Review

Biologically Active Compounds from Aphyllophorales (Polypore) Fungi

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Biologically Active Compounds from Aphyllophorales (Polypore) Fungi[⊥]

Jordan K. Zjawiony*

Department of Pharmacognosy and National Center for Natural Product Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, Mississippi 38677-1848

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This review describes biologically active natural products isolated from Aphyllophorales, many of which are known as polypores. Polypores are a large group of terrestrial fungi of the phylum Basdiomycota (basidiomycetes), and they along with certain Ascomycota are a major source of pharmacologically active substances. There are about 25 000 species of basidiomycetes, of which about 500 are members of the Aphyllophorales, a polyphyletic group that contains the polypores. Many of these fungi have circumboreal distributions in North America, Europe, and Asia and broad distributions on all inhabited continents and Africa; only a small number of the most common species with the most obvious fruiting bodies (basidiocarps) have been evaluated for biological activity. An estimated 75% of polypore fungi that have been tested show strong antimicrobial activity, and these may constitute a good source for developing new antibiotics. Numerous compounds from these fungi also display antiviral, cytotoxic, and/or antineoplastic activities. Additional important components of this vast arsenal of compounds are polysaccharides derived from the fungal cell walls. These compounds have attracted significant attention in recent years because of their immunomodulatory activities, resulting in antitumor effects. These high molecular weight compounds, often called biological response modifiers (BRM), or immunopotentiators, prevent carcinogenesis, show direct anticancer effects, and prevent tumor metastasis. Some of the protein-bound polysaccharides from polypores and other basidiomycetes have found their way to the market in Japan as anticancer drugs. Finally, numerous compounds with cardiovascular, phytotoxic, immunomodulatory, analgesic, antidiabetic, antioxidant, insecticidal, and nematocidal activities, isolated from polypores, are also presented. In fact many of the fungi mentioned in this paper have long been used in herbal medicine, including polypores such as *Ganoderma lucidum* (Reishi or Ling Zhi), *Laetiporus sulphureus* (Chicken-of-the-Woods), *Trametes versicolor* (Yun Zhi), *Grifola umbellata* (Zhu Lin), *Inonotus obliquus* (Chaga), and *Wolfiporia cocos* (Hoelen).

Polypores and corticioid fungi are members of the Aphyllophorales, a group of morphologically complex, terrestrial basidiomycetes. A phylogenetic classification for these fungi is under development, but the groups are probably not monophyletic.[1] As a result of updates in nomenclature and systematics information over the last thirty years, escalating even more from DNA sequence analyses, there are numerous changes in the names of these fungi to reflect the phylogenetic situation. This causes a problem in evaluating the older literature and in comparing studies of the same fungus that has been known by one or more different names. The fungal names used in this paper generally follow those of Gilbertson and Ryvarden or other recent monographic materials.[2]

Many of these fungi are saprobic wood decayers, and as such, these fungi are most often found on logs, stumps, or other dead wood. Many polypores are typically tough and woody and produce basidiospores on walls of tubes of the undersurface hymenophore (the tissue that bears the fertile layer). Common names for the fruiting bodies or basidiocarps of polypores include conks, shelf, and bracket fungi. Some basidiocarps are perennial, and others often do not rot readily; they may remain undecayed to the point that algae or mosses begin to grow on their surfaces. As mentioned above, the majority of polypores absorb nutrients from the dead woody plant parts and as such are saprobic. These may include polypores that grow on living trees and cause decay of the nonfunctional heartwood. A few of these fungi invade conducting plant tissues and a parasite, and as such are parasites; a few others are mycorrhizal and exchange nutrients and carbon with the roots of plants.

Several excellent review articles have been published on the subject of biologically active secondary metabolites from basidiomycetes.[3−13] This review focuses exclusively on polypores, which are considered by many authors as a major source of pharmacologically active natural products. The secondary metabolites of polypores exhibit a wide range of biological activities such as antimicrobial, antiviral, antifungal, anticancer, cardiovascular, antiinflammatory, antioxidant, immunostimulating, nematocidal, and other activities.[4]

Antimicrobial Metabolites (Antibacterial and Antifungal)

According to a recent biological evaluation of over 200 mushroom species, more than 75% of screened polypores showed strong antimicrobial activity.[14] These activities are associated not only with small molecule secondary metabolites but also with high molecular weight cell wall polysaccharides. The major philosophy of the search for antimicrobial compounds from basidiomycetes is that humans (and animals) share common microbial pathogens with fungi, such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas areuginosa*, so that we can benefit from defensive strategies used by fungi against microorganisms. No wonder so many antibiotics have been derived from fungi.

Basidiomycetes, especially polypores, have a long history of medicinal use. For instance, the tinder polypore, *Fomes fomentarius*, was used in the 18th and 19th centuries in hemostatic dressings and bandages.[15] The same polypore together with the birch polypore (*Piptoporus betulinus*), which has had a variety of medicinal and other uses, was found with the body of the famous 5300 year old "Ice Man"

[⊥] Dedicated to the late Dr. Monroe E. Wall and to Dr. Mansukh C. Wani of Research Triangle Institute for their pioneering work on bioactive natural products.

* Corresponding author. Tel: (662) 915-7290. Fax: (662) 915-6975. E-mail: jordan@olemiss.edu.

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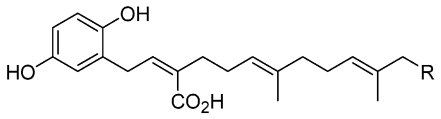
in a glacier of Italian Alps in 1991. It is not known, however, how he used either of these fungi.[4,16]

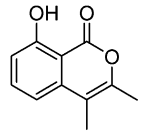
There are numerous publications describing antimicrobial properties of secondary metabolites isolated from various polypores.[17−39] Screening of crude extracts of Ganoderma basidiocarps, such as *Ganoderma lucidum* (Reishi mushrooms), *Ganoderma pfeifferi*, and *Ganoderma resinaceum*, revealed selective activity against *Bacillus subtilis*.



1 R=OH
2 R=H

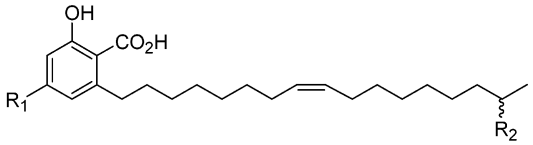
For example, two secondary metabolites, ganomycin A (**1**) and ganomycin B (**2**), isolated from *G. pfeifferi* showed moderate growth inhibition of several bacterial strains, particularly Gram-positive strains such as *B. subtilis*, *S. aureus*, and *Micrococcus flavus*.[17]

The antifungal isocoumarin oospolactone (**3**) was identified as a secondary metabolite of *Gleophyllum sepiarium*.[18] This compound was most active against strains of the asexual ascomycete *Alternaria*, showing MIC values of 12.5−25 μg/mL.



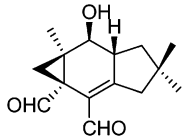
oospolactone (**3**)

Another group of antimicrobial metabolites of polyketide origin are merulinic acids A, B, and C (**4**−**6**) isolated from the fruiting bodies of the polypores *Merulius tremellosus* and *Phlebia radiata*.[19]



merulinic acid A (**4**) R_1=OH, R_2=H
merulinic acid B (**5**) R_1=H, R_2=OH
merulinic acid C (**6**) R_1=H, R_2=H

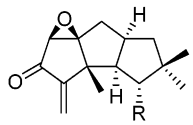
The merulinic acids showed antimicrobial activity with MIC values of 0.4−10 μg/mL, particularly against *Arthrobacter citreus*, *B. subtilis*, *Corynobacterium insidiosum*, *Micrococcus roseus*, and *Sarcina lutea*. *Mycobacterium phlei* was selectively inhibited by **5** and **6**, while **4** was inactive. Similarly, *S. aureus* and *Proteus vulgaris* were inhibited only by merulinic acid B (**5**). It is interesting that mycelial cultures of *Merulius tremellosus* do not produce merulinic acids, but instead a highly antifungal sesquiterpenoid, merulidial (**7**).[19] This occurrence serves as an example of the influence of different life cycle stages on the production of fungal secondary metabolites.



