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Bioactive metabolites from macrofungi: ethnopharmacology, biological activities and chemistry

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Abstract Exploration of natural sources for novel bioactive compounds has been an emerging field of medicine over the past decades, providing drugs or lead compounds of considerable therapeutic potential. This research has provided exciting evidence on the isolation of microbe-derived metabolites having prospective biological activities. Mushrooms have been valued as traditional sources of natural bioactive compounds for many centuries and have been targeted as promising therapeutic agents. Many novel biologically active compounds have been reported as a result of research on medicinal mushrooms. In this review, we compile the information on bioactive structure-elucidated metabolites from macrofungi discovered over the last decade and highlight their unique chemical diversity and potential benefits to novel drug discovery. The main emphasis is on their anti-Alzheimer, anti-diabetic, anti-malarial, anti-microbial, anti-oxidant, anti-tumor, anti-viral and hypocholesterolemic activities which are important medicinal targets in terms of drug discovery today. Moreover, the reader's attention is brought to focus on mushroom products and food supplements available in the market with claimed biological activities and potential human health benefits.

Keywords Medicinal mushrooms · Anti-oxidant · Anti-tumor · Anti-HIV · Anti-microbial · Anti-viral · Hypocholesterolemic · Anti-diabetic · Anti-Alzheimer · Anti-malarial · Food supplements

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Introduction

Exploration of natural sources for novel bioactive agents may provide leads or solutions for drug discovery and development (Newman and Cragg 2007; Lindequist et al. 2010; Liu et al. 2010b; Pan et al. 2010; Xu et al. 2010; Aly et al. 2011; Debbab et al. 2011, 2012). As the second most diverse group of organisms, it has been postulated that fungal diversity (up to 3 to 5 million species) exceeds that of terrestrial plants by an order of magnitude (Blackwell 2011; Dai 2010). Only a fraction of all fungal species have been described so far (about 100,000) and an even smaller number explored for the production of pharmacologically important metabolites. Yet, some of the most successful drugs and agrochemical fungicides on the market

have been developed from fungal secondary metabolites. Those include antibiotics (penicillins, cephalosporins and fusidic acid), anti-fungal agents (griseofulvin, strobilurins and echinocandins) and cholesterol-lowering agents such as statin derivatives (mevinolin, lovastatin and simvastatin), and immunosuppressive drugs (cyclosporin) (Liu 2002; Li and Vederas 2009; Smith and Ryan 2009; Aly et al. 2011; Hansen et al. 2012; Kozlovskii et al. 2013). Even some potent mycotoxins such as the ergot alkaloids have yielded drugs to treat neurological disorders, such as migraine and mental decline in the elderly, after optimisation by medicinal chemistry (Rosen 1975; Hyde 2001; Liu 2002; Li and Vederas 2009; Zhong and Xiao 2009; Aly et al. 2011; Mulac et al. 2012; Young 2013).

Mushroom forming fungi (phylum Basidiomycota and some Ascomycota) traditionally believed as remedies of many diseases (Sullivan et al. 2006; Petrova et al. 2008, 2009; Aly et al. 2011; de Silva et al. 2012a, b) are known to be prolific producers of bioactive metabolites (Abraham 2001; Kawagishi 2010; Wasser 2011). Particularly in Asia, a variety of mushrooms have been used for centuries as popular medicines to prevent or treat different diseases (Ying et al. 1987; Francia et al. 1999, 2007; Rapior et al. 2000; Lindequist et al. 2005; Poucheret et al. 2006; Ferreira et al. 2010; Aly et al. 2010; Jakopovich 2011; Xu et al. 2011; Wasser 2011; de Silva et al. 2012a, b).

Less intensively investigated organisms such as the macrofungi seem greatly promising in terms of compounds with potential biological activities. In recent decades, interesting compounds of different biogenetic origins have been isolated from Basidiomycota and were found to have antibacterial, antifungal, phytotoxic, cytostatic, antiviral, and other pharmacological activities (Francia et al. 1999, 2007; Rapior et al. 2000; Bao et al. 2001; Keller et al. 2002; Petrova et al. 2005; Poucheret et al. 2006; Zhang et al. 2007; Jeong et al. 2011; de Silva et al. 2012a, b). The aim of this review is to survey the novel bioactive metabolites from mushrooms discovered mainly through the past 10 years and highlights their reported bioactivities and unique chemical diversity, giving potential benefits to novel drug discovery. The reader's attention is also brought to focus on mushroom products and functional food supplements available in market with claimed biological activities and potential benefits on human health.

Medicinally important bioactive metabolites

Medicinal mushrooms have shown therapeutic benefits, primarily because they contain a number of biologically active compounds (Bao et al. 2001; Petrova et al. 2005; Chen and Seviour 2007; Zhang et al. 2007; Lee and Hong 2011).

These includes mainly high molecular weight compounds such as polysaccharides, proteins and lipids as well as a variety of complex low molecular weight metabolites with diverse chemical compositions such as terpenoids, polyketides, alkaloids and metabolites derived from non-ribosomal peptide synthesis (NRPS) (Kidd 2000; Zaidman et al. 2005; Liu 2007; Erkel and Anke 2008; Zhong and Xiao 2009; Ferreira et al. 2010; Lau et al. 2012; Wiemann et al. 2012; Gallo et al. 2013). Although this review mainly focuses on low molecular weight bioactive metabolites, there are many novel high molecular weight compounds which have promising bioactivities. In particular, many polysaccharides (β-glucans), proteins and protein–polysaccharide complexes have been extensively studied for their effective immunostimulatory and other bioactivities (Dai et al. 2012; Li et al. 2012; Maity et al. 2012; Ren et al. 2012; Silva et al. 2012; Wiater et al. 2012; Xu et al. 2012a, b; Yue et al. 2012; Synytsya and Novák 2013).

Low molecular weight metabolites that are not involved in the central metabolic processes of the fungi (the generation of energy and the formation of the building blocks of proteins, nucleic acids, and cell membranes) are known secondary metabolites (Abraham 2001; Petrova et al. 2008; Schüffler and Anke 2009; Kozlovskii et al. 2013). These arise as intermediates of primary metabolism, but they can be classified according to five main metabolic sources. These are (a) amino acid-derived pathways, including NRPS (b) the shikimic acid pathway, giving rise to aromatic compounds, which arise from similar biosyntheses as the aromatic amino acids (c) the acetate–malonate pathway, leading to so-called olyacetylenes or polyketides (d) the mevalonic acid pathway, resulting in the biosynthesis of terpenoids and (e) the polysaccharides and peptidopolysaccharides pathways (Isaac 1997; Zaidman et al. 2005; Erkel and Anke 2008; Lung and Hsieh 2011; Silva et al. 2012). Whereas polyketides and terpenoids have most often been reported from Basidiomycota, Ascomycota frequently also produce polyketides, but the NRPS-derived metabolites are predominant over the terpenoids. Notably, several compounds in Ascomycota are biosynthesised by mixed polyketide–NRPS-derived molecules (Brakhage 2013; Wiemann et al. 2012; Gallo et al. 2013), while mixed terpenoid/polyketides may occur in Basidiomycota such as *Armillaria* (Engels et al. 2011).

Fungal metabolism is also widely used as a method of bioconversion of pharmacologically important metabolites which do not have a fungal origin (Rozman and Komel 1991; Kollerov et al. 2010; Mabinya et al. 2010). Particularly, enzymes from mushrooms are commercially developed for bioconversion of natural metabolites into bioactive products (Asada et al. 2011; Ntougias et al. 2012; Trincone et al. 2012). Several studies have tested for the possibility of producing optimised derivatives of plant-derived pharmaceutical components by fungal fermentation (Kumaran et al. 2008; Yang et al. 2010).

Today, the majority of commercial mushroom products are taken from the fruit bodies collected in the wild or grown

commercially. The field collection often results in unpredictable metabolite profiles, rendering the standardisation of the resulting extract preparations very difficult. Moreover, field collection of large quantities of wild mushrooms is season-dependent, not ecologically sustainable, and may turn into a time-consuming and labor-intensive process as the respective species are becoming harder to find (Yang et al. 2012). The commercial production of fruiting bodies can also sometimes present problems with respect to standardisation of resulting extracts as the optimal conditions to attain reproducible metabolite profiles from the fruit bodies has not yet been fully understood.

Therefore, submerged cultivation of edible and medicinal mushrooms has received increasing attention around the world and is viewed as a promising alternative for efficient production of biomass and valuable metabolites for some mushroom species. The main advantages with cultivation is the faster production of both mycelial biomass and high value-added metabolites, in a shorter period within reducing space and less chance of contamination (Tang et al. 2007; Papaspyridi et al. 2011, 2012; Liu et al. 2012b; Nguyen et al. 2012). Optimization of culture medium composition and the physiological conditions of fungal growth provides a high yield of biomass and large amounts of specific substances of constant composition (Sánchez 2004; Jasinghe et al. 2007; Zheng et al. 2010; Ding et al. 2012; Nguyen et al. 2012; Lam et al. 2012). Optimization of fermentation of basidiomycetes in submerged culture for biotechnological production of bioactive compounds can be accomplished by employing innovative technologies such as bioreactor conversion, and statistical analysis ensures for the maximum biomass production (Lung and Hsieh 2011; Papaspyridi et al. 2011, 2012). Methods based on design of experiments (DOE), for example, the central composite rotatable design (CCRD) have been used to improve the simultaneous production of mycelial biomass and polysaccharides by submerged cultures (Malinowska et al. 2009). The submerged fermentation of the mycelium was advertised to be a promising alternative for production of various bioactive compounds on an industrial scale (Enman et al. 2012; He et al. 2012; Hamedi et al. 2012). However, it cannot be taken for granted that all bioactive metabolites that can readily be obtained from fruit bodies are also produced in the corresponding cultures of the same species or strain. Therefore, we have always emphasized whether the compounds listed in the current review were obtained from the sporocarps or the cultured mycelia.

Anti-oxidant activity

All aerobic life forms existing on earth are associated with oxidation processes, which is vital for their survival. Metabolic oxygen consumption is involved in the biochemical process of cellular respiration that allows energy production. Reactive oxygen species (ROS) derived from oxygen are highly reactive molecules that damage living matter and organisms by oxidation (Davies 2000; Nagy 2001; Halliwell 2006; Valko et al. 2007). Paradoxically, this vital mechanism may also lead to cell and tissue damages causing aging process through production of free radicals and various reactive oxygen species (Turkoglu et al. 2007; Thetsrimuang et al. 2011). These radicals get stabilized by reacting with structural and functional cell components including cellular lipids, proteins and DNA, affecting normal function and leading to various detrimental effects in the long term. These cellular and tissue impairments are recognized as one of the major underlying mechanistic bases of aging and development of pathologies such as diabetes, cardiovascular diseases, neurodegenerative diseases, Alzheimer's disease and cancers (Petersen et al. 2005; Waris and Ahsan 2006; Pham-Huy et al. 2008; Alfadda and Sallam 2012). Therefore the section on anti-oxidative activity of molecules is extremely important, because of the significant implications of oxidative processes, which are the major reason for the development of most other pathological diseases (Lynch et al. 2000; Kregel and Zhang 2007). On the other hand, ROS generation induced by phenols appears to play a key role in the innate immune defense system and its sequential effects, such as tumor cell apoptosis (Wei et al. 2008). Collectively, ROS exert a multitude of biological effects on the whole body energetic, metabolism, state of health and disease and even lifespan.

An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Antioxidants terminate the oxidation chain reactions by removing free radical intermediates, and inhibit other oxidation reactions (Mattill 1947; Sies 1997; Benzie 2003; Halliwell 2012). Recent research on favorable therapeutic effects of natural antioxidants to control certain diseases and to delay aging processes in general, has raised great interest in the pharmaceutical and food industry (Fang et al. 2002; Devasagayam et al. 2004; Valko et al. 2006, 2007; Pandey and Rizvi 2009; Krishnaiah et al. 2010).

The antioxidant properties of wild mushrooms, in particular, have been extensively studied (Song and Yen 2002). For instance, a study carried out with several wild mushroom species revealed very high phenolic concentrations (388 mg GAE/g extract) in basidiocarps of *Fomitopsis pinicola*, along with powerful antioxidant properties, mainly with reducing power (EC_{50} value 60 μg/mL similar to the standard Trolox®) (Reis et al. 2011). Another study tested the anti-oxidant activities of methanol extracts of 16 mushroom species by 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging method (Akata et al. 2012). Among them, *Pleurotus ostreatus* showed the most potent free radical scavenging activity (96.16 %) at 2.72 mg/mL of extract concentration (Akata et al. 2012).

Numerous wild mushroom species were reported to have antioxidant activity, which was mainly related to their

phenolic content, tocopherols, ascorbic acid, and carotenoids, which could be extracted for the purpose of being used as functional ingredients against chronic diseases related to oxidative stress (Ferreira et al. 2009; Oboh and Shodehinde 2009; Huang et al. 2010b; Heleno et al. 2011; Mohsin et al. 2011). The reported compound classes found in these mushrooms were mainly phenolic acids and flavonoids. Notably, these studies rarely used state-of the art of analytical chemistry including analytical and preparative HPLC, high resolution mass spectrometry and NMR spectroscopy. Therefore, the results, e.g. on the occurrence of plant polyphenols in mushrooms must be regarded with caution. For instance, it cannot be excluded that e.g., flavonoid-containing substrates of plant origin, such as cotton seed meal and soybean flour, which are sometimes used in fermentations, are the true sources of the respective metabolites. Other phenolic compounds such as the styryl pyrones treated in detail further below, however, have been isolated to purity and identified by state of the art methods of analytical chemistry from both the sporocarps and the mycelia of various basidiomycete species and are definitely genuine fungal secondary metabolites that even possess chemotaxonomic significance.

Phenolics are aromatic hydroxylated compounds, possessing one or more aromatic rings with one or more hydroxyl groups. The overall effectiveness of a natural phenolic antioxidant depends on the involvement of the phenolic hydrogen in radical reactions, the stability of the natural antioxidant radical formed during radical reactions, and the chemical substitutions present on the structure (Ferreira et al. 2009; Robaszkiewicz et al. 2010). Natural phenolic compounds of many fungi accumulate as end-products from the shikimate-chorismate pathway and can range from relatively simple molecules (phenolic acids, phenylpropanoids (Tsao 2010) to highly polymerized compounds (melanins, tannins) (Ayodele and Okhuoya 2009; Li et al. 2012). Moreover, aromatic products which have developed through shikimate metabolism may be further elaborated to pigments (Gill and Steglich 1987). The initial steps in the biogenesis of these pigments are the well known reactions of primary metabolism which lead from shikimate to chorismate and hence to four precursor groups including arylpyruvic acids, aromatic amino acids (e.g. phenylalanine and tyrosine), hydroxycinnamic acids and *p*-hydroxybenzoic acid (Gill and Steglich 1987; Zhou and Liu 2010; Pazarlioglu et al. 2011; Velíšek and Cejpek 2011).

Many research groups have begun identification of active low-molecular weight compounds in medicinal mushrooms, with a focus on the yellow polyphenol pigments which are referred as styrylpyrones. Interestingly, a representative group of medicinal fungi, mainly belonging to the *Hymenochaetaceae*, including *Phellinus* and *Inonotus* species, were shown to produce a large and diverse range of styrylpyrone-type polyphenol pigments. Sytrylprones are also common in the genera *Pholiota* and *Hypoholoma*, where they constitute bitter principles of inedible mushrooms. Styrylpyrone pigments in mushrooms have various biological activities, including anti-oxidative, anti-tumor, anti-proliferative, anti-diabetic and anti-viral effects important in pharmaceutical applications (Lee et al. 2008a; Lee and Yun 2011; Ayala-Zavala et al. 2012).

