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Entry

Fungal Metabolites in Human Health and Diseases—An Overview

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Definition: Fungi produce a wide range of secondary metabolites. Some of these metabolites are toxic to humans and cause various health disorders, ranging from acute poisoning to chronic diseases. Contrary to this, some fungal metabolites are valuable sources in therapeutics, such as penicillin. Herein, researchers briefly highlight the role played by different fungal metabolites in human health and diseases and give an overview of the most common fungal genera.

Keywords: fungi; secondary metabolites; mycotoxin; *Aspergillus*; *Penicillium*; *Fusarium*; antibiotic; anticancer



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1. Introduction

Fungi are extraordinary in their ability to produce numerous natural products known as fungal secondary metabolites, which exhibit various biological activities [1,2]. Considering the reported biological properties of fungi toward human health, they can be classified as toxic “mycotoxins” or non-toxic metabolites [3]. Mycotoxins are natural contaminants of food commodities and pose a measurable health risk for animal and human health [4]. Health risks are classified based on organs that are affected by the toxins, for instance, they possess carcinogenic, immunosuppressive, hepatotoxic, nephrotoxic, and neurotoxic effects [4,5]. Hundreds of mycotoxins have been identified [6,7]. The mycotoxins that receive the most significant concern from scientists are aflatoxin B1 and M1, cyclopiazonic acid, ochratoxin A, patulin, T-2 toxin, deoxynivalenol, zearalenone, ergot alkaloids, and macrocyclic trichothecenes, due to their health and economic effects. For instance, aflatoxin B1 is classified as the most potent hepatocarcinogen and mutagen [8,9]. However, human exposure to mycotoxins is still underestimated as scientists only focus on economically important mycotoxins. Therefore, it is important to intensify efforts to discover more toxic fungal metabolites that contribute to diseases of unknown aetiology.

On the contrary, some fungal metabolites are beneficial for human health and are used to treat many human diseases, such as antibiotics. Therefore, researchers from different fields work together towards understanding the fungal secondary metabolites in terms of their regulation, function, and applications, and evaluate their toxicity [10–13]. These fungal metabolites are characterized by their chemical structures and effects on human health [1]. A recent review mentioned that more than 1,500 fungal metabolites had been isolated and half of them have been used for primary health care. The other half is still under safety and toxicity investigation [1].

The scientific community has recently celebrated the 90th anniversary of Sir Alexander Fleming’s discovery of penicillin, which was the starting point of the antibiotic era [10]. Since then, scientists worldwide have started to consider and use innovative approaches

to study fungi due to their health and biotechnological significance. Although drug discovery from fungal metabolites is increased due to the development of bioinformatics and genomics [14], researchers expressed the need to ramp up the discovery of fungal metabolites to improve food quality or discover novel antibiotics. This was obvious during the pandemic when researchers initially struggled to find drugs to treat the SARS-CoV-2.

In the coming section, researchers will briefly discuss the importance of different fungal metabolites in human health and diseases with an overview of the fungal genera most frequently involved.

2. Mycotoxin Involved in Human Diseases

Mycotoxins are produced by hundreds of thousands of species of fungi, such as *Aspergillus* spp., *Penicillium* spp., *Fusarium* spp., *Claviceps* spp., and *Stachybotrys* spp. [15,16]. Therefore, mycologists classified mycotoxins based on the fungal species that produce them, see Table 1. These toxins can cause several health issues, such as liver and kidney cancers [6].