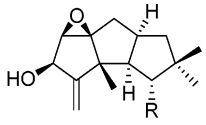
merulidial (**7**)

Biological activities of merulidial (**7**) are associated with the presence of two aldehyde functions in the molecule. The triol obtained by the reduction of merulidial is inactive.[20]

Antimicrobial sesquiterpenes, desoxyhypnophilin (**8**), hypnophilin (**9**), 6,7-epoxy-4(15)-hirsutene-5-ol (**10**), and 6,7-epoxy-4(15)-hirsutene-1,5-diol (**11**), with a hirsutane skeleton were isolated from the wood-decaying polypore *Lentinus crinitus*.[21]

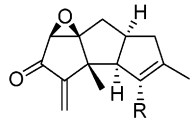


8 R=H
9 R=OH



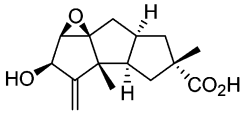
10 R=H
11 R=OH

Desoxyhypnophilin (**8**) and hypnophilin (**9**) are active against the Gram-positive bacterium *Bacillus cereus*, and spores of *Aspergillus niger*, *Aspergillus flavus*, and *Mucor rouxii* with MIC values of 1−5 μg/mL. The α,β-unsaturated exomethylene ketone system, present in these compounds, is responsible for antimicrobial activity. Reduction of the carbonyl group in **8** leads to a significant drop in antimicrobial activity of **10**.[21] Hypnophilin (**9**) together with pleurotellol (**12**) and pleurotellic acid (**13**) also were isolated from fermentation of the gilled mushroom *Pleurotellus hypnophilus* (Agaricaceae).[22] Hypnophilin (**9**) and pleurotellol (**12**) act in addition as the plant growth inhibitors.[12]



12 R=CH_2OH
13 R=CO_2H

Two other hirsutane derivatives, hirsutic acid (**14**) and complicatic acid (**15**), were isolated from the wood-decaying polypore *Stereum complicatum*.[23] Similar to other hirsutanes with an α,β-unsaturated exomethylene ketone system, complicatic acid (**15**) showed moderate antimicrobial activity against *S. aureus*.[24]



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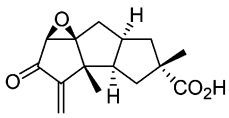
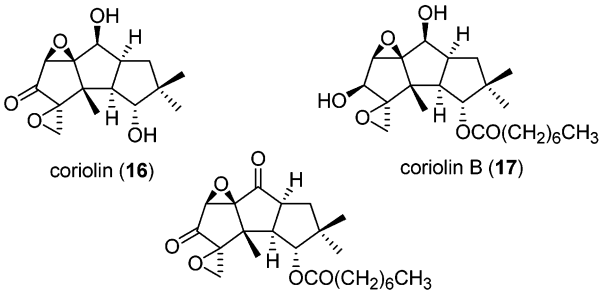


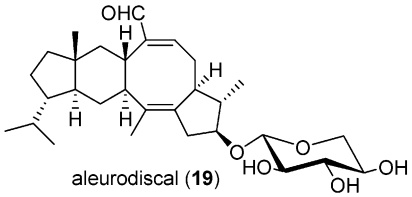
15

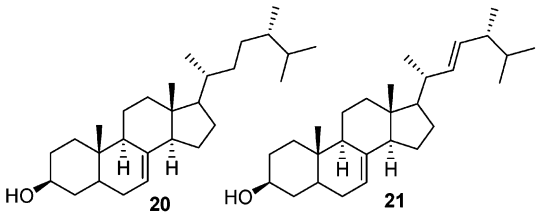
Another antimicrobial hirsutane sesquiterpene, coriolin (**16**), was isolated from the white-rot basidiomycete *Coriolus consors*.[25] Coriolin is active against *S. aureus*, *M. flavus*, *B. subtilis*, and *B. anthracis* with the same MIC values of 12.5 μg/mL. A closely related compound isolated from the same fungus, coriolin B (**17**), did not show any antimicrobial activity, but its synthetic derivative, diketocoriolin B (**18**), obtained by oxidation of coriolin B (**17**) showed antimicrobial activity similar to that of coriolin (**16**).[26]

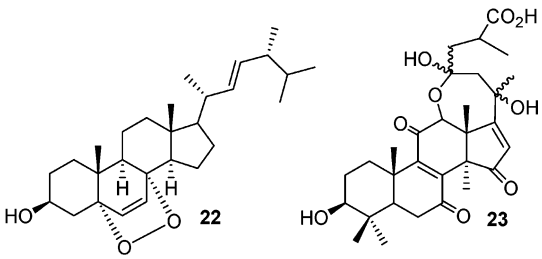
A potent antifungal sesterterpene β-D-xyloside, aleurodiscal (**19**), was isolated from another wood-rotting polypore, *Aleurodiscus mirabilis*.[27] Aleurodiscal (**19**) is selectively active against zygomycetes, especially against *Mucor miehei*.

Ganoderma applanatum, known commonly as the artist's conk, provides the sterols 5α-ergost-7-en-3β-ol (**20**), 5α-ergost-7,22-dien-3β-ol (**21**), 5,8-epidioxy-5α,8α-ergost-6,22-dien-3β-ol (**22**), and a novel lanostanoid (**23**) that are active predominantly against Gram-positive bacteria.[28]

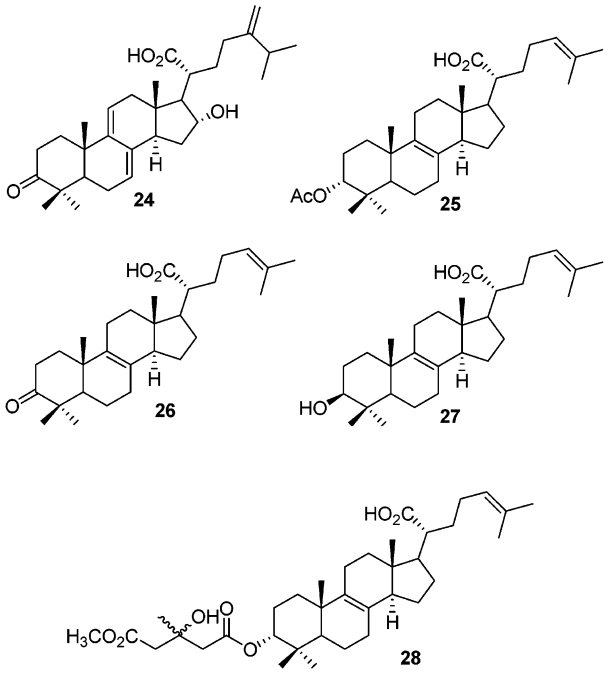




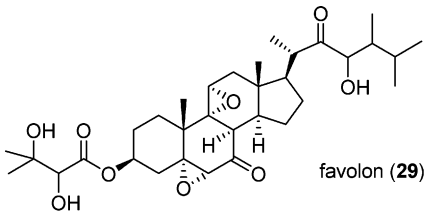




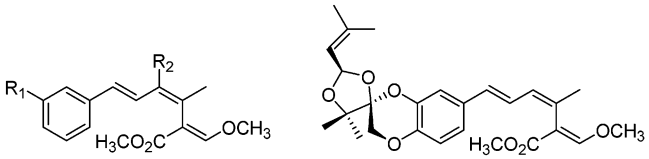
Several lanostanoid derivatives, polyporenic acid C (**24**), 3α-acetyloxylanosta-8,24-dien-21-oic acid (**25**), pinicolic acid A (**26**), trametenolic acid B (**27**), and fomitopsic acid (**28**), isolated from the polypore *Fomitopsis pinicola* have shown antimicrobial activity against *B. subtilis* in a TLC-bioautography assay in quantities from 0.01 to 1 μg, but did not inhibit *B. subtilis* in a classic agar dilution assay at concentrations up to 50 μg/mL.[29]