Phelligridins are interesting styrylpyrone derivatives from *Inonotus* and *Phellinus* species. Phelligridins C-F showed in vitro selective cytotoxicity against a human lung cancer cell line and a liver cancer cell line. In particular phelligridins C (**1a**) and D showed potent anti-proliferative activities against A549 and Bel7402 with IC_{50} values in the range of 100 nM (Mo et al. 2004). The highly oxygenated phelligridins D, E and G also exhibited significant free radical scavenging activity (Lee et al. 2007b; Lee and Yun 2007), and phelligridin G showed anti-oxidant activity inhibiting rat liver microsomal lipid peroxidation (Wang et al. 2005). The phelligridins H, I, J (**1b,1c,1d**) were isolated from the ethanolic extract of *P. igniarius* showed antioxidative and cytotoxic effects (Wang et al. 2007b; Lu et al. 2009; Huang et al. 2010a, b) (Fig. 1).

The free radical scavengers, inoscavins A-E (Wang et al. 2005; Jung et al. 2008), and methylinoscavins A-D (Lee et al. 2007a, b, c; Jung et al. 2008) were isolated from the fruiting bodies of *I. xeranticus.* Apart from these, interfungins A-C (Lee et al. 2006, 2007c), phelligridins D, F, davallialactone and methyl-davallialactone (Mo et al. 2004; Lee et al. 2006, 2008a, b; Lee and Yun 2006) were also detected in the fungal extract.

A co-culture of *I. obliquus* with *P. punctatus* led to the development of a cost-effective strategy for upregulating biosynthesis of bioactive metabolites with potent anti-tumor and anti-proliferative effects on HeLa 229 cells (Zheng et al. 2011). Increased production and changes in metabolic profiles with metabolites, including phelligridin C (**1a**), phelligridin H (**1b**), methylinoscavin A (**2**), inoscavin B (**3**), inoscavin C (**4**), davallialactone (**5**), methyldavallialactone (**6**), provide an interesting prospect for future on novel bioactive compound discovery from dual cultures of different mushrooms (Zheng et al. 2011). In addition, davallialactone isolated from *Inonotus xeranticus* was found to have potential in the treatment of Diabetes mellitus or age-related disease complications. It is found this can reduce the premature senescence and inflammation on glucose oxidative stress through down-regulation of senescence-associated β-galactosidase (SA β-gal) (Lee et al. 2008b; Yang et al. 2013) (Fig. 1).

An investigation of the methanolic sporocarp extract of *Inonotus obliquus* for free radical scavengers resulted in the identification of several styrylpyrones, including inonoblins A, B **(7)**, and C and the above mentioned phelligridins D, E, and G. These compounds exhibited significant scavenging activity against the ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)) radical cation and DPPH (2,2-diphenyl-1-picrylhydrazyl) radical, and showed moderate activity against the superoxide radical anion (Lee et al. 2007b).

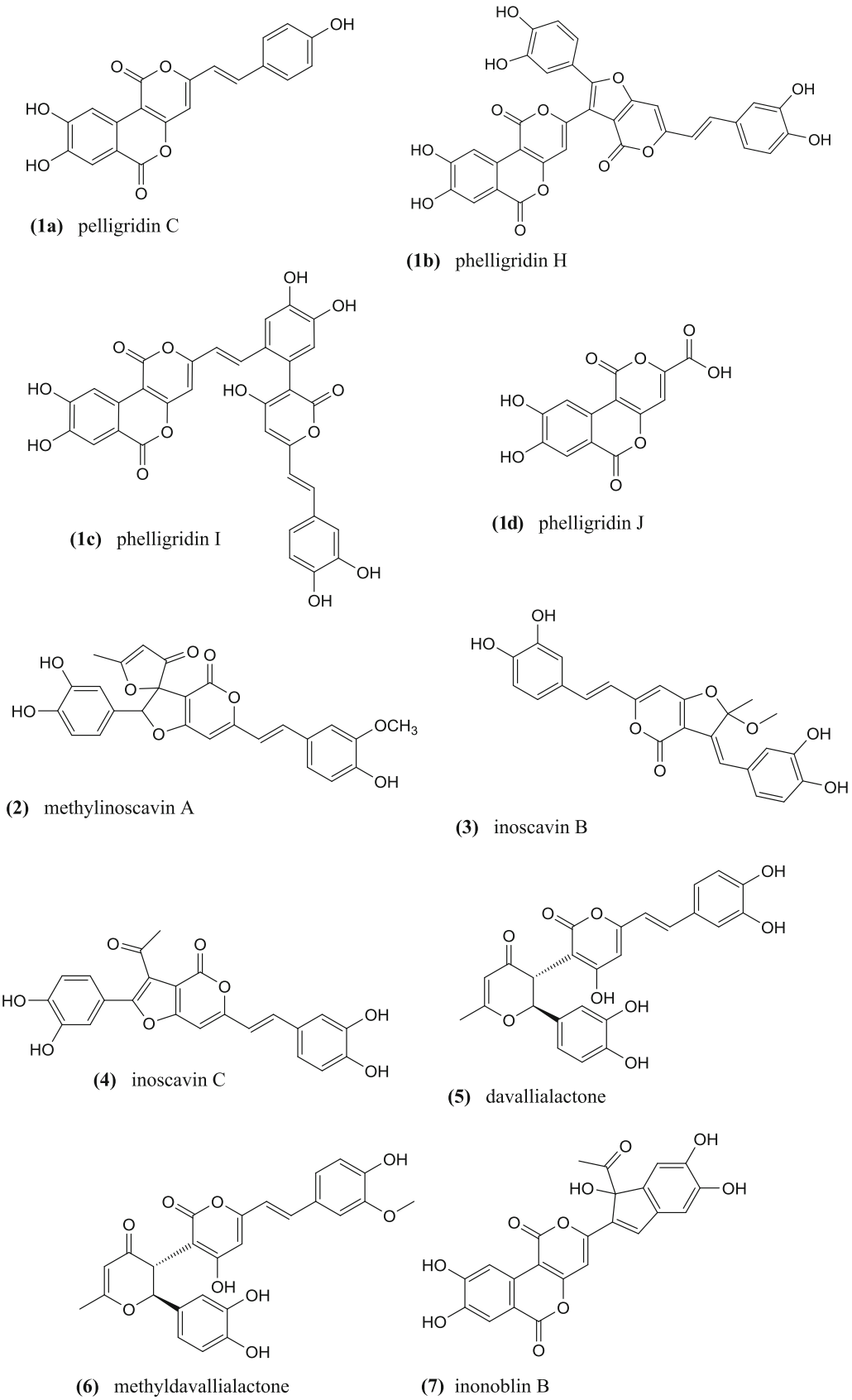


Fig. 1 Chemical structures of selected styrylpyrone derivatives from *Hymenochaetaceae* (genera *Phellinus* and *Inonotus*). The methyl derivatives may constitute artefacts

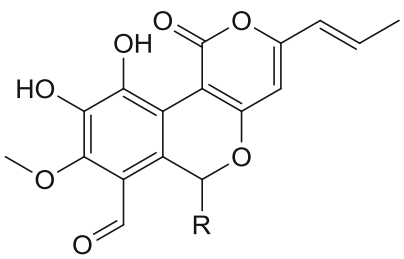
Three new polyketide-type antioxidative compounds, cyathusals A (**8**), B (**9**), and C (**10**), and the known pulvinatal (**11**) were obtained from cultures of the coprophilous mushroom *Cyathus stercoreus* (Kang et al. 2007). These compounds are also polyphenols, despite not being derived from the shikimate pathway (Fig. 2).

Anti-tumor activity

Tumor is a generic term for malignant neoplasms, an abnormal mass of tissue which results due to the autonomous (abnormal proliferation) growth of cells (Nowell 1986; Franks 1997; Ruddon 2007; Anand et al. 2008; Place et al. 2011). Essentially, this term circumscribes several types of diseases that may occur in different parts or organs of the human body (NCI 2011). A compound that is capable of counteracting or preventing the formation of malignant tumors is called anti-tumor agent. Biologically active metabolites found in medicinal mushrooms may provide anti-cancer action with a minimum of side effects. Many recent studies found that bioactive metabolites isolated from mushrooms provide favorable effects in controlling and preventing development of tumors (de Silva et al. 2012a; Petrova 2012; Xu et al. 2012b).

Although it has been reviewed previously, as this is one of the major chronic disease affects millions worldwide, the section on anti-tumor effect is extremely important (Jemal et al. 2009; CDC 2011; de Silva et al. 2012a). Table 1 recapitulates the bioactive compounds with potent anti-tumor activities detected in various mushrooms.

Triterpenes isolated from *Ganoderma* species have been identified as a potent anti-cancer agents (Paterson 2006; Cheng et al. 2010; de Silva et al. 2012a; Wu et al. 2012). Triterpenoids such as ganoderic acids, lucidimols,



(8) cyathusal A R = H
(9) cyathusal B R = OH
(10) cyathusal C R = $OCH(CH_3)_2$
(11) pulvinatal R = OCH_3

Fig. 2 Antioxidant polyketides from cultures of *Cyathus stercoreus*

ganodermanondiol, ganoderiol F and ganodermanontriol have been demonstrated to exert cytotoxic effects on various cancer cells (Chen and Chen 2003; Sliva 2003; Chang et al. 2006; Tang et al. 2006a; Weng and Yen 2010; Chin et al. 2011).

Those cytotoxic triterpenoids have been reported to inhibit human cervical cancer cells, and were also considered as an alternative dietary approach for the prevention of colitis associated cancer (Cheng et al. 2010; Xu et al. 2010). Triterpene-enriched extracts from *Ganoderma lucidum* inhibit the growth of hepatoma cells via suppressing protein kinase C, activating mitogen-activated protein kinases (Lin et al. 2003). Ganoderic acid T (**12**) (Fig. 3) also induces apoptosis of metastatic lung tumor cells through an intrinsic pathway related to mitochondrial dysfunction (Tang et al. 2006b). Recently, semisynthetic modification of ganoderic acid T resulted in more effective anticancer agents (Liu et al. 2012c). Cytotoxicity of a ganoderic acid fraction called GA-Me has been tested on human colon cancer cells (Chen et al. 2008). The activation of the intrinsic mitochondria-dependent apoptotic pathway was identified and the data suggest that GA-Me is a potent natural apoptosis inducing agent for human colon tumors (Zhou et al. 2011).

Another triterpenoid isolated from *G. lucidum* (Fig. 3), ganoderic acid DM **(13)** ADM) effectively inhibited cell proliferation and colony formation in MCF-7 human breast cancer cells. It exerted its antiproliferative effect by inducing cell cycle (G1) arrest and apoptosis in MCF7 cells (Liu et al. 2012d; Wu et al. 2012). In addition, lucidenic acids A, B, C, and N **(14–17)** have been isolated from fruiting bodies of a new strain of *G. lucidum* (YK-02), whose extracts showed anti-invasive effects on hepatoma cells, owing to extraordinary highs level of lucidenic acids (Weng et al. 2007). Moreover, a new ganoderic acid named 3α, 22β-diacetoxy-7α-hydroxy-5α-lanosta-8,24*E*-dien-26-oic acid (**18**) isolated from *G. lucidum* mycelia with considerable cytotoxic activity (Li et al. 2013). Recent research on *Ganoderma* has focused on the antlered form of *G. lucidum* (*G. lucidum* AF) which have stronger pharmacological effects. Investigations showed that *G. lucidum* AF contains a higher amount of triterpenes than normal *G. lucidum* giving potent immunomodulatory and anti-tumor effects (Nonaka et al. 2008; Watanabe et al. 2011).

Lanostane-type triterpenoids, steroids and a benzene derivative were also isolated from ethyl acetate crude extract of *G. zonatum* (Kinge and Mih 2011). Among those, the novel highly oxygenated lanostane triterpenoid, ganoderic acid Y (**19**) showed moderate cytotoxicity against two human tumor cell lines, SMMC-7721 (liver cancer) and A549 (lung cancer)

Table 1 Bioactive compounds with potent anti-tumor activities detected in mushrooms

Mushroom type	Bioactive compound	Biological activity	Reference
Coprinellus radians (*Coprinus radians*)	Guanacastane-type diterpenoids	Antitumor activity	Ou et al. 2012
Fomitopsis nigra	Fomitoside-K	Induce apoptosis via ROS-dependent mitochondrial dysfunction	Bhattarai et al. 2012; Lee et al. 2012
Ganoderma lucidum	Ganoderic acid Me (ganoderic derivative)	Anti-metastatic effect, reduce tumor invasion	Chen et al. 2008
	Ganoderic acids A, F and H	Inhibition of 1. expression of CDK4 2. secretion of uPA 3. adhesion, migration and invasion	Jiang et al. 2008
	Ganoderic acid DM	Anti-proliferative effect	Wu et al. 2012
	Lucidenic acids A, B, C, and N	Inhibition of 1. PMA-induced MMP-9 activity 2. invasion	Weng et al. 2007
Ganoderma lucidum	Ganoderic acid T, Ganoderic acid F	Antimetastatic effect	Xu et al. 2010; Tang et al. 2006a
	11β-Hydroxy-3,7-dioxo-5α-lanosta-8,24(E)-dien-26-oic acid 4,4,14α-Trimethyl-3,7-dioxo-5α-chol-8-en-24-oic acid 12β-Acetoxy-3,7,11,15,23-pentaoxo-5α-lanosta-8-en-26-oic acid ethyl ester	Cytotoxic effect	Cheng et al. 2010
Hexagonia speciosa	Oxygenated cyclohexanoids, speciosin B	Cytotoxicity against tumor cell lines	Jiang et al. 2009, 2011a
Inonotus obliquus	Lanostane-type triterpenoids	Anti-tumor activities	Nakata et al. 2007; Handa et al. 2010
Wolfiporia extensa (*Poria cocos*)	Lanostane-type triterpene acids 25-methoxyporicoic acid A	Antitumor activity	Akihisa et al. 2009

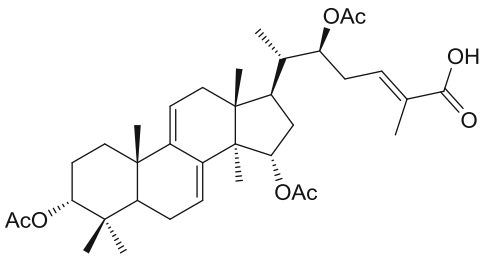
with IC_{50} values of 33.5 and 29.9 μM, respectively and further studies on these compounds may be useful.

Out of several lanostane-type triterpene acids isolated from the epidermis of the sclerotia of *Wolfiporia extensa (Poria cocos)*, the new derivative 25-methoxyporicoic acid A inhibited skin tumor promotion in an in vivo two-stage carcinogenesis test using 7,12-dimethylbenz[*a*]anthracene (DMBA) as an initiator and TPA (12-*O*-tetradecanoylphorbol-13-acetate) as promoters (Akihisa et al. 2009).

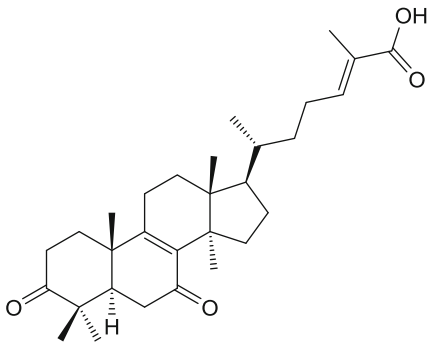
A recent review by Ríos et al. (2012) compiled the most relevant studies on lanostanoids studied recently, principally those isolated from *Ganoderma lucidum* and related species with potential anticancer activity.

Investigation of the fermentation products of *Coprinellus radians (Coprinus radians)* led to isolation of 13 new guanacastane-type diterpenoids, named radianspenes (Fig. 4) (**20**–**24**). These compounds were evaluated for antitumor activity against MDA-MB-435 cells, and radianspene C (**20**) showed inhibitory activity with an IC_{50} of 0.91 μM (Ou et al. 2012).

