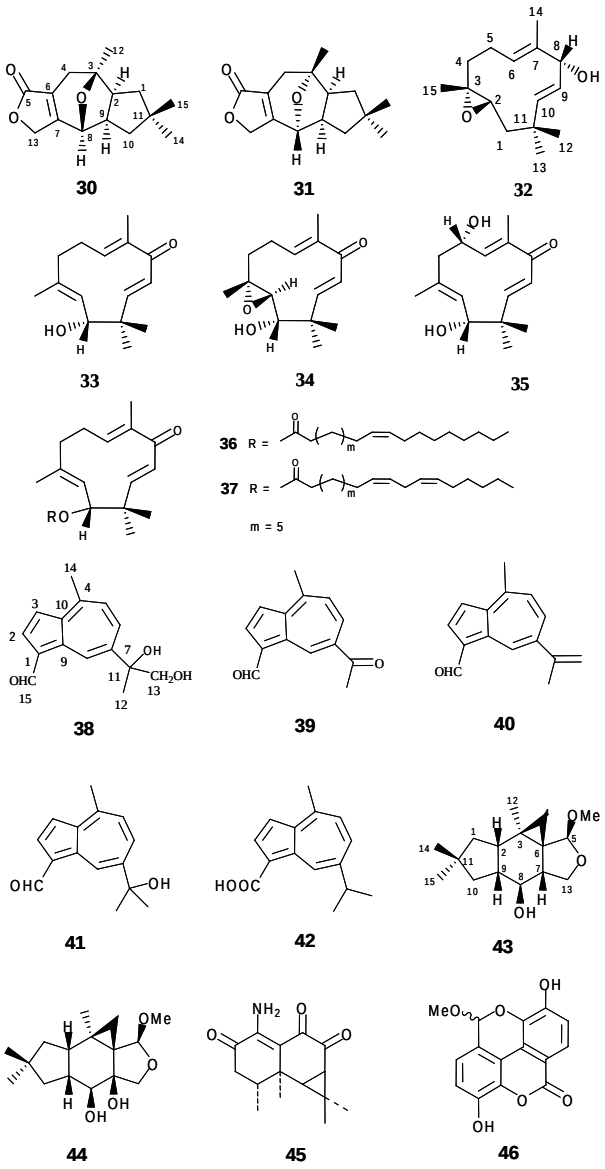


Figure 5. Described chemical compounds.

compounds have been reported to display antibacterial, antineoplastic, and antileukemia activity (*53-55*).

Pigments from *Pulveroboletus ravenelii* and *Xylaria euglossa*

A new butenolide-type fungal pigment, pulverolide (**47**), was isolated from the fresh fruiting bodies of *Pulveroboletus ravenelii* (*56*). *Xylaria euglossa* is a rot-wood-inhibiting ascomycete, mainly occurring on stumps and fallen branches of forested areas in the southwest of China. Many unique secondary metabolites have been found in the fungi of this genus. During the study of *Xylaria sp.*, various new metabolites were discovered, including cytochalasins, globoscin, lactones, maldoxin, sesquiterpenoids, xylaramide, xylarin, and xyloketals (*57*). Detailed chemical investigation of the fungus *Xylaria euglossa* has been performed and a new nitrogen-containing

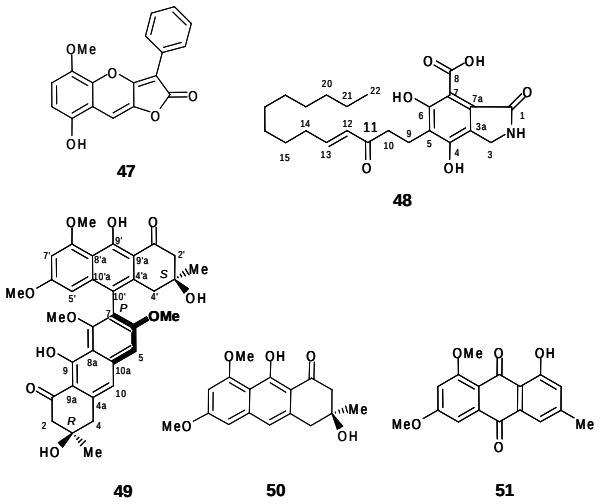


Figure 6. Described chemical compounds.