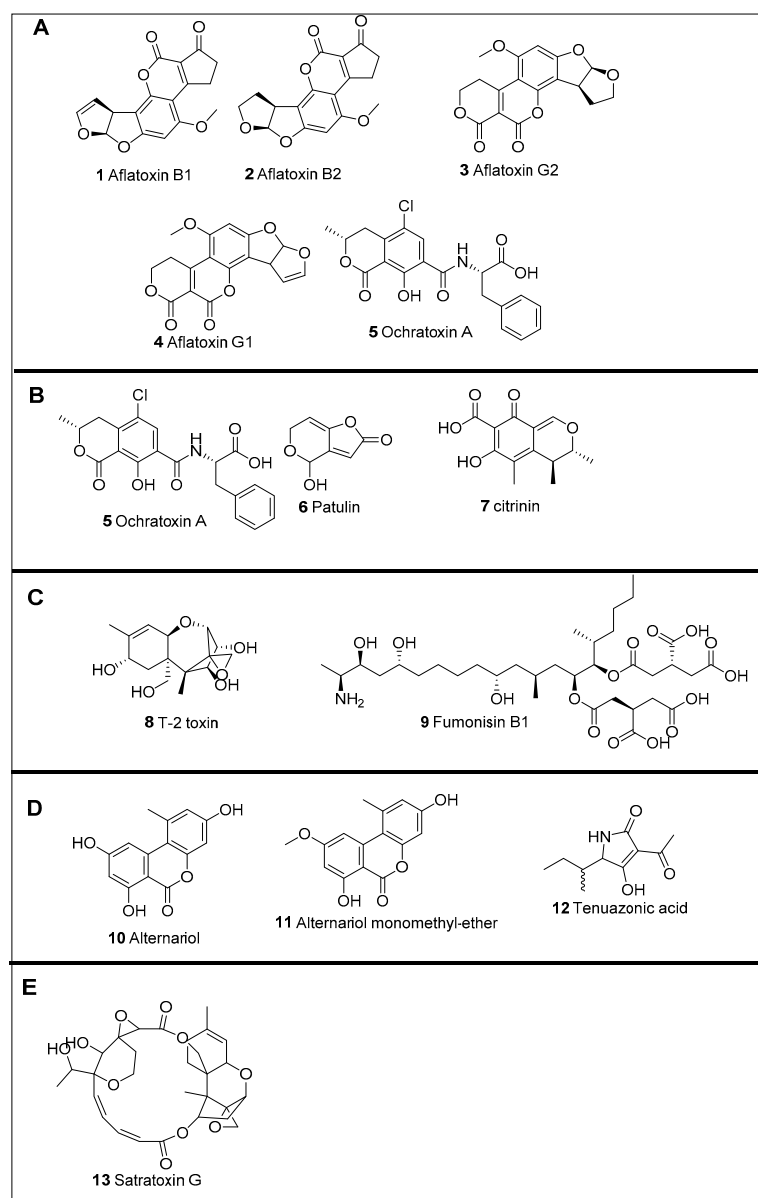


Figure 1. Common mycotoxins—(A). *Aspergillus* spp. (B). *Penicillium* spp. (C). *Fusarium* spp. (D). *Alternaria* spp. (E). *Stachybotrys* spp.

Table 1. Common toxigenic species of fungi and their chronic effects.

Fungal Species	Toxin *	Toxin Classification	Chronic Effect	Refs.
<i>Aspergillus flavus</i>	Aflatoxins B1, B2	<i>Aspergillus</i> toxins	Hepatotoxic	[8,17]
<i>A. parasiticus</i>	Aflatoxins B1, B2, G1, G2	<i>Penicillium</i> toxins		
<i>A. ochraceus</i>	Ochratoxin A	<i>Aspergillus</i> toxins	Nephrotoxic	[18–20] [21–23]
<i>Penicillium verrucosum</i>	Ochratoxin A, Citrinin	<i>Penicillium</i> toxins		
<i>P. purpurogenum</i>	Ochratoxin A, Citrinin			
<i>P. expansum</i>	Patulin, Citrinin		Cytotoxic effects	[21–25]
<i>Fusarium sporotrichioides</i> <i>F. graminearum</i> <i>F. verticillioides</i> <i>F. proliferatum</i>	T-2 toxin, Fumonisin	<i>Fusarium</i> toxins	Gastrointestinal, skin, thyroid, and bone marrow, disorders	[26–32]
<i>Alternaria alternata</i>	Alternariol, Aternariol monomethyl-ether, Tenuazonic acid	<i>Alternaria</i> toxins	Oesophageal cancer, hematologic disorder	[33,34]
<i>Stachybotrys atra</i>	Satratoxins	<i>Stachybotrys</i>	Sick building syndrome	[35,36]

* View chemical structure in Figure 1.