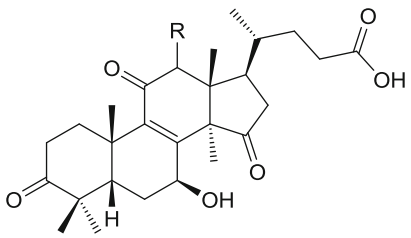
Biologically active metabolites isolated from *Inonotus obliquus* are claimed to provide many health benefits. Aside from the abovementioned stryrylpyrones, a number of novel lanostane-type triterpenoids with potent anti-cancer effects have been reported from the same fungus (Zheng et al. 2010; Kim et al. 2011). The extract of this species also contains polysaccharides and was reported to possess anti-tumor activity with high potential for apoptosis induction in cancer cells (Kim et al. 2006; Song et al. 2008; Nakajima et al. 2009; Youn et al. 2009). A recent study demonstrated the in vitro anticancer activity of fraction IO4 isolated from *I. obliquus* which was attributed to decrease tumor cell proliferation, motility and induction of morphological changes (Lemieszek et al. 2011). Previous studies reported the structures of new lanostane-type triterpenoids from the sclerotia of this mushroom: inonotsuoxides A (**25**) and B (**26**) (Nakata et al. 2007), inonotsulides A, B, and C (Taji et al. 2007), inonotsutriols A, B, and C (Taji et al. 2008a), inonotsutriols D (**27**), and E (**28**) (Tanaka et al. 2011; Fig. 5), lanosta-8,23*E*-diene-3β,22*R*,25-triol (**29**), lanosta-7:9(11),23*E*-triene-3β,22*R*,25-triol (**30**) and 3β-hydroxylanosta-8,24-dien-21-al (**31**) (Taji et al. 2008b), as well as the anti-tumor promoting activities of the most abundant triterpene, inotodiol (**32**). The latter compound



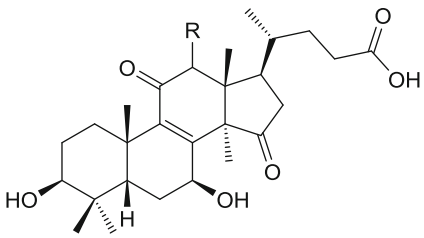
(12) ganoderic acid T



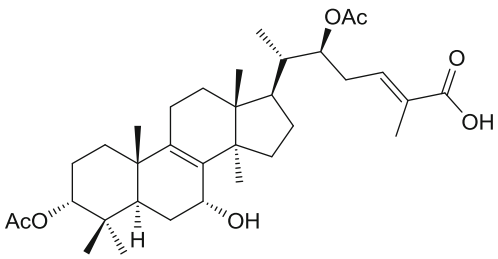
(13) ganoderic acid DM



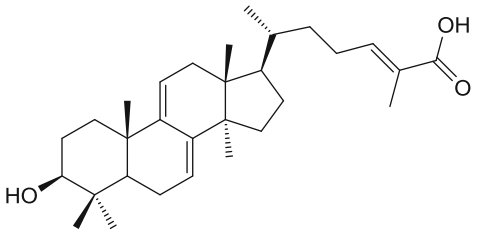
(14) lucidenic acid A R = H
(15) lucidenic acid B R = β-OH



(16) lucidenic acid C R = β-OH
(17) lucidenic acid N R = H



(18) 3α,22β-diacetoxy-7α-hydroxy-5α-lanosta-8,24*E*-dien-26-oic acid



(19) ganoderic acid Y

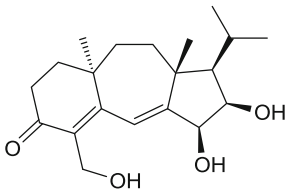
Fig. 3 Chemical structures of selected novel triterpenoids with anticancer activity from *Ganoderma lucidum*

inhibited cell proliferation through caspase-3-dependent apoptosis (Nomura et al. 2008).

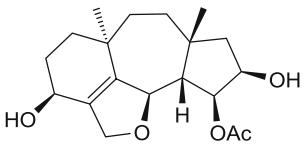
Sclerotia of *I. obliquus* also yielded an unusual lanostane-type triterpene and named spiroinonotsuoxodiol (**33**) and two further new lanostane-type triterpenoids, inonotsudiol A (**34**) and inonotsuoxodiol A (**35**) with moderate cytotoxic activity. Their structures were determined by NMR spectroscopy (Handa et al. 2010).

Cordycepin (**36**) or 3′-deoxyadenosine (Fig. 6), is a derivative of the nucleoside adenosine, isolated from *Cordyceps*

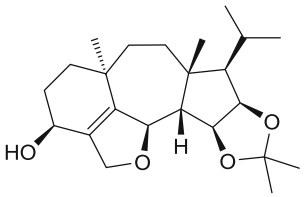
Fig. 4 Chemical structures of selected radianspenes with anticancer activities from cultures of *Coprinellus radians*



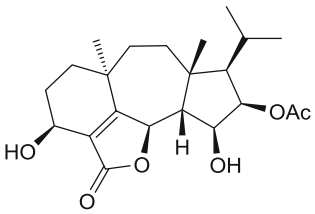
(20) radianspene C



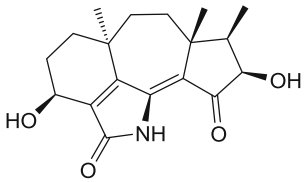
(21) radianspene E



(22) radianspene F



(23) radianspene H



(24) radianspene J

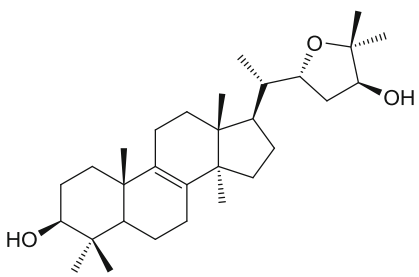
sinensis and *C. militaris* with anti-cancer and anti-proliferative effects (Yoshikawa et al. 2004; Khan et al. 2010; Paterson 2008; Wong et al. 2010; Jeong et al. 2011). Numerous studies have been undertaken to understand the mechanism of action of cordycepin against cancer cells. According to Wong et al. (2010) the two main effects of cordycepin appear to be the inhibition of polyadenylation at low doses and the activation of AMP-activated kinase pathway at higher doses. A recent study stressed on activity as cordycepin sensitizes cells to TNF-α induced apoptosis via induction of particular stress signaling and consequent suppression of NF-kB (Kadomatsu et al. 2012). Even though cordycepin analogues and derivatives seem to be weakly active, many research groups are still working on their potential bioactivities (Wong et al. 2010; Jeong et al. 2011; Lee et al. 2012).

A new sesquiterpene with a novel carbon skeleton, flammulinol A **(37)**, new isolactarane sesquiterpene and six isolactarane-related norsesquiterpenes, flammulinolides A-G (**38**–**44**), as well as sterpuric acid, were isolated from the solid culture of *Flammulina velutipes* (Fig. 6). Several of these compounds showed moderate cytotoxicity against KB cells with IC_{50} between 3.6 and 4.7 μM. Flammulinolide C (**40**) also showed cytotoxicity against HeLa cells with an IC_{50} of 3.0 μM (Wang et al. 2012a). In addition, solid culture extracts of *F. velutipes* grown on cooked rice yielded bioactive sesquiterpenoids with weak to moderate cytotoxic activities against human cancer cell lines (Wang et al. 2012b).

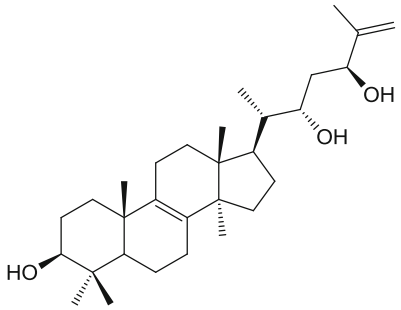
A new lanostane triterpene glycoside named fomitoside-K **(45)** (Fig. 7) from the fruiting bodies of the polypore mushroom *Fomitopsis nigra* induced apoptosis of human oral squamous cell carcinomas (YD-10B) via the ROS-dependent mitochondrial dysfunction signaling pathway (Bhattarai et al. 2012; Lee et al. 2012).

Extracts of mycelia and fruiting bodies of *Antrodia camphorata* are potential chemotherapeutic agents against many cancer types, including leukemia, hepatic, prostate, breast, bladder, and lung cancer cells in adjuvant cancer therapy (Hsu et al. 2007; Peng et al. 2007; Lu et al. 2009; Yang et al. 2011; Yue et al. 2012). Five lanostanes (3β,15α-dihydroxylanosta-7,9(11),24-triene-21-oic acid (**46**), dehydroeburicoic acid (**47**), 15α-acetyl-dehydrosulphurenic acid (**48**), dehydrosulphurenic acid (**49**) and sulphurenic acid **(50)**) and three ergostane-type triterpenes (methyl zhankuic acid A (**51**), zhankuic acid A (**52**) and zhankuic acid C (**53**) (Fig. 7), all isolated from fruiting bodies of *A. camphorata*, exhibited in vitro cytotoxic effects against various cancer cell lines, including human breast cancer cells (Yeh et al. 2009). Antrocin (**54**) (Fig. 7), from the fruiting bodies of *A. camphorata* showed the strongest anti-proliferative effect against MDA-MB-231 and MCF-7 cells with an IC_{50} value of 0.6 μM (Rao et al. 2011). 4,7-dimethoxy-5-methyl-1,3-benzodioxole (**55**) (Fig. 7) isolated from the fruiting bodies of *A. camphorata* showed potent in vivo antitumor effects through activation of the p53-mediated p27/Kip1 signaling pathway (Tu et al. 2012). Moreover, antroquinonol, a ubiquinone derivative, induced a concentration-dependent inhibition of cell proliferation in pancreatic cancer PANC-1 and AsPC-1 cells through an inhibitory effect on PI3-kinase/Akt/mTOR pathways that down-regulate cell cycle regulators (Yu et al. 2012).

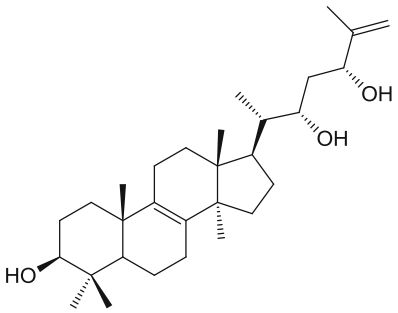
Investigations of the mushroom *Hexagonia speciosa* (*Polyporaceae*), which is widely distributed in the tropical and subtropical regions of China (Zhao 1998) have resulted in the discovery of a series of oxygenated cyclohexanoids (Fig. 8) (Jiang et al. 2009; Fig. 8). The cyclohexanoids,



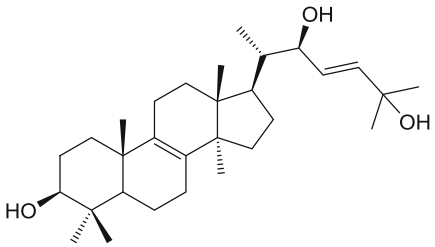
(25) inonotsuoxide A (*22R*-Form)
(26) inonotsuoxide B (*22S*-Form)



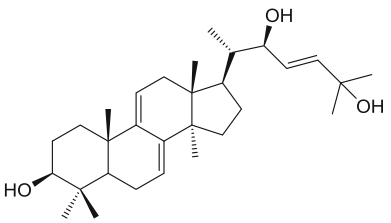
(27) inonotsutriol D



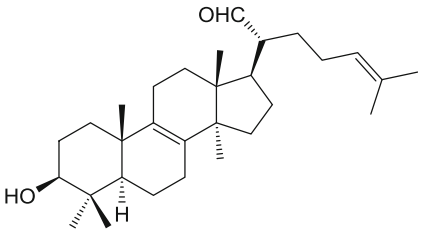
(28) inonotsutriol E



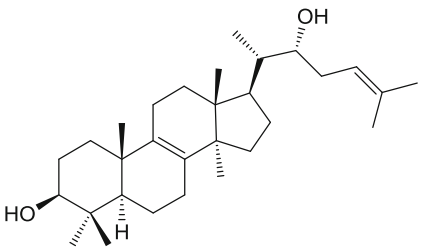
(29) lanosta-8,23*E*-diene-3β,22*R*,25-triol



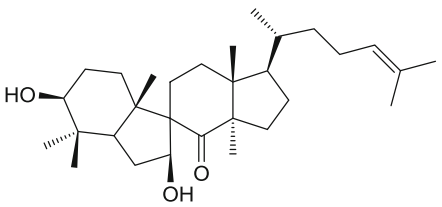
(30) lanosta-7,9(11),23*E*-triene-3β,22*R*,25-triol



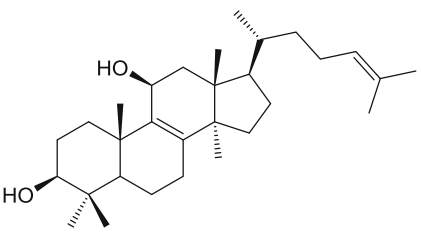
(31) 3β-hydroxylanosta-8,24-dien-21-al



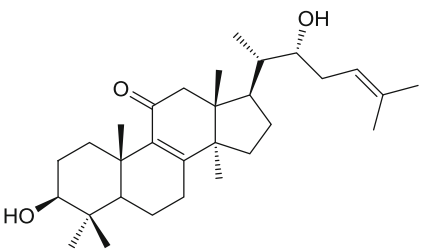
(32) inotodiol



(33) spiroinonotsuoxodiol



(34) inonotsudiol A



(35) inonotsuoxodiol A

Fig. 5 Chemical structures of triterpenoids with anticancer activities from *Inonotus* species

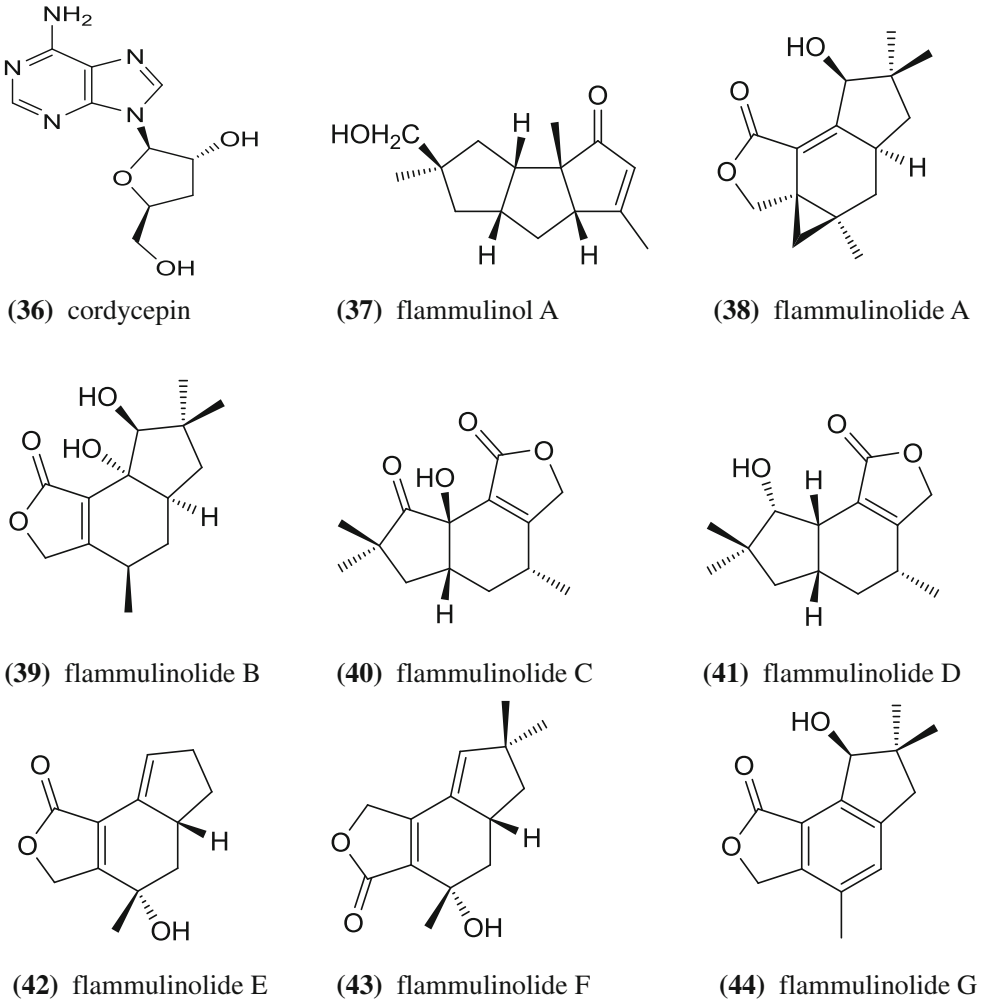


Fig. 6 Chemical structures of cordycepin **(36)**, and cytotoxic terpenoids (**37**–**44**) from *Flammulina velutipes*

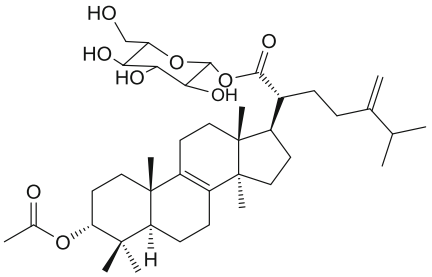
speciosins L–T (**57**–**65**), as well as the 5*H*-furan-2-one metabolite, 5′-O-acetylaporpinone A (**66**) were obtained together with the known speciosins A, B, D, E, F, I and K (**67**–**73**) and aporpinone A **(74)** from scale-up cultures of the fungus. Among these compounds, speciosin B (**68**) showed significant cytotoxicity against several tumor cell lines with IC_{50} values in the range of 0.23–3.30 μM (Jiang et al. 2009, 2011a).

