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Review

SECONDARY METABOLITES FROM HIGHER FUNGI IN VIET NAM: DISCOVERY, CHEMODIVERSITY, AND BIOACTIVITY

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Abstract. Medicinal higher fungi such as *Ganoderma, Phellinus and Hexagonia* have been used as alternative medicinal remedies to promote health and longevity for people in Viet Nam and other regions of the world since ancient times. Nowadays there is an increasing public interest in the secondary metabolites of Vietnamese higher fungi for discovering new drugs or lead compounds. Current research in drug discovery from medicinal higher fungi involves a multifaceted approach combining mycological, biochemical, pharmacological, metabolic, biosynthetic and molecular techniques. In recent years, many new secondary metabolites from Vietnamese higher fungi have been isolated and are more likely to provide lead compounds for new drug discovery, which may include chemopreventive agents possessing the bioactivity of immunomodulatory, anticancer, etc. However, numerous challenges of secondary metabolites from higher fungi are encountered including separation, identification, biosynthetic metabolism, and screening model, etc. Commercial production of secondary metabolites from medicinal mushrooms is still limited mainly due to less information about secondary metabolism and its regulation. Therefore, strategies for enhancing secondary metabolite production have been continuously developed. At present, Vietnamese higher fungi secondary metabolites can be divided into over 20 major groups according to their chemical types. In this paper, roughly three groups of secondary metabolites derived from higher fungi reported in the past decade are overviewed.

Keywords: higher fungi, secondary metabolites, chemodiversity, bioactive

Classification numbers: 1.2.1, 1.4.4

1. BIODIVERSITY OF HIGHER FUNGI IN VIET NAM

The fungal kingdom contains heterogeneous organisms, with over 100,000 species described. However, the number of fungal species, in fact, can be up to 5,100,000 species [1]. Nowadays, fungi have practical applications in many aspects, including food processing: *Pleurotus*, *Lentinula edodes*, *Auricularia auricula-judae*, *Volvariella volvacea*, *Tremella fuciformis*, *Hypsizygus tessellatus* [2]; medicinal products: *Ganoderma lucidum*, *Trametes versicolor*, *Cordyceps*; and others applied in pharmaceutical technology. Scientifically, many species (*Lentinus tigrinus*, *Schizophyllum commune*) were the subjects of study on physiology, biochemistry, and genetics. In addition, many species of fungi are harmful to plants and animals, even more some poisonous fungi cause coma and death for humans.

At the end of the 19th century, studies on macrofungi in Viet Nam were started (Patouillard, 1890), which were carried out by Vietnamese and some foreign mycologists but most of their publications were interpreted in Vietnamese. Today about 1400 species of macrofungi have been reported from Viet Nam, including Basidiomycota (90 %), Ascomycota (8 %), Myxomycota (1.5 %), and Glomeromycota (0.5 %) [3 - 5]. Vietnamese macrofungi have high resource values, such as edible mushrooms (about 250 species), pharmaceutical mushrooms (230 species), poisonous mushrooms (35 species), and many species that can be used in biotechnology and for environmental conservation [3, 4]. It is estimated that the number of possible mushroom species in Viet Nam is six times higher than that of higher plant species, which can be up to 72,000 species. That means more than 90 % of the possible mushroom species in Viet Nam have not yet to be identified and listed. In the mushroom section (2001) of the list of Vietnamese plants, the number of fungal species is only about 2,250 species, of which Ascomycota species are rare compared to Basidiomycota species. Meanwhile, the number of fungal species is estimated to account for 2/3 of the total described species in the world [5]. In addition, the aquatic fungi species in freshwater and saltwater of Viet Nam are almost unpublished. Even for macrofungi, the work regarding the number of named taxons is just at the beginning stage.

Vietnamese macrofungi species have proved to be of considerable resource values in manyaspects. There are more than 200 species, of which about 50 species are precious edible mushrooms. The vast majority of edible mushrooms in Viet Nam belongs to the representatives of the fungus Basidiomycota and a few species of the fungus Ascomycota, including species of *Auricularia* (7 species), *Tremella* (5 species), *Lentinulaedodes*, *Volvariellavolvacea*, *Termitomyces* (3 species), *Boletusedulis*, *Boletusaff. Felleus*, *Macrocybegigantea*, *Entolomaclypeatus*, *Pleurotus* spp., *Cantherelluscibarius*, *Hypsizigusmarmoreus*, and *Flammulinavelutipes*. Notably, a representative of *Ustomycetes* is *Ustilagoesculenta* - *Yeniaesculenta*, which parasitizes on the root of the plant used as food, formerly sold in the market, now becomes very rare. Moreover, 200 species of fungi can be used as medicinal herbs (Trinh Tam Kiet, 2008), of which many species are valuable medicinal herbs such as *Ganodermalucidum*, *Ganodermacapense*, *Ganodermaapplanatum*, *Ganodermaaustrale*, *Tomophaguscolossus*, *Lariciformesofficinalis*, *Inonotusobliquus*, *Trametesversicolor*, *Schizophyllumcommune*, *Lentinulaedodes*, *Flammulinavelutipes*, *Auricularia*, *Tremella*, *Cordycepsinensis*, and *Cordycepmilitaris*. Initial studies on some higher fungi of Viet Nam were focused on bioactive substances that have anti-inflammatory effects, enhance immune response, and/or support the treatment of cancer, immunodeficiency, urology, and cardiology. About 50 species of fungi can be used to produce enzymes and some valuable active ingredients that can be applied in biotechnology and environmental protection [5].

In general, Vietnamese macrofungi have only been initially studied. Meanwhile, the higher fungi of Viet Nam are very diverse, made up of many geographical factors, and have great resource values. In order to overcome the lagging situation in research and application of higher fungi, to conserve large fungal genetic resources, and to promote valuable resource values, we need to invest appropriately to promote comprehensive study on higher fungi in Vietnam in the near future**.**

2. CHEMODIVERSITY OF SECONDARY METABOLITES FROM HIGHER FUNGI IN VIET NAM

Interestingly, almost all drug screening models can have corresponding active substances from higher fungi or other microbial secondary metabolites [6], and higher fungi are recognized as cell factories producing diversified bioactive compounds. More importantly, most secondary metabolites from higher fungi possess the drug-like characteristics of chemical structures, which can act as a major natural compound library for new drug discovery [6, 7]. Generally speaking, the drug-like properties of secondary metabolites from higher fungi mainly include the following. Their molecular weights are in the range of 150 - 1,000 Da, and the metabolites usually contain C, H, O, and N, even S, P, and halogen atoms such as Cl, Br, and F. Their chemical structures commonly contain some important functional groups such as hydroxyl, carboxyl, carbonyl, amino, etc., which can provide multipharmacophore points. Their molecular properties such as relative molecular mass, log P values, and the number of the donor and receptor of hydrogen bonding usually meet the rules of drug-like properties. According to statistical data, the total number of bioactive microbial metabolites recognized has doubled nearly every decade. As shown in Table 1, more than 19 species of higher fungi have now been reported for the composition of second metabolites in Viet Nam. In addition, around 100 secondary metabolites need to be further examined for any biological activity. At present, higher fungi secondary metabolites can be divided into over 20 major groups according to their chemical types [8]. In this work, roughly three groups of secondary metabolites reported in the past decade, which derive from higher fungi (Tables 2 - 4), are overviewed as follows.

