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Review

The Genus *Chrysosporium*: A Potential Producer of Natural Products

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Abstract: *Chrysosporium*, a genus of ascomycete fungi in the family *Onygenaceae*, has the ability to produce abundant new bioactive natural products, providing a structural foundation in drug development. This review includes the sources, distribution, biological activities and structural characteristics of the compounds isolated from *Chrysosporium* from 1984 to 2021. The results show that 66% of the compounds isolated from *Chrysosporium* are new natural products. More than half of the *Chrysosporium*-isolated compounds are from marine-derived *Chrysosporium*. The chemical structures of *Chrysosporium*-derived compounds have different skeletons, which are concentrated in alkaloids, polyketides, and lactones. Eighty percent of the natural products isolated from *Chrysosporium* have been found to have various biological activities, including cytotoxic, antibacterial, antifungal and enzyme-inhibitory activities. These results demonstrate the potential of *Chrysosporium* for producing new bioactive secondary metabolites, which can be used as the structural basis for developing new drugs.

Keywords: *Chrysosporium*; secondary metabolites; bioactivities; medicinal potentiality

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1. Introduction

The fungus *Chrysosporium* is classified into the *Onygenaceae* family, *Onygenales* order, *Euascomycetes* class and *Ascomycota* phylum, and was first established by Corda in 1833, identified as the model species *C. corii* [1]. The colonies of *Chrysosporium* are basically flat, white to beige to tan in color, often with a powdery or granular surface texture. The mycelial mesh of *Chrysosporium* is almost transparent, with a smooth wall and more or less irregular vertical branches [2]. In 1901, Saccardo took the genus *Chrysosporium* as a synonym of *Sporotrichum* Link ex Fr. [3], and there has been little research since then. In 1958, Hughes reintroduced the genus *Chrysosporium* [4]. Since then, Oorschot has greatly revised the classification and identification of *Chrysosporium*. The difference between the genus *Chrysosporium* and its related genera was redefined, a large number of strains were reconfirmed and identified, and 22 species of *Chrysosporium* were identified [5].

Chrysosporium is widely distributed and can be separated from many materials and environments, such as different soils from the equator to the polar regions, oceans, air, plants, river bed sludge, livestock manure, sewage, the surfaces or bodies of animals and birds, low-temperature caves, salt ponds, high-humidity bird nests, deserts, nuclear radiation areas, baked food, etc. [6–11]. The reason that *Chrysosporium* has such strong environmental adaptability is its capacity to produce different and unique enzymes and secondary metabolites, including alkaloids, polyketides and lactones [2].

Natural products have always been the structural inspiration of drug development because of their unique, complex structures and huge range of biological activities. Almost 50% of the approved drugs are natural products and their analogues, or are derived from natural products and inspired by them [12]. In 1984, chryscandin was found as a new

antibiotic in the culture broth of the fungi *C. pannorum* No. 4629 by Michio Yamashita et al. [13,14], which is the first natural product discovered from the genus *Chrysosporium*. Although the first research on secondary metabolites of the genus *Chrysosporium* in 1984 occurred more than one century after the first identification of the genus *Chrysosporium* in 1833, the discovery of this antibiotic opened the door to the study of natural products from *Chrysosporium*.

The secondary metabolites isolated from *Chrysosporium* have various bioactive activities, including cytotoxic activity [15,16], antibacterial activity [13,14,17], antifungal activity [17,18], enzyme inhibition [17,19] and other biological activities [13,14,19]. They also show a diversity of structural frameworks, including polyketides [20,21], alkaloids [16], peptides [15,22], lactones [17], terpenoids [23] and steroids [18]. The activity and structural diversity of natural products isolated from *Chrysosporium* reflect its great potential to reveal new bioactive natural products. Until now, no review has summarized the secondary metabolites of the genus *Chrysosporium*. In view of this situation, the sources, distribution, biological activities and structural characteristics of the compounds isolated from *Chrysosporium* from 1984 to 2021 are reviewed in this paper.

2. Cytotoxic Activity

Two antibiotic components, C_{3368}-A (**1**) and C_{3368}-B (**2**) (Figure 1), were isolated from the fermentation broth of *C. verrucosum* Tubaki, which was obtained from the soil of King George Island, Antarctica [20]. Their structures were determined to be the same as those of *R*-(–)-bisdechlorogeodin and questin, respectively [21]. They had a strong inhibitory effect on the nucleoside transport of tumor cells and nucleoside uptake by spleen lymphocytes of mice. The IC_{50} values of the inhibition of nucleoside transport in Ehrlich ascites tumor cells of **1** and **2** were 4 μM and 6 μM (Table 1). Compounds **1** and **2** showed inhibition of nucleoside uptake by splenic lymphocytes in mice, with IC_{50} values of 5.8 μM and 2.0 μM (Table 1). This was the first Antarctic soil fungal-isolated antibiotic with the above-mentioned effects.

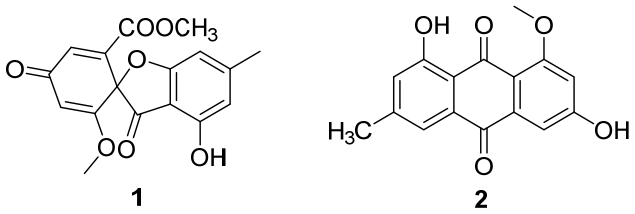

Figure 1. Structure of polyketides **1** and **2** [20].

A new antitumor antibiotic, adenopeptin (**3**) (Figure 2), was isolated from the culture medium of *Chrysosporium* sp. PF1201 [15]. By using transformed rat glial cells and rat 3Y1 fibroblasts to study the antitumor activity of adenopeptin [24–26], the IC_{50} values of adenopeptin on normal and transformed cells were obtained (Table 1) [15]. Compound **3** showed significant antitumor activity against glial cells of RG-E1A-7 (oncogene E1A) and RG-E1-4 (oncogene E1A, E1B), with IC_{50} values of 4.5 nM and 34 pM, respectively (Table 1). Compound **3** also displayed strong antitumor activity against 3Y1 fibroblast Adl2-3Y1 (oncogene E1A, E1B), with the IC_{50} value of 11 pM (Table 1). It was found that adenopeptin (**3**) induced apoptotic cell death in the cells transformed by adenovirus type 12 oncogene (including E1A). However, **3** showed weak cytotoxicity against normal rat glial cells and rat 3Y1 fibroblasts (Table 1), indicating the potential of **3** to be developed into a selective anticancer drug.

Table 1. Compounds with cytotoxic activity.

Compound	Cell	IC_{50} Value	Ability	Pro	Con	Prospect
1/**2** (μM) [20] (1992)	Inhibition of nucleoside transport in Ehrlich ascites tumor cells	4/6	Strong	Strong inhibitory effect on nucleoside transport of tumor cells and nucleoside uptake by spleen lymphocytes of mice		Structural foundation for antitumor drug development
	Inhibition of nucleoside uptake by splenic lymphocytes in mice	5.8/2.0				
3 [15] (1998)	Glia	9.1 μM	Weak	Selective cytotoxicity to transformed cell lines and normal cell lines		Potential to be developed into antitumor agent
	RG-E1A-7	4.5 nM	Strong			
	RG-E1-4	34 pM	Strong			
	3Y1	11 μM	Weak			
	Adl2-3Y1	11 pM	Strong			
	SR-3Y1	590 nM	Strong			
	HR-3Y1	3.2 μM	Moderate			
	SV-3Y1	6.0 μM	Moderate			
4/**5**/**6** (μM) [27] (2001)	HL-60	0.43/-/0.10	Strong	Strong cytotoxicity against a series of cell lines	Compound **4** was unstable	
	WiDr	1.87/-/0.47				
	HeLaS3	4.92/-/0.23				
	HCT-116	6.79/6.0/0.77				
	B16	6.56/7.6/1.87				
	P388D1	6.56/6.8/0.94				
	SK-BR3	7.96/-/1.17				
7/**8** (μM) [28] (2013)	A549	2.10/13.91	Weak	Broad-spectrum cytotoxic activity	Weak activity	To provide structural inspiration for new antitumor drugs
	MDA MB-231	9.34/1.3				
	MCF-7	11.19/21.89				
	HeLa	21.01/25.64				
	COLO 205	7.9/-				
9/**10**/**11** (μM) [29] (2013)	A549	147.3/63.2/34.5	Weak		Weak activity	
	K562	164.0/63.0/25.4				

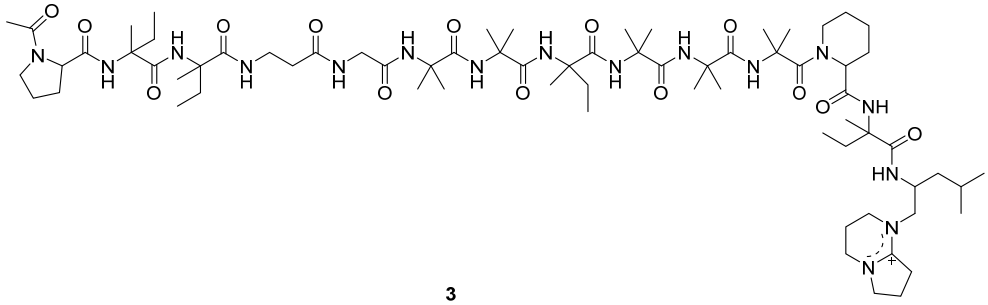

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Figure 2. Structure of peptide **3** [15].