Arnamial (**75**), a new Delta(2,4)-protoilludane everninate ester (Fig. 9) from cultures of the fungus *Armillaria mellea*, showed cytotoxicity against Jurkat T cells, MCF-7 breast adenocarcinoma, CCRF-CEM lymphoblastic leukemia, and HCT-116 colorectal carcinoma cells at IC_{50}=3.9, 15.4, 8.9, and 10.7 μM, respectively (Misiek et al. 2009; Misiek and Hoffmeister 2012).

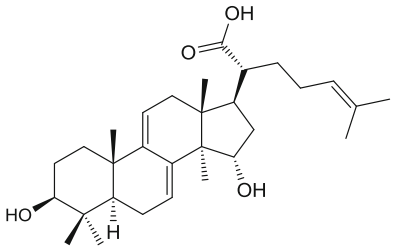
Irofulven (**56**) (Fig. 7), also known as 6-hydroxymethylacylfulvene and MGI-114, is a promising semi-synthetic anti-cancer agent derived from illudin-S, a sesquiterpenoid originally isolated from cultures of the mushroom *Omphalotus illudens* with improved therapeutic potential (McMorris et al. 1996; McMorris 1999; Schobert et al. 2011).

Irofulven acts as potent inhibitor of DNA synthesis and induces apoptosis in the nanomolar range (Woynarowski et al. 1997; Kelner et al. 2008). However, its cytotoxicity seems to be more specifically directed against malignant cells and the redox homeostasis that is maintained protects normal cells from the effects of irofulven (Leggas et al. 2002; Raymond et al. 2004). The exact mechanism of action of this compound is still under investigation (Gregerson et al. 2003; Wiltshire et al. 2007). However, an enhanced anti-tumor activity of irofulven was observed in combination with other anti-cancer agents (Poindessous et al. 2003; Serova et al. 2006; Kelner et al. 2008), other anti-angiogenic or chemotherapeutic drugs (Alexandre et al. 2004; Woo et al. 2005; Hilgers et al. 2006; Dings et al. 2008).

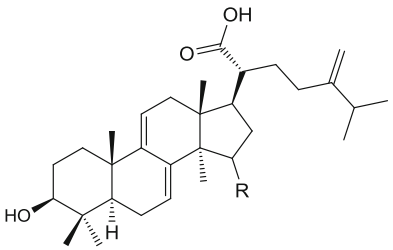
Irofulven produced different results in phase I and II trials of human cancer cell lines, including advanced melanoma (Pierson et al. 2002), advanced renal cell carcinoma (Alexandre et al. 2007) and pretreated ovarian carcinoma



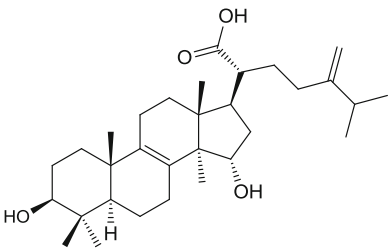
(45) fomitoside-K



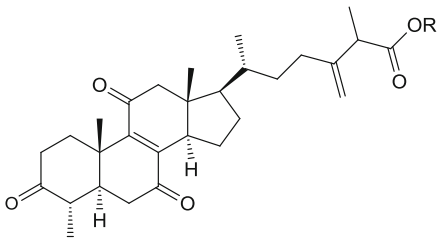
(46) 3β,15α-dihydroxylanosta-7,9(11),24-trien-21-oic acid



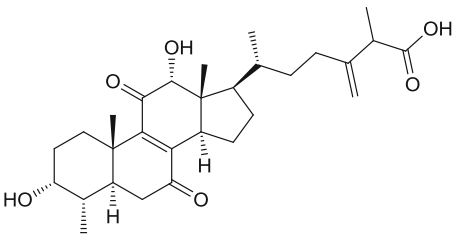
(47) dehydroeburicoic acid R = H
(48) **15**α-acetyl-dehydrosulphurenic acid R = α-OAc
(49) dehydrosulphurenic acid R = α-OH



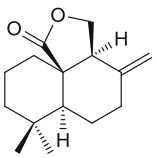
(50) sulphurenic acid



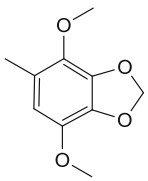
(51) methyl antcinate B R = CH_3
(52) zhankuic acid A R = H



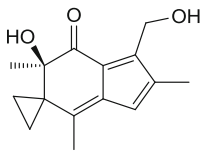
(53) zhankuic acid C



(54) antrocin



(55) 4,7-dimethoxy-5-methyl-1,3-benzodioxole



(56) irofulven

Fig. 7 Chemical structures of triterpenoids and other compounds with anticancer activity from *Fomitopsis nigra* (**45**), *Antrodia camphorata* (**46**–**55**), and of the investigational drug, irofulven (**56**), which is inspired from the illudin sequiterpenoids, derived from *Omphalotus spp*.

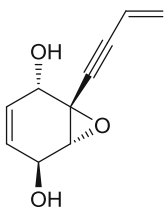
(Seiden et al. 2006; Schilder et al. 2010). In addition to these investigations, another class of semisynthetic analogs of the natural product illudin S, acylfulvenes (AFs) serve as a useful tool for evaluating protein and nucleic interactions, and considerable cytotoxic activities (Pietsch et al. 2011).

Most recent research on the analysis concerning the draft genome sequence of *O. olearius* revealed a diverse network of sesquiterpene synthases and two metabolic gene clusters associated with illudin biosynthesis. Genomic methods may soon substantially facilitate discovery and biosynthetic production of unique pharmaceutically relevant bioactive compounds from Basidiomycota (Wawrzyn et al. 2012a).

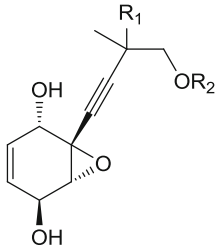
Anti-viral activity

Despite the advances in modern medicine, human viral infections continue to kill millions throughout the world (Merican

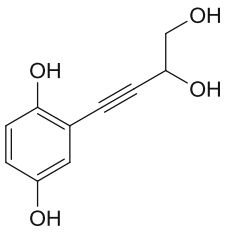
Fig. 8 Bioactive polyketides *from Hexagonia speciosa*



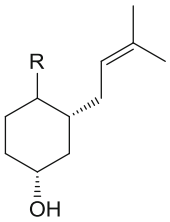
(57) speciosin L



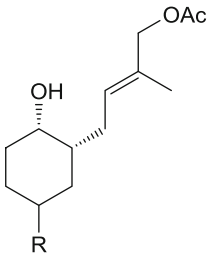
(58) speciosin M $R_1 = H$, $R_2 = Ac$
(59) speciosin N $R_1 = OH$, $R_2 = H$
(60) speciosin O $R_1 = OH$, $R_2 = Ac$



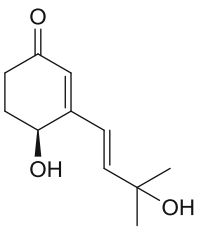
(61) speciosin P



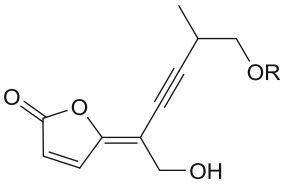
(62) speciosin Q R = β-OH
(72) speciosin I R = α-OH



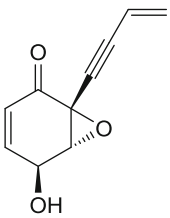
(63) speciosin R R = α-OH
(64) speciosin R R = β-OH



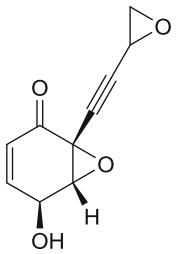
(65) speciosin T



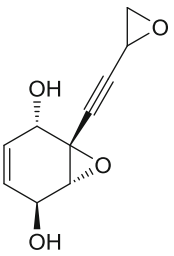
(66) 5'-O-acetylaporpinone A R = Ac
(74) aporpinone A R = H



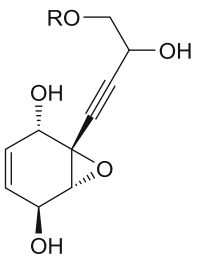
(67) speciosin A



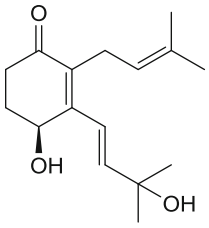
(68) speciosin B



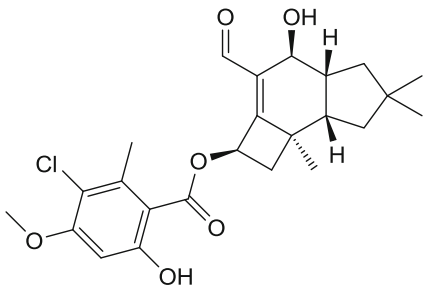
(69) speciosin D



(70) speciosin E R = H
(71) speciosin F R = CH_3



(73) speciosin K



(75) arnamial

Fig. 9 Chemical structure of arnamial

et al. 2000; Kuiken et al. 2003; Shepard et al. 2005). A major difficulty in designing safe and effective antiviral drugs is the fact that viruses use the host's cells to replicate and the virus subtypes often show considerable variability (Jones 1998; De Clercq and Field 2006). Furthermore, this makes it hard to find targets for the drug that would interfere with the virus without also harming the host organism's cells. Antiviral drugs are a group of medication used specifically for treating viral infections. Nowadays, about 40 synthetic and semi-synthetic drugs (the latter of which are derived from plant or bacterial metabolites) have been approved for clinical use in the treatment of viral infections (De Clercq and Field 2006; DeChristopher et al. 2012). However, in recent decades many natural products have been recognized by the pharmaceutical industry because of their wide structural diversity, as well as a variety of pharmacological activities (Jones 1998; De Clercq and Field 2006). Above all, fungal metabolites, especially from basidiomycetes, have stimulated interest from investigators.

Antiviral effects of mushrooms are exerted not only by their crude extracts but also from isolated compounds. These active principles may act directly by inhibition of viral enzymes, synthesis of viral nucleic acids or adsorption and uptake of viruses into mammalian cells. The triterpenoids, ganodermadiol (**76**), lucidadiol (**77**) and applanoxidic acid G (**78**), isolated from *Ganoderma pfeifferi* (Fig. 10) and known from other *Ganoderma* species, possess in vitro antiviral activity against influenza virus type A (IC_{50} values in MDCK cells >0.22; 0.22 and 0.19 mM, respectively). Further, ganodermadiol is active against herpes simplex virus type 1, an important virus causing lip exanthema and other symptoms (IC_{50} in Vero cells 0.068 mM) (Mothana et al. 2003). Antiviral activity against type A influenza virus of birds and humans A/Aichi/2/68 (H3N2) was investigated for aqueous extracts from mycelia of 11 basidiomycete species. The most promising species identified as potential producers of antiviral agents in these studies were *Daedaleopsis confragosa, Datronia mollis, Ischnoderma benzoinum, Laricifomes officinalis*, *Lenzites betulina, Trametes gibbosa* and *T. versicolor* (Kabanov et al. 2011; Teplyakova et al. 2012).

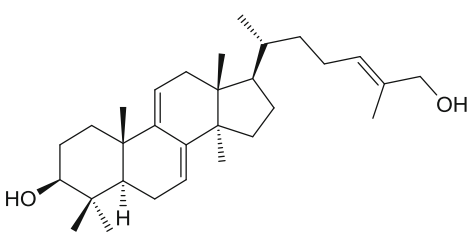
Aqueous and ethanol extracts, as well as polysaccharide fractions of *Lentinula edodes* showed antiviral activity against the replication of poliovirus (PV-1) and bovine herpes virus (BoHV-1) (Rincão et al. 2012). The authors concluded that extracts act on the initial processes of the replication of both strains of virus. However, it remains unclear how such hydrophilic macromolecules with unfavorable pharmaceutical properties can eventually find application in antiviral therapy, perhaps aside from viral skin diseases.

A novel illudane–illudane bis-sesquiterpene, agrocybone (**79**), from the basidiomycete *Agrocybe salicacola*, found to exhibit weak antiviral activity against respiratory syncytial virus (RSV) with IC_{50} value of 100 μM (Zhu et al. 2010). Notably, the above mentioned bioactivities were all determined in vitro, and it may need further research to develop a pharmaceutical drug from these fungi.

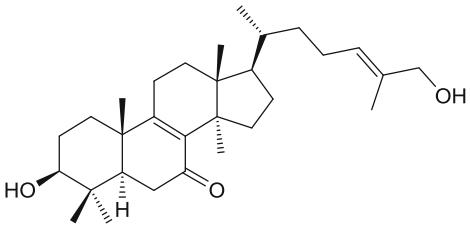
The human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS) which has become a serious disease worldwide and is responsible for a great number of deaths. The general effects found in patients of HIV infected encompass immunodeficiency, decline in ability to combat infections, opportunistic infections, malignant tumors, and nerve handicaps (Mallery et al. 1999; Spano et al. 2006; Rumbaugh and Nath 2006). The distribution of AIDS is worldwide, and it has become one of the most difficult viral diseases to treat.

Recent advances in research have made renewal interest on finding cures for HIV from natural products (Ng et al. 1997; Ngai and Ng 2003; Cassels and Asencio 2011; DeChristopher et al. 2012). There is currently no cure for AIDS. However, it is encouraging to note that novel treatments have been made with the discovery of new drugs and the combination therapy. Bioactive compounds isolated from mushrooms act as Reverse-Transcriptase Inhibitors (RTIs), and help in inhibition of HIV multiplication. Highly active antiretroviral therapy (HAART) is a powerful HIV treatment that was introduced in the mid-90s. Reverse-transcriptase inhibitors (RTIs) are a class of antiretroviral drug used to treat HIV infection, which inhibit activity of reverse transcriptase (a viral DNA polymerase enzyme that retroviruses need to reproduce). RTIs block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying (Ravichandran et al. 2008). The extract of *Russula paludosa* demonstrated inhibitory activity on HIV-1 RT (97.6 %). A peptide isolated from the extract, exhibited potent inhibitory activity on HIV-1 RT at concentrations of 1 mg/ml, 0.2 mg/ml, and 0.04 mg/ml, the inhibition ratios were 99.2 %, 89.3 %, and 41.8 %, respectively, giving an IC_{50} of 11 μM (Wang et al. 2007a).