2.1. Terpenoids

Terpene is known as an important variety of naturally occurring bioactive metabolites produced by many higher fungi species. Especially diterpenoid, triterpenoid, and sesquiterpenoid are typical representatives of terpenes with interesting biological activities. The main terpenes isolated from Vietnamese macrofungi include diterpenoids, triterpenoids, and sesquiterpenoids. Diterpenoids and sesquiterpenoids possess rich pharmacological effects. Thang's group reported that two new diterpenoids **1-2** were isolated from *N. melanoporus* [9]. Their stereochemical structures were established as drimane-type sesquiterpenoids possessing a rare dioxabicyclooctane moiety by X-ray crystallographic studies. Moreover, the diterpenes **3-4** were also found in this species [10].

Triterpenes are widely distributed in traditional medicines. Their structures are considered to be derived from the acyclic precursor squalene. More than 20,000 triterpenes have been isolated and identified from natural sources, including squalene, lanostane, dammarane, lupane, oleanane, ursane, and hopane structure types [11, 12]. The triterpenoids are more isolated from the species of the genus *Ganoderma, Phellinus, Hexagonia, and Trametes* in Viet Nam. The triterpenoids from *Ganoderma*are have been quite popularly studied recently. The characteristic secondary metabolites of *Ganoderma* genus are also found in these fungi in Viet Nam. The

compounds **5-15** were isolated from the extract of five species (*G.applanatum*, *G.pfeifferi*, *G.australe*, *G.mastoporum*, and *G. colossum*) belonging to the genus *Ganoderma* (Table 2) [13-17]. These compounds are characteristically presented in the composition of *Ganoderma* species reported worldwide. Most of them contain 30 or 27 carbon atoms. A few have 24 carbon atoms. These compounds possess the same skeleton, namely a *trans* configuration of rings A/B, B/C, C/D and 10β, 13β, 14α, 17β substituents. Moreover, substituents are always found at the C-3, 7, 11, 12, 15, 22, 23, 24 and 25 positions of the parent nucleus.

The species of *Phellinus* genus in Viet Nam including *P.igniarius*, *P.gilvus*, *P.baumii*, *and P.pini* were studied for their chemical composition. Their triterpenoid composition has also been investigated (**16-19**), showing that their structures mainly possess a tirucallane-type triterpenoid basic skeleton [18 - 20]. Most of them contain 30 atoms. A few have furane moiety on the side chain. For the genus *Hexagonia*, only two species were investigated for the composition of secondary metabolites including *H. apiaria*, and *H. tenuis*. The triterpenoid compounds (**20-25**) from these species exhibit a very characteristic structure of the lanostane-type skeleton with oxygenate in C-3 position and spiroannulated ring E and ring F being an α,β-unsaturated-γ-lactone [21 - 23]. In addition, there is also a triterpene with ursane skeleton (**26**) found in these species [22].

2.2. Steroids

Ergosterol (**27**) and ergosterol peroxides (**28**) are steroids isolated mainly from most of the Vietnamese macrofungi [13-16, 18, 19, 22-25]. This is also easily explained because these two compounds are structural components of the cell membrane of fungi. These compounds are not only essential for fungal growth and development but also important for adaptation to stress in fungi. Therefore, ergosterol and ergosterol peroxides from ten mushrooms (cultivated and wild mushrooms) in Viet Nam were analyzed by high-performance liquid chromatography coupled with the ultraviolet detection. The contents of ergosterol in *Fomitopsis dochmius* were 0.03061 g/L. Ergosterol content in *Fomitopsis dochmius* is the highest among the ten fungal samples analyzed. In contrast, only a very small quantity of ergosterol was found in *Phellinus igniarius*. As shown in Table 2, the contents of ergosterol peroxide in *Fomitopsis dochmius* were 0.00237 g/L. At the meantime, only a very small quantity of ergosterol peroxide was found in *Phellinus igniarius* and *Ganoderma applanatum*. The results show that the contents of ergosterol and ergosterol peroxides in ten mushrooms samples have significant differences [26].

The ergostane skeleton (**29-33**) is the main structure of steroid compounds published on higher fungi in Viet Nam. The substituents are always found at the C-3, 4, 7, 6, 8, 14, 22 positions of this skeleton [14, 15, 19]. Moreover, the diversity of Vietnam's macrofungal species is also reflected in the appearance of some steroids with a very special carbon skeleton such as three novel steroids (**34-37**), named cattienoids A-C and schisanlactone A (**37**) isolated from the fruiting bodies of *Tomophaguscattienensis* (a new mushroom recently collected from Cattien National Park, Viet Nam). They possess an unusual seven-membered lactone ring, derived from lanostane-type triterpenoids [27]. The same carbon skeleton of steroids (Colossolactone C-G, **38-42**) was found from *G. colossum* [17]. Moreover, a new steroid, phellinol (**43**), and a known steroid compound, senexonol (**44**) were isolated from the extracts of the *Phellinus* sp..

According to the above-mentioned reports, in addition to the similar structures with those observed in other macrofungi in the world, the steroid composition from Vietnamese macrofungi has special structural forms that need to be studied further.

2.3. Phenolic and other compounds

Recently, these medicinal fungi in Viet Nam have been reported to produce a variety of yellow polyphenol pigments, known as styrylpyrones (**45-47**), which have significant biological effects, such as antioxidant, anti-cancer, anti-platelet, anti-diabetic, anti-inflammatory, and antiviral activities [28]. Styrylpyrone pigments are common constituents of fungi, mainly those belonging to the Hymenochaetaceae family, including *Phellinus* and *Inonotus*. They also exist in primitive angiosperm families, including Piperaceae, Lauraceae, Annonaceae, Ranuculaceae and Zingiberaceae, where they play an important role in protecting against mechanical wounding or microbial attack, and show potent biological activities, including anti-cancer and sedative effects. Biogenesis of fungal styrylpyrones and their intrinsic roles in fungi, like the phenylpropanoid derivatives of plants, which have important ecological and physiological values, have attracted much attention. Styrylpyrones are regarded as phenylalanine (Phe)-derived fungal metabolites with a variety of functions, including defense, pigmentation and signaling molecules. In our ongoing research of natural phenolic compounds, chemical investigation on the fruit bodies of *Phellinus* and *Nigrofomes* genus has led to the characterization of three flavonoids, including daidzin (**48**), pterocarpin (**49**), and 5-hydroxy-7methoxy-flavone (**50**), along with ten known phenolic compounds (**51-60**) [10, 28-32]. Chemical investigation on extracts from the fruiting body *Inonotus* sp. using open column and preparative HPLC yielded several phenolic compounds such as hispidin (**61**), iso-hispidin (**62**), inonotic acid methyl ester (**63**), and inotilone (**64**) [33].

Moreover, the polychlorinated compounds were observed from higher fungi, including 1,2,4,5-tetrachloro-3,6-dimethoxybenzene (**65**) and 4,4’-dihydroxy-3,3’,6,6’-tetramethyl-[1,1’-bi(cyclohexane)]-3,3’,6,6’-tetraene-2,2’,5,5’-tetraone (**66**) [30, 31]. Many chlorinated compounds were reported to exhibit antimicrobial activity.