TMC-69 (**4**) (Figure 3) is a new antitumor antibiotic that was isolated from the fermentation broth of *Chrysosporium* sp. TC 1068 [16]. However, compound **4** was unstable, so more stable derivatives, diacetyl TMC-69 (**5**) and hexahydro TMC-69 (**6**), were prepared to research their structures and biological activities. TMC-69 (**4**) and its derivatives, **5** and **6**, showed strong cytotoxicity to many tumor cell lines (Table 1). The survival time of mice-transplanted B16 melanoma and P388 leukemia was significantly prolonged by hexahydro TMC-69 (**6**). TMC-69 (**4**) had cytotoxicity on mouse tumor cells (P388D1 and B16) and human tumor cells such as HCT-116, HeLa S3, SK-BR3, WiDr and HL-60 cell lines, and showed the strongest cytotoxicity to HL-60 human promyelocytic leukemia cells, with an IC_{50} value of 0.43 μM (Table 1). Diacetyl TMC-69 (**5**) exhibited strong cytotoxicity against tumor cell lines HCT116, B16 and P388D1, with IC_{50} values ranging from 6.0 to 7.6 μM (Table 1) [16]. Hexahydro TMC-69 (**6**) also showed significant cytotoxicity to all tested cells, with IC_{50} values ranging from 0.1 to 1.87 μM (Table 1) [27]. The free *N*-hydroxyl group and the triene moiety are not necessary for cytotoxicity by analyzing the IC_{50} values of **4**–**6** (Table 1).

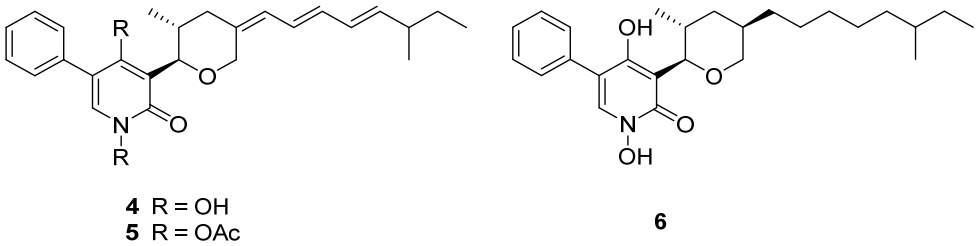


Figure 3. Structure of alkaloids **4**–**6** [16].

Strain BK-3 was identified as *C. lobatum*, which was isolated from forest soil samples collected in Kaziranga National Park, Assam, India [17]. Two bioactive compounds were isolated through biological activity-oriented purification and identified as *α*,*β*-dehydrocurvularin (**7**) and curvularin (**8**) (Figure 4), respectively [28]. Cytotoxicity tests were carried out on them and found that **7** and **8** showed similar antitumor activity towards HeLa, A549, MCF-7 and MDA MB-231. Furthermore, compound **7** was active towards COLO 205, with an IC_{50} value of 7.9 μM, while compound **8** was inactive (Table 1). The cytotoxic activities of compound **7** were better than those of compound **8**, except for the MDA-MB-231 cell line, caused by the oxidation of **8** to format the unsaturation double bond in **7** (Figure 4), which was the only difference between these two compounds.

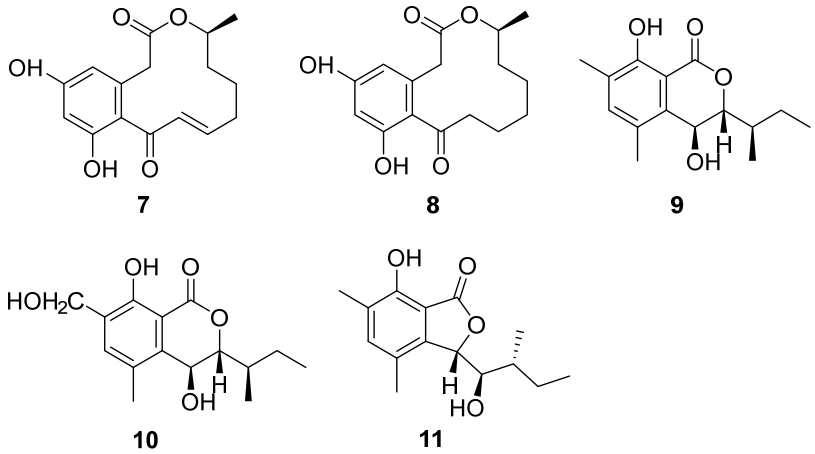


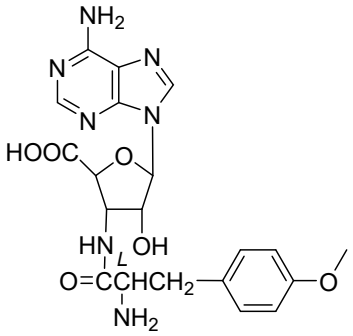
Figure 4. Structure of lactones **7**–**11** [17,29].

The fungal strain *C. articulatum*, a marine-derived fungus, was isolated from an unidentified marine sponge collected in Gagu-do, Korea in October 2008. The strain was numbered F085 and stored in the Laboratory of Natural Product and Structure Determination, College of Pharmacy, Seoul National University [29]. Elin et al. isolated three new benzolactone metabolites, chrysoarticulins A–C (**9**–**11**) (Figure 4). Chrysoarticulins A–C were, respectively, identified as a new isocoumarin metabolite with a *sec*-butyl side chain, a benzyl oxidant of A and a new benzolactone metabolite. The new compounds showed weak cytotoxicity towards the A549 and K562 cell lines, and the activity of compound **11** was higher than that of other compounds, with IC_{50} values of 34.5 μM and 25.4 μM (Table 1). However, its cytotoxicity was far weaker than that of doxorubicin.

There are nine natural products (**1**–**4** and **7**–**11**) isolated from the genus *Chrysosporium*, along with two chemical derivatives (**5** and **6**), that exhibit cytotoxic activities. The cytotoxic isolated compounds include one peptide (**3**), three polyketides (**1**, **2** and **4**) and five lactones (**7**–**11**). Among them, compound **1** displays significant antitumor activity against transformed cell lines and weak cytotoxicity against normal cell lines (Table 1), indicating the potential of **1** to be developed into an antitumor agent.

3. Antibacterial Activity

Yamashita et al. found a new antibiotic, chryscandin (**12**) (Figure 5) [14], from the fungus *Chrysosporium pannorum* in 1984. This was the first discovery of a secondary metabolite from the genus *Chrysosporium*. Compound **12** was found in the culture broth of the strain *C. pannorum* and had a unique structure, with an adenine nucleus and a 3-aminoribofuranuronic acid. The antimicrobial activity of **12** was tested and it showed activity against Gram-positive bacteria. The MIC value towards *Staphylococcus aureus* 209P JC-1 was 12.5 μg/mL (Table 2).



12

Figure 5. Structure of alkaloid **12** [14].

An antibacterial naphthoquinone antibiotic complex was isolated from the culture medium of *C. queenslandicum* IFM 51121, which was kept in the Microbial Strain Collection Center of the Research Center of Pathogenic Fungi and Microbial Toxicology, Chiba University, Japan [30]. The compounds of the complex were identified as altersolanols A–C (**13**–**15**) (Figure 6) [31,32]. They were active against all the tested Gram-positive bacteria and *Pseudomonas aeruginosa* IFO 3080, including *Staphylococcus aureus* IFO I2732, *Micrococcus luteus* IFO 3333 (**13** MIC = 12.5, **14** MIC = 25, **15** MIC = 25) and *Baccillus subtilis* IFO 3007 (**13** MIC = 50, **14** MIC = 25, **15** MIC = 25) [33] (Table 2). The MIC values of **13**–**15** against *P. aeruginosa* IFO 3080 and *S. aureus* IFO I2732 were all 12.5 μg/mL (Table 2) [33]. *P. aeruginosa* IFO 3080 was used to study the antimicrobial mechanism of **13**. The incorporation of radioactive precursors into macromolecules (DNA, RNA and protein) in whole *P. aeruginosa* IFO 3080 cells was nonspecifically suppressed by compound **13**. Moreover, the respiration of *P. aeruginosa* cells was enhanced; however, the proton conduction was unchanged through **13**. In addition, compound **13** increased the oxidation of NADH in the membrane fraction isolated from *P. aeruginosa*. In addition, it stimulated the oxidation of NADH by the enzyme preparation of cytochrome *c* reductase in the absence of cytochrome *c*. In summary, altersolanol A (**13**) seemed to inhibit bacterial growth by interfering with the respiratory chain in the bacterial membrane as an electron acceptor [34]. In addition to the above metabolites, *C. queenslandicum* IFM 51121 co-produced new antibacterial compounds related to the members of the dihydro-naphthoquinone group [35–37], named chrysoqueen (**16**) and chrysolandol (**17**) [30]. They showed activity against Gram-positive bacteria such as *Micrococcus luteus* IFM 2066 and *Bacillus subtilis* PCI 219, which had the same MIC value of 33 μg/mL.