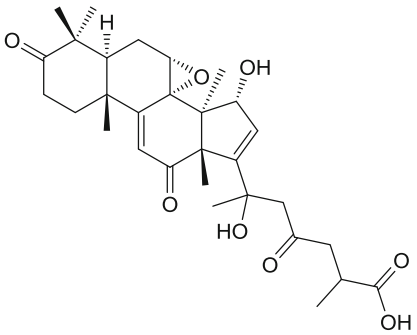
Three antioxidant compounds, namely adenosine (**80**), dimethylguanosine (**81**) and iso-sinensetin (**82**) from fruiting bodies of *Cordyceps militaris* were also found to possess moderate HIV-1 protease inhibiting activities (Jiang et al.



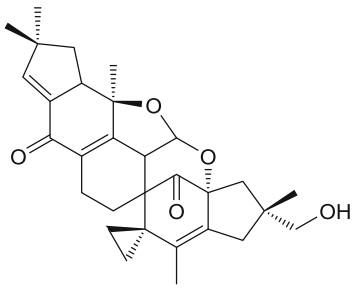
(76) ganodermadiol



(77) lucidadiol



(78) applanoxidic acid G



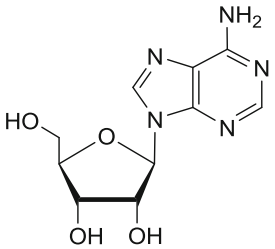
(79) agrocybone

Fig. 10 Chemical structures of antiviral triterpenes (**76**–**78**) from *Ganoderma pfeifferi*, and of the antiviral sesquiterpene dimer agrocybone (**79**) from *Agrocybe salicacicola*

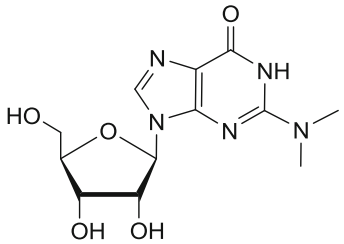
2011b) (Fig. 11). Whereas nucleosides have been very frequently reported from *Cordyceps*, the flavonoids could be derived from the substrate, rather than from the fungus itself.

Previous studies confirmed the close relationship between oxidative stress and AIDS, suggesting that antioxidants might play an important role in treatment of AIDS (Foster 2007). Moreover, HIV-1 protease (HIV-1 PR) is a retroviral aspartyl protease (retropepsin) that is essential for the life-cycle of HIV, which causes AIDS. Further investigations on their antioxidant and anti-HIV-1 PR mechanisms might be rewarding, as HIV-1 PR has been a prime target for drug therapy. In addition, the new diketopiperazines, epicoccins E-H, isolated from the culture of a *Cordyceps*-colonizing fungus (*Cordyceps sinensis*), *Epicoccum nigrum* and showed inhibitory effects on HIV-1 replication in C8166 cells (Guo et al. 2009). Epicoccin G **(83)** showed inhibitory effects on HIV-1 replication in C8166 cells, with EC_{50} value of 13.5 μM (Fig. 11).

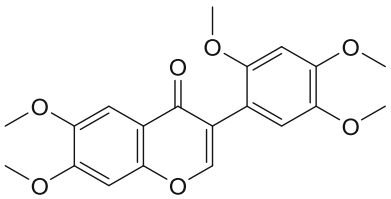
Apart from the above proteineaous compounds reported from mushrooms several low molecular weight terpenoids showed potent inhibitory activity against human



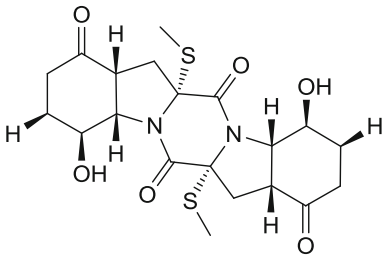
(80) adenosine



(81) dimethylguanosine



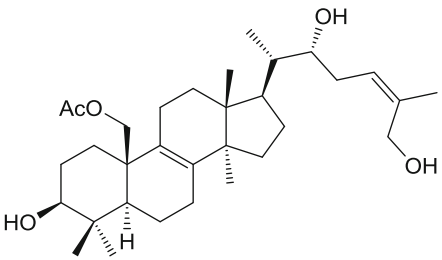
(82) iso-sinensetin



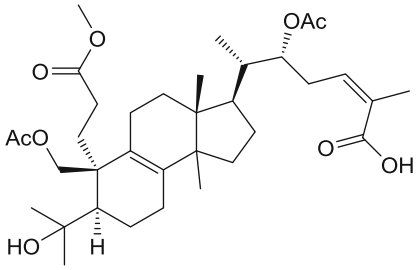
(83) epicoccin G

Fig. 11 Chemical structures of adenosine (**80**), dimethylguanosine (**81**), iso-sinensetin (**82**) from cultures of *Cordyceps militaris* and epicoccin G (**83**) from *Cordyceps sinensis*-colonizing fungus *Epicoccum nigrum*

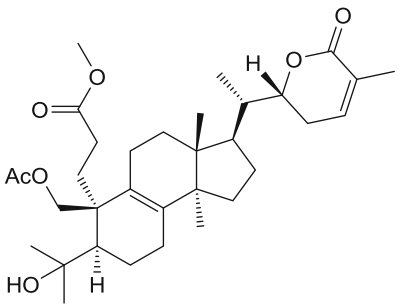
Fig. 12 Chemical structures of antiviral triterpenoids (**84**–**93**) from *Ganoderma* species



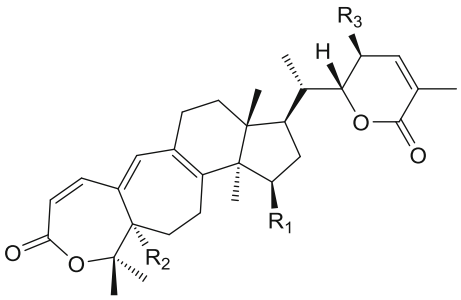
(84) colossolactone A



(85) colossolactone V



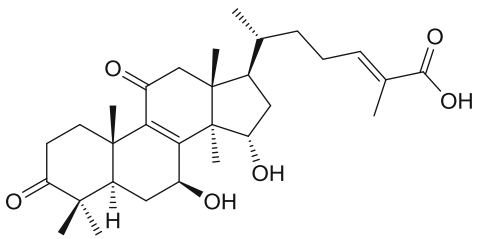
(86) colossolactone VII



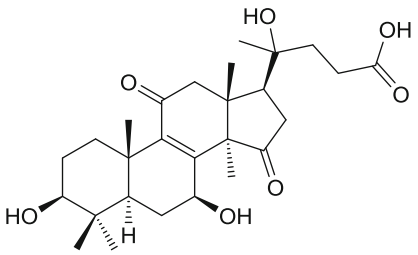
(87) colossolactone VIII R_1 = OAc, R_2 = H, R_3 = OH

(88) colossolactone G R_1 = OAc, R_2 = OH, R_3 = H

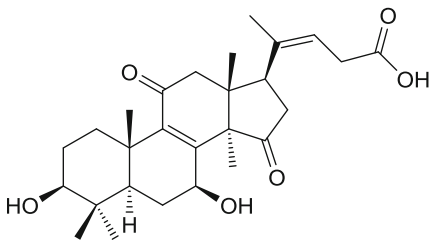
(89) schisanlactone A $R_1 = R_2 = R_3$ = H



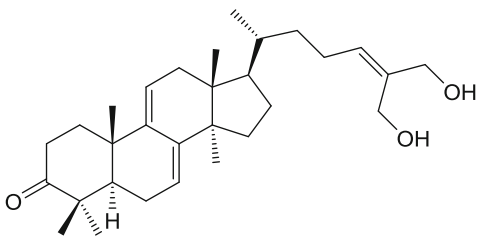
(90) ganoderic acid GS-2



(91) 20-hydroxylucidenic acid N



(92) 20(21)-dehyrolucidenic acid N



(93) ganoderiol F

immunodeficiency virus. Several lanostane triterpenes named colossolactones (Fig. 12; Table 2) have been isolated from the fruiting bodies of *Ganoderma colossum* (Min et al. 1998; Kleinwächter et al. 2001; El Dine et al. 2008). These were tested for inhibition of HIV-1 protease, and several showed IC_{50} values in the 5–39 μg/mL range, with colossolactone V (**85**), colossolactone G (**88**), and schisanlactone A (**89**) exhibiting values below 10 μg/ml (El Dine et al. 2008). Five new and six previously known lanostane-type triterpenoids (**84**–**93**) (Fig. 12) were isolated from the fruiting body of *Ganoderma sinense* and tested for inhibition of HIV-1 protease. Of these, the new ganoderic acid GS-2(90), and the previously described 20-hydroxylucidenic acid N (**91**), 20(21)-dehydrolucidenic acid N (**92**), and ganoderiol F (**93**), were active at IC_{50} values of 20–40 μM (Sato et al. 2009).

Table 2 Fungal bioactive compounds potent anti-HIV and other activities detected in mushrooms

Mushroom species	Bioactive compound	Biological activity	References
Cordyceps militaris	Adenosine, iso-sinensetin and dimethylguanosine	Inhibition of HIV-1 protease	Jiang et al. 2011b
Ganoderma lucidum	Lucidenic acid O, lucidenic lactone, ganoderiol, ganoderic acid (24*S*)-24,25-dihydroxylanost-8-ene-3,7-dione and 3β,7β-dihydroxy-11,15-dioxolanosta-8,24(*E*)-dien-26-oic acid	Anti-HIV-1 Anti-HIV-1-Protease	Min et al. 1998
Ganoderma colossum	Colossolactones	Inhibition of HIV-1 protease	Kleinwächter et al. 2001; El Dine et al. 2008
Ganoderma sinense	Ganoderic acid GS-2, 20-hydroxylucidenic acid N, 20(21)-dehydrolucidenic acid N, ganoderiol F	Inhibition of HIV-1 protease	Sato et al. 2009
Russula paludosa	Peptides	Inhibition of HIV-1 RT	Wang et al. 2007a

Anti-microbial activity

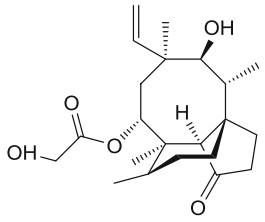
An antimicrobial agent is a substance that inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Mushrooms are rich sources of natural antibiotics. For instance, the cell wall glucans are not only well- known for their immunomodulatory properties, but many of the excreted secondary metabolites of the mycelium combat bacteria (Deyrup et al. 2007) and fungi (Kettering et al. 2005; Gilardoni et al. 2007). A well known example of diterpenoid antibiotic pleuromutilin (**94**) (Fig. 13) has been isolated previously which was derived from the fungus *Clitopilus passeckerianus* (former name: *Pleurotus passeckerianus*) (Novak and Shlaes 2010). Further research led to the discovery of retapamulin, which is a C_{14}-sulfanyl-acetate derivative of pleuromutilin with improved pharmacological properties and was developed as an antibiotic drug (Nagabushan 2010).

There is a renewed interest regarding the finding of antibacterial compounds as many pathogenic bacteria species have acquired antibiotic resistance mechanisms that have limited treatment options (Boucher et al. 2009). Several studies have concluded that some of these antibiotic drugs could lead to drug induced hepatotoxicity, which would be more severe in patients with hepatitis or HIV (Sharma and Mohan 2004; Andrade and Tulkens 2011). This renewed interest on exploration for natural antimicrobial compounds from mushrooms has resulted in numerous mushroom extracts being tested with considerable positive activities reported (Barros et al. 2007; Iwalokun et al. 2007; Ramesh and Pattar 2010; Gazzani et al. 2011; Ochoa-Zarzosa et al. 2011; Harikrishnan et al. 2011, 2012; Alves et al. 2012a, b; Schwan 2012).

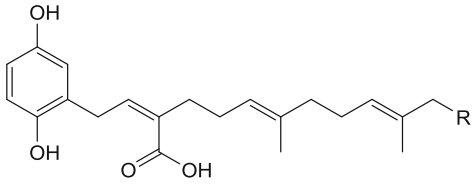
Numerous studies on antimicrobial potential of *G. lucidum* are well documented. Two new farnesyl hydroquinones named ganomycin A **(95)** and ganomycin B **(96)** were isolated from *G. pfeifferi* (Fig. 13). Both compounds exhibited antimicrobial activity against several Gram-positive and Gram-negative bacteria (Mothana et al. 2000). *Staphylococcus aureus* infections are a major cause of illness and death and impose serious economic costs on patients worldwide (Boucher and Corey 2008). Infections with *S. aureus* are especially difficult to treat because of evolved resistance to antimicrobial drugs and there is an urgent need for novel anti-bacterial drugs (Klein et al. 2007). Antimicrobial activities of *Ganoderma lucidum, G. praelongum* and *G. resinaceum* were evaluated against 30 strains of clinical isolates of methicillin-resistant and -sensitive *Staphylococcus aureus.* The ethyl acetate extract of *G. praelongum* containing sesquiterpenoids exhibited the maximum activity (35.67± 0.62 μm) and minimum inhibitory concentration (MIC) of 0.390–6.25 mg/mL (Ameri et al. 2011).

Tuberculosis, mediated by *Mycobacterium tuberculosis* is one of the most serious chronic infectious diseases, causing about 2–3 million deaths per year (Corbett et al. 2003). There is urgent need for new anti tubercular compounds, especially those from natural products in order to overcome the difficulties of side effects of current medicines and minimize the multi-drug resistant of the organism (Ginsberg 2010; Barrios-Garcia et al. 2012). Lanostane triterpenes with moderate activity against *M. tuberculosis* were characterized from the Earth Star mushroom, *Astraeus pteridis* as astraodoric acid A (**97**) and B (**98**), (Fig. 13) from *A. odoratus* having MICs of 50 and 25 μg /mL, respectively (Stanikunaite et al. 2008; Arpha et al. 2012). In addition novel butenolides, ramariolides A–D, isolated from the fruiting bodies of the coral mushroom *Ramaria cystidiophora*, showed in vitro antimicrobial activity against *Mycobacterium smegmatis* and *M. tuberculosis* (Centko et al. 2012). Among the novel lanostane triterpenoids, ganorbiformins A–G, isolated from *Ganoderma orbiforme* BCC 22324, the C-3 epimer of ganoderic acid T also exhibited significant antimycobacterial activity with MIC 1.3 μM (Isaka et al. 2013).

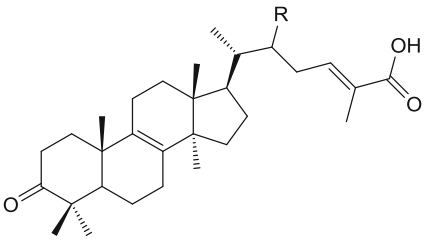
Other lanostane triterpenoids from *Fomitopsis rosea*, *F. pinicola*, *Jahnoporus hirtus*, and *Albatrellus flettii* displayed activities against *Bacillus* and *Enterococcus* species (Popova



(94) pleuromutilin



(95) ganomycin A R = OH
(96) ganomycin B R = H



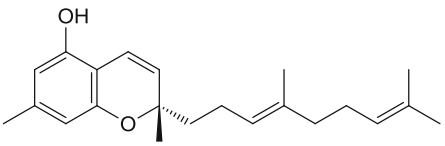
(97) astraodoric acid A R = α-OAc
(98) astraodoric acid B R = α-OH

Fig. 13 Chemical structures of pleuromutilin (**94**) from *Clitopilus passeckerianus*, ganomycins A (**95**) and B (**96**) from *Ganoderma pfeifferi* and astraodoric acids A and B (**97**, **98**) from *Astraeus odoratus*

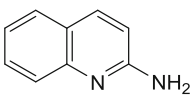
et al. 2009; Liu et al. 2010a, b). Important clinical infections caused by *Enterococcus* include urinary tract infections, bacterial endocarditis, diverticulitis, and meningitis and an important feature of this genus is the high level of intrinsic antibiotic resistance (Fisher and Phillips 2009).