3. BIOACTIVITY OF SECONDARY METABOLITES FROM HIGHER FUNGI IN VIET NAM

3.1. Antimicrobial activity

Most compounds have been tested for antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Lactobacillus fermentum*, *Salmonella enterica*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* as well as an inhibition of tyrosinase enzyme [27]. Colossolactones (A-G) displayed no antimicrobial activity against a spectrum of bacteria and fungi [17].

3.2. Anti-inflammatory activity

Those purified triterpenoids (**20**-**25**, **27**, **28**) in sufficient quantities were examined for their inhibition of superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB. Among the constituents examined, hexatenuin A (**25**) displayed the most significant inhibition of superoxide anion generation and elastase release with IC_{50} values of 1.9 ± 0.2 and 4.3 ± 1.4 μM, compared with the reference compound LY294002, with IC_{50} values of 0.4 ± 0.02 and 1.5 ± 0.3 μM, respectively. In addition, the following structure-activity relationships could be deduced from the bioactivity data. Hexagonins B (**21**) and D (**23**), possessing a basic triterpenoid skeleton without malonyl substitution at C-3, did not show anti-inflammatory bioactivity. Comparatively, hexagonin A (**20**), with the triterpenoid skeleton and

malonyl and methyl ester functions, also did not exhibit significant activity. Hexatenuin A, having the triterpenoid skeleton and a free malonic acid group, displayed the most significant inhibitory effects in the bioactivity examination. Consequently, the free malonic acid function is important for anti-inflammatory activity. From the above data, the purified triterpenoids of *H. apiaria* are potential new leads for anti-inflammatory drug development. This fungus is also a good source of healthy food with a possibly known mechanism of action [22].

From a Vietnamese Wood-Rotting *Phellinus* sp., compound **30** was shown to inhibit the production of nitric oxide (NO) in RAW 264.7 cells with an IC_{50} value of 28.96 μM. Compounds **19**, **43**, and **44** were also evaluated regarding their inhibitory activities against NO production stimulated by LPS in RAW 264.7 cells. They moderately suppressed the LPS-induced production of NO with IC50 values of 22.6, 31.3 and 85.4 μM, respectively [20].

All compounds from the fruiting body *Inonotus* sp. exhibited significant inhibitory activities against key enzymes involved in inflammatory processes: hydroxysteroid dehydrogenase (3a-HSD), cyclooxygenase (COX) and xanthine oxidase. They were evaluated for their inhibitory activities in 3a-HSD, COX-1, COX-2 and XO enzyme assays according to previously documented procedures. Their inhibitory potencies, expressed as IC_{50} values are compared with those of the references, indomethacin and allopurinol. The results demonstrated that the phenolic compounds exhibit strong COX inhibitory effects with a prevalence for COX-2 in the case of compounds hispidin (**61**), iso-hispidin (**62**), inonotic acid methyl ester (**63**), and inotilone (**64**). It should be highlighted that hispidin (**61**) and the novel inotilone (**64**) selectively inhibit COX-2 at concentrations as low as those of the marketed selective inhibitors meloxicam and nimesulide. In all cases, except for compound **64**, strong 3a-HSD inhibitory effects were noted, as well as moderate inhibitory effects toward XO, except hispidin (**61**), which exhibited an inhibitory activity at a level comparable with that of the standard allopurinol. As far as the tautomeric compounds **61** and **62** are concerned, it seems that the α-pyrone is more active than the γ-pyrone [33]. Moreover, colossolactones (A-G) inhibited 3*R*-hydroxysteroid dehydrogenase (3*R*-HSD) at concentrations comparable to indomethacin as standard drug, suggesting anti-inflammatory properties for them [17].

3.3. Anticancer activity

To assay on the growth inhibitory activity of nigrofomins A (**1**) (purity > 96 %) and B (**2**) (purity > 91 %) towards tumor cell lines, three different cells from different organs, including acute T-cell leukemia (Jurkat), human nasopharyngeal carcinoma (NPCTW01), and lung cancer (NCI-H661) cell lines, were used. Treatment with compounds **1** and **2** showed inhibition of Jurkat cell lines with IC_{50} values of 125 μM and 99 μM, respectively. However, NPC-TW01 and NCI-H661 cells were less susceptible to treatment with **1** and **2** with IC_{50} values ranging from 159 to 238 μM for **1** and from 188 to 246 μM for **2**, respectively. Furthermore, our results showed that only acute T-cell leukemia cells are sensitive to both **1** and **2** treatments. Our results clearly demonstrated a significant increase of G_0/G_1 population with concomitant loss of the S phases when Jurkat cells are treated with both **1** and **2** for 48 hours. The accumulation of the G_0/G_1 population increased with treatment dosage enhancement, suggesting that the cell cycle arrest phenomena by **1** and **2** are in a concentration-dependent manner [9].

Three compounds (**33**-**35**) were tested for their cytotoxicity, and it was found that cattienoid B (**35**) and schisanlactone A (**37**) have moderate cytotoxicity against KB cells with IC_{50} values of 91.2 and 63.3 μM [27]. The compounds (**28**, **31**, and **33**) showed cytotoxic activity against KB cells with their IC50 values of 12.68, 10.72 and 87.95 μg/mL, respectively [24].

Colossolactones (A-G) showed moderate cytotoxicity against L-929, K-562, and HeLa cells with IC_{50} values ranging from 15 to 35 μg/mL [17].

4. CONCLUDING REMARKS

Medicinal higher fungi such as *Ganoderma*, *Phellinus*, *Hexagonia*, and *Trametes* have been used as alternative medicine remedies to promote health and longevity for people in Viet Nam and other regions of the world since ancient times. In addition to the similar structures reported from higher fungi in the world, the chemical compositions from Vietnamese macrofungi also have a lot of special structural forms that need further attention and investigation according to previous publications. Moreover, the bioactivity of secondary metabolites isolated from higher fungi in Viet Nam has been characterized and is likely to provide lead compounds for new drug discovery, which may include chemopreventive agents possessing various bioactivities such as anti-inflammatory, anticancer, etc. Therefore, more studies focusing on this subject are needed to develop this valuable resource.

Structures of Secondary Metabolites

Table 1. Name, location of higher fungi from Viet Nam.

Number	Name	Location	Reference
Ganoderma			
1	*Ganoderma applanatum*	Pu Huong National Park, Nghe An	[15]
2	*Ganoderma pfeifferi*	Pu Huong National Park, Nghe An	[16, 34]
3	*Ganoderma austral*	Pu Huong National Park, Nghe An	[13]
4	*Ganoderma mastoporum*	Pu Huong National Park, Nghe An	[14]
5	*Ganodermaneo-japonicum*	Cat Tien National Park, Lam Dong	[24]
6	*Ganodermamirabile*	Lao Cai	[25]
7	*Ganoderma colossum*	Culture collection of the Mycological Center, University Hanoi	[17]
Phellinus			
8	*Phellinusigniarius*	Pu Huong National Park, Nghe An	[18, 28]
9	*Phellinus gilvus*	Pu Mat National Park, Nghe An	[31]
10	*Phellinus baumii*	Pu Mat National Park, Nghe An	[30]
11	*Phellinuspini*	Pu Mat National Park, Nghe An	[19]
12	*Phellinus* sp.	Nho Quan, Ninh Binh	[20]
Hexagonia			
13	*Hexagonia apiaria*	Pu Huong National Park, Nghe An	[22]
14	*Hexagonia tenuis*	Pu Mat National Park, Nghe An	[21]
Other higher fungi			
15	*Tomophaguscattienensis*	Cat Tien National Park, Lam Dong	[27]
16	*Nigrofomes melanoporus*	Pu Mat National Park, Nghe An	[9, 10]
17	*Trametes cubensis*	Ky Son, Nghe An	[32]
18	*Inonotus* sp.	Viet Nam	[33]

Table 2. Name, source, and bioactivities of terpenoids from fungi in Viet Nam.