2.1. Mycotoxin Involved in Liver Diseases

Aflatoxins are difuranocoumarin derivatives produced by many species of *Aspergilli*, particularly *A. flavus*, *A. parasiticus*, *A. bombycis*, *A. coracles*, *A. nomius* and *A. pseudotamarii* [6,15,37]. These fungi grow on particular foods under favourable temperature and humidity conditions and produce aflatoxins before and after harvesting [17,38]. Aflatoxins are primarily found in cereals, oilseeds, tree nuts, spices, milk, and dairy products [39–41]. *A. flavus* is the most common producer of aflatoxins. It was first isolated and characterized following the death of more than 100,000 turkeys due to an unidentified disease, named turkey X disease. The toxin was traced to a mould-contaminated peanut meal consumed by the turkeys [6]. Eighteen types of aflatoxins have been identified, with the major four being AFB1, AFB2, AFG1 and AFG2 (Figure 1A, 1–4, respectively). Due to high toxicity, aflatoxin B1 was classified as a Group 1A human carcinogen [8,42]. Aflatoxin B1 (AFB1) is the most potent natural toxin and may cause liver cancer [16]. The Food and Agriculture Organization emphasized that children under 5 years in Africa are at a high risk of consuming milk contaminated with aflatoxin M1 and M2 which cause growth retardation [17]. AFM1 and AFM2 are metabolism products of AFB1, and thus can be found in milk. Therefore, several regulations have been implemented worldwide to control aflatoxin consumption [15,16].

2.2. Mycotoxins Involved in Kidney Diseases

Members of the ochratoxin family have been found in varied species of *Aspergillus*, in particular *A. alliaceus*, *A. melleus*, *A. carbonarius*, *A. glaucus*, and *A. niger*, and other related fungal species, including *Penicillium viridicatum* [6,43]. These toxins are found in various cereal grains, dried fruits, wine, and coffee. Ochratoxin A (OTA) (Figure 1A, 5) is the most toxic compound in the ochratoxin family [19]. Early studies have connected OTA exposure within human diseases, such as Balkan endemic nephropathy (BEN), chronic interstitial nephropathy (CIN), and other renal diseases. The effect of OTA was reported by IARC and is considered nephrotoxic, teratogenic, immunotoxic, and has been classified by IARC as a class 2B carcinogen, and a possible human carcinogen [20,44]. However, a recent European Food Safety Authority report showed that ochratoxins cause nephrotoxicity and renal tumours in various animal species. The information related to the effect of this toxin on human health is still limited, and more clinical studies are needed to confirm the hazardous extent of ochratoxins [18].

2.3. Mycotoxins Involved in Genotoxicity, Immunotoxicity, and Neurotoxicity

Patulin (PAT) (Figure 1B, 6) is a secondary metabolite produced by *Aspergillus*, *Byssoschlamys*, and *Penicillium* spp. [25,45] and is common infestation of fruit- and vegetable-based products. The risk of human exposure to patulin through the consumption of juices and jams occurs at an early age [24].

Patulin is an α , β -unsaturated γ -lactone that has broad-spectrum antimicrobial activity but has been classified as mycotoxin [25]. Patulin has chronic health effects, including genotoxicity, immunotoxicity, and neurotoxicity in rodents, but insufficient evidence exists for carcinogenicity. Therefore, the IARC has classified it as Group 3B, however, its effects on humans are not yet clear [24,25].

2.4. Mycotoxins Involved in Damage to Organs

Citrinin (Figure 1B, 7) is mycotoxin that was isolated from *Penicillium* cultures that contaminated stored food for long periods of time [21]. Initially, citrine aimed to be used as a drug before World War II; unfortunately, it also displayed toxicity, so it was discontinued [22]. Several *Penicillium* strains were found to produce citrinin such as *P. citrinum*, *P. expansum*, *P. radicola*, *P. verrucosum* [21,22]. Chemically citrinin is a quinone methide with two intramolecular hydrogen bonds [23].

Moreover, numerous *Aspergillus* species were also able to produce it. Citrinin has also been isolated from *Monascus ruber* and *Monascus purpureus*, which are used industrially to produce pigments for the food industry as a preservative or for food colouring. Although citrinin mainly targets the kidney, reports indicated it targets other organs, such as the liver and bone marrow. However, regulating this toxin in food or animal feed would meet an acceptable level in many countries including Europe [21,22].