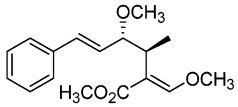


A culture of an Ethiopian *Favolaschia* species produced favolon (**29**), an unusual ergosterone with a B/C-*cis* ring junction. This compound displayed strong antifungal activity against numerous fungal pathogens, with the strongest inhibitions in the agar diffusion assay for *Mucor miehei*, *Paecilomyces varioti*, and *Penicillium islandicum*.[30]



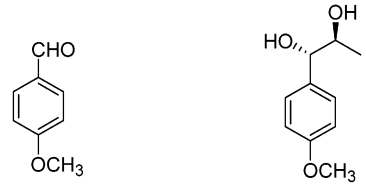
Basidiocarps of the genera of *Agaricus*, *Favolaschia*, and *Filoboletus* produced strobilurins A (**30**), E (**31**), and F1 (**32**), 9-methoxystrobilurin A (**33**), and oudemansin A (**34**), aromatic antifungal compounds derived by way of the shikimic acid pathway. These compounds exhibited potent antifungal activity (MIC values of 0.1−1 μg/mL), but they had no discernible antibacterial properties.





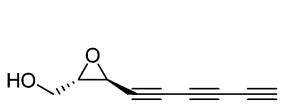
The strobilurins and oudemansins also inhibited the growth of a number of fungal plant pathogens at very low concentrations.[12] They have a unique mode of action, selectively inhibiting the respiration of fungi by interfering with the ubiquinol oxidation center of the mitochondrial bc1 complex.[12] These compounds have served as natural product prototypes for the design and development of synthetic analogues. Their lack of mammalian toxicity has made them good lead compounds for the development of commercial agricultural fungicides.[31]

Very simple aromatic compounds, such as anisaldehyde (**35**) and (4-methoxyphenyl)-1,2-propanediol (**36**), showing weak antifungal activity, were isolated from *Pleurotus pulmonarius* and *Bjerkandera adusta*.[32]

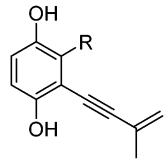


One of the first antimicrobial compounds ever isolated from a polypore was biformin (**37**), a polyacetylenic carbinol. Biformin (**37**) is produced by *Trichaptum biforme* (as

Polyporus biformis) and is active against a wide variety of bacteria and fungi.[33]



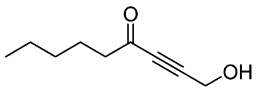
biformin (**37**)



frustulosin (**38**) R=CHO
frustulosinol (**39**) R=CH_2OH

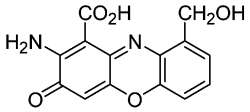
The aromatic acetylene derivatives frustulosin (**38**) and frustulosinol (**39**) isolated from the liquid cultures of *Stereum frustulosum* were active against several bacteria such as *S. aureus*, *Bacillus mycoides*, and *B. subtilis* and also moderately active against *Vibrio cholera* and *V. cholera* phage.[34,35]

Another example of an acetylenic compound exhibiting antifungal activity is the 1-hydroxy-2-nonyn-3-one (**40**) isolated from the fermentation of the polypore *Ischnoderma benzoinum*.[36]



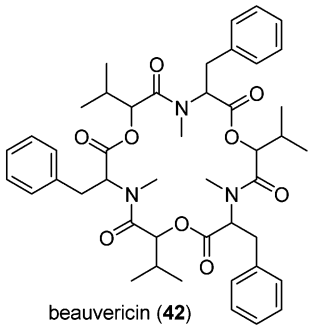
1-hydroxy-2-nonyn-3-one (**40**)

The red polypore *Pycnoporus sanguineus* produces cinnabarin (**41**), a phenoxazinone with antimicrobial activity. *B. cereus* and *Leuconostoc plantarum* were the most sensitive to cinnabarin, each being inhibited with an MIC value of 62.5 μg/mL.[37,38]



cinnabarin (**41**)

A large group of antimicrobial secondary metabolites isolated from polypores also includes a cyclodepsipeptide, beauvericin (**42**). Beauvericin (**42**) is produced by the bright yellow polypore *Laetiporous sulphureus* (as *Polyporus sulphureus*), commonly known as "Chicken-of-the-Woods".[39] Beauvericin also is considered as a mycotoxin produced by hypocrealean ascomycetes in grain.[40]



beauvericin (**42**)

A number of polypores exhibit immunoprotective activity and provide protection against a variety of infectious diseases. This kind of activity is associated mainly with the presence of polysaccharides. PSK, a protein-bound polysaccharide isolated from *Trametes versicolor* (as *Coriolus versicolor*), was found to increase resistance in mice against infection with *Listeria monocytogenes* by enhancing oxygen metabolism of the host macrophages.[41]

Antiviral Metabolites

In their excellent review article on mushroom antivirals, Brandt and Piraino divided the antiviral compounds from fungi into two major classes: (i) those that act indirectly as biological response modifiers (usually from polysaccharide fractions); and (ii) those that act directly as viral inhibitors.[8] In polypores, however, several polysaccharide fractions display direct inhibitory effects on various viruses. The polysaccharide preparation, PSK from *T. versicolor* (as *C. versicolor*), commonly known as turkey tail, was found to have an antiviral effect on human immunodeficiency virus (HIV) in vitro.[42,43] One of the mechanisms of this effect was due to inhibition of the binding of HIV with lymphocytes. PSK inhibited reverse transcriptase of avian myeloblastosis virus in vitro.[44] PSK isolated from *T. versicolor* (as *Polyporus versicolor*) also has been shown to provide protection against exogenous and endogenous infections by the murine cytomegalovirus (MCMV).[45]

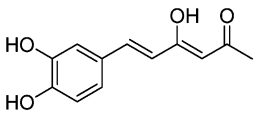
In contrast with PSK, another protein-bound polysaccharide, PSP, isolated from *T. versicolor* (as *C. versicolor*), is not a "true" antiviral and acts indirectly by immunostimulation.[8] PSP was reported to inhibit the binding of HIV-1 gp120 to immobilized CD4 receptor with an IC_{50} value of 150 μg/mL and recombinant HIV-1 reverse transcriptase with an IC_{50} of 6.25 μg/mL.[46] Both the polysaccharides PSK and PSP are heteroglucans with α-(1→4)- and β-(1→3)glucosidic linkages, with a protein or polypeptide component. The presence of fucose in PSK and rhamnose and arabinose in PSP distinguishes the two protein-bound polysaccharides, which are otherwise chemically similar.[47]