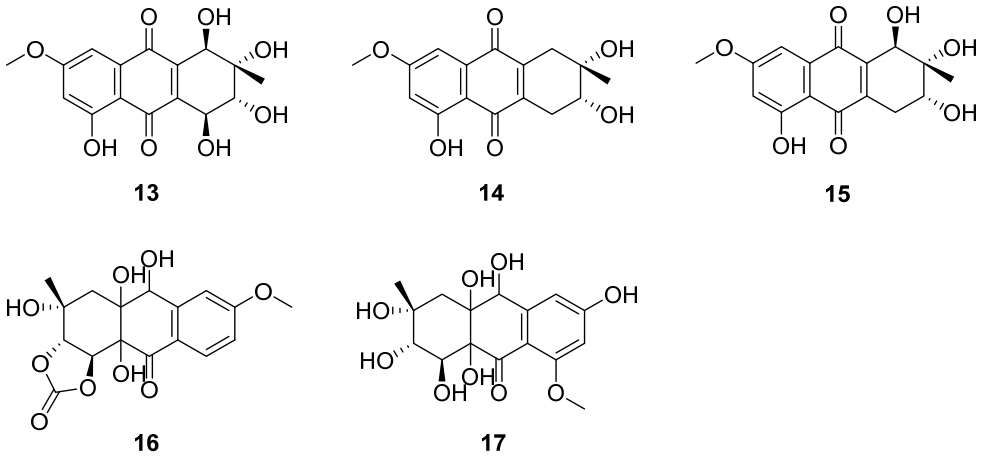


Figure 6. Structure of polyketides **13**–**17** [30–32].

α,*β*-Dehydrocurvularin (**7**) and curvularin (**8**) (Figure 4) were isolated from the strain *C. lobatum* BK-3. Compound **7** exhibited weak antibacterial activity against Gram-positive and Gram-negative bacteria, such as *B. subtilis*, *S. aureus* and *Escherichia coli*, which had the same MIC value of 40 µg/mL [38] (Table 2). The possible antibacterial mechanism of 7 was its efflux pump inhibitory potential in ethidium bromide (EtBr) fluorescence. Compound 7 suppressed the efflux pump by 0.84-fold, decreasing in ethidium bromide (EtBr) fluorescence with the concentration of 100 µg/mL [39]. Curvularin (**8**) (Figure 4) could completely inhibit the growth of *B. subtilis* on the seeds of *Phaseolus mungo* at a concentration of 100 ppm [40].

The fungus *C. multifidum* was isolated from the gut of *Hermetia illucens* BSF larvae [22]. The BSF larvae were taken from the breeding colony established by the Universidad Peruana Cayetano Heredia (Lima, Peru). The samples were fed with fresh and unsterilized chicken manure for 11 days. *Chrysosporium* was also isolated from chicken feces [41], which may be the *Chrysosporium* obtained from the diet of BSF larvae. Seven compounds were separated from the fungus *C. multifidum*, six *α*-pyranone derivatives (**18**–**23**) and a diketopiperazine (**24**) (Figure 7), and compound **24** was first reported in the *Chrysosporium* genus. The extract from the culture supernatant of *C. multifidum* showed moderate activity against methicillin-resistant *Staphylococcus aureus* (MRSA), with an MIC value of 62.5 µg/mL. Among these compounds, compound **21** had the highest activity towards MRSA (MIC = 62.5 µg/mL) (Table 2). These data suggest that the fungus *C. multifidum* isolated from the *H. illucens* gut may be a useful source to produce antimicrobial compounds that are active against other drug-resistant pathogens.

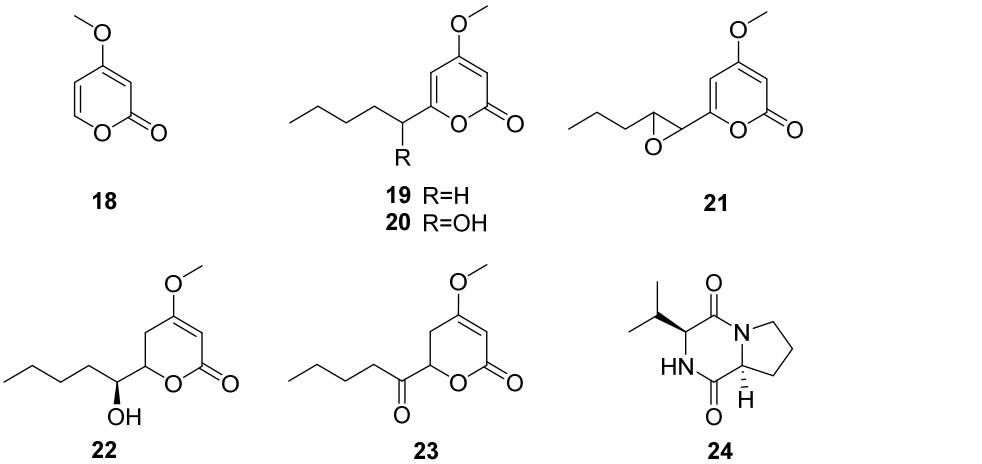


Figure 7. Structure of lactones **18**–**23** and cyclic dipeptide **24** [22].

Table 2. Compounds with antimicrobial activity.

Compound	Strain	MIC Value (μg/mL)	Ability	Pro	Con	Prospect
12 [14] (1984)	*Staphylococcus aureus* 209P JC-1 *Candida albicans* FP-614 *C. albicans* FP-616 *C. albicans* FP-618 *C. albicans* FP-620 *C. albicans* FP-622 *C. albicans* FP-633	12.5 0.8 0.2 0.8 0.2 3.1 1.6	Weak	Broad-spectrum antimicrobial activity	Weak activity	Structural foundation for new antibiotics
13/**14**/**15** [33] (2002)	*S. aureus* IFO I2732 *Micrococcus luteus* IFO 3333 *Baccillus subtilis* IFO 3007 *Pseudomonas aeruginosa* IFO 3080 *C. albicans* IFO 1061 *Aspergillus niger* IFO 6275 *Saccharomyces cereoisiae* IFO 0203	12.5/12.5/12.5 12.5/25/25 50/25/25 12.5/12.5/12.5 >100 >100 >100	Weak	Broad-spectrum antibacterial activity and the antibacterial mechanism of **13** was studied.	Weak activity	To provide structural inspiration for new antibiotics
16/**17** [30] (2002)	*Bacillus subtilis* PCI 219 *Micrococcus luteus* IFM 2066	33/33 33/33	Weak		Weak activity	Structural foundation for developing new antibiotics
25 (Zone of inhibition) [42] (2002)	*Aspergillus nidulans* IFM 5369	52.1 mm	Strong	Significant antifungal activity against *A. nidulans* IFM 5369 and broad-spectrum antifungal activity		Potential to be developed into new antifungal drugs
	Penicillium chrysogenum IFM 40614 *Paecilomyces variotii* IFM 40913 *A. terreus* IFM 40851 *A. fumigatus* IFM 41088 *Alternaria alternata* IFM 41348 *A. niger* IFM 5368 *A. niger* IFM 41934		Moderate			
26 [18] (2003)	*Candida albicans* (FLZ-S) *C. albicans* (FLZ-R) *C. dubliniensis* (FLZ-R) *C. krusei* *C. glabrate* (FLZ-S) *C. glabrate* (FLZ-R) *Saccharomyces cerevisiae* *Cryptococcus neoformans*	1 0.5 8 2 0.1 0.5 <0.06 16	Weak Weak Weak Weak Moderate Weak Moderate Weak	Broad-spectrum antifungal activity	Weak activity	Structural foundation for developing new antibiotics
27 [23] (2009)	*S. cerevisiae* (PM 503)	60	Weak		Weak activity	
7 [38] (2013)	*B. subtilis* *S. aureus* *Escherichia coli* *Cladosporium herbarum*	40 40 40 -	Weak	The antibacterial mechanism was studied	Weak activity	

Table 2. *Cont.*

Compound	Strain	MIC Value (μg/mL)	Ability	Pro	Con	Prospect
8 [40] (2013)	*Chaetomium indicum* Corda *Phoma hibernicaa* Grimes et al. *Aspergillus flavus* Link ex Fr. *Drechslera tetramera* McKiuney *Fusarium oxysporum* Schl.	Completely suppressed in 50 ppm	Strong	Completely suppressed the growth of a series of fungi on the seeds of *Phaseolus mungo* Roxb		Potential to be developed into agricultural antimicrobial drugs
	B. subtilis	Completely suppressed in 100 ppm				
	Curvularia lunata (Walker) Boedijn Papulaspora sp.	Completely suppressed in 200 ppm				
	Alternaria alternata Nees.	Reduced considerably in 200 ppm				
21	methicillin-resistant *Staphylococcus aureus* (MRSA)	62.5	Moderate	With antibacterial activity against drug-resistant strain	The low activity	Potential to be developed into antimicrobial resistance drugs
18–**20**, **22**–**24** [41] (2019)			Weak			

4. Antifungal Activity

Besides antibacterial activity, chryscandin (**12**) (Figure 5) showed antifungal activity against *C. albicans*. The inhibition rates against *C. albicans* FP-614, FP-616, FP-618, FP-620, FP-622 and FP-633 were tested, and all the MIC values were less than 4 μg/mL [14] (Table 2). Such inhibition was accompanied by swelling of the *Candida* cells [43]. The acute toxicity of compound **12** was very low in mice, indicating the good drug safety performance of **12**. The anti-infective experiment in vivo due to *C. albicans* of **12** was examined with the ED_{50} value of 10 mg/kg by the subcutaneous route and 25 mg/kg by the oral route [14], which was almost the same as the positive control, 5-fluorocytosine.