2.5. Mycotoxins Involved Gastrointestinal, Skin, Thyroid, and Bone Marrow Disorders

Trichothecenes are a large group of toxic fungal secondary metabolites produced by various fungi, including *Fusarium* spp., *Myrothecium* spp., *Stachybotrys* spp., and *Trichoderma* spp. [46,47]. These toxins cause many health issues for humans and animals [26,47]. Over 200 trichothecene toxins were reported. They share a common tricyclic 12,13-epoxytrichothec-9-ene (EPT) core structure and are classified into four groups A, B, C, and D based on the substitution pattern of EPT, with groups A and D recognised as the most toxic compounds [27,47].

T-2 toxin (Figure 1C, 8) is related to trichothecenes group A and is considered the most toxic fungal secondary metabolite produced by *Fusarium* species, including *F. sporotrichioides*, *F. poae*, and *F. acuminatum*. T-2 toxicity effects depend on several factors, such as the dosage, age, and exposure (oral, dermal, and aerosol). T-2 toxin causes a gastrointestinal disorder known as Alimentary Toxic Aleukia that affects humans after consuming moldy food. Several toxicological studies were conducted to evaluate the cytotoxic and genotoxic impact of T-2 toxin [26,27,46]. They found that this toxin could inhibit protein synthesis and has immunomodulatory insults [26,27,46]. This inhibitory effect is visible in proliferating cells, such as the gastrointestinal tract, skin, thyroid, and bone marrow cells [26,31].

2.6. Mycotoxins Involved in Cancer and Heart Failure

Fumonisin are mycotoxins produced by *Fusarium* spp. such as *F. proliferatum* and *F. verticillioides*. Fumonisin are classified into four major groups; FA, FB, FC, and FP, of which fumonisin B1 (Figure 1C, 9) is the most toxic member. FB1 contaminates corn, rice, oat, rye, barley and wheat [48]. However, the risk of contamination with these toxic fungal metabolites depends on several environmental factors, such as humidity and temperature [49].

FB1 (9) poses a health risk for animals and humans. It was reported that FB1 causes oxidative stress, cellular autophagy, apoptosis, and kidney diseases. Exposure to high levels of fumonisins in diet during early pregnancy induces a high risk of bearing a child

with a brain or spinal cord deficiency. Therefore, worldwide regulations and legislation have restricted a maximum limit of fumonisin in human foods and animal feeds [28,49].

2.7. Mycotoxins Involved in Oesophageal Cancer and Hematologic Disorder

Alternaria spp. is a widespread fungal genus that infects various crops, causing economic loss [50]. *Alternaria* toxins are a large group of more than seventy toxins, however, only a few have been reported and chemically characterised, including alternariol (AOH), alternariol monomethyl-ether (AME), and tenuazonic acid (TeA) (Figure 1D, 10–12, respectively) [33,51,52]. These toxins contaminate food products, such as fruits, vegetables, cereals, and grains. According to EFSA, the information on the toxicological profile of *Alternaria* mycotoxins is not enough for a proper health hazard assessment [50,53]. Many studies described these toxins as having cytotoxic, genotoxic, mutagenic, fetotoxic and teratogenic exchange consequences among their effects [54]. Other studies reported these toxins to cause mutagenic, oestrogenic and clastogenic effects [50,55]. However, most of the published studies focus on a single toxin, although *Alternaria* toxins, in general, are produced simultaneously. Although one study investigated the effect of binary or ternary combinations in vitro on relevant human cell lines [34], more data is still needed to understand the impact of these toxins on human health.

2.8. Mycotoxins Involved in Cause Respiratory Illness

Satratoxins are macrocyclic trichothecene mycotoxins produced by *Stachybotrys* species. Satratoxin G (Figure 1E, 13) is one of the most known toxins in this family [56]. *Stachybotrys chartarum* is associated with dampness and is called saprophytic black mould [36,57]. Many researchers suggested that satratoxins contribute to sick building syndrome with different symptoms, such as upper respiratory tract symptoms including wheezing and coughing, and in some cases they may exacerbate chronic lung diseases, such as asthma [35].