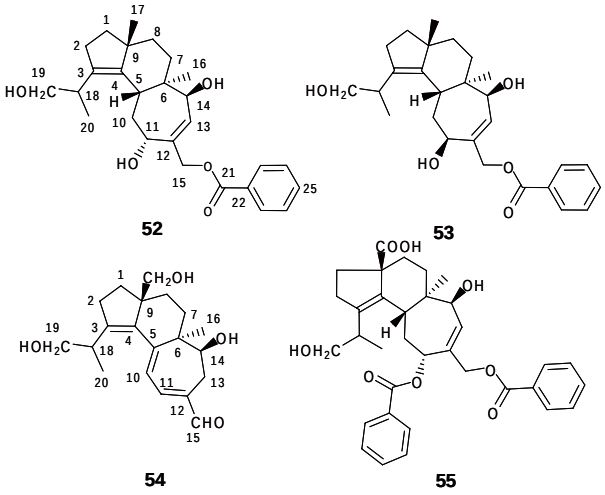


Figure 7. Described chemical compounds.

compound, xylactam (**48**), was isolated along with two known alkaloids, penochalasin B 2 and neoechinulin A, from extracts of the fruiting bodies (*57*).

A new pigment, 8,8'-*O*,*O*-dimethylphlegmacin A (**49**), was isolated from the fruiting bodies of ascomycete *Xylaria euglossa* along with two known fungi pigments, (**50**) and **(51)**. The structure of compound **49** was established as (3*R*,3'*S*,*P*)-2,2',3,3'-tetrahydro-3,3',9,9' -tetrahydroxy-6,6',8,8'-tetramethoxy-3,3'-dimethyl-[7,10'-bianthracene]-4,4' (1H,1'H)-dione by spectroscopic means. Its absolute configuration was deduced from CD and ^{1}H NMR spectra. It represents the first isolation of a phlegmacin-type pigment from an ascomycete (*58*).

Diterpenoids from *Sarcodon sp.* and *Hydnum sp.*

Novel cyathane-type diterpenoids, scabronines G and H and sarcodonin I **(52-54),** were isolated from the fruiting bodies of the basidiomycete *Sarcodon scabrosus* together with four known diterpenoids, allocyathin B_2, sarcodonin A, sarcodonin G, and scabronine F (*59*,*60*). *Sarcodon scabrosus* is a mushroom belonging to the family *Thelephoraceae* and has a bitter taste. Diterpenoids, including sarcodonins A-H, scabronines A-F, and scabronines L and M, have previously been isolated from this mushroom as bitter principles (*61-63*). All of these diterpenoids posses a cyathane skeleton consisting of angularly condensed five-, six- and seven-membered rings and display activity to stimulate nerve growth factor (NGF)-synthesis *in vitro*.

Eleven compounds have been isolated from the fruiting bodies of the basidiomycete *Hydnum repandum*. Their structures were established as sarcodonin A, scabronine B (**55**), 3β-hydroxy-5α,8α-epidioxyergosta-6,22-dien, (22*E*,24*R*)-ergosta-7,22-diene-3β,5α,6β-triol, (22*E*,24*R*)-ergosta-7,22-diene-3β-ol, benzoic acid, 4-hydroxylbenzaldehyde, 4-monopropanoylbenzenediol, ethyl-β-*D*-glucopyranoside, thioacetic anhydrid, and (2*S*,2'*R*,3*S*,4*R*)-2-(2-hydroxytricosanoylamino) hexadecane-1,3,4-triol by spectral methods. Among them, sarcodonin A and scabronine B were first reported from *Hydnum* genus, and the other compounds were isolated from thisfungus for the first time (*64*).