Water-soluble preparations from carpophores of *Ganoderma applanatum* (as *Elfvingia applanata*) exhibited potent antiviral activity against vesicular stomatitis virus Indiana serotype VSV (IND).[48]

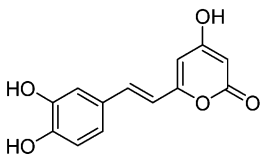
Aqueous extracts from four polypores, *Fomitella supina*, *Phellinus rhabarbarinus*, *Trichaptum perrottotti*, and *Trametes cubensis*, showed strong anti-HIV-1 activity without toxicity toward lymphocytic cells. It was demonstrated that the active compounds of these extracts act by a mechanism of direct virion inactivation and inhibition of syncytium formation in an in vitro culture system.[49]

Water-soluble lignins isolated from the sclerotia of the polypore *Inonotus obliquus*, commonly known as "Chaga", inhibited HIV protease with an IC_{50} value of 2.5 μg/mL.[50]

Recently, two phenolic compounds, hispolon (**43**) and hispidin (**44**), isolated from the basidiocarps of *Inonotus hispidus* showed considerable antiviral activity against influenza viruses type A and B.[51]



hispolon (**43**)

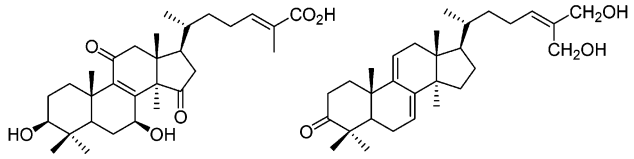


hispidin (**44**)

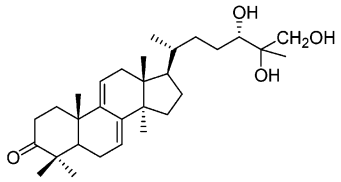
The filtrate from the culture of polypore *Fomes fomentarius*, "tinder conk", is highly active against the mechanical transmission of tobacco mosaic virus (TMV) with an IC_{50} value of 10 μg/mL, and it has similar effects against the TMV infection on bell pepper and tomato plants.[52]

The fruiting bodies of *Ganoderma lucidum* are the source of antiviral triterpenoids. Ganoderic acid β (**45**) isolated

from the spores of *G. lucidum* showed significant anti-HIV-1 protease activity, with an IC_{50} value of 20 μM.[53] The same species also produced ganoderiol F (**46**) and ganodermanontriol (**47**), which have anti-HIV-1 activity.[54]

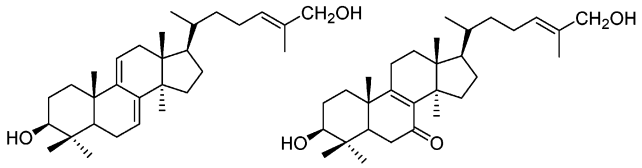


ganoderic acid β (**45**) ganoderiol F (**46**)

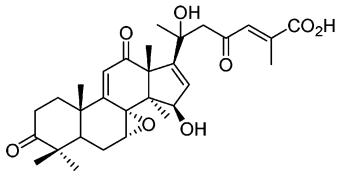


ganodermanontriol (**47**)

Recently, antiviral triterpenes also were isolated from the European polypore *Ganoderma pfeiferri*. Ganodermadiol (**48**), lucidadiol (**49**), and applanoxidic acid (**50**) showed antiviral activity against influenza virus type A and HSV-1.[55]



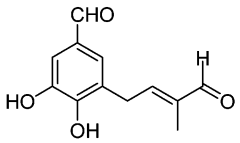
ganodermadiol (**48**) lucidadiol (**49**)



applanoxidic acid (**50**)

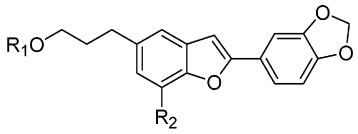
Cytotoxic, Antineoplastic, and Immunomodulatory Substances

The cytotoxic, antineoplastic, and immunomodulatory activities of polypore extracts are mostly associated with the presence of polysaccharides, although numerous smaller molecular weight cytotoxic polypore metabolites also are known.[56,57] A rare example of a cytotoxic monoterpene is montadial A (**51**), isolated from the polypore *Bondarzewia montana*.[58] Montadial A is cytotoxic (IC_{50}) against lymphocytic leukemia L1210 cells in mice at a concentration of 10 μg/mL as well as against promyelocytic human leukemia HL60 cells at 5 μg/mL.



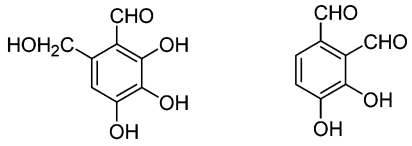
montadial A (**51**)

Extraction of *Laetiporus sulphureus* var. *miniatus* provided several secondary metabolites, among which compounds such as egonol (**52**), demethoxyegonol (**53**), and egonol glucoside (**54**) showed low cytotoxicity against Kato III cells with IC_{50} values of 28.8, 27.5, and 24.9 μg/mL, respectively.[59]



egonol (**52**) R_1=H, R_2=OMe
demethoxyegonol (**53**) R_1=H, R_2=H
egonol glucoside (**54**) R_1=Glc, R_2=OMe

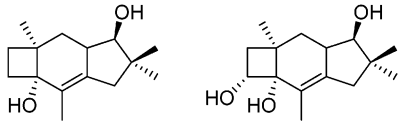
Two highly oxygenated phenols, fomecin A (**55**) and B (**56**), were isolated from the polypore *Pyrofomes demidoffii* (as *Fomes juniperinus*).[60] Fomecin B is cytotoxic against HeLa, MDCK, and FL cells with IC_{50} values of 20, 14, and 17 μg/mL, respectively.[61]



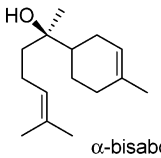
fomecin A (**55**) fomecin B (**56**)

The semisynthetic analogue of coriolin B (**17**) mentioned above, the antimicrobial diketocoriolin B (**18**), also exhibited antitumor activity.[62,63] Also discussed earlier, the antimicrobial hirsutane sesquiterpenes, hypnophillin (**9**), pleurotellol (**12**), and pleurotellic acid (**13**), isolated from *Pleurotellus hypnophilus* have shown a strong cytotoxic activity.[22] Two other hirsutane compounds, desoxyhypnophilin (**8**) and 1-desoxyhypnohilol (**11**), obtained by fermentation of *Lentinus crinitus*, are also cytotoxic against L929 mouse fibroblast cells with IC_{50} values of 2.4 and 0.9 μg/mL, respectively.[21]

The effective antifungal metabolites from *Merulius tremellosus*, merulidial (**7**) and its co-isolates tremediol (**57**), tremetriol (**58**), and α-bisabolol (**59**), were shown to be cytotoxic. Merulidial inhibits DNA synthesis in ECA cells at a concentration of 9 μg/mL and is also mutagenic.[20] Three other compounds (**57**−**59**) induce apoptosis in human promyelocytic leukemia cells HL-60 and interfere with signal transduction in COS-7 cells.[12]

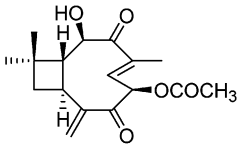


tremediol (**57**) tremediol (**58**)

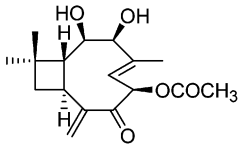


α-bisabolol (**59**)