3. Fungal Metabolites against Human Disease

3.1. Fungal Metabolites Used as Antibiotics

An antibiotic is a chemical substance generally produced by microorganisms and able to inhibit the growth or destroy different microbial pathogens. Literature indicated that most filamentous fungi could produce different antibiotic compounds against pathogenic bacteria, fungi, etc. [58]. Most currently used antibiotics are derived from *Streptomyces* species and other actinobacteria, with relatively few compound classes derived from fungi. This includes *Penicillium*-derived penicillins (Figure 2, 14) and *Cephalosporium*-derived cephalosporins (Figure 2, 15), which belong to the β -glucan antibiotics, as well as the steroid fusidic acid (Figure 2, 16) from *Fusidium coccineum* and pleuromutilin (Figure 2, 17) [59–61].

The discovery of the penicillin- and cephalosporin-type β -lactams has shaped the modern pharmaceutical industry, and they have remained the most important antibiotics for around 70 years after their discovery. Afterwards, thousands of fungal metabolites were discovered; however, only a few have entered clinical development, which could be attributed to the exit of most of the Big Pharma companies from the field of novel antibiotics discovery [62].

Although penicillin G was the first fungal natural product to develop the first antibiotic, mycophenolic acid was discovered even earlier in 1893, from a *Penicillium brevicompactum* strain identified to inhibit the growth of *Bacillus anthracis*. It was claimed to be the first purified natural product antibiotic [63]. Due to its toxicity, it was recently dismissed as an antibiotic but developed as the immunosuppressant drug mycophenolate mofetil.

Recently, the antibacterial antibiotics pipeline showed that most compounds under development had been optimised from old classes with known modes of action [64]. Hence, antibiotic resistance is likely to happen once launched. The inhibition of biofilm formation is one of the most promising strategies to discover antibiotics that combat resistant pathogens. Two recent examples are coprinuslactone (Figure 2, 18) derived from the mush-

room *Coprinus comatus* against *Pseudomonas aeruginosa* biofilm [11], and roussoellenic acid (Figure 2, 19) from a *Rousoella* spp., against *Staphylococcus aureus* biofilm [12].

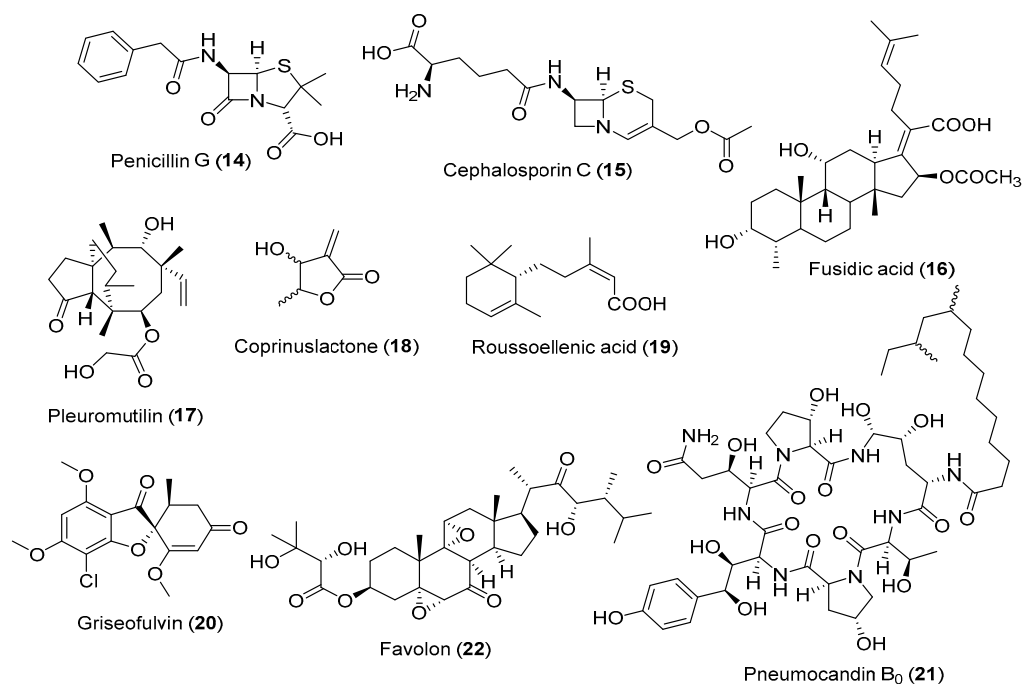


Figure 2. Selected fungal metabolites with antibiotic effect.