Miscellaneous

A novel *N*-containing compound, vibratilicin (**56**), was isolated from the fruiting bodies of the basidiomycete *Cortinarius vibratilis* (*65*). Compound **56** is a representative of a rare natural substance containing hydroxamic acid moieties and can be viewed as a derivative of neoengleromycin from the fungus *Engleromyces goetzii* (*66*).

Fruiting bodies of the basidiomycete *Thelephora aurantiotincta* contain a *p*-terphenyl, named aurantiotinin A (**57**), together with ganbajunin C and atromentin (*67*). Fruiting bodies of the basidiomycete *Cortinarius umidicola* contain a natural pyridine derivative (3-aldehyde-2-amino-6-methoxypyridine, (**59**), together with (*R*)-glycidyl octadecanoate (**58**) (*68*).

An unique fungal pigment, hypocrellin D (**60**), together with three known perylenequinone derivatives, hypocrellin A (**61**), B, C, was isolated from the fruiting bodies of *Shiraia bambusicola* (*69*). The ROESY experiment and CD of hypocrellin D required that the absolute configuration of the asymmetric carbons of the alicyclic ring of **60** be the same as those of hypocrellin A; *i.e.* 14*S* and 15*R*. *Shiraia bambusicola* (Hypocreaceae), an ascomycete parasitic on bamboo twigs, is recorded only in China and Japan. It has been commonly used as medicinal fungi under the name of "Zhu Huang" in China for treatment of rheumatism and pneumonia in traditional Chinese medicine (TCM). The new perylenequinone pigments hypocrellin A-C and shiraiachrome A-C were previously isolated from *S. bambusicola* as fungal metabolites that exhibit photodynamic activity on bacteria and fungi (*70*,*71*). Recently, the methanolic extract of the mycelium of the fungus *S. bambusicola* was found to show significant cytotoxicity in A-549 and HCT-8 solid tumor cells.