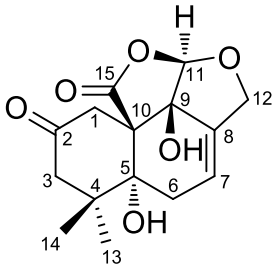
Number	Name	Bioactivities	Source	Reference
Sesquiterpenoids				
1	Nigrofomin A (**1**)	Anticancer	*N. melanoporus*	[9]
2	Nigrofomin B (**2**)	Anticancer	*N. melanoporus*	[9]
Diterpenoids				
3	Madolin A (**3**)		*N. melanoporus*	[10]
4	Dehydrovomifoliol (**4**)		*N. melanoporus*	[10]
Triterpenoids				
5	Ganoderal A (**5**)		*G. australe*	[13]
6	Ganoderic acid Y (**6**)	Cytotoxicity	*G. austral* *G. mirabile*	[13, 25]
7	Ganoderic acid SZ (**7**)		*G. australe*	[13]
8	Ganodermanondiol (**8**)		*G. mastoporum*	[14]
9	Δ^1 -Lupenone (**9**)		*G. mastoporum*	[14]
10	Lucidumol B (**10**)		*G. mastoporum*	[14]
11	Ganodermadiol (**11**)		*G. pfeifferi* *G. applanatum*	[15, 16]
12	*3β*-Hydroxy-5α-lanosta-7,9,24 (*E*)-trien-26-oic acid (**12**)		*G. pfeifferi* *G. applanatum*	[15, 16]
13	7-Oxo-ganoderic acid Z (**13**)		*G. pfeifferi*	[16]
14	Colossolactone A (**14**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
15	Colossolactone B (**15**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
16	Igniarine (**16**)		*P. igniarius*	[18]
17	Gilvsin A (**17**)		*P. pini*	[19]
18	Gilvsin B (**18**)		*P. pini*	[19]
19	Trametenolic acid B (**19**)	Anti-inflammatory	*Phellinus* sp.	[20]
20	Hexagonin A (**20**)	Anti-inflammatory	*H. apiaria*	[22]
21	Hexagonin B (**21**)	Anti-inflammatory	*H. apiaria*	[22]
22	Hexagonin C (**22**)	Anti-inflammatory	*H. apiaria*	[22]
23	Hexagonin D (**23**)	Anti-inflammatory	*H. apiaria*	[22]
24	Hexagonin E (**24**)	Anti-inflammatory	*H. apiaria*	[23]
25	Hexatenuin A (**25**)	Anti-inflammatory	*H. apiaria* *H. tenuis*	[21-23]
26	Ursolic acid (**26**)		*H. apiaria*	[22]

Table 3. Name, source, and bioactivities of steroids from higher fungi in Viet Nam.

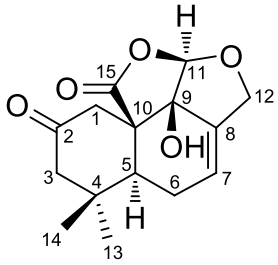
Number	Name	Bioactivities	Source	Reference
1	Ergosterol (**27**)	cytotoxicity	*G. pfeifferi* *G. applanatum* *G. austral* *G. neo-japonicum* *G. mirabile* *N. melanoporus* *P. igniarius* *P. pini* *P. gilvus*	[13-16, 18, 19, 22-25]
2	Ergosterol peroxide (**28**)	cytotoxicity	*G. pfeifferi* *G. mastoporum* *G. applanatum* *G. austral* *G. mirabile* *N. melanoporus* *H. apiaria* *P. igniarius* *P. pini* *P. gilvus*	[13-16, 18, 19, 22, 23, 25]
3	Ergosta-7,22-dien-3-one (**29**)	Anti-inflammatory	*G. mastoporum*	[14]
4	Ergosta-4,6,8(14),22-tetraen-3-one (**30**)	Cytotoxicity	*G. mastoporum* *G. neo-japonicum*	[14, 20, 24]
5	3*β*,5*α*-Dihydroxy-(*22E,24R*)-Ergosta -7,22-dien-6-one (**31**)	Anti-inflammatory	*G. mastoporum*	[14]
6	Ergosta-7,22-dien-3*β*-ol (**32**)	Cytotoxicity	*G. mastoporum* *G. applanatum* *P. pini* *G. neo-japonicum*	[14, 15, 19, 24]
7	Cerevisterol (**33**)		*G. pfeifferi*	[16]
8	Cattienoid A (**34**)	Cytotoxicity	*T. cattienensis*	[27]
9	Cattienoid B (**35**)	Cytotoxicity	*T. cattienensis*	[27]
10	Cattienoid C (**36**)	Cytotoxicity	*T. cattienensis*	[27]
11	Schisanlactone A (**37**)	Cytotoxicity, anti-inflammatory	*T. cattienensis*	[27]
12	Colossolactone C (**38**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
13	Colossolactone D (**39**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
14	Colossolactone E (**40**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
15	Colossolactone F (**41**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
16	Colossolactone G (**42**)	Cytotoxicity, anti-inflammatory	*G. colossum*	[17]
17	Phellinol (**43**)	Anti-inflammatory	*Phellinus* sp.	[20]
18	Senexonol (**44**)	Anti-inflammatory	*Phellinus* sp.	[20]

Table 4. Name, source and bioactivities of polyphenols and other compounds from higher fungi in Viet Nam.

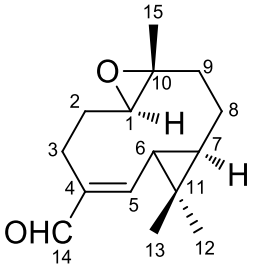
Number	Name	Bioactivities	Source	Reference
Styrylpyrone				
1	Inoscavin A (**45**)	Antioxidant, anti-diabetes	*P. igniarius* *P. baumii*	[29]
2	Meshimakobnol A (**46**)	Cytotoxic	*P. igniarius*	[18, 28]
3	Meshimakobnol B (**47**)	Cytotoxic	*P. igniarius*	[18, 28]
Flavonoids				
4	Daidzin (**48**)		*P. igniarius*	[29]
5	Pterocarpin (**49**)		*P. igniarius*	[29]
6	5-Hydroxy-7methoxy-flavone (**50**)		*P. igniarius*	[29]
Phenolic compounds				
7	3,4-Dihydroxylbenzoic aldehyde (**51**)		*P. baumii*	[30]
8	Methyl 3,4-dihydroxybenzoate (**52**)		*P. baumii*	[30]
9	(*E*)-4-(3,4-dihydroxyphenyl)but-3-en-2-one (**53**)		*P. gilvus* *P. baumii*	[31]
10	Benzoic acid (**54**)		*N. melanoporus*	[10]
11	Methyl(2-hydroxyphenyl) acetate (**55**)		*N. melanoporus*	[10]
12	Ferulic acid (**56**)		*N. melanoporus*	[10]
13	*Trans-p*-hydroxycoumaric acid (**57**)		*N. melanoporus*	
14	γ-(4-Methylphenyl)-γ-methyl-γ- butyrolactone (**58**)		*N. melanoporus*	[10]
15	Oospolactone (**59**)		*T. cubensis*	[32]
16	Oospoglycol (**60**)		*T. cubensis*	[32]
17	Hispidin (**61**)		*Inonotus* sp.	[33]
18	Iso-hispidin (**62**)		*Inonotus* sp.	[33]
19	Inonotic acid methyl ester (**63**)		*Inonotus* sp.	[33]
20	Inotilone (**64**)		*Inonotus* sp.	[33]
Other compounds				
17	1,2,4,5-Tetrachloro-3,6-dimethoxybenzene (**65**)		*P. gilvus* *P. baumii*	[30, 31]
18	4,4’-Dihydroxy-3,3’,6,6’-tetramethyl-[1,1’-bi(cyclohexane)]-3,3’,6,6’-tetraene-2,2’,5,5’-tetraone (**66**)		*P. gilvus*	[31]