Altersolanols A–C (**13**–**15**) (Figure 6) and queenslandon (**25**) (Figure 8), isolated from *C. queenslandicum* IFM 51121, were found to have antifungal activity [31,32,42,44]. The MIC values of **13**–**15** towards *C. albicans* IFO 1061, *Saccharomyces cereoisiae* IFO 0203 and *Aspergillus niger* IFO 6275 were all over 100 μg/mL (Table 2). Queenslandon (**25**) belonged to the zearalenone family of mycotoxins [44]. Compound **25** exhibited significant antifungal activity, with a 52.1 mm maximum inhibition diameter against *A. nidulans* IFM 5369 by the 8 mm paper disc containing 50 μg of **25** [42], and its antifungal activity was even stronger than that of positive control amphotercin B. It also showed moderate antifungal activity against *Penicillium chrysogenum* IFM 40614, *Paecilomyces variotii* IFM 40913, *A. terreus* IFM 40851, *A. fumigatus* IFM 41088, *Alternaria alternata* IFM 41348, *A. niger* IFM 5368 and *A. niger* IFM 41934 [42] (Table 2). The inhibition diameters of the reference drug amphotercin B against *A. niger* IFM 5368 and *A. nidulans* IFM 5369 were 13 and 32 mm, respectively.

In order to search for antifungal drugs, a new antifungal agent, sch 601324 (**26**) (Figure 8), was separated from the fungal culture *Chrysosporium pilosum* [18], which belongs to sterol sulfates and has antifungal activity against various candidal strains, such as *Candida albicans*, *C. dubliniensis*, *C. krusei*, *C. glabrate* and *Saccharomyces cerevisiae*. The MIC values were under 2 μg/mL (Table 2). The collected microorganisms were purchased from commercial sources and named SPRI-IL15503. Four new caryophyllene sesquiterpenes (**27**–**30**) (Figure 8) were found by further study of the secondary metabolites of the microorganism [23]. Compound **27** showed antifungal activity, and its MIC value towards *S. cerevisiae* (PM 503) was 60 μg/mL (Table 2). Compounds **27**–**30** possess three oxygen atoms on C-6, C-7 and C-15, but their different oxidation states or cyclization positions may be related to the strength of their antifungal activity. The results show that *C. pilosum* has the ability to produce antimicrobial secondary metabolites, which provide a chemical structural foundation for drug development.

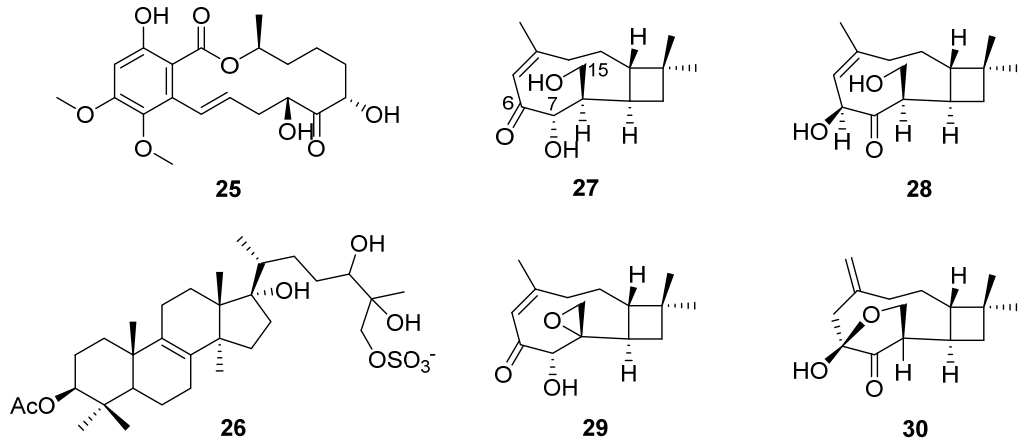


Figure 8. Structure of lactone **25**, steroid **26** and terpenoids **27**–**30** [18,23,42].

Two bioactive compounds, α,β-dehydrocurvularin (**7**) and curvularin (**8**) (Figure 4), isolated from the strain *C. lobatum* BK-3, showed antifungal activities. α,β-Dehydrocurvularin (**7**) exhibited antifungal activity against *Cladosporium herbarum* [45]. An antifungal activity evaluation indicated that curvularin (**8**) could completely suppress the growth of a series of fungi on the seeds of *Phaseolus mungo* Roxb with a concentration of 50 ppm (Table 2) [40].

Eighteen *Chrysosporium*-isolated compounds exhibit antimicrobial activities. Fifteen of these compounds show antibacterial activities (**7**, **8**, **12**–**24**), nine of the compounds display antifungal activities (**7**, **8**, **12**–**15**, **25**, **26**, **27**), and six compounds reveal both antibacterial and antifungal activities (**7**, **8**, **12**–**15**). Nine of the antimicrobial compounds belong to lactones (**7**, **8**, **18**–**23**, **25**), five of the compounds belong to the family of polyketides (**13**–**17**), and others include an alkaloid (**12**), cyclic peptide (**24**), terpenoid (**27**) and steroid (**26**). Among them, compound **8** can completely suppress the growth of a series of fungi and bacterium *B. subtilis* on the seeds of *Phaseolus mungo* Roxb, meaning that it has the potential to be developed into agricultural antimicrobial drugs. Compound **25** exhibits stronger antifungal activity against *A. nidulans* IFM 5369 than positive control amphotercin B, which could be developed into antifungal drugs.

5. Enzyme Inhibition

Inhibition of $p21^{ras}$ protein's farnesylation is considered a potential strategy for antitumor chemotherapy research [46]. A new compound, R113228 (**31**) (Figure 9), was isolated from a fungus, *C. lobatum*, which was a new type of farnesyl protein transferase (FPTase) inhibitor [47]. This strain was numbered CBS12395 and is conserved in the Centraalbureau voor Schimmel Culturen, Baarn, Holland. Compound **31** showed selective inhibition towards FPTase. Because its IC_{50} towards human geranyl-geranyl protein transferase was 59 μM (Table 3), it showed no inhibitory effect on rat liver squalene synthase. This secondary metabolite represents a new and effective inhibitor of Ras post-translational processing and thus can be used as an anticancer agent.

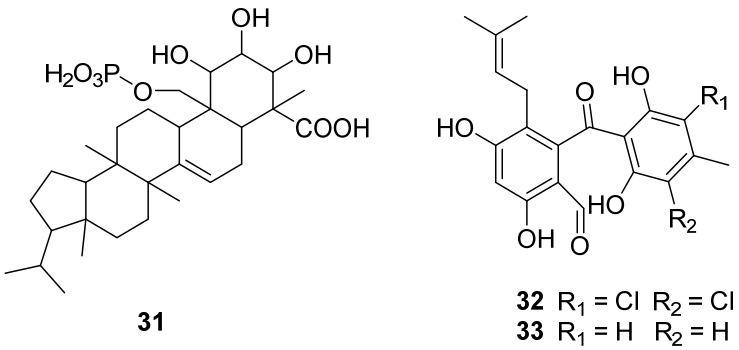


Figure 9. Structure of triterpene **31** and polyketides **32** and **33** [47,48].

SB87-Cl (**32**) and SB87-H (**33**) (Figure 9) [48] were isolated from *Chrysosporium* sp. Compound **32** could inhibit reductase (Table 3), but had different structural characteristics from other inhibitors with chlorination. It also could be safely used as an active ingredient in hair growth stimulators [49].

In the search for HIV-1 protease inhibitors in microbial secondary metabolites, inhibitors from the fungus *C. merdarium* P-5656 were identified [19]. P-5656 came from the soil samples collected from a coconut forest near Tenacaita, Mexico, from which the known bisalkylated 2,5-dihydroxybenzoquinones didemethylasterriquinone D (**34**) and isocochliodinol (**35**), as well as the new metabolites semicochliodinol A (**36**) and B (**37**) (Figure 10), were separated. Compounds **34**–**36** exhibited strong enzyme inhibition activity against HIV-1 protease (HIV-1 prt), with IC_{50} values from 0.18 μM to 0.37 μM (Table 3). Compound **37** was a weak HIV-1 protease inhibitor. The IC_{50} values of compounds **34**–**37** for human cathepsin D (CD) were from 2.5 μM to 4.9 μM (Table 3). Nakikiqinones C and D, with a similar central hydroxybenzoquinone ring, have been described as c-ErbB-2 kinase

inhibitors [50]. Compounds **34**–**37** inhibited epidermal growth factor receptor protein tyrosine kinase (EGF-R PTK) by approximately 20 μM (Table 3). The overlap of **34** with known EGF-R PTK [51] inhibitors or DAHP 1 [52] suggests that new derivatives of **34** with meta substitution on the benzoquinone ring can be more effective as inhibitors of this enzyme. Downregulation of PTK activity in tumor cells is associated with malignant transformation. EGF-R PTK inhibitors may have therapeutic potential as anticancer agents. Studies have shown that **34** and its derivatives are attractive lead compounds for HIV-1 protease and EGF-R PTK inhibitors.