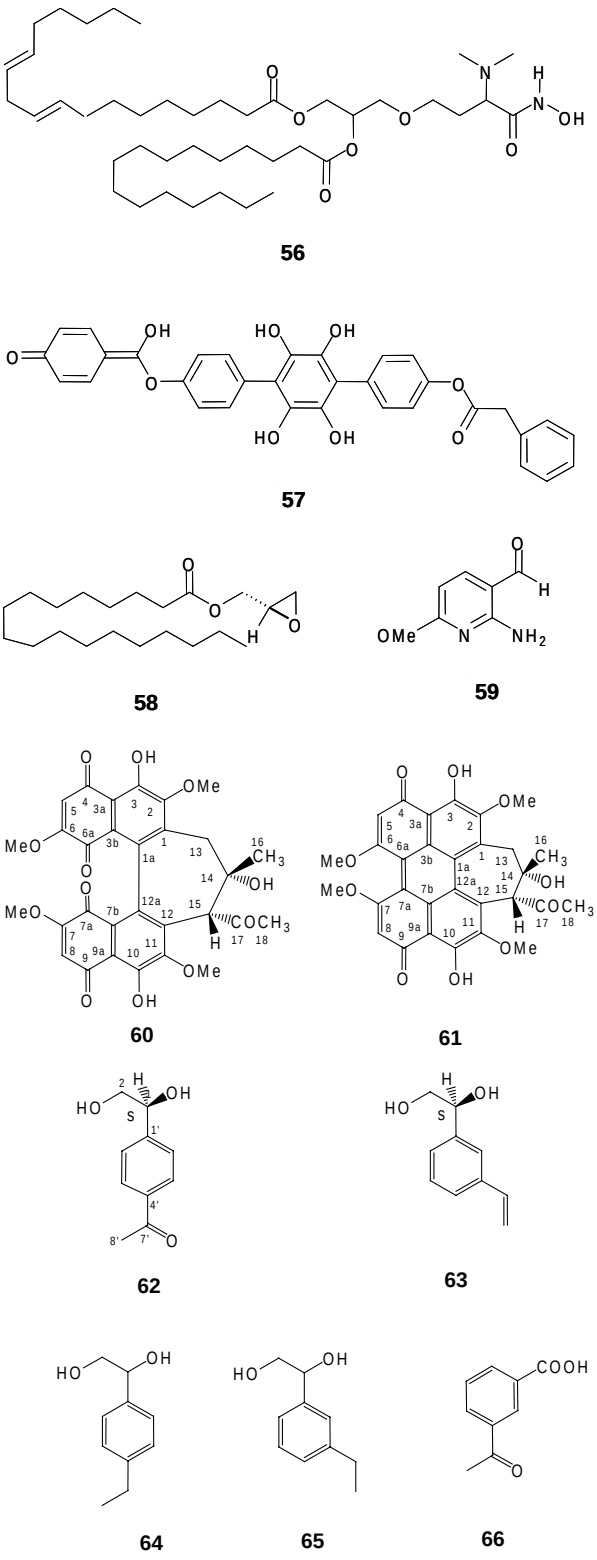


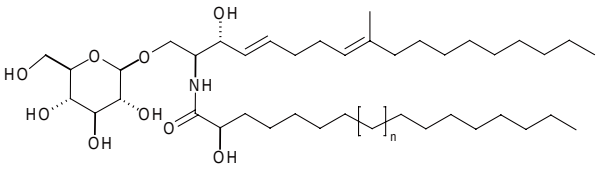
Figure 8. Described chemical compounds.

Subsequent bioassay-guided fractionation in HCT-8 *in vitro* led to the isolation and characterization of shiraiachromes A and B as two major cytotoxic principles (*72*). A series of new perylene derivatives related to shiraiachrome-A and -B as well as calphostin-C has been synthesized and evaluated for its cytotoxicity, antiviral activity, and inhibitory activity against protein kinase C (*72*).

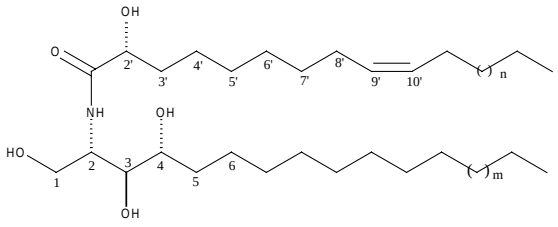
When grown in culture, the basidiomycete *Boletus edulis* produces two phenyl-ethanediols, 1-(3-ethenylphenyl)-1,2-ethanediol **62** and 1-(4-acetylphenyl)-1,2-ethanediol **63**, together with three known compounds, 1-(3-formylphenyl)-ethanone **64,** 1-(3-ethylphenyl)-1,2-ethanediol **65,** and 1-(4-ethylphenyl)-1,2-ethanediol **66** (*73*). Compound **62** has often been used as a type of rubber composition and was isolated for the first time as a new natural substance.

Five cerebrosides, including three new ones named cortenuamide A (**67**), cortenuamide B (**68**), and cortenuamide C (**69**), were isolated from the fruiting bodies of the Basidiomycetes *Cortinarius tenuipes*. The structures of those compounds were elucidated as (4*E*,8*E*)-*N*-*D*-2'-hydroxytetracosanoyl-1-*O*-β-*D*-glucopyranosyl-9-methyl-4,8-sphinga-dienine (**67**), (4*E*,8*E*)-*N*-*D*-2'-hydroxytricosanoyl-1-*O*-β-*D*-gluco-pyranosyl-9-methyl-4,8-sphingadienine (**68**), (4*E*,8*E*)-*N*-*D*-2'-hydroxyl-docosanoyl-1-*O*-β-*D*-glucopyranosyl-9-methyl-4,8-sphingadienine (**69**), (4*E*,8*E*)-*N*-*D*-2'-hydroxyoctasanoyl-1-*O*-β-*D*-glucopyranosyl-9-methyl-4,8-sphingadienine, and (4*E*,8*E*)-*N*-*D*-2'-hydroxypalmitoyl-1-*O*-β-*D*-gluco-pyranosyl-9-methyl-4,8-sphingadienine by spectral and chemical methods (*74*). A new ceramide, named hygrophamide (**70**), was isolated from the fruiting bodies of the Basidiomycetes *Hygrophorus eburnesus*. The structure of the compound was elucidated as (2*S*,3*R*,4*R*,2'*R*)-2-(2'-hydroxy-9'*Z*-ene-tetracosanoylamino)-octadecane-1,3,4-triol (**70**) by spectral and chemical methods (*75*).