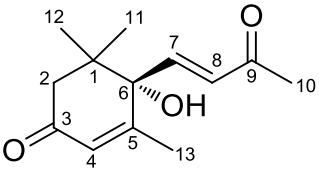
nigrofomin A (**1**)



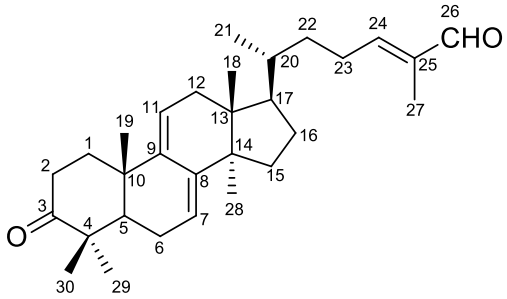
nigrofomin B (**2**)



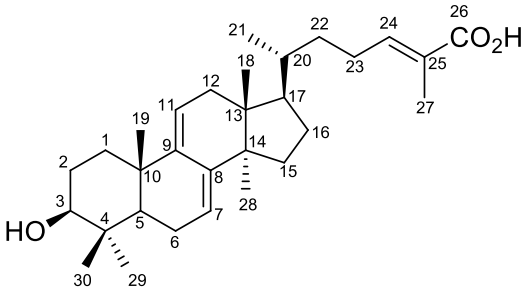
madolin A (**3**)



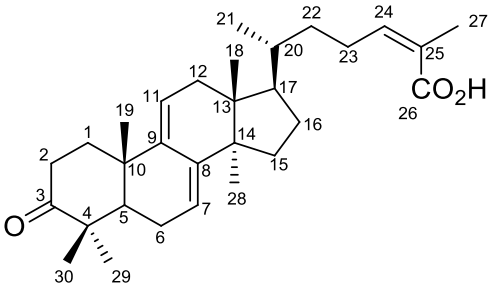
dehydrovomifoliol (**4**)



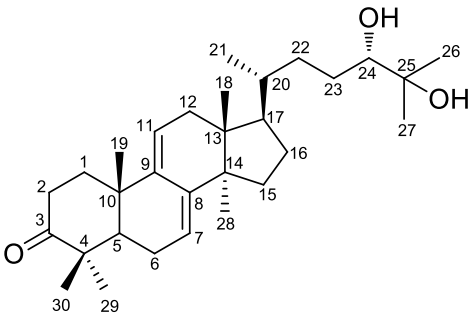
ganoderal A (**5**)



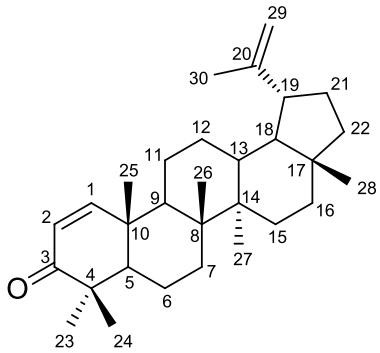
ganoderic acid Y (**6**)

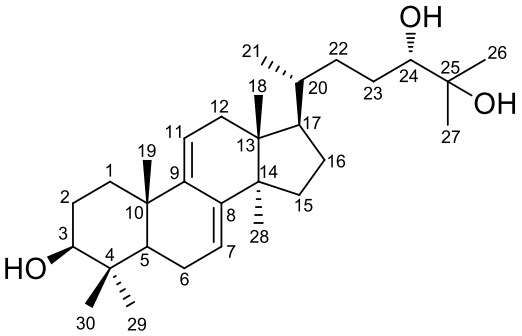


ganoderic acid SZ (**7**)

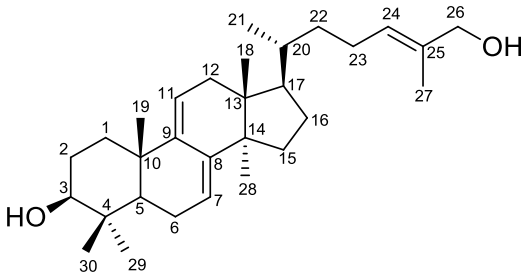


ganodermanondiol (**8**)

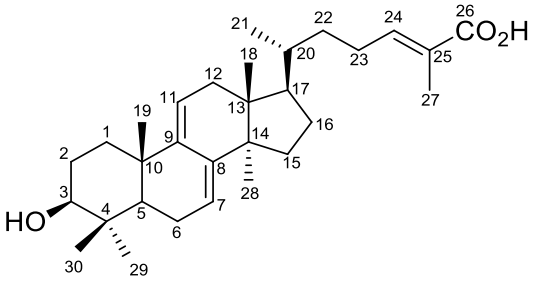




Δ^1-lupenone (**9**)

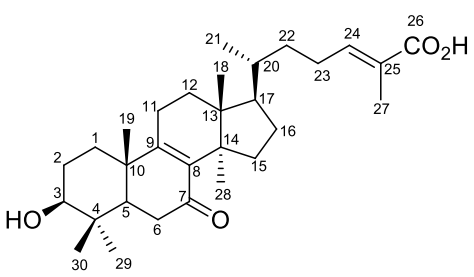


lucidumol B (**10**)

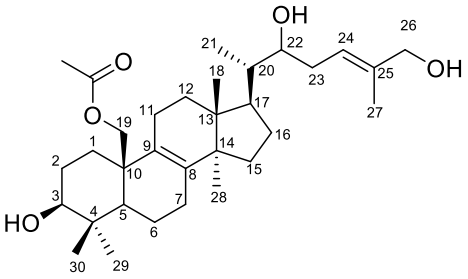


ganodermadiol (**11**)

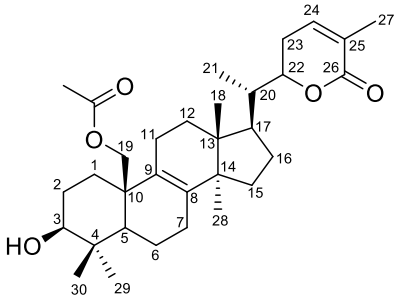
3β-hydroxy-5α-lanosta-7,9,24(*E*)-trien-26-oic acid (**12**)