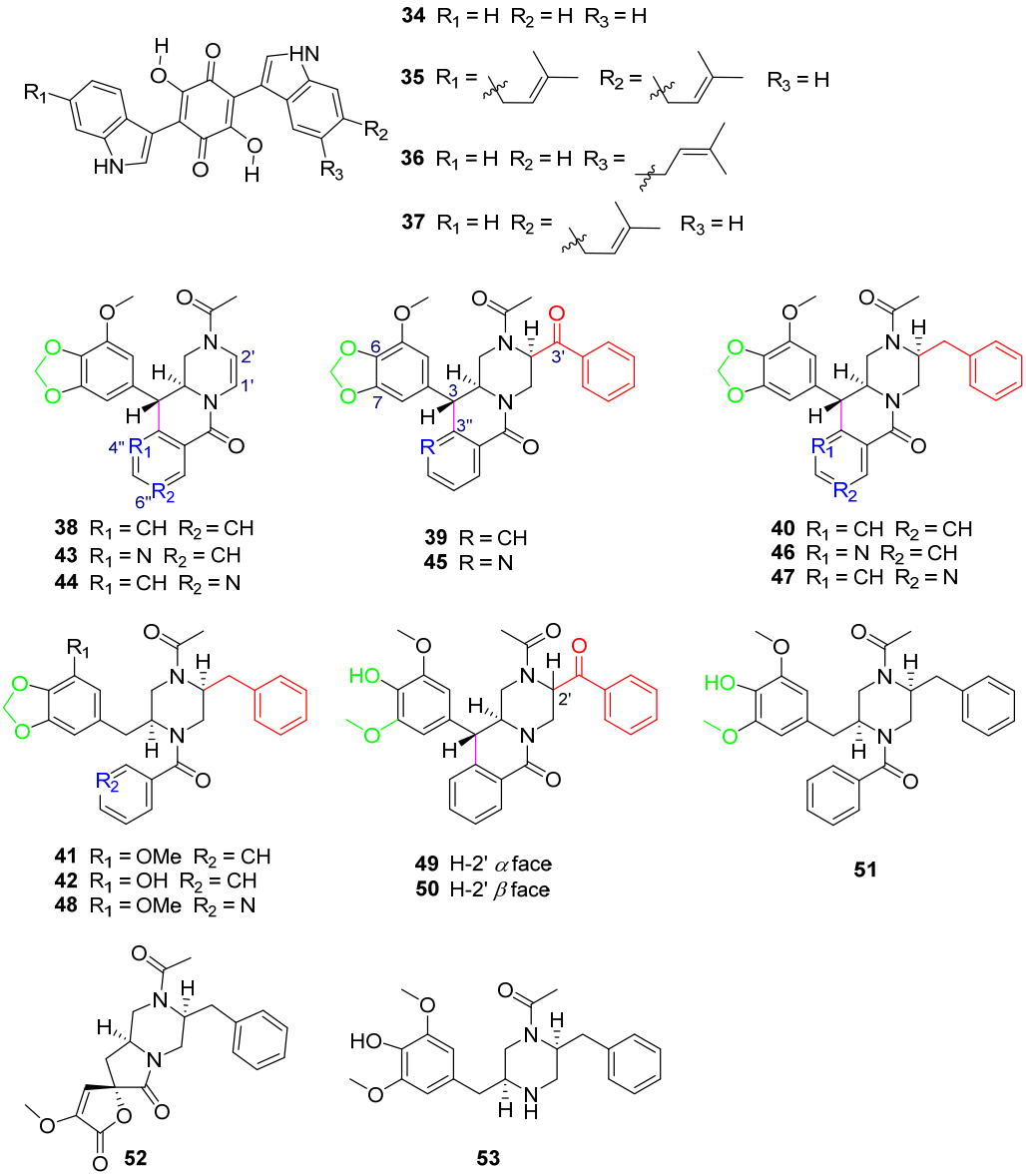


Figure 10. Structure of alkaloids **34**–**53** [19,53,54]. The different color highlighted the different structural characteristics of **38**–**51**.

Table 3. Compounds with enzyme inhibition.

Compound	Enzyme	Inhibition Value	Ability	Pro	Con	Prospect
31 (IC_{50}/μM) [47] (1995)	FPTase	59	Moderate			Potential to be developed into new antitumor drugs
32 [49] (1995)	Reductase	-	-			
34/**35**/**36**/**37** (IC_{50}/μM) [19] (1997)	HIV-1 prt	0.24/0.18/0.37/>0.5	Strong/weak (**37**)	Strong inhibition against HIV-1 prt	Weak inhibition against CD and EGF-R PTK	Attractive lead compounds for HIV-1 protease
	CD	4.2/4.1/2.5/4.9	Weak			
	EGF-R PTK	15/20/20/60	Weak			
6 (IC_{50}/μM) [27] (2001)	Cdc25A	3.1	Strong	Strong inhibition against Cdc25A and Cdc25B		Potential to be developed into new antitumor drugs
	Cdc25B	4.4				
8 (IC_{50}/μM) [28] (2013)	AChE	1.36	Strong	Strong inhibition		Potential to be developed into AChE inhibitory drugs to treat Alzheimer's disease
11 (IC_{50}/μM) [29] (2013)	Sortase A	95.1	Moderate			Potential to be developed into new antimicrobial drugs
	ICL	236.4	Weak		Weak inhibition	Structural foundation for developing new anti-tuberculosis drugs
38–**42** (GS) [53] (2019)	P-gp	3.6/7.2/6.3/1.6/1.8	Weak	Compounds **43**, **45**, **46**, **47** and **54** display significant enzyme inhibitory activity against P-gp and could reverse doxorubicin resistance in human colon cancer cells		Potential to be researched as assisted antitumor drugs to reduce the occurrence rate of drug resistance
43/**44** (GS)	P-gp	9.5/6.8	Moderate			
45/**46**/**47** (GS)		20.5/21.3/19.8	Strong			
48–**53** (GS) [54] (2021)		1.62/0.81/1.11/1.13/1.39/1.27	Weak			
54 (GS)	P-gp	14	Strong			
55/**58**/**59** (GS)	P-gp	5.6/4.5/6.0	Moderate			
56/**57**/**60**/**61** [55] (2020)	P-gp	-	-			

TMC-69-6H (**6**) (Figure 3), a hexahydro derivative of **4**, caused a dose-dependent inhibition of phosphatase Cdc25A (Cdc25 phosphatases are classified as dual-specificity protein phosphatases) activity, with an IC_{50} value of 3.1 μM, and also inhibited Cdc25B, with an IC_{50} of 4.4 μM (Table 3) [27].

The initial crude extract of the strain *C. lobatum* BK-3 showed 60% inhibition of acetylcholinesterase (AChE) [28]. Chemical investigation of the fungus led to the isolation of compound curvularin (**8**) (Figure 4), which showed strong AChE inhibitory activity, with 80% inhibition, and the IC_{50} value was 1.36 μmol/mL (Table 3), compared to the positive control galanthamine, with 75% inhibition and an IC_{50} value of 2.625 μmol/mL.

Chrysoarticulin C (**11**) (Figure 4), isolated from the fungus *C. articulatum*, had moderate activity on sortase A, the key enzyme related to the adhesion and invasion of Gram-positive bacteria, with the IC_{50} value of 95.1 μM. Compound **11** displayed weak inhibition against isocitrate lyase (ICL, a key enzyme in microbial biosynthesis), with an IC_{50} value of 236.4 μM (Table 3) [29].

Five new phenylpropyl piperazines, chrysosporazines A–E (**38**–**42**) (Figure 10), featuring an unprecedented hexahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-6-one scaffold [53], were obtained from the fungus *Chrysosporium* sp. CMB-F214 in the gastrointestinal tract of a *Mugil* mullet purchased from an Australian market. Chrysosporazines showed P-glycoprotein (P-gp) inhibition and could reverse doxorubicin resistance in human colon cancer cells (SW620 Ad300, P-gp overexpressing cell lines) with a 2.5 μM co-treatment,

significantly improving the sensitivity of **38**–**40** to doxorubicin, with the GS (the ratio of doxorubicin IC_{50} without and with the addition of either **38**–**40** or verapamil) values of 3.6, 7.2 and 6.3, respectively, and the GS of verapamil as the positive control was 8.3 (Table 3).