Ceramide fractions were isolated from the fruiting bodies of *Tuber indicum* and separated into three kinds of molecular species, **71**, **72**, and **73,** by normal and reverse phase silica gel-column chromatography. According to NMR spectroscopy, FAB-MS, and chemical degradation experiments, the component sphingoid base for **71** and **72** was uniformly



67 n=9, **68** n=8, **69** n=7



70 n=11, m=4

Figure 9. Described chemical compounds.

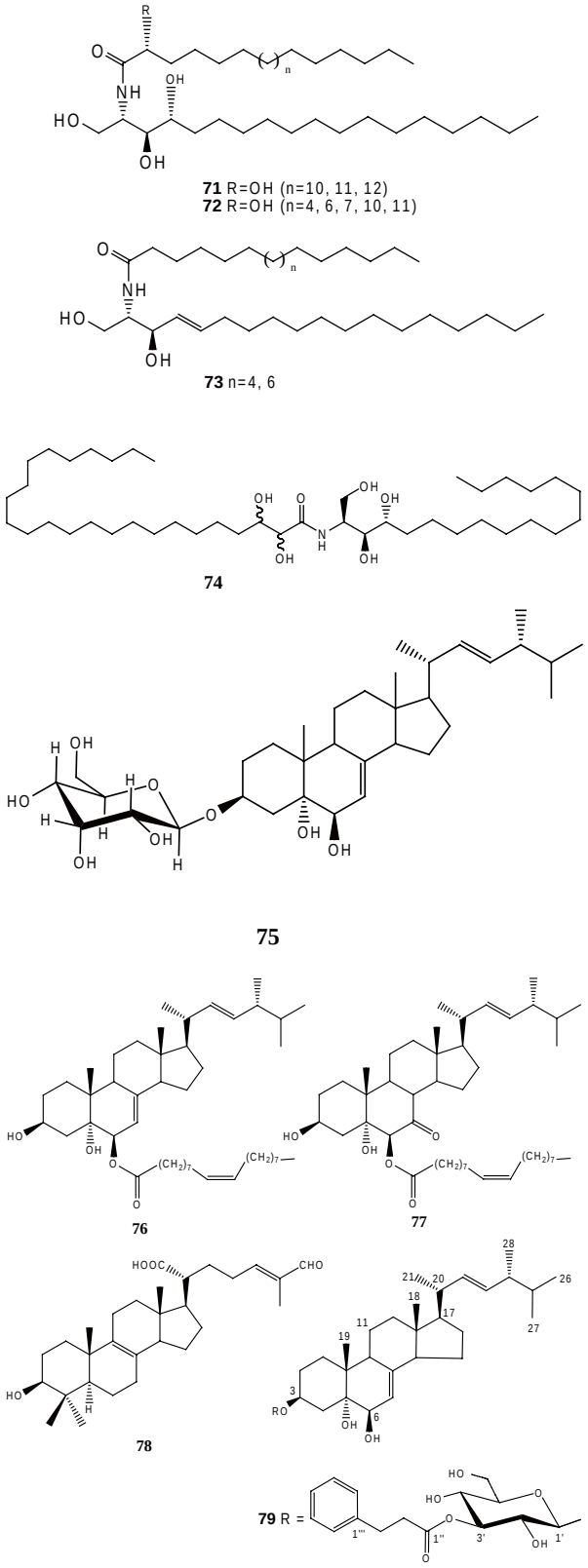


Figure 10. Described chemical compounds.