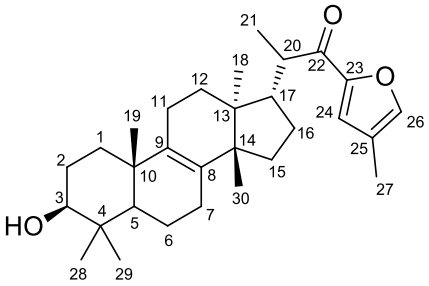
7-oxo-ganoderic acid Z (**13**)



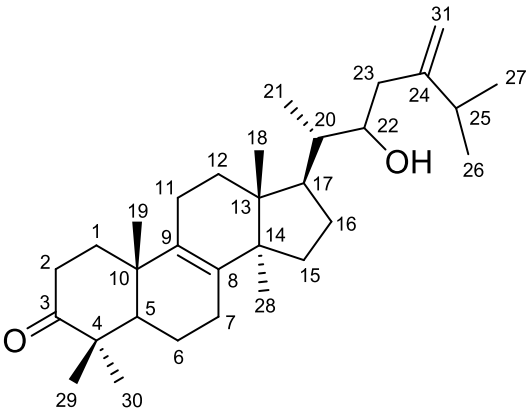
colossolactone A (**14**)



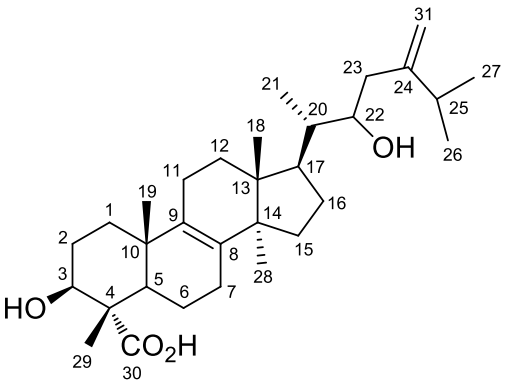
colossolactone B (**15**)



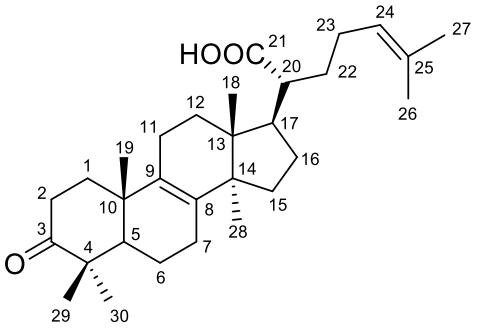
igniarine (**16**)



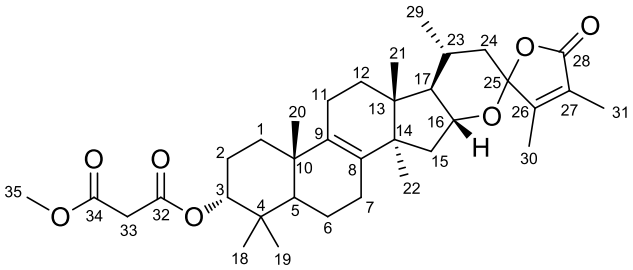
gilvsin A (**17**)



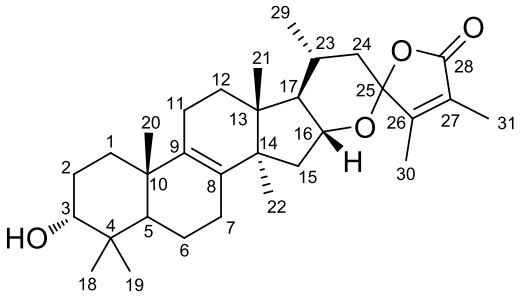
gilvsin B (**18**)



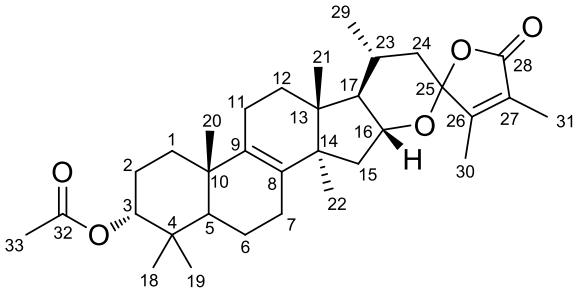
trametenolic acid B (**19**)



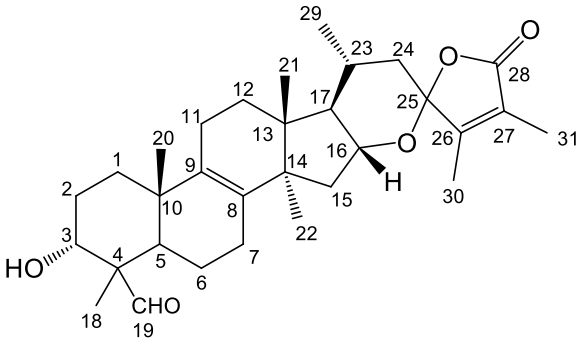
hexagonin A (**20**)



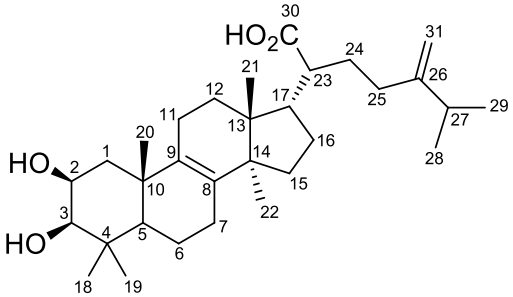
hexagonin B (**21**)



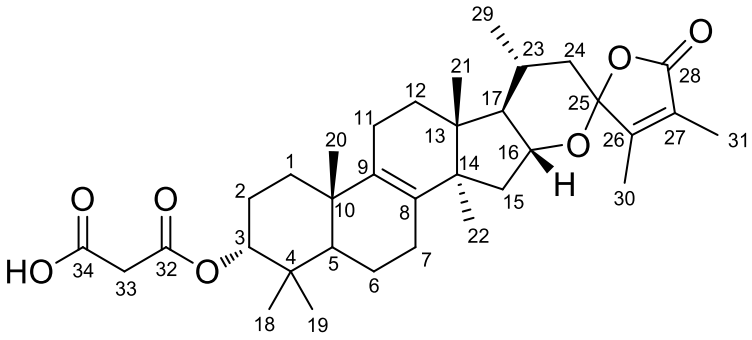
hexagonin C (**22**)



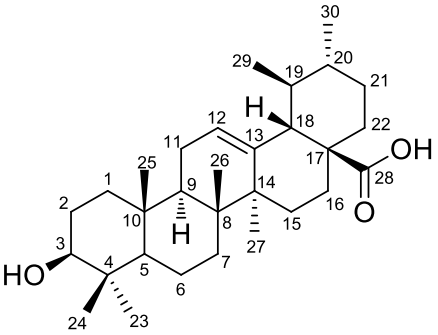
hexagonin D (**23**)



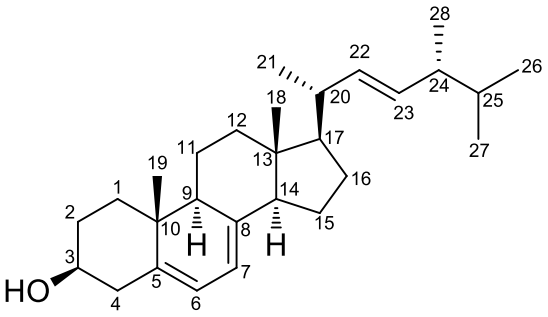
hexagonin E (**24**)