Further chemical investigation of the fungus CMB-F214 led to the isolation of azachrysposorazines A1, A2, B1, C1, C2 and D1 (**43**–**48**), chrysosporazines N–P (**49**–**51**), spirochrysosporazine A (**52**) and known chrysosporazines A–D (**38**–**41**) (Figure 10), with the method of precursor-directed biosynthesis-mediated amplification [54]. The fungus CMB-F214 was cultured in an M1 agar plate medium containing sodium nicotinate. The new natural product chrysosporazine Q (**53**) was produced by the fungus CMB-F214 in an M2 medium without sodium nicotinate. Compounds **43**–**53** reversed the drug resistance of SW620 Ad300 cancer cells to doxorubicin. The doxorubicin sensitivity (GS) induced by C-2′-substituted analogues **45**–**47** was more than 2.5-times higher than that of the positive control, verapamil (Table 3).

Further investigation of the structure–activity relationship of the chrysosporazines and their derivatives found that the influences of the structures on reversing the doxorubicin resistance bioactivity of the compounds are mainly caused by the following aspects: C-2′ substitution by benzaldehyde or benzyl groups, C-3/C-3″ cyclization, whether there is a methylenedioxy ring and whether there is a replacement of CH by N in the location of 4″ or 6″.

The reduction of the double bond between C-1′ and C-2′ and the substitute in the location of C-2′ by a benzaldehyde group in **39** and **45** (Figure 10) or a benzyl group in **40** and **46** (Figure 10) can lead to significantly higher GS values (**38** GS = 3.6, **39** GS = 7.2, **40** GS = 6.3, **43** GS = 9.5, **45** GS = 20.5, **46** GS = 21.3) (Table 3), when comparing the structures of **38**/**39**/**40**, **43**/**45**/**46** (Figure 10), respectively.

The cyclization of C-3/C-3″ leads to higher activity when comparing the structures of **40** and **41** (Figure 10) (**40** GS = 6.3, **41** GS = 1.6), and **46** and **48** (Figure 10) (**46** GS = 21.3, **48** GS = 1.62), respectively (Table 3). The breakage of the C–C bond in C-3/C-3″ in **41**, **42**, **48** and **51** (Figure 10) leads to a lower ability to reverse doxorubicin resistance (**41** GS = 1.6, **42** GS = 1.8, **48** GS = 1.62, **51** GS = 1.13) (Table 3), which further explains the importance of C-3/C-3″ cyclization to the activity of compounds.

The only difference in the structures of **39** and **49**/**50** (Figure 10) is whether the left sides of C-6 and C-7 contain a methylenedioxy ring, which causes their different GS values (**39** GS = 7.2, **49** GS = 0.81, **50** GS = 1.11) (Table 3). It is found that the GS values of the compounds containing a methylenedioxy ring are higher than those of the compounds not containing it.

When comparing the structures of **38** and **43**/**44** (Figure 10) (**38** GS = 3.6, **43** GS = 9.5, **44** GS = 6.8) (Table 3), substitution of CH with N at 4″ or 6″ significantly increases the activity of the compounds. The structure analysis of **39** and **45** (Figure 10) (**39** GS = 7.2, **45** GS = 20.5) and **40** and **46**/**47** (Figure 10) (**40** GS = 6.3, **46** GS = 21.3, **47** GS = 19.8) (Table 3) also reaches the same conclusion. The alternative CH by N at 4″ or 6″ has a positive impact on the activity of the compounds.

Compounds **45**–**47** (Figure 10), which have structures with all of the above characteristics, including C-2′ substitution, C-3/C-3″ cyclization, the methylenedioxy ring and alternative CH by N at 4″ or 6″, exhibited the best activity (**45** GS = 20.5, **46** GS = 21.3, **47** GS = 19.8) (Table 3), with GS values > 2.5-fold higher than that of the positive control, verapamil (GS = 8.1), which further illustrated that these four structural features are the key determinants to improve the P-gp inhibition of chrysosporazines and their derivatives.

The fungus *Chrysosporium* sp. CMB-F294, derived from the *Mugil* mullet gastroint estinal-derived fungal isolate library, showed a potential ability to produce P-pg inhibitory compounds [55]. Chemical investigation of the fungus CMB-F294 led to the isolation of eight new alkaloids, chrysosporazines F–M (**54**–**61**) (Figure 11), belonging to phenylpropanoid piperazines. The cyclized analogues chrysosporazines F, G, J and K (**54**, **55**, **58** and **59**) showed significant inhibition towards the enzyme P-gp. Chrysosporazine F (**54**),

with a 2.5 μM co-treatment, also induced an increase in doxorubicin sensitivity (GS = 14) (Table 3), which was over two times than that of positive control verapamil (GS = 6.0).

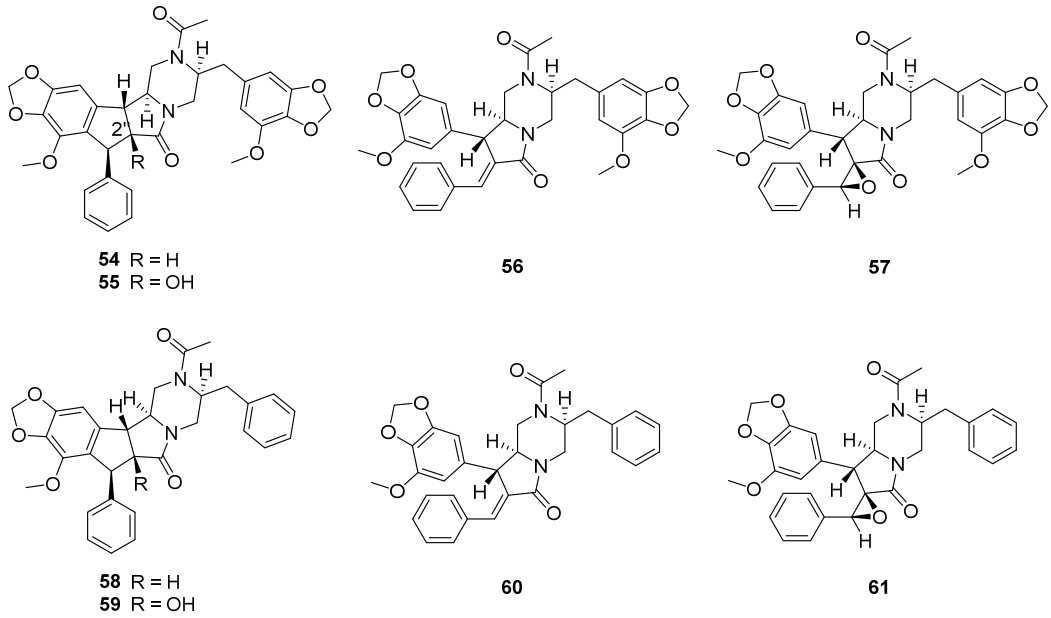


Figure 11. Structure of alkaloids **54**–**61** [55].

Chrysosporazines and their derivatives (**38**–**61**), belonging to the rare class of phenylpropanoid piperazines, are the characteristic natural products of the genus *Chrysosporium*. Compounds **38**–**51** feature an unprecedented hexahydro-6*H*-pyrazino[1,2-*b*]isoquinolin-6-one scaffold, and **54**–**61** feature unprecedented carbocyclic and heterocyclic scaffolds.

Thirty-two compounds isolated from *Chrysosporium* sp. show enzyme inhibition. Most of the enzyme inhibitory compounds are alkaloids (**34**–**61**); others are lactones (**8** and **11**), a terpenoid (**31**) and a polyketide (**32**). Among them, compound **8** exhibits stronger enzyme inhibitory activity against AChE than that of the positive control galanthamine, meaning that **8** could be developed into AChE inhibitory drugs to treat Alzheimer's disease. Moreover, compounds **43**, **45**, **46**, **47** and **54** display significant enzyme inhibitory activity against P-gp and could reverse doxorubicin resistance in human colon cancer cells, which shows that they could be researched as assisted antitumor drugs to reduce the occurrence rate of drug resistance.

6. Other Biological Activities

A new biphenyl dicarboxylic acid, sporandol (**62**) (Figure 12), was isolated from *C. meridarium* under the guidance of antiparasitic activity [56]. This compound is much less toxic to mammals than other members of the binaphthyl group. Compound **62** is active against many parasites. At a dose of 190 mg/kg, it could inhibit the growth of the endoparasite (fluke) *Fasciola hepatica* and the ectoparasite *Dipetalogaster maximus* in a mouse [56]. When 620 mg/kg was administered daily for six consecutive days, the mouse did not suffer from serious poisoning. Therefore, Sporandol (**62**) has the potential to become an antiparasitic agent.