While resistant bacterial pathogens are a pressing topic, relatively low attention is paid to the resistant pathogenic fungi. There are only a few antimycotic compound classes on the market, including the oldest griseofulvin (Figure 2, 20), which was discovered from *Penicillium griseofulvum* in 1952 [13]. The newest class of fungi-derived antifungal agents are the echinocandin lipopeptides, such as pneumocandin B₀ (Figure 2, 21) derived from *Glarea lozoyensis* [65]. Another example is favolon (Figure 2, 22), isolated from *Favolaschia calocera* and exhibiting a potent antifungal effect [66]. Strobilurin is also considered an antifungal agent. Strobilurin A and B are extracted from *Strobilurus tenacellus* and used in agriculture as fungicides [67].

3.2. Fungal Metabolites Used as Anticancer Agents

Although most anticancer agents were discovered from plants and bacteria, fungi are also considered as an essential source for anticancer drug discovery. Illudin S (Figure 3, 23) is a fungal toxin isolated from *Omphalotus illudens* (Jack O'Lantern mushroom) and showed promising anticancer effects against different cancer cell lines [68]. Its semi-synthetic derivative irifolven (Figure 3, 24) interferes with DNA replication complexes and cell division in DNA synthesis. It passed phase II clinical trials with promising effects against brain, breast, blood, colon, prostate, lungs, ovarian, and pancreatic cancer cell lines [69]. Aphidicolin (Figure 3, 25) is a tetracyclic diterpene isolated from *Cephalosporium aphidicola* (currently changed to *Akanthomyces muscarius*) with antimetabolic properties that acts via the specific binding on DNA polymerases and is still under intensive clinical trials [70].

In 1971, a novel diterpene was isolated from the bark of the northwest Pacific yew tree, *Taxus brevifolia* and named taxol or paclitaxel (Figure 3, 26). It demonstrated moderate *in vivo* activity against different cancer cell lines. After more than 20 years of its initial report, it was FDA-approved against breast and ovarian cancers with a unique mechanism of action. However, the supply to the market was a real problem due to its very low yield. With many different trials to solve this issue, Stierle et al. [71] focused on discovering a new production source; endophytes that colonize the yew tree. They isolated 50 ng/L of the drug for the first time from *Taxomyces andreanae* [70]. The continuous search for

paclitaxel led to the discovery of over 20 endophytic fungal genera that could produce either paclitaxel or its analogues [72].

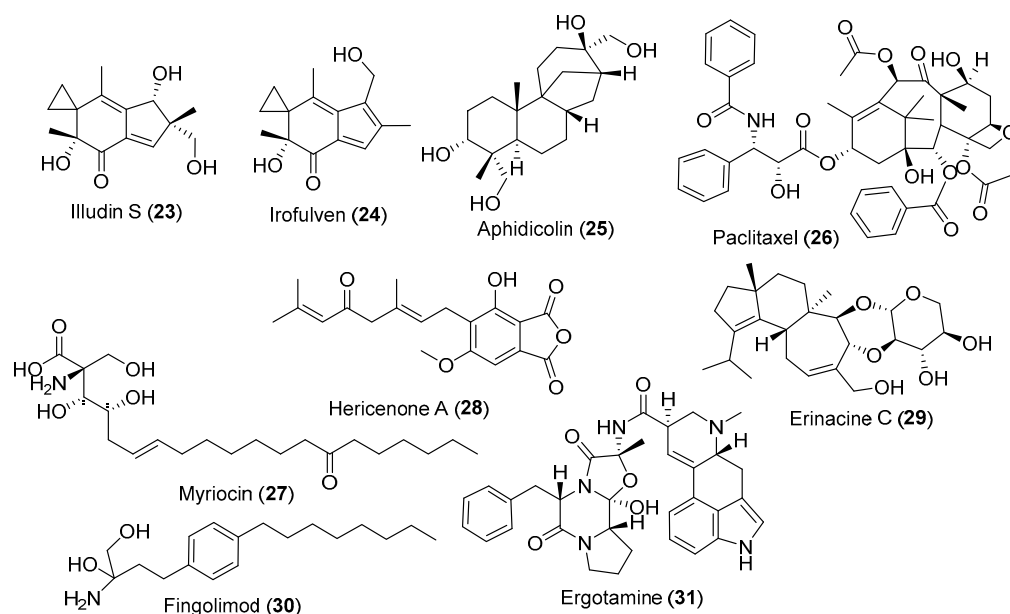


Figure 3. Selected fungal metabolites with anticancer and CNS-related effects.