A basidiocarp reported as a species of *Panus* contained two caryophyllane sesquiterpenes, naematolon (**60**) and naematolin (**61**).[64] The cytotoxicity of these compounds is probably associated with the presence of an α,β-unsaturated keto system in their structures. Naematolon (**60**), possessing two such systems, is about 5 times more cytotoxic than naematolin. Naematolon inhibits the incorporation of thymidine into the DNA of ECA cells with an IC_{50} value of 2 μg/mL. It did not, however, show any significant antitumor activity in vivo with P-388 lymphocytic leukemia, Lewis lung carcinoma, or B-16 melanocarcinoma. The LD_{50} in mice was determined as high as 225 mg/kg of body weight.[12]

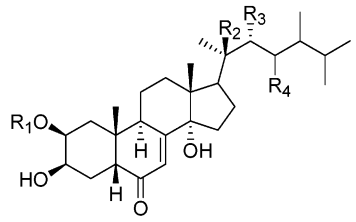


naematolon (**60**)

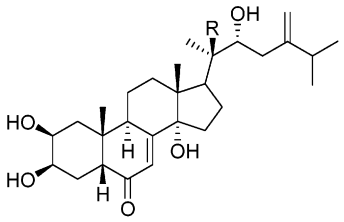


naematolin (**61**)

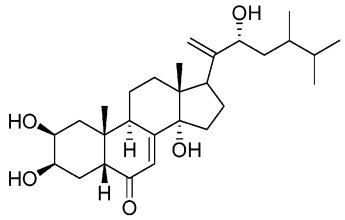
The crude drug "Chorei", prepared from the dried fruit body of *Polyporus umbellatus*, is known in Japan and the People's Republic of China as a remedy for kidney and other diseases. Seven new ecdysterone analogues, polyporusterones A−G (**62**−**68**), were isolated from the extract of this polypore. All of these showed cytotoxic activity against leukemia L-1210 cells with IC_{50} values of 10−64 μg/mL.[65]



polyporusterone A (**62**) R_1=R_4=H, R_2=R_3=OH
polyporusterone C (**64**) R_1=H, R_2=OH, R_3=R_4=O
polyporusterone E (**66**) R_1=R_2=H, R_3=R_4=O
polyporusterone F (**67**) R_1=R_2=R_4=H, R_3=OH



polyporusterone B (**63**), R=OH
polyporusterone G (**68**), R=H



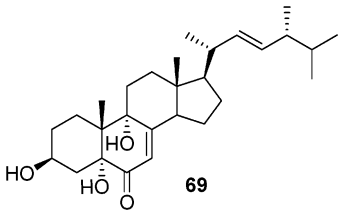
polyporusterone D (**65**)

The crude extract of the European wood-rotting fungus *Trametes versicolor* (as *Polyporus versicolor*) contains cytotoxic, polyoxygenated ergosterol derivatives. The active compounds 3β,5α,9α-trihydroxyergosta-7,22-dien-6-one (**69**) and 3β,5α,9α-trihydroxy-6β-methoxyergosta-7,22-diene (**70**) were isolated by bioassay-guided fractionation using rat hepatoma cells.[66]

The polypore *Antrodia cinnamomea*, a parasite of the heartwood of the Taiwanese evergreen tree *Cinnamomum micranthum*, has been utilized in Chinese medicine for the treatment of various disorders including liver cancer. Bioassay-guided fractionation of this polypore provided three new steroids, zhankuic acids A−C (**71**−**73**).

Biological study revealed that zhankuic acid A (**71**) exhibits cytotoxic activity against P-388 murine leukemia cells with an IC_{50} value of 1.8 μg/mL.[67]

Numerous cytotoxic triterpenoids have been isolated from various species of the Polyporaceae. An excellent review of their structures was published several years ago by Mizuno and his colleagues.[57] Just two polypores, *Ganoderma lucidum* and *G. applanatum*, provided 113 lanostane derivatives, and their isolation and biological activities were the subject of 35 publications. Moreover, 47 triterpenoids were isolated from yet other polypores including species reported in the genera *Trametes*, *Fomes*, *Polyporus*, *Coriolus*, *Laetiporus*, *Fomitopsis*, *Piptoporus*, *Poria*, and *Cryptoporus*, and accounted for another 35 publications. This review will not describe those compounds, and the reader is referred to Mizuno's paper for detailed information.[57]



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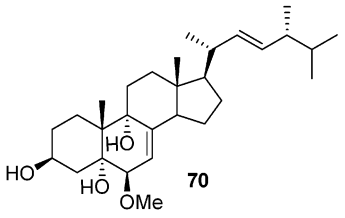

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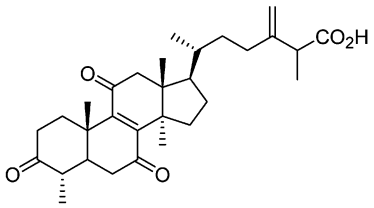
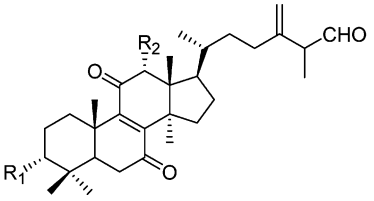


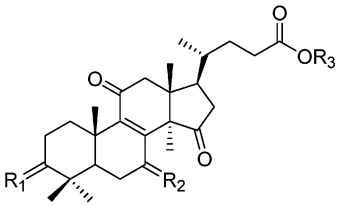
zhankuic acid A (**71**)



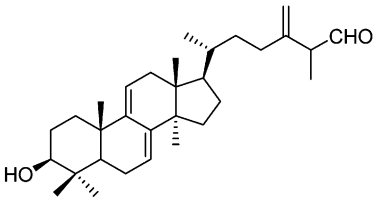
zhankuic acid B (**72**) R_1=OH, R_2=H
zhankuic acid C (**73**) R_1=R_2=OH

Ganoderma lucidum is well known in Korea, Japan, the People's Republic of China, and other countries in eastern Asia, where it is used as a folk remedy for the treatment of such disparate conditions as cancer, hepatitis, chronic bronchitis, asthma, hemorrhoids, and fatigue symptoms.[68] After providing over 130 pharmacologically active triterpenoids, there are yet additional new triterpenes isolated from this polypore and published in the recent literature.[69,70] Two more new triterpenoids, lucidenic acid N (**74**) and methyl lucidenate F (**75**), were isolated from the dried fruiting bodies of *G. lucidum*. Lucidenic acid N (**74**) showed significant cytotoxic effects on the Hep G2, Hep G2,2,15, and P388 cell lines with IC_{50} values of 2.06×10^{-4}, 1.66×10^{-3}, and 1.2×10^{-2} μM, respectively.[69]

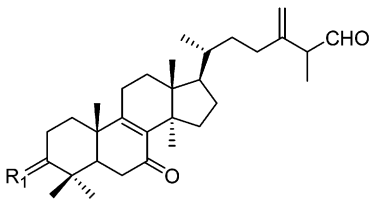
Lucialdehydes A−C (**76**−**78**), three new lanostane-type triterpene aldehydes, also were isolated from *G. lucidum*. The most active of these compounds, lucialdehyde C (**78**), was found to be cytotoxic against murine sarcoma Meth A, sarcoma S-180, human breast cancer T-47D, and Lewis lung carcinoma LLC cells with ED_{50} values of 3.8, 7.1, 4.7, and 10.7 μg/mL, respectively.[70]



lucidenic acid N (**74**) R_1=αH,OH, R_2=αH,OH, R_3=H
methyl lucidenate F (**75**) R_1=R_2=O, R_3=CH_3