α,*β*-Dhydrohydrohcurvularin (**7**) (Figure 4) showed significant antioxidant properties. Its superoxide anion scavenging activity was much better than the positive controls (ascorbic acid, EC_{50} = 21.01 μg/mL, luteolin, EC_{50} = 31.01 μg/mL), with an EC_{50} value of 16.71 μg/mL. Moreover, compound **7** also showed DPPH scavenging activity, lipid peroxidation inhibition and erythrocyte hemolytic inhibition. The EC_{50} values were 50.75 μg/mL, 159.09 μg/mL and 141.79 μg/mL, respectively [28]. Among them, Curvularin (**8**) (Figure 4) was a potential nematicide against the root lesion nematode *Pratylenchus penetrans* [57]. Compounds **7** and **8** were found to have phytotoxicity. When the concentrations of **7**

and **8** were as low as 0.1 and 0.33 mg/mL, respectively, it caused stem collapse and vascular necrosis in zinnia (*Zinnia elegans* Jacq. (Compositae)) seedlings within 24 h [45]. These two compounds led to the necrosis of cuttings of Canada thistle (*Cirsium arvense* (L.) Scop. (Compositae)) at a concentration of 0.33 mg/mL for 16 h. The activity of **7** and **8** toward oats (*Avena byzantina* cv. Coast Black) was low. Both of the compounds caused chlorosis at the lowest concentration tested (0.1 mg/mL) by 64 h of incubation [45]. *α*,*β*-Dhydrohydrohcurvularin (**7**) caused extensive necrosis of the leaves of various weeds at 688 µM, while corn and soybeans were insensitive to it. However, the investigation of the host range showed that the toxin was non-specific. Compound **7** significantly inhibited the mitosis of root tip cells, which supports the potential of **7** to be used as a natural biological herbicide [58].

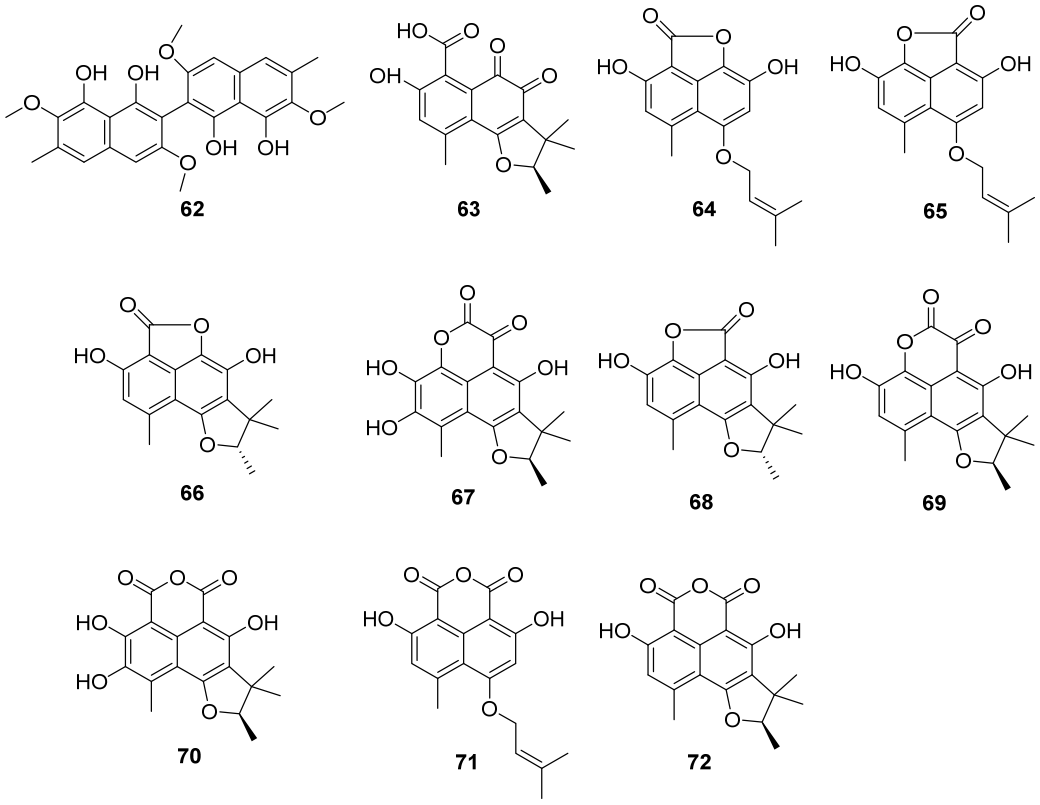


Figure 12. Structure of polyketides **62**–**72** [56,59].

The fungus *C. lobatum* TM-237-S5 was isolated from the sponge *Acanthella cavernosa*, which was collected from the coral ecosystem of the Red Sea [59]. Ten compounds (**63**–**72**) (Figure 12) related to phenylacetones were isolated and identified: peniciphenalenin D (**63**), isoconiolactone (**64**), coniolactone (**65**), (−)-peniciphenalenin F (**66**), (+)-8-hydroxyscleroderolide (**67**), (−)-7,8-dihydro-3,6-dihydroxy-1,7,7,8-tetramethyl-5H-furo-[2′,3′:5,6] naphtho [1,8-bc]furan-5-one (**68**), (+)-scleroderolide (**69**), (+)-8-hydroxyslerodin (**70**), conioscleroderin (**71**) and (+)-sclerodin (**72**). Among them, **64**, **66**, **67** and **70** were new compounds.

7. Purification Techniques for the Compounds Isolated from *Chrysosporium*

The natural products isolated from the genus *Chrysosporium* were mainly purified through different chromatographic techniques, including silica gel column chromatography (CC) [22,28,30,42,56], medium-pressure liquid chromatography (MPLC) [22], Sephadex LH-20 CC [16,22,30,55], CM-Sephadex C-25 [14], Sepabeads SP20SS CC [15], MCI-gel CHP 20P CC [30], Diaion HP 20 CC [14,15,28], ODS CC [49], C_{18} reversed-phase vacuum flash chromatography [19,29], semi-preparative high-performance liquid chromatography (HPLC) [16,18,19,23,29,42,54,55,59] and preparative thin-layer chromatography (TLC) [30,42],

combined with extraction, recrystallization [14,19,30,42], UPLC-DAD and UPLC-QTOF analyses [54], and bioactivity-guided isolation [30,42]. In the process of separation, most of the compounds could be disclosed on the TLC plates in UV_{254} light [28,30,42] and TLC-direct bioautography (DB) tests [22], conveniently.

The liquid culture medium of the genus *Chrysosporium*, concentrating most of the secondary metabolites, was first filtrated to discard the mycelium and obtain the supernatant fluid. The filtrate could be eluted through polymeric resin Diaion HP-20 [14,15,28] or MCI-gel CHP 20P CC [30] to remove the sugars and minerals and acquire the crude extract, or directly extracted by ethyl acetate (EA) to obtain the crude extract. Most of the fermentation broth was extracted by EA; however, the crude extracts of the fungi *C. pilosum* and *Chrysosporium* sp. were extracted with acetonitrile and then purified to obtain terpenoids **27**–**30** [23] and steroid **26** [18], respectively. Almost all of the compounds were in the organic phase, except polypeptide **3** [15]. The acetone–0.2 M HCl (1:1) eluate of the Diaion HP-20 column was partitioned between EA and water. The aqueous layer was extracted with chloroform, and the extract was subjected to Sepabeads SP20SS CC to obtain **3** [15]. Some of the fungi *Chrysosporium* were cultured in agar plates containing PDA medium [59], M1 agar media [54], M2 agar [54] or Yeast Extract Sucrose (YES) agar [55], and then extracted with EA, filtered and concentrated in a vacuum, to obtain the crude extract. The crude extract could be purified by different chromatographic techniques according to the different properties of the isolated compounds.

8. Conclusions

From 1984 to 2021, a total of 70 natural products were isolated from the genus *Chrysosporium* (Table 4), with 66% of these compounds being discovered for the first time. These findings demonstrate that the genus *Chrysosporium* has great potential to produce compounds with novel structures. The structures of the isolated compounds, with diverse skeletons, are mainly concentrated in the classes of alkaloids, polyketides and lactones (Figure 13). Forty-three percent of the compounds isolated from the genus *Chrysosporium* belong to the family of alkaloids (Figure 13); 29% are polyketides, and 17% are lactones. Terpenoids and peptides are both less than 10%. In addition, only 1% of the compounds belong to steroids (Figure 13).

Chrysosporazines, as well as their derivatives, belonging to the rare family of phenylpropanoid piperazine alkaloids, are the characteristic natural products of the genus *Chrysosporium*. Moreover, they are also the main secondary metabolites of the genus *Chrysosporium*, accounting for over one third of all the compounds isolated from *Chrysosporium*.

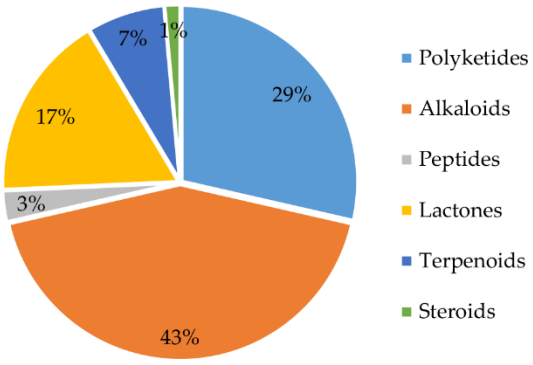


Figure 13. Structural types of compounds isolated from *Chrysosporium* from 1984 to 2021.

Table 4. Compounds isolated from *Chrysosporium* in 1984–2021.