3.3. Fungal Metabolites Used as CNS-Disease-Related Agents

Hericium erinaceus is a medical mushroom that produces two terpenoid classes, hericenones, such as hericenone A (Figure 3, 27), and erinacines, such as erinacine C (Figure 3, 28), which can stimulate the synthesis of the nerve growth factor and nerve regeneration in vitro and in vivo [73]. During the synthesis process to produce myriocin (Figure 3, 29) derivatives, a compound produced by the insect-associated ascomycete *Isaria sinclairii*, fingolimod (Figure 3, 30) was one of the final products. Fingolimod is a potent immunosuppressant that was FDA-approved in 2010 as a new treatment for multiple sclerosis [74]. Ergotamine (Figure 3, 31) is the principal alkaloid produced by the ergot fungus *Claviceps purpurea*. It has a similar structure to a few neurotransmitters and exhibits a vasoconstrictor effect. It is used to prevent post-partum haemorrhage (bleeding after childbirth) and is currently used for treating acute migraine attacks [75].

3.4. Fungal Metabolites Control Cardiovascular Diseases

Cardiovascular diseases include the malfunctioning of the heart and blood vessels due to elevated plasma cholesterol levels. Cardiovascular diseases are the leading cause of death worldwide, with more than eighteen million deaths yearly. Inhibition of de novo synthesis of cholesterol through 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors is an effective method to reduce plasma cholesterol and hence cardiovascular diseases. The fungal metabolites statins are the most important class of HMG-CoA reductase inhibitors. Compactin or mevastatin (Figure 4, 32) was isolated from *Penicillium brevicompactum* and exhibited promising hypocholesterolemic activity, and since then has been known under the name “ML-236B” [76,77]. Later, the first FDA-approved statin as an HMG-CoA reductase inhibitor was lovastatin (Figure 4, 33). Although different fungal species produce it, the commercial product is derived from *Aspergillus terreus* [78].