(2*S*,3*S*,4*R*)-2-amino-1,3,4-octadecantriol, while the sphingoid of **73** was *D-erythro*-sphingosine, and their structures have been determined unequivocally to be (2*S*,2'*R*,3*S*,4*R*)-2-(2'-*D*-hydroxyalkanoylamino) octadecane-1,3,4-triol, the fatty acid composition of which consists of 2-hydroxydocosanoic, 2-hydroxytetracosanoic, and 2-hydroxytricosanoic acids; (2*S*,3*S*,4*R*)-2-(alkanoyl-amino) octadecane-1,3,4-triol, the fatty acid composition of which is unusual and consists of docosanoic, hexadecanoic, tricosanoic, octadecanoic and nonadecanoic acids; and (2*S*,3*R*,4*E*)-2-(alkanoylamino)-4-octadecene-1,3-diol, the component fatty acids of which were hexadecanoic (predominant) and octadecanoic acids, respectively (*76*). A new phytosphingosine-type ceramide **74**, named paxillamide, was isolated from the fruiting bodies of the basidiomycete *Paxillus panuoides* (*77*).

A new steroidal glucoside with a polyhydroxy ergosterol nucleus, tuberoside (**75**), has been isolated from the fruiting bodies of ascomycete *Tuber indicum*. This is the first example of isolation of a polyhydroxylated ergosterol glucoside from higher fungi in nature (*78*). Two new oleate esters of polyhydroxylated ergostane-type nucleus, 3β,5α-dihydroxy-(22*E*,24*R*)-ergosta-7,22-dien-6β-oleate (**76**) and 3β,5α-dihydroxy-(22*E*,24*R*)-ergosta-22-en-7-one-6β-oleate (**77**), were isolated from the fruiting bodies of the basidiomycete *Tricholomopsis rutilans* along with three known sterols (*79*). A new cytotoxic lanostane triterpenoid (**78**) was isolated from the basidiomycete *Hebeloma versipelle* (*80*). **78** exhibited cytotoxic activity against the tumor cell lines HL60, A549, SGC-7900 and Bel-7402, with IC_{50} values of 11.2, 20.9, 22.6, and 25.0 μg/mL, respectively. A new ergostane-type glycoside, named tylopiloside (**79**), was isolated from the fruiting bodies of the basidiomycete *Tylopilus virens*. Its structure was elucidated as (22*E*,24*R*)-ergosta-7,22-dien-5α,6β-diol-3β-*O*-[3-(3-phenylpropanoyloxy)]-β-*D*-glucopyranoside (*81*).

The fungus *Bondarzewia berkeleyi* (Fr.) Bond. et Singer of the family Bondarzewiaceae (Basidiomycota) grows at the base or roots of *Abies* and other conifers of the family Fagaceae. There are no reports of its chemical constituents in the literature. Steglich and Anke reported a cytotoxic metabolite, montadial A, isolated from the polypore *B. Montana* (*82*). They noted that treatment of these mycelial roots with aqueous KOH causes an intense yellow color. Taxonomically, the genus *Bondarzewia* has been placed in the order Russulales, which is supported by the occurrence of stearoyl-velutinal, the chemotaxonomic marker compound for this order (*82*).

Summary

Among many diverse organisms, higher fungi are a major source of biologically active natural substances. They have often been found to contain biologically active compounds, and they provide a rich variety of active secondary metabolites. There are potentially many compounds still to be discovered in higher fungi since until now only a relatively small number of higher fungi have been chemically investigated, and many

of the remaining species are involved in interesting biological phenomena. These as yet unstudied species hold the promise of providing new natural substances. That these fungi are often involved in interesting biological processes indicates not only that the new metabolites involved will be chemically interesting but also that the new metabolites may be biologically interesting and significant. The large biodiversity of higher fungi provides a huge resource for extending the chemodiversity of natural substances and for finding new lead structures for medicinal chemistry.

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