Coprinol, a new antibacterial cuparane-type terpenoid from cultures of a *Coprinus* sp. exhibited activity against multidrug-resistant Gram-positive bacteria (Johansson et al. 2001). Micaceol, a sterol and (*Z, Z*)-4-oxo-2,5-heptadienedioic acid were isolated from "*Coprinus"* (currently valid name *Coprinopsis*) *micaceus* with activities against *Corynebacterium xerosis* and *S. aureus* (Zahid et al. 2006). Coloratin A [3,5-dimethoxy-2-(6-oxo-5-pentyl-6H-pyran-3-carbonyl)-benzoic acid] and coloratin B (2-carbomethoxyl-3,5-dimethoxybenzoic acid) extracted from a fungus named *Xylaria intracolorata* had reasonable antimicrobial activity against several microbes (Quang et al. 2006). Liu et al. (2010b) isolated novel compounds with effective antimicrobials from two American mushroom species, *Jahnoporus hirtus* and *Albatrellus flettii* (Fig. 14). 3,11-dioxolanosta-8, 24(*Z*)-diene-26-oic acid, a new lanostane-type triterpene from *J. hirtus* and confluentin **(99)**, grifolin (**100**), and neogrifolin (**101**) from *A. flettii*. Grifolin showed promising activities against *Bacillus cereus* (10 μg/mL) and *Enterococcus faecalis* (0.5 μg/mL). Fungal extracts and compounds screened for anti bacterial activity among thirteen microorganisms and 2-aminoquinoline (2-AQ) (**102**), isolated from *Leucopaxillus albissimus*, showed strong inhibitory activity against *Cytophaga johnsonae* (Schwan et al. 2010).

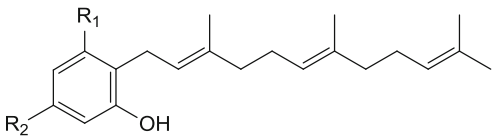
Plectasin, a macromolecular peptide, the first defensin (cysteine-rich host defense peptide) that has been isolated from the saprotrophic ascomycete *Pseudoplectania nigrella* demonstrated strong antimicrobial activity against gram-positive bacteria including *Streptococcus pneumoniae* (Mygind et al. 2005). Extracts from the fruit bodies of the medicinal mushroom *Hericium erinaceus* inhibited the adverse in vivo effects of *Salmonella* in mice via stimulation of the immune system (Kim et al. 2012). *Armillaria* species,



(99) confluentin



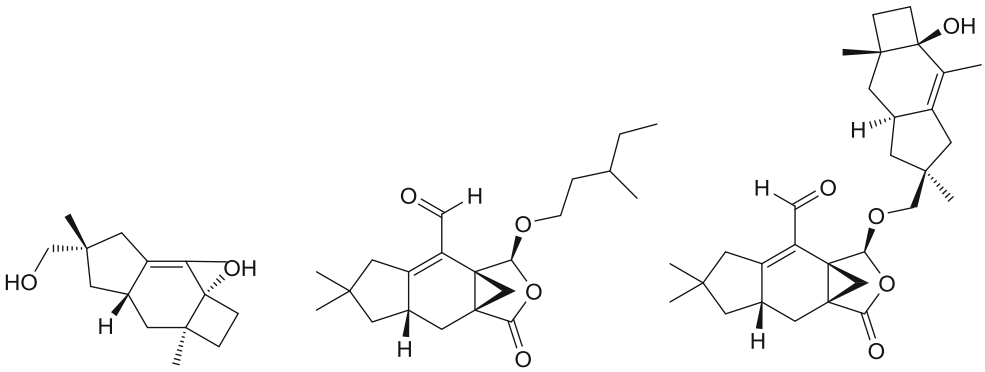
(102) 2-aminoquinoline



(100) grifolin R_1 = OH, R_2=CH_3
(101) neogrifolin R_1 = OH_3, R_2=CH

Fig. 14 Chemical structures of confluentin (**99**), grifolin (**100**) and neogrifolin (**101**) from *Albatrellus* spp. and 2-aminoquinoline (**102**) from *Leucopaxillus albissimus*

Fig. 15 Chemical structures of antifungal sesquiterpenoids from cultures of *Phlebia uda*



(103) udasterpurenol A **(104)** udalactarane A **(105)** udalactarane B

having great potential of anti-microbial effect with capacity to produce many sesquiterpene aryl esters while arnamial is a most active compound and showed a minimum inhibitory concentration of <5 μg/mL on four basidiomycetes and *Penicillium oxalicum* (Misiek and Hoffmeister 2012).

Three new sesquiterpenoids, named udasterpurenol A (**103**) and udalactaranes A (**104**) and B (**105**), have been isolated from a new basidiomycete *Phlebia uda* (Fig. 15). The compound inhibited the spore germination of the plant pathogenic fungus *Fusarium graminearum* (Schüffler et al. 2012).

Although there are number of studies available in the literature, they are almost entirely focused on the screening of antibacterial properties of mushroom extracts. In fact, there is a gap in the identification of the individual compounds responsible for those properties, and only a few low-molecular weight compounds and some peptides and proteins have been described. Antibiotic resistance with evolution of superbug bacterial species is a serious and growing phenomenon in modern medicine and this information illustrates the new avenues opens with novel anti-microbial compounds from medicinal mushrooms.

Anti-malarial agents

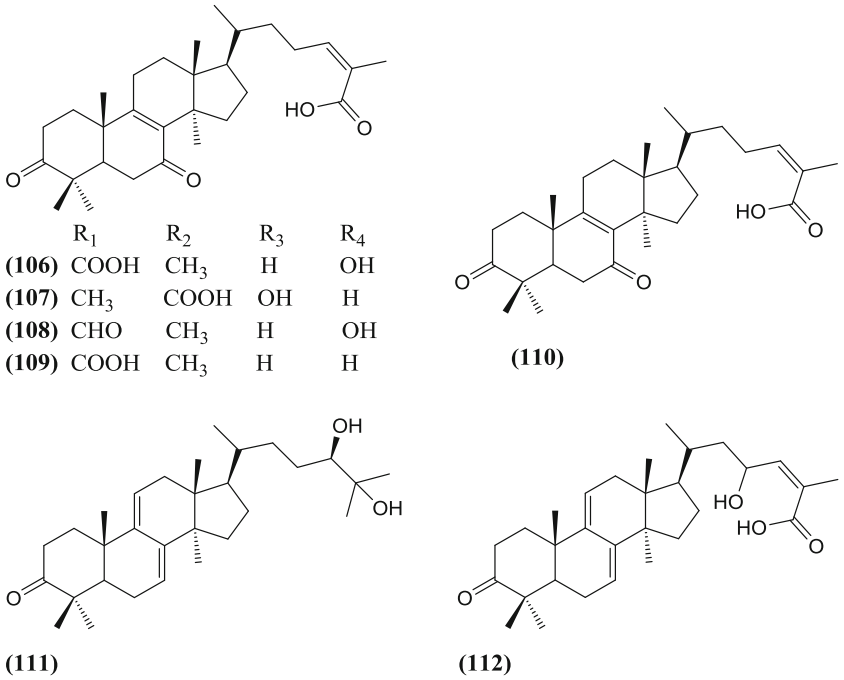
Malaria remains the world most devastating human parasitic infection, afflicting more than 500 million people and causing about 2.5 million deaths each year. It is an infectious disease caused by main four protozoan species of the genus *Plasmodium* (*Plasmodium falciparum*, *P. malariae*, *P. ovale,* and *P. vivax*) (Mendis et al. 2009). There are still very few drugs that are active against malaria (artemisinin, atovaquone, and chloroquine analogues) (Wells et al. 2009; Gamo et al. 2010) and any direct therapeutic agents were not yet available (Wells et al. 2009; Anthony et al. 2012; Kulangara et al. 2012).

The increasing resistance to existing antimalarial drugs demands the exploration of novel drugs and treatment efforts to eliminate this deadly disease. Natural products contain a great variety of chemical structures and have been screened for antiplasmodial activity as potential sources of new antimalarial drugs (Batista et al. 2009; Kaur et al. 2009; Katsayal et al. 2009; Krettli 2009; Gamo et al. 2010; Nogueira and Lopes 2011).

HPLC-based activity profiling and subsequent chromatography of the ethyl acetate extract of *Ganoderma lucidum* yielded six lanostanes (**106**–**112**) of which three (**107**, **108**, **112**) were new (Fig. 16). These lanostanes exhibited moderate in vitro antiplasmodial activity with IC_{50} values of 6 to 20 μM (Adams et al. 2010).

Investigation of the chemical constituents of fungus, *Cordyceps nipponica* BCC 1389 led to the identification of four isolates of *N*-hydroxy- and *N*-methoxy-2-pyridones compounds (Fig. 17), namely cordypyridones A-D (**113**–**116**). Out of these, the cordypyridones A and B, which are atropisomers of each other, exhibited potent in vitro antimalarial activity with IC_{50} values of 0.066 and 0.037 μg/mL, respectively (Isaka et al. 2001). *Cordyceps unilateralis* BCC 1869 was found to produce bioactive naphthoquinones, which possess anti-malarial activity (Kittakoop et al. 1999; Wongsa et al. 2005). Previously reported bioxanthracenes of ES-242s and their analogues from the insect pathogenic fungus *Cordyceps pseudomilitaris* BCC 1620 (on a Lepidoptera larva) showed moderate antimalarial activity (Jaturapat et al. 2001), while ES-242s derivative exhibited similar activity (IC_{50} 3.3 μM) in another study (Isaka et al. 2007). The sterostreins are five novel terpenoids from cultures of the mushroom *Stereum ostrea* BCC 22955 and out of those, sterostrein A (**117**) (Fig. 17) exhibited considerable antimalarial activity (IC_{50} 2.3 μg/mL) against *P. falciparum* as well (Isaka et al. 2011, 2012).

Neonothopanus nambi Speg. (*Marasmiaceae*) is a novel poisonous luminescent mushroom which is phylogenetically related to *Omphalotus*. Six new sesquiterpenes, a known aristolane dimeric sesquiterpene and aurisin A were recently isolated and characterized as antiparasitic principles from cultures of this fungus (Kanokmedhakul et al. 2012). Aurisin A (**118**) as well as a new dimeric sesquiterpene, aurisin K (**119**)



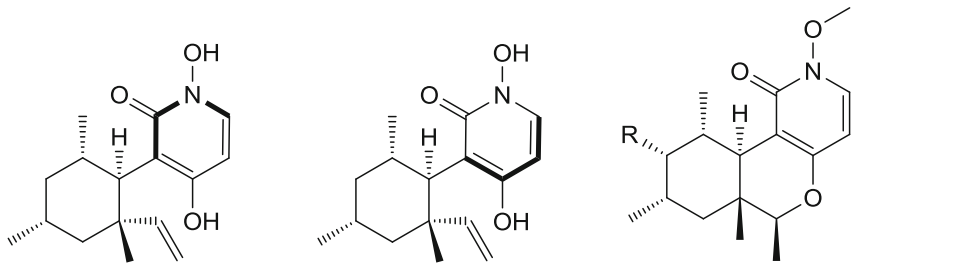
	R_1	R_2	R_3	R_4
(106)	COOH	CH_3	H	OH
(107)	CH_3	COOH	OH	H
(108)	CHO	CH_3	H	OH
(109)	COOH	CH_3	H	H

(110)

(111)

(112)

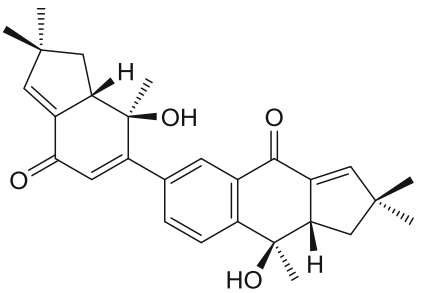
Fig. 16 Chemical structures of antiplasmodial triterpenoids (**106**–**112**) from *Ganoderma lucidum*



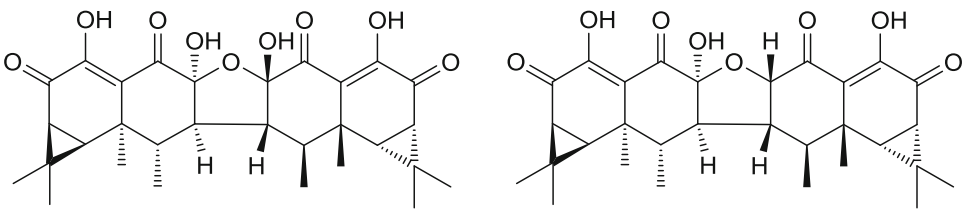
(113) cordypyridone A

(114) cordypyridone B

(115) cordypyridone C R = H
(116) cordypyridone D R = OH



(117) sterostrein A



(118) aurisin A

(119) aurisin K

Fig. 17 Chemical structures of antiparasitic agents from fungi: cordypyridones A-D (**113**–**116**) from *Cordyceps nipponica*, sterostrein A (**117**) from *Stereum ostrea*, aurisins A (**118**), and K (**119**) from *Neonothopanus nambi*

(Fig. 17) exhibited excellent antimalarial activity against *Plasmodium falciparum* and antimycobacterial activity against *Mycobacterium tuberculosis* (Kanokmedhakul et al. 2012).

Anti-Alzheimer's disease

Alzheimer's disease is the most common form of dementia (Salmon 2012). Most often, this is diagnosed in people over 65 years of age. Alzheimer's disease is a progressive neurologic disease of the brain leading to the irreversible loss of neurons and the loss of intellectual abilities, including memory and reasoning, which becomes severe enough to impede social or occupational functioning (Shen 2004). During the course of the disease plaques and tangles develop within the structure of the brain. This causes brain cells to die. Patients with Alzheimer's also have a deficiency in the levels of some vital brain chemicals which are involved with the transmission of messages in the brain- neurotransmitters.

According the National Institute on Aging, there are estimated to be between 2.4 million and 4.5 million Americans who have Alzheimer's (Anonymous 2008). The main characteristic of the brains of Alzheimer's disease patients is the accumulation of insoluble fibrillar senile plaques around the neuron cells and neurofibrillary deposits of hyperphosphorylated tau proteins (Duyckaerts et al. 2009). The main component of these plaques is an amino acids peptide called amyloid β-peptide (Aβ). This then causes a deficiency of neurotransmitters, general loss of neural functions, and death of neural cells, which all eventually lead to the development of Alzheimer's disease (Christen 2000; Smith et al. 2000; Sastre et al. 2006). So far, several drug candidates have been developed to cure Alzheimer's disease. However, neuroprotective activity of current drugs for curing Alzheimer's disease is still under debate (Khan et al. 2009; Mangialasche et al. 2010). Therefore, many studies worldwide have concentrated on exploration of novel treatment methods and drugs from natural sources (Khan et al. 2009; Wender et al. 2011; Pasinetti 2012; Young 2013). Moreover, alternative methods such as traditional/oriental medicinal practices are also being evaluated for their therapeutic utility in combating these devastating diseases (Seo et al. 2010a, b; Jeon et al. 2011).