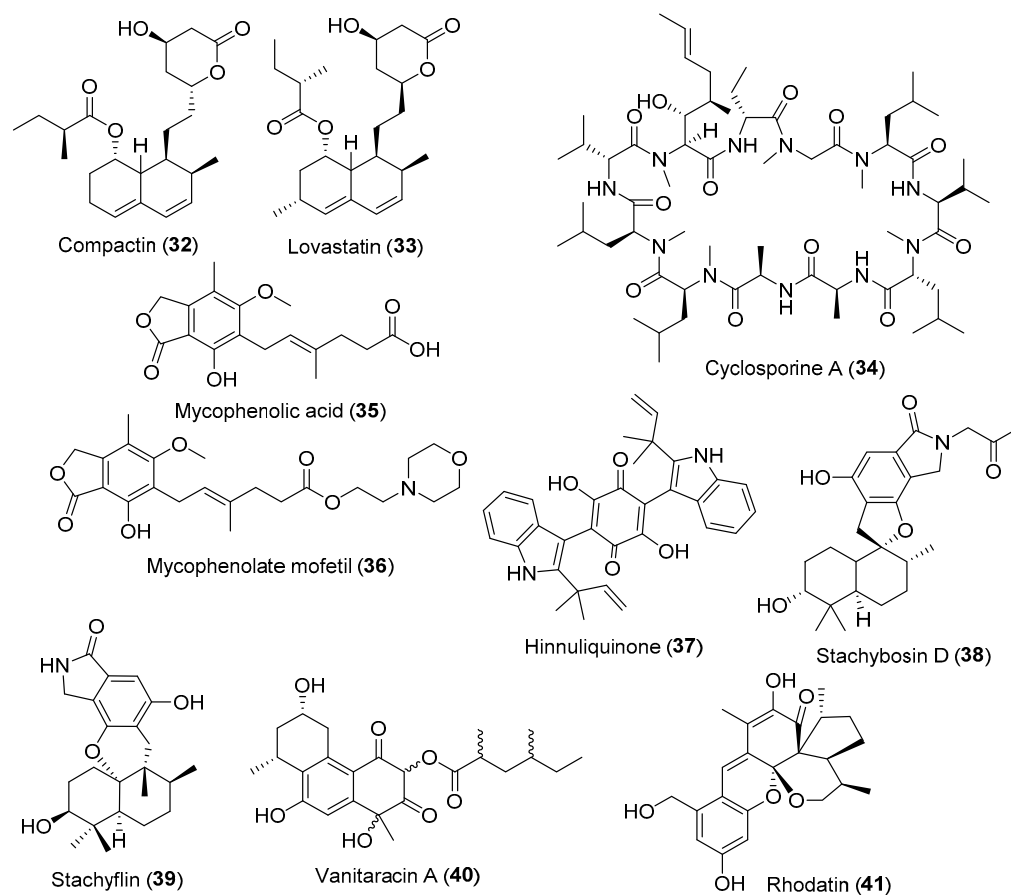


Figure 4. Selected fungal metabolites with antiviral, immunomodulatory and cardiovascular-related effects.

3.5. Fungal Metabolites Used as Immunomodulatory Agents

In the global market, some of the crucial immunomodulatory drugs are biotechnologically produced by bacterial or fungal fermentation. Cyclosporine A (Figure 4, 34) was first isolated from the ascomycete *Tolypocladium inflatum* and exhibited a mild antifungal effect. After many years, it was discovered that this cyclopeptide possesses a precise mode of action by selectively binding to cyclophilin A. This protein inhibits calcineurin, which in turn inhibits interleukine II production cascade, and hence the immune response of the human body is suppressed [63]. This is usually used in crucial immunosuppressant therapy to prevent the rejection of organ transplants.

Mycophenolic acid (Figure 4, 35) was the first discovered meroterpenoid antibiotic and produced by *Penicillium* spp., including *P. brevicompactum* and *P. roquefortii*. However, it has never been marketed as an antibiotic [79]. Its use as an immunosuppressant became evident, as it selectively inhibits inosine monophosphate dehydrogenase (IMPDH), an essential enzyme for the T- and B-lymphocytes, and thereby suppresses the immune system [80]. It can also prevent peroxynitrite tissue damage through the depletion of tetrahydrobiopterin, a co-factor to induce nitric oxide synthase (iNOS). Consequently, its prodrug mycophenolate mofetil (Figure 4, 36) is used to prevent organ rejection and manage psoriasis and other immunological disorders.

3.6. Fungal Metabolites Used as Antiviral Agents

Viral diseases usually cause severe global epidemics/pandemics, especially when vaccines or antiviral drugs are not available. So, a continuous search is urgently needed for new antiviral agents from natural sources. A lot of potentially active fungal natural products have shown antiviral activity; however, none of them have reached the market. The bis-

indolyl quinone hinnuliquinone (Figure 4, 37) isolated from an unknown fungus recovered from *Quercus coccifera*, inhibited the wild-type and clinically-resistant HIV-1 protease, a key enzyme in the replication and maturation of the HIV-1 virus [81]. Stachybosin D (Figure 4, 38), a phenylspirodrimane metabolite isolated from a sponge-derived fungus *Stachybotrys chartarum*, was able to inhibit HIV-1 replication in both NNRTIs-resistant strain and wild-type HIV-1 by targeting reverse transcriptase [82].

The terpenoid stachyflin (Figure 4, 39), isolated from a marine-derived isolate of *Stachybotrys* spp. showed good activity against the influenza A virus (H1N1) [83]. The novel tricyclic polyketide vanitaracin A (Figure 4, 40) isolated from a culture broth of *Talaromyces* spp., was reported to inhibit all hepatitis B genotypes (A–D) viral entry processes through direct interaction with the HBV entry receptor correlated to the hepatitis D virus [84]. Recently, the novel meroterpenoid rhodatin (Figure 4, 41) with its unprecedented carbon skeleton, was isolated from cultures of the rare basidiomycete *Rhodotus palmatus* and exhibited significant anti-HCV activities [85].

4. Summary

This review has emphasised the importance of fungal metabolites in human health and disease. The fungal metabolites are divided into mycotoxin and non-toxic metabolites. While mycotoxin contaminations are almost non-avoidable and thus constitute a serious risk for food safety, other non-toxic metabolites may even become beneficial for human health. This is further underlined by the recent pandemic that dragged attention to the need for the discovery of new metabolites that can be used as treatments in the future.

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