Type	Compound	Source	Distribution	Bioactivity	Year
Alkaloids	**4**	*Chrysosporium* sp. TC 1068		Cytotoxicity	2001 [16]
	12	*C. pannorum* No. 4629		Antibacterial and antifungal activities, and acute toxicity in mice	1984 [14]
	34–37	*C. merdarium* P-5656		Enzyme inhibition	1997 [19]
	38–42	*Chrysosporium* sp. CMB-F214 from Gastrointestinal tract of *Mugil* mullet	Australia	Enzyme inhibition	2019 [53]
	43–53	*Chrysosporium* sp. CMB-F214 from Gastrointestinal tract of *Mugil* mullet	Australia	Enzyme inhibition	2021 [54]
	54–61	*Chrysosporium* sp. CMB-F294 from Gastrointestinal tract of *Mugil* mullet	Australia	Enzyme inhibition	2020 [55]
Polyketides	**1, 2**	*C. verrucosum* Tubaki from soil	King George Island, Antarctica	Cytotoxicity	1992 [20]
	13–15	*C. queenslandicum* IFM 51121 from soil	Egypt	Antibacterial and antifungal activities	2002 [30]
	16, 17	*C. queenslandicum* IFM 51121 from soil	Egypt	Antibacterial activity	2002 [30]
	32	*Chrysosporium* sp.		Enzyme inhibition	2004 [48]
	33	*Chrysosporium* sp.			2004 [48]
	62	*C. meridarium*		Antiparasitic activity	1997 [58]
	63–72	*C. lobatum* TM-237-S5 from the sponge *Acanthella cavernosa*	The mesophotic coral ecosystem of the Red Sea		2019 [59]
Lactones	**7**	*C. lobatum* BK-3 from soil	Kaziranga National Park, Assam, India	Cytotoxicity, phytotoxicity, antibacterial, antifungal and antioxidant activities	2013 [28]
	8	*C. lobatum* BK-3 from soil	Kaziranga National Park, Assam, India	Cytotoxic, phytotoxic, enzyme inhibitory, antifungal and antibacterial activities	2013 [28]
	9, 10	*C. articulatum* from a dictyoceratid sponge	The coast of Gagu-do, Korea	Cytotoxicity	2013 [29]
	11	*C. articulatum* from a dictyoceratid sponge	The coast of Gagu-do, Korea	Cytotoxicity and enzyme inhibition	2013 [29]
	18–23	*C. multifidum* from the gut of *Hermetia illucens* larvae	The Universidad Peruana Cayetano	Antibacterial activity	2019 [22]
	25	*C. queenslandicum* IFM 51121 from soil	Egypt	Antifungal activity	2002 [30]
Terpenoids	**27**	*C. pilosum*		Antifungal activity	2009 [23]
	28–30	*C. pilosum*			2009 [23]
	31	*C. lobatum* from soil		Enzyme inhibition	1995 [47]
Peptides	**3**	*Chrysosporium* sp. PF1201		Cytotoxicity	1998 [15]
	24	*C. multifidum* from the gut of *Hermetia illucens* larvae	The Universidad Peruana Cayetano Heredia (Lima, Peru)	Antibacterial activity	2019 [22]
Steroids	**26**	*C. pilosum*		Antifungal activity	2003 [18]

The sources of *Chrysosporium* are distributed in different ecosystems, including the Antarctic, forests and oceans. Half of the isolated natural products were separated from marine organism-derived *Chrysosporium*, including sponge, seaweed and mullet. The first marine-derived natural product was isolated from an unidentified sponge-derived *Chrysosporium* in 2013 [29]. Since then, more than 80% of the compounds have been isolated from the marine-derived genus *Chrysosporium*, indicating that marine fungi have great potential to produce new compounds.

The genus *Chrysosporium* has the potential to produce a variety of secondary metabolites with diverse bioactivities, including cytotoxicity, antimicrobial, enzyme inhibition, antiparasitic, antioxidant and phytotoxicity (Figures 14 and 15). The activities of the *Chrysosporium* isolated compounds mainly focus on the categories of enzyme inhibition (46%), antimicrobial (34%) and cytotoxic (13%) activities (Figure 15). Around 80% of the compounds have biological activity, of which nine (**3**, **7**, **8**, **25**, **43**, **45**, **46**, **47**, **54**) showed stronger activities than those of the positive controls. Compound **3** shows intense cytotoxicity against transformed oncogene tumor cell lines, while it exhibits weak cytotoxicity to normal cell lines, indicating that **3** has the potential to be developed into a selective antitumor agent. Compound **7** shows strong antioxidant activity, which could be exploited for its anti-oxygen activity. Compound **8** exhibits strong enzyme inhibitory activity against AChE. Meanwhile, compounds **43**, **45**, **46**, **47** and **54** display significant enzyme inhibitory activity against P-gp and could reverse doxorubicin resistance in human colon cancer cells, which shows that they could be developed into antitumor drugs to reduce the occurrence of drug resistance. Compound **25** exhibits significant antifungal activity and could be used as an antibiotic. Compounds **7** and **8** display a variety of different activities, including antimicrobial, antioxidant, cytotoxic, phytotoxic and enzyme inhibitory activities (Figure 14), which could be used in the medical, agricultural and industrial fields. All these results indicate that the genus *Chrysosporium* is a potential source of rich bioactive compounds.

In this review, we have summarized the chemical structure type, bioactivity, source and distribution of the secondary metabolites isolated from *Chrysosporium* from 1984 to 2021. The results of the literature survey show that *Chrysosporium* has great potential to produce a variety of new bioactive natural products. However, there are few studies about the bioactive mechanisms, which limits the practical application of the isolated compounds from *Chrysosporium*. The results demonstrate that the genus *Chrysosporium* is a promising germplasm resource for the discovery of novel compounds with pharmacological and biological activities, which have the potential to be developed into new drugs.

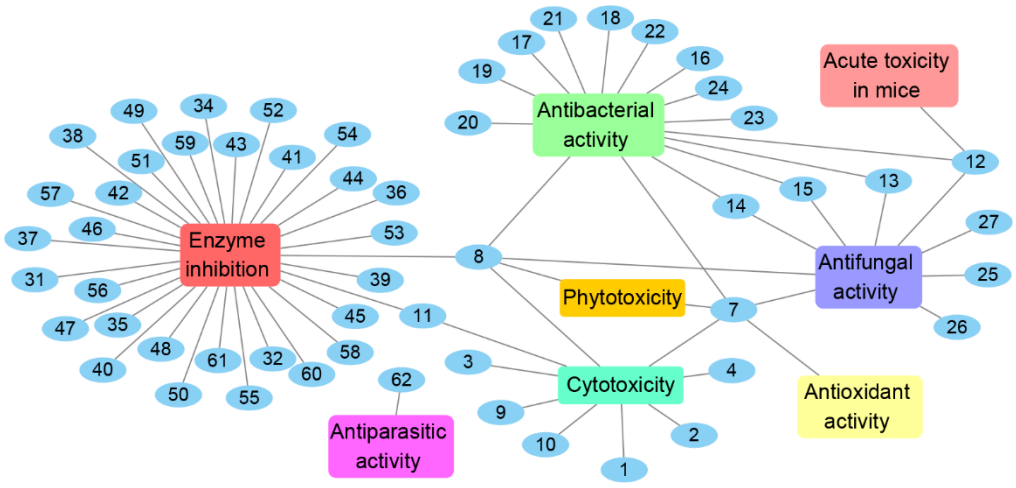


Figure 14. Bioactivities of natural products isolated from *Chrysosporium* from 1984 to 2021.

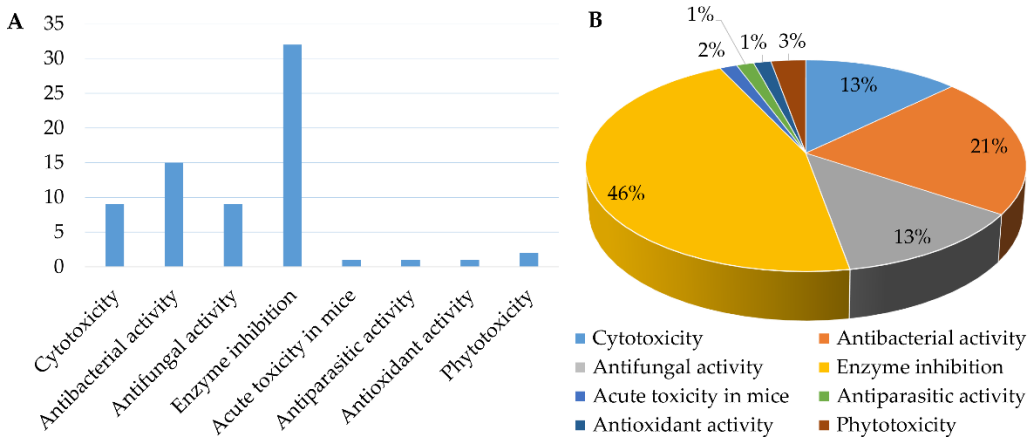


Figure 15. The number (**A**) and percentage (**B**) of *Chrysosporium* isolated compounds with different bioactivities from 1984 to 2021.

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