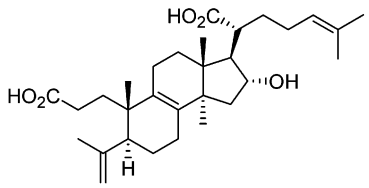


lucialdehyde A (**76**)

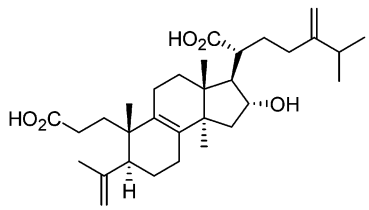


lucialdehyde B (**77**) R_1=O
lucialdehyde C (**78**) R_1=αH,OH

Recently, two new 3,4-secolanostane-type triterpenes were isolated from the sclerotium of *Poria cocos*.[71] These two new compounds, poricoic acid G (**79**) and poricoic acid H (**80**), showed potent inhibitory effects on Epstein−Barr virus early antigen (EBV-EA) activation induced by the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Poricoic acid G (**79**) was found to be significantly cytotoxic to leukemia HL-60 cells with a GI_{50} (concentration that yields 50% growth of cancer cells) value of 39.3 nM, with only moderate cytotoxicity to the other cells.



poricoic acid G (**79**)

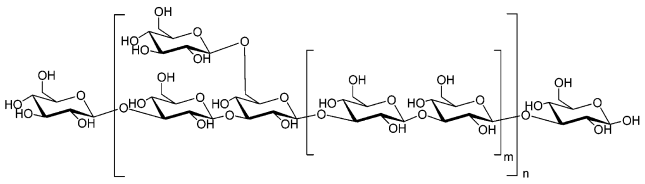


poricoic acid H (**80**)

The use of hot water extracts of medicinally important basidiomycetes as a remedy against cancer is known in the folk medicine of many countries. This kind of therapy was used for centuries in Korea, Japan, the People's Republic of China, Russia, and other eastern countries. Most of the pharmacologically active, anticancer basidiomycetes belong mainly to the Polyporaceae. The water extracts of those basidiocarps contain predominantly polysaccharides, which are the principal components of the fungal cell walls. These polysaccharides have attracted significant attention in recent years due mainly to their immunomodulatory activity, which results in their antitumor effects. These high molecular weight compounds often are called biological response modifiers (BRM), or immunopotentiators, which are able to prevent carcinogenesis and carcinostasis. Several excellent review articles about the isolation, biological activity, and development of antitumor-active polysaccharides were published in the late 1990s.[9,10,56,57]

The first written reports (*Compendium of Materia Medica*) associated with the medicinal value of polypore mushrooms date back to Eastern Han Dynasty (25−220 AD) in China.[72] Modern research with polypore polysaccharides can be said to have started in 1969 in Japan with the work of Ikegawa, who reported a marked host-mediated antitumor activity of hot water extracts of numerous edible polypores with Sarcoma 180 grafted on Swiss albino mice.[73] Since that time, numerous publications have appeared on the isolation and characterization of anticancer polysaccharides. The majority of these compounds can be classified as β-D-glucans, i.e., polysaccharides yielding only D-glucose after acid hydrolysis.[57] In addition, a number of other polymeric compounds such as heteropolysaccharides, glycoproteins and glycopeptides, chitin derivatives, lectins, RNA, and indigestible polysaccharides (dietary fibers) were isolated from polypores.

The vast majority of antitumor β-D-glucans isolated from polypores are β-(1→3)-D-glucopyranans with 500 000−2 000 000 mean molecular weight and characteristic β-(1→6)-D-glucosyl branches (**81**). The level of their activity is closely related to their molecular weight, branching, and solubility in water. Among these preparations, higher antitumor activity is correlated with the higher molecular weight, lower level of branching, and greater water solubility of β-glucans.[74]



β-D-glucan [(1-6)-D-glucosyl branched β-(1-3)-D-glucopyran] (**81**)

Relatively large quantities of β-glucans can be obtained from basidiocarps by extraction with dilute alkali, but in this case the product is insoluble in water.[75] Attempts have been made to increase β-glucan solubility in water by chemical modifications such as hydroxymethylation, carboxymethylation, periodic acid oxidation followed by sodium borohydride reduction, lowering (1→6) branching by mild Smith degradation, and partial conversion of glucopyranosyl residues in the main chain of β-glucans to corresponding 3,6-anhydro derivatives or other sugar residues.[10,75−77]

The structures of the β-glucans have been elucidated by NMR and X-ray crystallography and a combination of chemical methods such as methylation, periodic acid oxidation, Smith degradation, and enzymatic hydrolysis.[78,79] The results of X-ray diffraction studies have shown that the β-glucans have a secondary structure of a right triple-stranded helix.[80] High-resolution solid state ^{13}CNMR spectroscopy detects at least three types of secondary structures of β-D-glucans: single-chain, single-helix, and triple-helix forms.[57] The first two correspond to anhydrous and hydrated forms and are readily interconvertible by hydration and dehydration. The third one, the triple-helix form, is associated with the presence of an annealed gel form of β-D-glucan.[81] According to conformation−activity relation-

ship studies, the single-helical β-D-glucans are more effective as antitumor agents as compared to triple-helical ones, although this distinction is less clear for branched glucans.[82]

One of the examples of antitumor β-D-glucans from polypores is compound D-II isolated from the cultured mycelium of *Trametes versicolor* (as *Coriolus versicolor*). D-II strongly inhibited the growth of Sarcoma-180 transplanted subcutaneously in mice by intraperitoneal, intravenous, subcutaneous, and intramuscular administration at a dose of 5 mg/mL. The molecular weight of D-II was estimated as 2 000 000 by gel filtration or 6 500 000 by light-scattering analysis. The chemical structure of D-II was elucidated by a combination of oxidation, methylation, and degradation methods as a β-(1→3)-D-glucan in which one of every three glucose residues is branched at C-6 with a β-D-(1→6)-linkage.[83]

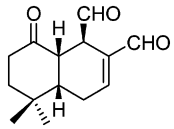
The polysaccharide fraction of polypore fungal extracts also may contain β-D-glucans with heterosaccharide residues, i.e., xylose, galactose, mannose, glucuronic acid, and other sugars, as well as glycopeptides or glycoproteins. Various antitumor-active heteroglucans and their protein complexes were isolated from the polypore *Ganoderma lucidum* (Reishi mushroom) including glucuronoglucan, xyloglucan, mannoglucan, xylomannoglucan, and other compounds.[10,57] The hot-water extract of *Albatrellus confluens* (as *Polyporus confluens*) also provides xyloglucan−protein complexes with strong antitumor activity.[84,85] Some heterogalactans were found in aqueous extracts of *Ganoderma applanatum*. None, however, showed antitumor activity.[86]

One of the most well-studied antitumor polysaccharide from polypores is PSK, also known as Krestin. PSK, isolated from *Trametes versicolor* (as *Coriolus versicolor*), is a protein-bound polysaccharide or glycoprotein that is effective against several animal cancer models.[87] Oral administration of PSK enhances the antitumor cytotoxicity of hepatic lymphocytes, preventing liver metastasis through the augmentation of organ-associated natural killer activity.[88] It also expresses superoxide dismutase mimicking activity and enhances in vitro anticancer activity of the known anticancer drug cisplatin.[89] PSK suppresses pulmonary metastasis of methylcholanthrene-induced sarcomas, human prostate cancer DU145M, and lymphatic metastasis of mouse leukemia P388, and it has prolonged the survival period in spontaneous metastasis models. PSK also suppresses the metastasis of rat hepatoma AH60C, mouse colon cancer colon 26, and mouse leukemia RL male 1 in artificial metastasis models.[90] PSK (Krestin) is currently marketed in Japan as an immunotherapeutic agent for colorectal, gastric, and lung cancers. In an excellent review on antitumor-active polysaccharides from medicinal basidiomycetes, Mizuno et al.[56] give an extensive overview of antitumor properties of polysaccharides isolated from various polypores.