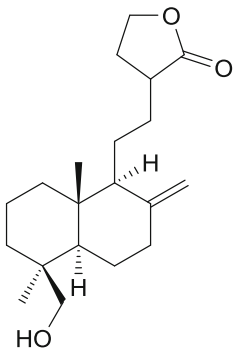
Three new labdane diterpenes (**120**–**122**), isolated from the fruiting body of *Antrodia camphorata* showed neuroprotective effects in vitro (Fig. 18) (Chen et al. 2006). The terpenoids isolated from *Antrodia* species also prevented serum deprivation-induced PC12 cell apoptosis, with potential neuroprotective effects (Huang et al. 2005; Lu et al. 2008) and potential in suppressing amyloid β-peptide (Aβ) accumulation. A recent study compared the in vitro and in vivo effects of the fruiting body and mycelium of *A. camphorata* against amyloid β-protein-induced neurotoxicity and memory impairment. The fruiting body possessed stronger abilities than that of the mycelium for inhibiting neurocytotoxicity, amyloid β-peptide 40 (Aβ40) accumulations in brain and suppression of hyperphosphorylated tau (p-tau) protein expression, both in vitro and in vivo. Tau protein is a highly soluble microtubule-associated protein (MAP) that stabilizes microtubules. Hyperphosphorylation of the tau protein (pTau) can result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved in the pathogenesis of Alzheimer's disease (Alonso et al. 2001). These comparisons supported the fact that the fruiting body extracts possessed more significant improvement effect on working memory ability than mycelium in the AD rats (Wang et al. 2012c).

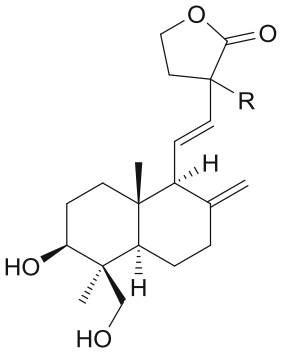
Neurotrophic factors are important in better neuronal function and hence neurotrophic factor-like substances or their inducers are expected to be applied to the treatment of neurodegenerative diseases such as Alzheimer's disease. Extracts from cultures of *Hericium erinaceus* showed neurotrophic effects and improved the mycelination process in the matue mycelinating fibers (Moldavan et al. 2007). A double-blind, parallel-group, placebo-controlled clinical trial was performed with oral administration of *H. erinaceus*, demonstrating significant improvement of cognitive impairment (Mori et al. 2009).

Some of the compounds responsible for these effects have already been identified. Hericenones and erinacines are terpenoids isolated from *H. erinaceus*, which can easily cross the blood–brain barrier (Moldavan et al. 2007; Kawagishi and Zhuang 2008; Ma et al. 2010). The erinacines in particular have potential as medicines for degenerative neuronal disorders and peripheral nerve regeneration, as oral administration of erinacine A significantly increases the level of nerve growth factor (NGF) in the rat's locus coeruleus and hippocampus, but not in the cerebral cortex (Shimbo et al. 2005). Another study also revealed that yet unknown active compounds that are not hericenones can stimulate NGF synthesis via activation of the JNK pathway (Mori et al. 2008).

Neuronal cell death is an essential cause of neurodegenerative disease including Alzheimer's, Parkinson's, Huntington's and the prion diseases and it is induced by endoplasmic reticulum (ER) stress (Kawagishi et al. 1994; Shimoke et al. 2004). Compounds able to reduce ER stress are useful in attenuation of neuronal cell death and, hence, in the reduction of the damage, which occurs in neurodegenerative disease (Kawagishi et al. 1994).

Dilinoleoyl-phosphatidylethanolamine, another compound from *Hericium erinaceus* protects against ER stress-dependent neuronal cell death of Neuro2a cells via protein kinase C pathway (Nagai et al. 2006). Further extensive studies on the bioactive constituents of the same mushroom resulted in the isolation of 3-hydroxyhericenone F **(123)**. This compound (Fig. 18) showed protective activity against endoplasmic reticulum (ER) stress dependent Neuro2a cell death (Ueda et al. 2008).

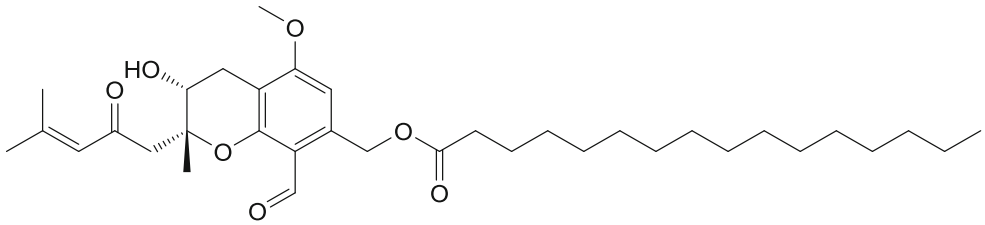




(120) 19-hydroxylabda-8(17)-en-16,15-olide

(121) 3β,19-dihydroxylabda-8(17),11*E*-dien-16,15-olide R = H (α or β)

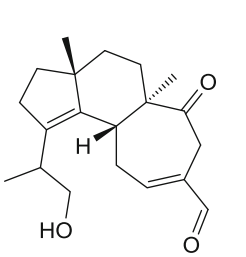
(122) 13-*epi*-3β,19-dihydroxylabda-8(17),11*E*-dien-16,15-olide R = H (β or α)



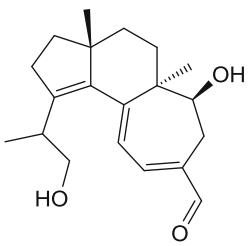
(123) 3-hydroxyhericenone F

Fig. 18 Chemical structures of neuroprotective labdane terpenoids (**120**–**123**) from *Antrodia camphorata*

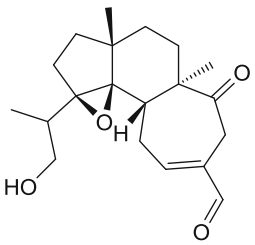
Some cyathane diterpenoids, named scabronines and sarcodonins (Fig. 19) were isolated from the fruiting bodies of the basidiomycete *Sarcodon scabrosus.* Sarcodonins G and A (**124, 125**) at 25 μM showed significant neurite outgrowth (neurite genesis)-promoting activity in the presence of 20 ng/mL NGF after 24 h treatment (Shi et al. 2011). Most recently



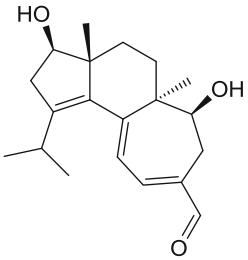
(124) sarcodonin G



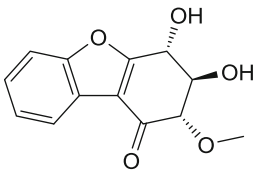
(125) sarcodonin A



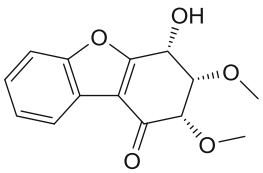
(126) scabronine M



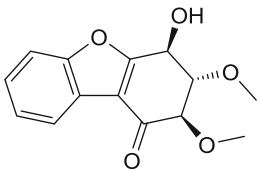
(127) cyrneine A



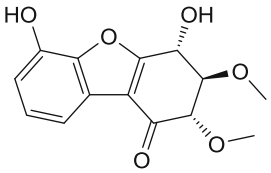
(128) ribisin A



(129) ribisin B



(130) ribisin C



(131) ribisin D

Fig. 19 Chemical structures of neuroprotective agents from basidiomycetes: cyrneine A (**127**) and other cyathanes (**124**–**126**) from *Sarcodon* species, benzofuran derivatives (**128**–**131**) from *Phellinus ribis*

scabronine M (**126**) significantly inhibited dose-dependently NGF-induced neurite outgrowth in PC12 cells without cytotoxicity, possibly through suppressing the phosphorylation of the receptor Trk A and the extracellular signal regulated kinases (ERK) (Liu et al. 2012e). Novel cyathane diterpenes, i.e., cyrneines A and B from *Sarcodon cyrneus*, induce neurite outgrowth in the PC12 cell model of neuronal differentiation and cyrneine A **(127)** even enhances neurite outgrowth in a Rac1-dependent mechanism in PC12 cells (Marcotullio et al. 2006; Obara et al. 2007).

In addition, four new benzofuran derivatives (Fig. 19), ribisin A **(128)**, ribisin B **(129)**, ribisin C **(130)**, and ribisin D **(131)**, were isolated from the methanolic extract of the fruiting bodies of *Phellinus ribis*. These compounds promote neurite outgrowth in NGF-mediated PC12 cells at concentrations ranging from 1 to 30 μM (Liu et al. 2012f).

Hypocholesterolemic activity

Hypercholesterolemia is the medical term for the presence of excess levels of cholesterol in the blood and it is a form of "hyperlipidemia" elevated levels of lipids in the blood and "hyperlipoproteinemia" elevated levels of lipoproteins in the blood (Biggerstaff and Wooten 2004). Epidemiological studies suggested that hypercholesterolemia and hyperglycemia were the major risk factors for cardiovascular disease and diabetes, which were largely influenced by diet (Kaur et al. 2002; Tourlouki et al. 2009; Mahdy et al. 2012). According to the recent records cardiovascular disease and diabetes are the major causes of morbidity and mortality in the world including majority of western countries and in the Asia-Pacific region (Eckel et al. 2006; Ali et al. 2012; Celermajer et al. 2012).

Fungal products have already been demonstrated to have effectiveness in lowering lipid levels such as red yeast rice which is the fermented byproduct of cooked rice with a strain of *Monascus purpureus* (Huang 2007; Becker et al. 2009). Indeed, edible mushrooms are an ideal food for the dietetic prevention of cardiovascular disease including atherosclerosis due to their high fiber and low fat content. A novel study reported that considerable production of lovastatin, a cholesterol-lowering drug obtained from the extracts of *Omphalotus olearius* OBCC 2002 and from *Pleurotus ostreatus* OBCC 1031 (Atli and Yamac 2012). Interestingly, Lovastatin, identified from *Pleurotus* species and its derivatives were reported to be a good therapeutic agents for ameliorating hypercholesterolemia (Gunde-Cimerman and Plemenitas 2001; Mattila et al. 2001; Alarcón and Aguila 2006). Even though the latter authors report the isolation of lovastatin by HPLC, such studies should be regarded with caution and further studies are warranted, since lovastatin and other statins have predominately been found in Ascomycota, and no NMR data of the compound isolated from the basidiomycetes were presented.

3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase is the key enzyme in cholesterol biosynthesis, which converts HMG-CoA to mevalonate. Therefore, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins are most commonly used in hyperlipidemic treatments (Steinberg et al. 1989; Shimada et al. 2003). HPLC analytical methods have determined significant amounts of this inhibitor in mushroom fruiting bodies of *P. ostreatus*, particularly in the pileus and sporocarps. The beneficial effects of oyster mushroom on blood serum parameters may be attributed to the presence of various biologically active compounds such as polysaccharides, mevinolin and other statins, linoleic acid, ergosterol, ergosterol derivatives, protocatechuic acid, chlorogenic acid, naringenin, hesperetin, and biochanin-A (Mattila et al. 2001; Alarcón and Aguila 2006; Alam et al. 2008, 2010; Schneider et al. 2011). Previous studies have also confirmed the hypocholesterolemic and hypolipidemic activity of this mushroom and recommended for consumption as a natural cholesterol-lowering agent in the human diet (Bobek et al. 1994, 1995, 1998; Gunde-Cimerman 1999).

Eritadenine [2(*R*), 3(*R*)-dihydroxy-4-(9-adenyl)-butyric acid] is an adenosine analogue from *Lentinula* (invalid name "*Lentinus*") *edodes*, which represents a well studied hypocholesteremic agent. The mechanism of hypocholesterolemic action of eritadenine was found to be associated with a modification in hepatic phospholipid (PL) metabolism by inducing phosphatylethanolamine N-methyltransferase deficiency (Sugiyama et al. 1995). The extra- and intracellular distribution of eritadenine by shiitake mycelial culture and the influence of reactor conditions on the mycelial morphology and eritadenine concentrations were studied and reliable analytical HPLC procedures for quantification of eritadenine was developed (Enman et al. 2007, 2008). A rapid method to produce eritadenine by liquid phase fermentation of *Lentinus edodes* without formation of the fruit body has been described in a patent (US Patent 8053217). A diet containing 5 % *Lentinus edodes* fruiting bodies given to hypercholesterolemic rats reduced plasma total cholesterol, triglyceride, low-density lipoprotein (LDL), total lipid, phospholipids, and the LDL/high-density lipoprotein ratio by 34.33, 53.21, 75.00, 34.66, 25.73, and 71.43 %, respectively (Yoon et al. 2011). These results suggest that shiitake mushrooms could also be recommended as a natural cholesterol lowering substance in the diet.

It has also been reported that *Pleurotus citrinopileatus* fruiting body extracts exert anti-hyperlipidemic effects. Serum triglyceride and total cholesterol levels were lowered in hyperlipidemic rats supplemented with the extracts, while high-density lipoprotein levels were significantly increased (Hu et al. 2006a). Similar effects were noted when powdered

P. ostreatus fruiting bodies or a water-soluble polysaccharide extracted from *P. citrinopileatus* fermentation broth were fed to hypercholesterolemic or diabetic rats, respectively (Hossain et al. 2003; Hu et al. 2006a, b). Recent investigation on the cholesterol lowering properties of an oyster mushroom diet in humans (20 subjects) found that decreased triacylglycerol concentrations (−0.44 mmol/L; $p=0.015$) and oxidized low density lipoprotein levels (−7.2 U/mL; $p=0.013$) significantly, and showed a significant tendency in lowering total cholesterol values (−0.47 mmol/L; $p=0.059$) (Schneider et al. 2011). However, study on antihyperlipidemic effects of *Pleurotus ostreatus* in HIV-infected individuals taking antiretroviral therapy did not give a satisfactory result of clinical magnitude (Abrams et al. 2011).

Laetiporus species are brown rot fungi commonly found in temperate Europe and North America) as well as tropical-subtropical areas (Ota et al. 2009). The study conducted to evaluate the inhibition and reduction effects of the dried mycelial extract of the mushroom on hypercholesteremia of rat model and a small human trial. The results showed a significant inhibition of blood cholesterol levels in rat models and 73.6 % (14 out of 19) reduction of blood cholesterol levels in human subjects suggesting that *Laetiporus* sp could be used as a hypocholesterolemic agent (Aryantha et al. 2010).

Several studies demonstrated that culture extracts of *Inonotus obliquus* significantly decreased serum content of free fatty acids (FFA), total cholesterol (TC), triglyceride (TG) and low density lipoprotein-cholesterol (LDL-C), whereas effectively increasing high density lipoprotein-cholesterol (HDL-C) in serum of diabetic mice (Sun et al. 2008; Lu et al. 2010). Investigation of the effects of ethanol extract of *Auricularia auricula* (AAE) containing polyphenolic compounds, on hypercholesterolemia in ICR mice showed a remarkable hypocholesterolemic effect, improving antioxidant status, decreasing the level of total cholesterol and atherosclerosis index, increasing the level of high-density lipoprotein cholesterol and fecal excretion of bile acids (Chen et al. 2011).

Extracts from the culture broth of *Tremella aurantialba* showed strong abilities to reduce the levels of total cholesterol and total triglyceride in serum of rats (Zhang et al. 2009). Moreover, Ohtsuki et al. (2007) investigated the effects of *Hypsizigus marmoreus* on serum and hepatic lipid levels in C57BL/6J mice, liver triacylglycerols and serum cholesterol level were significantly lower than that of the control group. High concentrations of blood cholesterol levels, hypercholesterolemia, can lead to a progression of hyperglycemia in type 2 diabetes in human and animals (Mathé 1995; Kuller 2006). Cholesterol directly effects β-cell metabolism and opens a novel set of mechanisms that may contribute to β-cell dysfunction and the onset of diabetes (Hao et al. 2007). Epidemiological studies suggest that higher levels of dietary fibre intake play a significant protective role in lowering the dietary glycemic load and shows potent hypocholesterolemic effects (Anderson 2009). Rats fed *A. bisporus* fruiting bodies exhibited significant anti-glycemic and anti-hypercholesterolemic effects (Jeong et al. 2010; Volman et al. 2010). Even oral administration of the common button mushroom, *Agaricus bisporus* for 4 weeks of animal model resulted in a significant decrease in plasma total cholesterol (TC) and low-density lipoprotein (LDL) (22.8 % and 33.1 %) accompanied by a significant increase in plasma high-density lipoprotein concentrations (Jeong et al. 2010) *Agaricus sylvaticus* showed preventive effects on the onset of atheroma plaques in hypercholesterolemic rabbits (Percario et al. 2008).