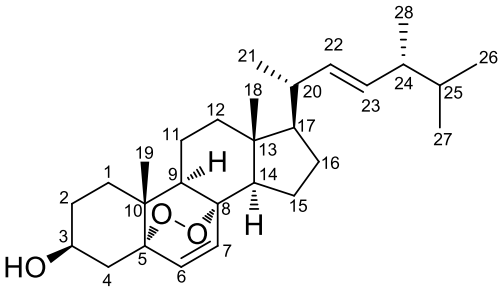
hexatenuin A (**25**)



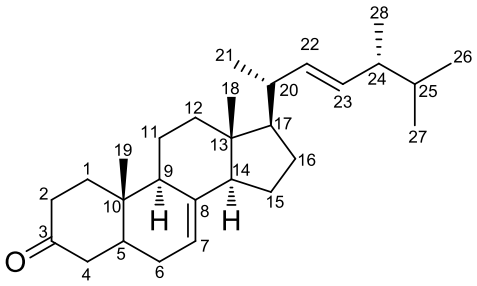
ursolic acid (**26**)



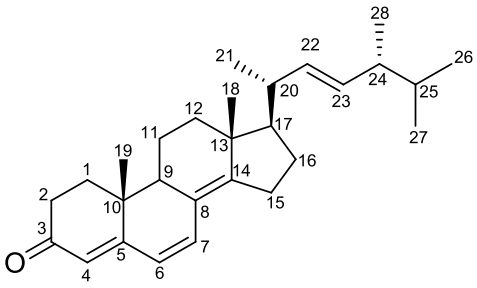
ergosterol (**27**)



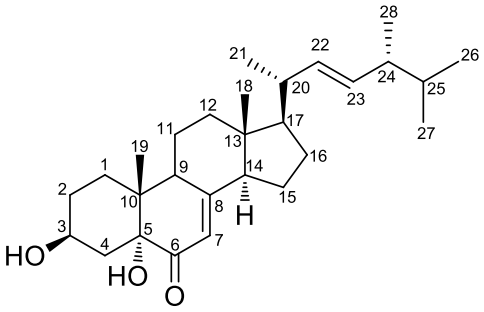
ergosterol peroxide (**28**)



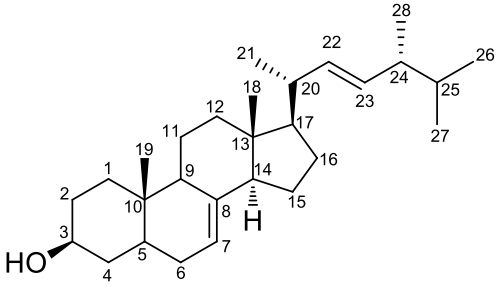
ergosta-7,22-dien-3-one (**29**)



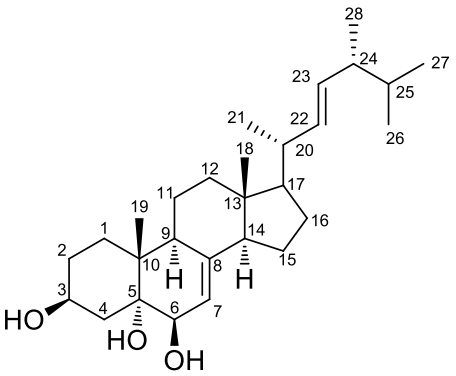
ergosta-4,6,8(14),22-tetraen-3-one (**30**)



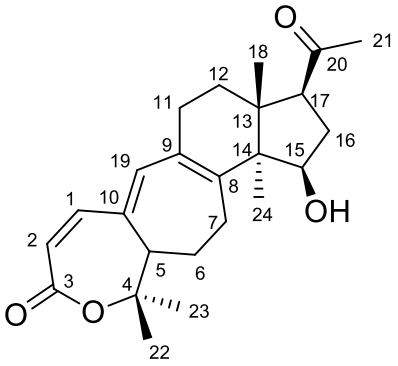
3β,5α-dihydroxy-(22E,24R)-ergosta-7,22-dien-6-one (**31**)



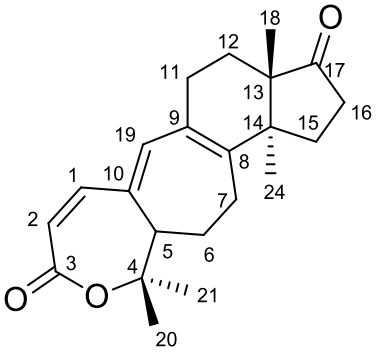
ergosta-7,22-dien-3β-ol (**32**)



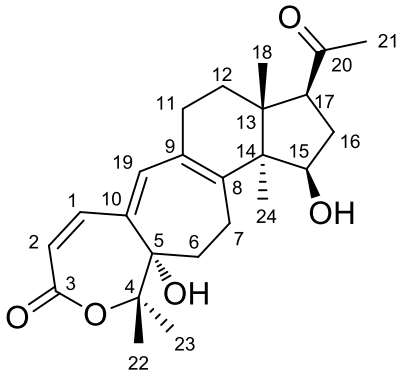
cerevisterol (**33**)



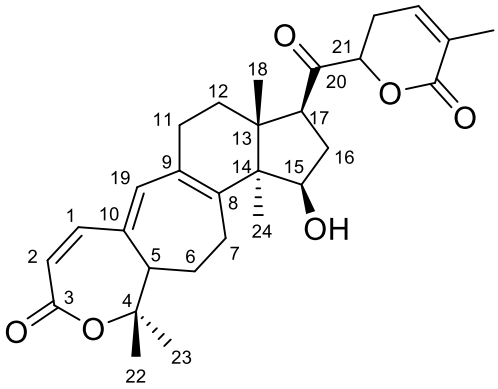
cattienoid A (**34**)



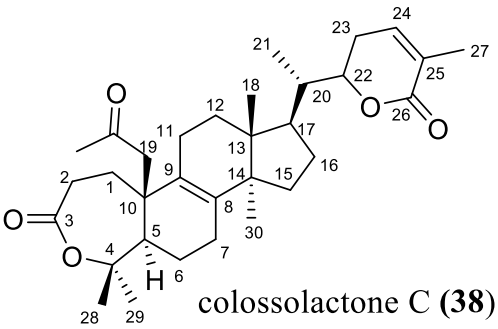
cattienoid B (**35**)



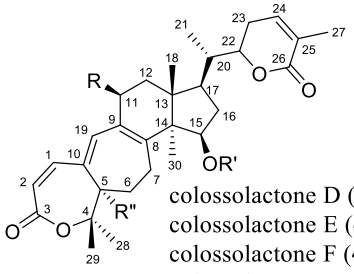
cattienoid C (**36**)



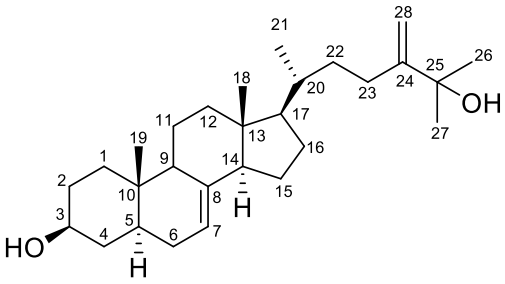
schisanlactone A (**37**)