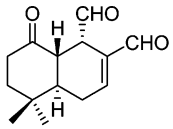
Compounds with Miscellaneous Biological Activities

An Australian polypore species of *Panus* biosynthesizes the drimane sesquiterpene panudial (**82**). This compound, with an A/B ring *cis* junction, is isomeric with kuehneromycin B (**83**), isolated from other fungi in addition to polypores. Panudial (**82**) is a potent inhibitor of bovine and human ADP-stimulated platelet aggregation, with IC_{30} values of 2.5 and 6 μg/mL, respectively.[64]

An ergostane derivative (**84**) isolated from *Grifola umbellata* (as *Polyporus umbellatus*) was found to inhibit rabbit platelet aggregation induced by collagen or ADP in vitro.[91]

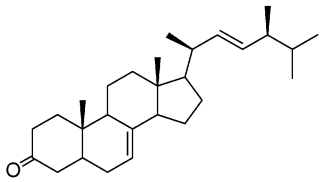


panudial (**82**)



kuehneromycin B (**83**)

The inhibitory effects on platelet responses to various aggregating agonists were also observed for ganodermic acid S (**85**), a triterpenoid isolated from the polypore *Ganoderma lucidum*. Ganodermic acid S potentiated the response of human gel-filtered platelets to prostaglandin PGE-1 and inhibited the platelet response to collagen.[92]



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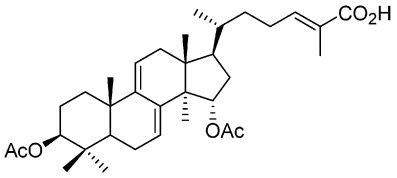
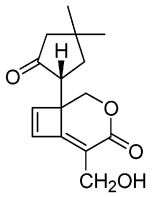
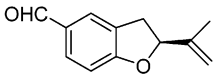


ganodermic acid S(**85**)

Several secondary metabolites from polypores show phytotoxic activity.[12] A parasite of conifers, the polypore *Heterobasidium annosum* (previously known as *Fomes annosus*), produces phytotoxic bicyclic sesquiterpenes, fomannosin (**86**) and fomannoxin (**87**). Both compounds are toxic to the green alga *Chlorella pyrenoidosa*.[93]



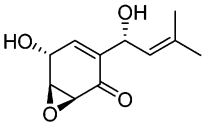
fomannosin (**86**)



fomannoxin (**87**)

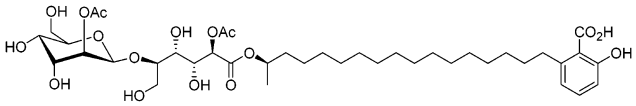
The above-mentioned hypnophilin (**9**) and pluerotellol (**12**) are phytotoxic. They inhibited indole-3-acetic acid-induced growth in the classic experiment using the *Avena* (oat) coleoptile bioassay.[22]

A prenylated shikimic acid derivative panepoxydone (**88**), isolated from the fermentation of cultured mycelia of *Panus conchatus*, *Panus rudis*, and *Lentinus crinitus*, was found to inhibit NF-κB-mediated signal transduction in African green monkey COS-7 cells.[12,94] Panepoxydone inhibited the NF-κB-activated expression of the reporter gene secreted alkaline phosphatase (SEAP) with an IC_{50} value of 1.5−2.0 μg/mL.[95]



panepoxydone (**88**)

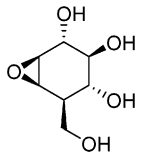
Some secondary metabolites from polypores are also known as enzyme inhibitors. Caloporoside (**89**) isolated from *Caloporus dichrous* inhibits pig's brain phospholipase C with a K_i value of 10 μg/mL.[96]



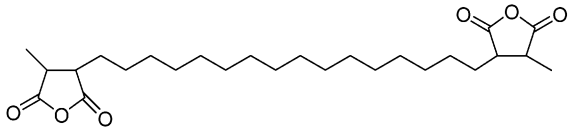
caloporoside (**89**)

As already mentioned above, diketocoriolin (**18**) exhibited immunomodulatory effects most probably by inhibition of Na^+-K^+-ATPase.[97]

A highly oxygenated metabolite, cyclophellitol (**90**), isolated from *Phelinus* spp., specifically inhibited almond β-glucosidase with an IC_{50} value of 0.8 μg/mL.[98] Another metabolite from *Tyromyces lacteus*, tyromycin A (**91**), specifically inhibited leucine and cysteine aminopeptidases of HeLa S3 cells.[99]

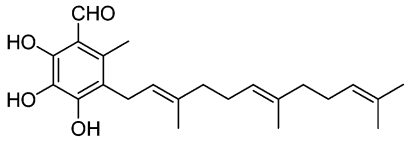


cyclophellitol (**90**)

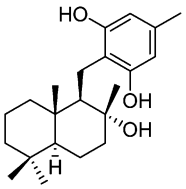


tyromycin A (**91**)

Scutigeral (**92**), a secondary metabolite isolated from fruiting bodies of *Albatrellus ovinus*, has affinity to the brain dopamine D1 receptors, stimulates rat dorsal root ganglion neurons, and may act as an orally active painkiller targeting vanilloid receptors (VR1).[100,101] The fruiting bodies of another polypore of the same genus, *Albatrellus confluens* from Yunnan, People's Republic of China, provided albaconol (**93**), which acted as a VR1 antagonist with an IC_{50} value of 5 μM.[102]



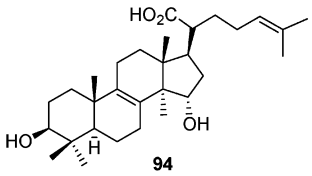
scutigeral (**92**)



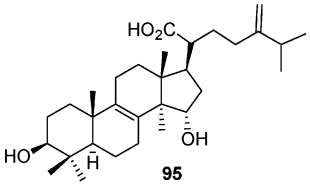
albaconol (**93**)

As mentioned earlier, *Laetiloporus sulphureus*, Chicken-of-the-Woods, well known for its spectacular size, color, and shape, was reported to cause visual hallucinations and ataxia in children upon ingestion.[103] Two triterpenoids, 15α-hydroxytrametenolic acid (**94**) and sulfurenic acid (**95**), isolated from this mushroom showed dopamine D_2 receptor agonistic activity in monkeys by intramuscular injection at a dose of 3.8 mg/kg/body weight.[102]

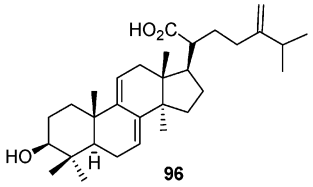
Dehydrotrametenolic acid (**96**) has been found in several polypores including *Wolfiporia cocos*, *Poria carbonica*, *Fomitopsis officinalis* (as *Fomes officinalis*), *Laetiloporus sulphureus* (as *Laetiporus versiporus*), and *Antrodia cinnamomea*. Dehydrotrametenolic acid (**96**) reduces hyperglycemia in mice with noninsulin-dependent diabetes mellitus (NIDDM) and acts as an insulin sensitizer in glucose tolerance tests.[104]



94

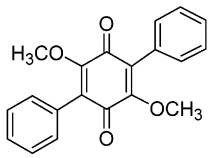


95

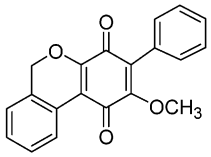


96

Two lipid peroxidation inhibitors, betulinans A (**97**) and B (**98**), were isolated from the methanol extract of *Lenzites betulina*.[105] Peroxidative damage of cells and organellar membranes by free radicals has been implicated in pathogenesis of various diseases such as atherosclerosis, arthritis, myocardial ischemia, and cancer. Betulinans A (**97**) and B (**98**) inhibited lipid peroxidation with IC_{50} values of 0.46 and 2.88 μg/mL, respectively. Betulinan A (**97**) was about 4 times more active as a radical scavenger than vitamin E.