Anti-diabetic activity

Diabetes mellitus is a life-threatening chronic metabolic disease causing several health problems to millions worldwide and has become a significant ailment in many countries (Wild et al. 2004; WHO 2011; Hagopian et al. 2011; Smith et al. 2012). In general, this is caused by lack of insulin and/or insulin dysfunction, characterized by high levels of glucose in the blood (hyperglycemia). Diets incorporated with mushrooms are ideal low energy foods for diabetes patients as they lack in fats and cholesterol, are low in carbohydrates, and high in proteins, vitamins and minerals (Mattila et al. 2002; Guillamón et al. 2011; Lau et al. 2012; Phillips et al. 2011a, b; Ulziijargal and Mau 2011). Thus, medicinal mushrooms are functional foods and a good solution to controlling diabetes and a potent source of biologically active compounds with anti-diabetic effects. A comprehensive literature survey on anti-diabetic effects of mushrooms has been given in our previous article, de Silva et al. (2012b) and this is only a brief focus and update on recent discoveries.

Alpha-glucosidase catalyzes the cleavage of carbohydrates to glucose and any compound that inhibits the activity of this enzyme is useful as a treatment for diabetes mellitus type 2. A lanostane triterpenoid isolated from *Ganoderma lucidum*, namely ganoderol B-[(3β,24*E*)-lanosta-7,9(11),24-trien-3,26-diol] had strong inhibitory activity on α-glucosidase (Fatmawati et al. 2011). An acid protein-bound polysaccharide, isolated from *Inonotus obliquus* exhibited an inhibitory activity against α-glucosidase with the IC_{50} value of 93.3 μg/mL and produced inhibitory activity lipid peroxidation in rat liver tissues (Chen et al. 2010). In vitro studies revealed that ganoderol B had a moderate α-glucosidase inhibition activity with an IC_{50} of 48.5 μg/mL (119.8 μM). The ethanol extracts of *Phellinus merrillii* (EPM) showed strong α-glucosidase and aldose reductase activities in vivo and the inhibitors were identified as hispidin, hispolon and inotilone (Lee et al. 2010; Huang et al. 2011). Among these hispidin, hispolon, and inotilone exhibited activity against α-glucosidase inhibitor with IC_{50} values of 297.06, 12.38, and 18.62 μg/mL,

respectively, and aldose reductase inhibitor activity with IC_{50} values of 48.26, 9.47, and 15.37 μg/mL, respectively. In addition, hispidin from *Phellinus linteus* indirectly showed hypoglycemic effects through protecting β-cells from the toxic action of reactive oxygen species in diabetes with scavenging activity of approximately 55 % at a concentration of 30 μM (Jang et al. 2010). Other strylpyrones and their antioxidant activities have been described further above.

Recently, a novel proteoglycan extract from the fruiting bodies of *Ganoderma lucidum* named Fudan-Yueyang-*G. lucidum* (FYGL), showed an efficient anti-diabetic potency (Teng et al. 2011, 2012). A proteoglycan extract administered orally to streptozotocin-induced diabetic rats showed a significant decrease (IC_{50}, 5.12±0.05 μg/mL) in plasma glucose levels (Teng et al. 2011). It was suggested that the hypoglycemic effect of FYGL is caused by inhibition of the protein tyrosine phosphatase PTP 1B, i.e., a key enzyme in blood sugar homeostasis that is regarded as validated biochemical target in the Pharma industry for screening (Popov 2011).

Oral administration an aqueous extract of *Pleurotus pulmonarius* also reduced the serum glucose level in alloxan treated diabetic mice. The extract also showed increased glucose tolerance in both normal and diabetic mice (Badole et al. 2006). A novel polysaccharide-peptide complex with hypoglycemic activities was isolated and identified from the abalone mushroom *Pleurotus abalones* (Li et al. 2011, 2012; Wang et al. 2011). *Pleurotus ostreatus* high concentrated extracts were found to be effective in decreasing the genetic alterations and sperm abnormalities in diabetes conditions and could reduce the high blood glucose level in hyperglycemic rats (Ghaly et al. 2011). The latter study does not necessarily relate to the hydrophilic macromolecule described above.

A recent study investigated the potential hypoglycemic and renoprotective effects of the solid-state fermented mycelium extract of *Cordyceps sinensis* with significant increase in β-cell survival, renal NKA activity and decreases collagen deposition, and mesangial matrix accumulation (Kan et al. 2012). Cordycepin isolated from *C. militaris* provides potential use as an immunomodulatory agent for treating diabetes by suppressing the diabetes regulating genes (Shin et al. 2009). It is evident that *C. militaris* has both insulin-like and insulin release promoting activity and potential anti-diabetic activity (Zhang et al. 2006). A recent research finding indicates that *C. militaris* can lower plasma glucose via the stimulation of insulin secretion and cholinergic activation and the extracts decreased the plasma glucose by 21 % and induced additional insulin secretion by 54.5 % after 30 min (Cheng et al. 2012).

Several clinical trials using diabetic patients demonstrated that consumption of medicinal mushrooms or combination of them as adjuvant treatment provided significant effects on reducing blood glucose levels and considerable therapeutic potential against diabetes mellitus. Clinical investigation in diabetic subjects confirms that Oyster mushroom consumption significantly decreased the blood pressure, plasma glucose, total cholesterol and triglycerides, without a direct adverse effect on body weight, on liver or kidney function (Khatun et al. 2007). Recently a clinical study (120 patients) concluded a significant association between mushroom supplementation and gradual reduction in hyperglycemia in type 2 diabetic patients and the potential use of oyster mushroom for better glycemic control, positive effects on lipid profiles and a better quality of life (Agrawal et al. 2010). A randomized, double-blinded, placebo-controlled clinical trial depicts significant reducing effect on the metabolic and blood pressure of 56 patients with colorectal cancer who supplemented with *Agaricus sylvaticus* (Fortes et al. 2008). Patients supplemented with dried mushroom extracts of *A. sylvaticus* showed a significant reduction of fasting plasma glucose and total cholesterol compared with a placebo group (Fortes et al. 2008, 2009; Fortes and Carvalho Garbi Novaes 2011).

Commercially available mushroom products and dietary supplements

Highly purified compounds derived from medicinal mushrooms are now being used in much of Asia as pharmaceutical products in medicine. In addition, there is a emerging interest in beneficial effects of these compounds not only as pharmaceutical drugs but also as a novel class of supportive products with overall immune enhancement (Cornillier et al. 2008; Hasan et al. 2009; Jiang and Sliva 2010; Jakopovich 2011). Constituents of these dietary supplements act as biological response modifiers in order to strengthen the natural defenses of individuals who are prone to recurrent infections and who are sensitive to allergens (Leung et al. 2006; NCI 2006; Carayol et al. 2010, 2013; Bobovcak et al. 2010). Most importantly they can minimize the side effects during risk periods, such as after radiotherapy and chemotherapy. In addition there is growing evidence for the effectiveness of using medical nutrition therapy in preventing and managing lifelong threatening chronic diseases such as diabetes cancers or cardiovascular diseases (Pastors 2003; Fortes et al. 2008; Hasan et al. 2009; Anonymous 2010; Igel et al. 2012).

Consumption of foods enclosed with medicinal properties is a cost effective means to achieve significant health benefits by preventing or altering the course of disease occurrence. A new concept arises with the modern science on foods in the pharma-nutrition interface; improve health or reduce disease risk has been progressively gaining interest (Eussen et al. 2011; Leal et al. 2013). Thus, incorporation of mushrooms as a daily food or as a supplement, containing many nutrients and bioactive substances, can assist in maintaining more normal cellular and immune function which helps in well

Table 3 Examples of marketed products of mushroom extracts with claimed biological activities

Product name[a]	Product function claim	Fungus/extract present	Web page
BIOIMMUNOGEN PSK-16™ - Polysaccharide Protein	Immunomodulating Support natural killer (NK) cell, T-cell, macrophage activity, and cytokine production	Blend of 16-Mushroom Complex	http://www.qualityahcc.com
BreastDefend™	Prevents inhibits proliferation and metastatic behavior of MDA-MB-231 invasive human breast cancer cells	Extracts from medicinal mushrooms (*Coriolus versicolor, Ganoderma lucidum, Phellinus linteus*),	Jiang et al. 2012
Breast-Mate®	Deliver targeted nutritional support specifically to breast cells and alternative treatment for cancer	*Phellinus linteus*	Sliva 2010 http://www.swansonvitamins.com/mushroom-wisdom-breast-mate-120-tabs
Coriolus-MRL	Enhance immunity and help to prevent chronic diseases	Mycelium and primordia (young fruit body) of *Coriolus versicolor*	http://www.mrlusa.com/products01.html Córdoba and Ríos 2012
Dr. Myco San products DIMEMYKON	Optimally regulate blood sugar levels and keep diabetes mellitus under control	Mixed of several mushroom species	www.mykosan.com Jakopovich 2011
MycoPhyto® Complex	Cytostatic effects through the inhibition of cell proliferation and cell cycle arrest at the G2/M phase of highly invasive human breast cancer cells MDA-MB-231	A blend of mushroom mycelia from *Agaricus blazei, Cordyceps sinensis, Coriolus versicolor, Ganoderma lucidum, Grifola frondosa* and *Polyporus umbellatus*, and β-1,3-glucan isolated from *Saccharomyces cerevisiae*	Jiang and Sliva 2010
Mycoformulas Memory	Promote healthy brain function and nervous system	*Hericium erinaceus*	http://mycoformulas.com/memory-mushroom-supplements.html
New Chapter® LifeShield® Immunity	Support the immune system, vitality, and overall wellness.	*Ganoderma lucidum* mycelium and fruiting bodies with combination of several other mushrooms	http://www.newchapter.com/mushrooms/lifeshield-immunity
ORIVEDA® *Coriolus* PSP extract	An excellent general immune supporter, adjuvant during anti-cancer therapy	PSP Extract *Trametes versicolor*	http://www.oriveda.com/coriolus_psp.php
Pleuran Imunoglukan P4H® capsules	Support the immune system	β-glucan from *Pleurotus ostreatus*	http://www.pleuran.com/ Bergendiova et al. 2011; Bobovcak et al. 2010
ReishiMax capsules	Inhibits adipocyte differentiation, stimulates glucose uptake and activates AMPK	Polysaccharides extracted from *Ganoderma lucidum*	Thyagarajan-Sahu et al. 2011

[a] The co-authors of the present paper have not confirmed these claims

Table 4 Examples of patented products of mushroom extracts with claimed biological properties

Claimed product / extract name	Biological activity	Patent Application No	Inventors
Food supplement prepared from *Grifola frondosa, Pleurotus eryngii, Hericium erinaceus*	Reducing blood sugar and regulating blood lipid levels	CN 101292726 A 20081029	Liu et al. 2008
Ganoderic acid T-amide derivative TLTO-A	Antitumor agent for inhibiting cancer cells and induce the apoptosis of tumor cells	CN102219822	Zhong et al. 2011
Method of eritadenine production in liquid phase fermentation of *Lentinus edodes*	Blood cholesterol reducing therapeutic agent	United States Patent 8053217	Berglund et al. 2011
Mushroom extracts from *Agaricus* spp *Hericium erinaceus*, and *Hypsizigus marmoreus*	Insulin secretion stimulators and health foods for prevention and therapy of diabetes mellitus	JP 2012077004A	Takeshi et al. 2012
Mushroom extract from *Hericium erinaceus*	Anti-dementia substance inhibit the neuronal toxicity of amyloid beta-peptide (Aβ) and induce the synthesis of nerve growth factor (NGF)	US2009274720 (A1)	Zhuang et al. 2009
Phytonutrient compositions prepared from *Agaricus bisporus*, *Lentinula edodes*, *Pleurotus ostreatus* and *Grifola frondosa*	Treatment of neurodegenerative diseases and radiation damage	WO2007US63984 20070314	Beelman et al. 2007
Terpenoid spiroketal compound from *Agaricus subrufescens* and related *Agaricus* spp.	Therapeutic potential on disease having Liver X Receptor (LXR) agonists activity	EP 2 468 253(A1)	Grothe et al. 2012

functioning of the whole body (Wachtel-Galor et al. 2004; Han et al. 2006; Cheung 2008; Borchers et al. 2008; Bobovcak et al. 2010; Jiang and Sliva 2010; Brennan et al. 2012). Examples of the available dietary supplements, commercial products developed from medicinal mushrooms that claim to provide beneficial effects in diseases prevention are shown in Table 3. Examples of patented mushroom extracts investigated in recent years are listed in Table 4.

Conclusion and future prospective

Since nature is the master chemist, bioactive compounds of natural origin have been the most consistent successful source for lead for new drugs. In this review, we have summarized the biological activities and chemical background of novel secondary metabolites and mushroom extracts which have been discovered in recent years. Moreover, a brief idea on commercially available mushroom products in the market sold as dietary supplements, functional foods and newly discovered patent products.

Today, the emergence of drug-resistant pathogens, drug-resistant cancer cells and occurrence of various side effects for the currently available drugs is an overwhelming problem of medical concern. There is an urgent need in exploration of novel compounds with natural origin and as well as further studies on exact mechanism of action of already identified compounds as they may have different modes of action targeting several sites (Strohl 2000; Wong et al. 2010; Clericuzio et al. 2012; Liu et al. 2012a, d; Yao et al. 2012).

According to recent research, many novel compounds from medicinal mushrooms and their respective biological activities have been identified (Khan and Tania 2012). Especially, bioactivities on anti-oxidant, anti-tumor, anti-diabetic and anti-microbial effects have been extensively identified. These benefits are primarily due to the presence of low molecular weight metabolites including triterpenes, phenols, polyketides and high molecular weight polysaccharides, proteins and polysaccharide-protein complexes. Most of the studies here reviewed are relatively recent and have been based on in vitro studies or animal models. Few studies have been performed at the level of clinical trials in patients. Future studies should emphasis on the improvement in methodological quality and warrant further clinical research on the effects of these compounds (Standish et al. 2008; Ramberg et al. 2010; Jin et al. 2012; Lima et al. 2012; Roupas et al. 2012). In addition, expert knowledge on mycology, molecular biology, chemistry, and pharmacology should be integrated in order to search for better outcomes (Moran et al. 2007; Hansen et al. 2011; Woolston et al. 2011; Wawrzyn et al. 2012a, b).

Mushroom derived commercial products, dietary supplements, and nutritional foods with claimed biological activities and overall immune enhancers have been illustrated. Most of these products are recommended for adjutant therapy or alternative mode of medicine but not for direct cure of any diseases. These can improve the comfort of patients' lives or prevent certain diseases or to support drug treatment in chronic diseases to reduce side effects. However, clearly defined protocols and medical standards on exact bioactive compounds and improved culture conditions should be incorporated in production, to ensure a level of quality control and reproducibility for clinical trials (Jasinghe et al. 2007; Tang et al. 2007; Papaspyridi et al. 2011, 2012; Nguyen et al. 2012; Maia et al. 2012; Wang et al. 2012a, b; Tepwong et al. 2012). In addition, despite of the claimed therapeutic potential of these products, intensive research in this area is still required

to meet the growing need for better therapeutics and drug leads.

It is well known that only a small fraction of the estimated fungal biodiversity worldwide has been investigated for bioactive compounds. Accordingly, more extensive collections of fungal species should be isolated, and correctly identified (Zhao et al. 2010, 2011; Chen et al. 2012; Wisitrassameewong et al. 2012a, b). Moreover, certain unique medicinal mushroom species are rare, endemic and restricted to certain small areas of the world. Therefore, identifying their ecological niches, conservation and sustainable harvest of these precious natural products is essential (Mortimer et al. 2012). Therefore, despite the promising published data, research on chemical investigation of mushroom species for bioactive metabolites, and search on their possible mechanism of action would satisfy the urging need for new therapies worldwide.

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