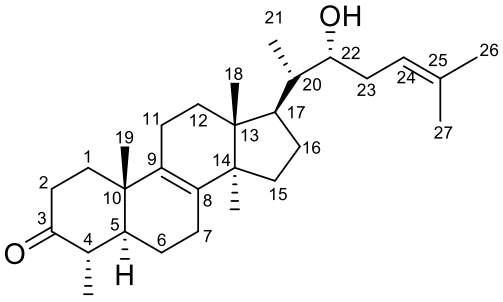
colossolactone C **(38)**



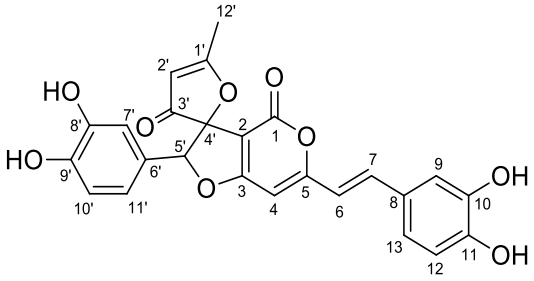
colossolactone D (**39**): R = H; R' = H; R" = H
colossolactone E (**40**): R = H; R' = Ac; R" = H
colossolactone F (**41**): R = OH; R' = Ac; R" = H
colossolactone G (**42**): R = H; R' = Ac; R" = OH



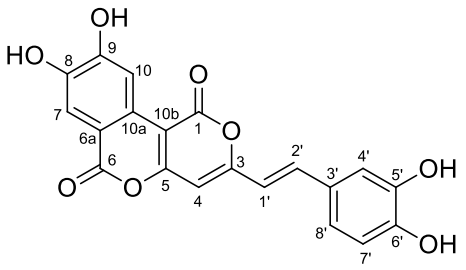
phellinol **(43)**



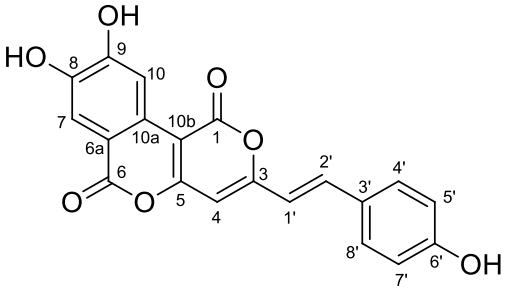
sexeanol **(44)**



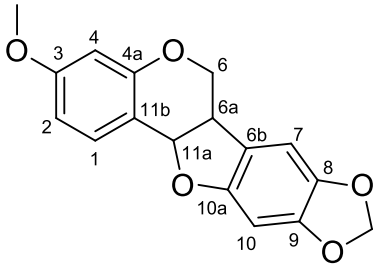
inoscavin A (**45**)



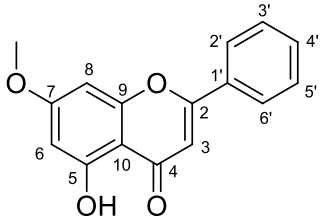
meshimakobnol A (**46**)



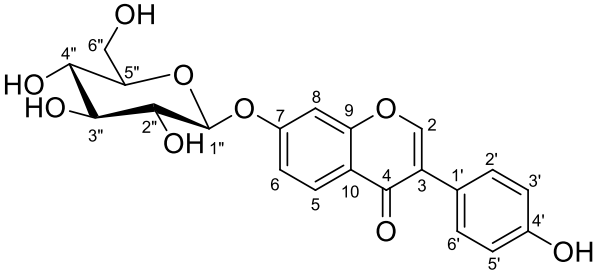
meshimakobnol B (**47**)



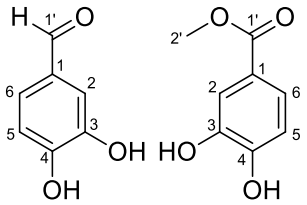
pterocarpin (**48**)



5-hydroxy-7-methoxy-flavone (**49**)

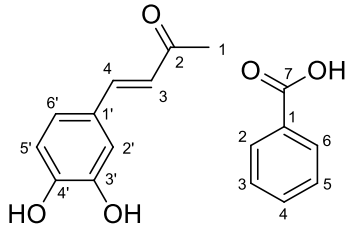


daidzin (**50**)



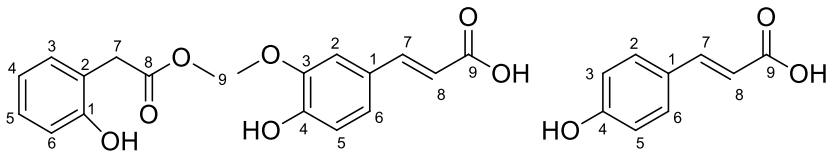
3,4-dihydroxylbenzaldehyde (**51**)

methyl 3,4-dihydroxybenzoate (**52**)

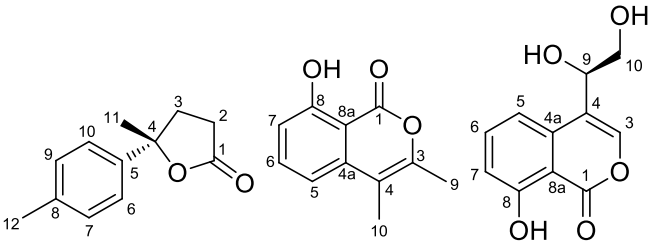


(*E*)-4-(3,4-dihydroxyphenyl)but-3-en-2-one (**53**)

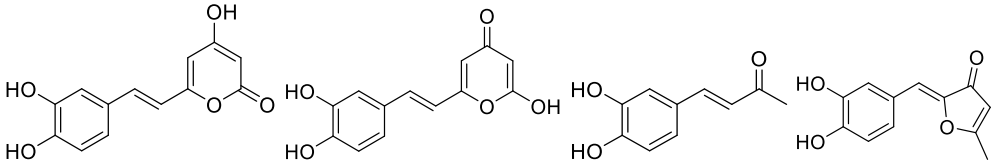
benzoic acid (**54**)



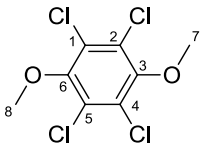
methyl (2-hydroxyphenyl)acetate (**55**) ferulic acid (**56**) trans-p-hydroxycoumaric (**57**)



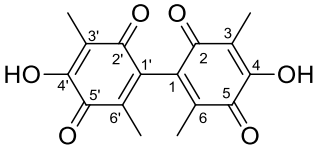
γ-(4-methylphenyl)-*γ*-methyl-*γ*-butyrolactone (**58**) oospolactone (**59**) oospoglycol (**60**)



hispidin (**61**) iso-hispidin (**62**)inonotic acid methyl ester (**63**) inotilone (**64**)



1,2,4,5-tetrachloro-3,6-dimethoxybenzene (**65**)



4,4’-dihydroxy-3,3’,6,6’-tetramethyl-[1,1’-bi(cyclohexane)]-

3,3’,6,6’-tetraene-2,2’,5,5’-tetraone (**66**)

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Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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