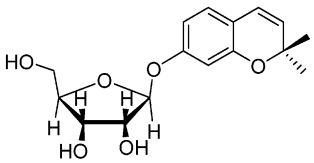


betulinan A (**97**)

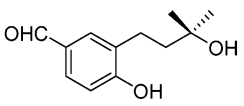


betulinan B (**98**)

An extract obtained from a tissue culture (i.e., mycelium) of the fruiting body of *Stereum hirsutum* also produced antioxidant metabolites, sterin A (**99**) and sterin B (**100**).[106] In the lipid peroxidation inhibition test using rat liver microsomes, sterin A (**99**) showed inhibition with an IC_{50} value of 8 μg/mL.



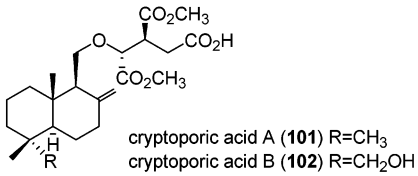
sterin A (**99**)

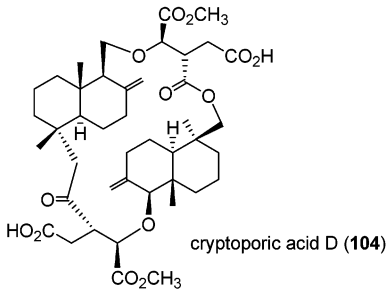


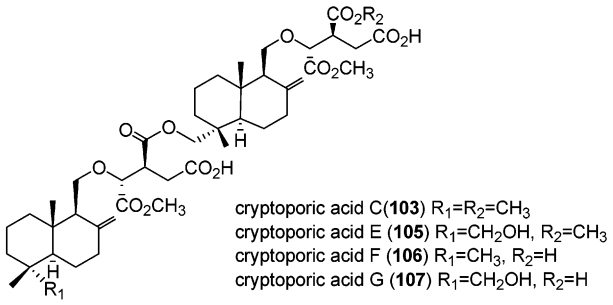
sterin B (**100**)

The inedible fruiting body of *Cryptoporus volvatus* (Polypopraceae) contains large amounts of the novel drimane sesquiterpenoids cryptoporic acids A−G (**101**−**107**). The intensely bitter tasting cryptoporic acids completely inhibited germination of rice in husk and elongation of the second coleoptile at a concentration of 200 ppm. Their main activity, however, was the strong inhibition of superoxide anion radical (SAR) release. Inhibitors of SAR release and radical scavengers are necessary to prevent human diseases caused by ischemia and inflammation. Cryptoporic acids inhibit the release of SAR from guinea pig peritoneal macrophages induced by the SAR stimulant formyl-me-

thionyl-leucyl-phenylalanine (FMLP) at concentrations from 0.05 to 25 μg/mL.[107]

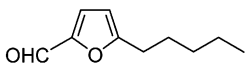




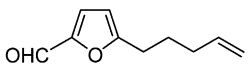


Cryptoporic acid E (**105**) inhibited the tumor promotion activity of okadaic acid in two-stage carcinogenesis experiments. The antitumorigenic effect of **105** on colon carcinogenesis also was observed.[107]

Some secondary metabolites isolated from polypores have insecticidal and nematocidal activity. Examples include beauvericin (**42**), already mentioned above, from *Laetiloporus sulphureus* (as *Polyporus sulphureus*), as well as several ascomycetes that exhibit significant insecticidal activites,[40] or anisalaldehyde (**35**) and (4-methoxyphenyl)-1,2-propandiol (**36**), with nematocidal properties.[108] Nematocidal activities against *Aphelencoides besseyi* also have been reported for two alkylated furaldehydes, 5-pentyl-2-furaldehyde (**108**) and 5-(4-pentenyl)-2-furaldehyde (**109**) isolated from *Irpex lacteus*.[109]



(**108**)



(**109**)

Concluding Remarks

Polypore fungi are the major source of biologically active natural products among the species of the diverse fungal phylum Basidomycota. They provide a rich variety of active secondary metabolites and polysaccharides. Over and over certain polypores have been found to contain active compounds. These include *Trametes versicolor*, *Laetiporus sulphureus*, and several species of *Ganoderma*, with long-lived fruiting bodies that ideally resist decay during their relatively long periods (weeks to months) of active basidiospore production. This is evident from the large number of compounds isolated from polypores that have proved to have significant antimicrobial activities, making them good candidates for critically needed new antibiotics. Sclerotia, the long-lived underground resistant mycelial structures of polypores such as *Grifola umbellata* and *Wolfiporia cocos*, also are good sources of secondary metabolites. Polysaccharide fractions of many polypores have shown remarkable anticancer effects in vivo through potentiation and stimulation of the entire immune system.

While a functional role for antibiotics can be assumed, a role for the compounds in the fungi that synthesize them, however, is unknown. Another neglected area of research in relation to the secondary metabolites of basidiomycetes is the difference in production of different compounds in different life history states, the mycelium (somatic assimilative state) and basidiocarp (reproductive state). They apparently are distinctive not only in function, but also in production of metabolites.

Of biologically active compounds from Basidiomycetes, a number from Aphyllophorales (polypores) have found their way to the market. In Japan, the polysaccharide anticancer drug PSK (Krestin) isolated from polypore *Trametes versicolor* (as *Coriolus versicolor*) is on the market, together with two other drugs from nonpolyporous wood-decaying fungi: Lentinan (Enzolen) from *Lentinus edodes* (Shiitake), and Schizophyllan (Sonifilan) from *Schizophyllum commune*. Several polysaccharide preparations from basidiomycetes, including polypores such as *Grifola frondosa*, *Ganoderma lucidum*, and *Trametes versicolor*, are in clinical trials in the People's Republic of China. Extracts from numerous Aphyllophorales are also available all over the world as nutritional supplements or herbal remedies. There is an intense interest in these so-called "mushroom nutriceuticals" by consumers. The market value of mushroom dietary supplement products from *Ganoderma lucidum* species alone worldwide is estimated to be $5−6 billion per year, with $1.6 billion for the United States.[110,111]

The major research on isolation of pharmacologically active compounds from polypores, as well as other Basidiomycetes, comes from Germany, Japan, Korea, and the People's Republic of China, the countries with the historically best established tradition of the use of medicinal mushrooms. Unfortunately, the United States has been poorly represented in this research field. Considering, however, the leading role of the U.S. in the study of natural products worldwide, this gap could soon be filled. The large and well-preserved natural resources of North America, with a rich diversity of higher fungi, including polypores, makes a good base for more extensive research on the isolation and biological evaluation of natural products from mushrooms.

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