REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Chemodiversity of the Genus *Chaetomium* Secondary Metabolites

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Abstract

Since Alexander Fleming discovered penicillin in 1982 fungi was used as a very important source of antibiotics and secondary metabolites due to their importance. Similar to higher plants and bacteria, fungi have the capacity to generate various secondary metabolites having biological effects, such as alkaloids, terpenoids and anthraquinones. The Ascomycete genus *Chaetomium* is a rich source of new and bioactive secondary metabolites, which are crucial compounds. A broad variety of biomolecules have been identified from genus *Chaetomium* as natural antioxidants, including nucleobases, polyketides, terpenoids, flavonoids, coumarins, xanthones, semiquinones, peptides, and phenolic acids. Other compounds belonging to diverse structural types of chaetoglobosins, epipolythiodioxopiperazines, azaphilones have been recorded. The majority of these *Chaetomium's* metabolites are characterized by antibiotic, anticancer, cytotoxic, antimalarial, enzyme inhibitory, and other medical and pharmaceutical activities. In this review we will focus on the chemistry of some important secondary metabolites produced by the genus *Cheatomium* and their biological uses.

Keywords: Fungi, Antimicrobial, Endophytes.

1. Introduction

Almost from the beginning of human civilization, there has been medicine. The majority of novel medications have historically been created from substances derived from natural sources and from natural products themselves (secondary metabolites) **(Lahlou, 2007)**. In 1990 eighty percent of all medications were either made from natural sources or from chemicals derived from them. **(Li & Vederas, 2009)**.

There have been numerous estimates of the number of fungus, with estimates ranging from 500,000 to approximately 10 million species, with mycologists tending to endorse estimates of 1.5 to 5 million species **(Hawksworth & Lücking, 2017)**. **(Locey & Lennon, 2016)** predicted up to a trillion species of microorganisms globally without any refereed to total number of fungal species. The estimated global diversity of fungus would be 1,000 times more than the highest estimate at 10 million species if this estimate is accurate and only 1% of these were fungi **(Hawksworth & Lücking, 2017)**. The conservative estimate of 1.5 million species of fungi proposed by **(Hawksworth, 2001)** and the recent range estimated at 2.2 to 3.8 million with 120,000 currently accepted species, it appears that at best just 8%, and in the worst case scenario just 3%, are named so far **(Hawksworth & Lücking, 2017)**.

There have been descriptions of about 500,000 secondary metabolites, often known as natural products. **(Bills & Gloer, 2016)**. Of these, 70,000 come from microorganisms, 350,000 from plants, and

100,000 from animals. **(Nett *et al.*, 2009; Bérdy, 2012)**. There have been described over 33,500 bioactive microbial metabolites **(Nett *et al.*, 2009**). Of these about 47% (15,600) are of fungal origin **(Bérdy, 2012).**

After discovery of penicillin, research has been directed to find novel myco-derived bioactive molecules with potential agricultural, pharmaceutical, and nutritional characteristics **(Abdel-Azeem *et al.*, 2016)**. Fungi are unexplored mine for pharmaceutically important natural products with a broad spectrum of activity such as antimicrobial, anti-hepatotoxicity, antioxidant, antitumor, etc **(Abdel-Azeem *et al.*, 2016, 2019; Prateeksha *et al.*, 2019; Moubasher *et al.*, 2022).** A huge number of taxa belonging to filamentous fungi (micro and macromycetes) have been proved to produce a broad variety of low molecular mass natural products (NPs) with unusual bioactive properties. Interestingly, the metabolites of filamentous fungi enriched with various natural compounds such as antibiotics, vitamins, fragrances or pigments **(Demain, 2014).**

Endophytic fungi are a large group of fungi colonized living tissues of plants without causing any apparent pathological symptoms **(Abdel-Azeem *et al.*, 2016)**. Many natural products known today are produced by a large number of endophytic taxa **(Abo Nahas, 2019)**. Paclitaxel, a powerful anticancer mediator, extracted from endophytic fungi e.g., *Taxomyces andreanae* and *Pestalotia spp*. Therefore, endophytes have been documented as potent new sources of anticancer **(Salem and Abdel-Azeem, 2014),** antimicrobial and antimalarial bioactive metabolites **(Ferreira *et al.*, 2017)**.These metabolites include alkaloids, steroids, xanthine, phenols, iso-coumarins, quinones, and terpenoids **(WU *et al.*, 2018).** The range of biological and biotechnological applications of its species in various fields, such as medical mycology, have made *Chaetomium* a prominent genus in the Ascomycota.**(Waksman & Bugie, 1944)**, introduced Chetomin as a new antibiotic substance recovered from *Chaetomium cochliodes*. **(Zhang *et al.*, 2010),** biotechnology **(Attia *et al.*, 2020; Darwish *et al.*, 2020),** and molecular studies **(Abdel-Azeem *et al.*, 2018; Agrawal *et al.*, 2021).**

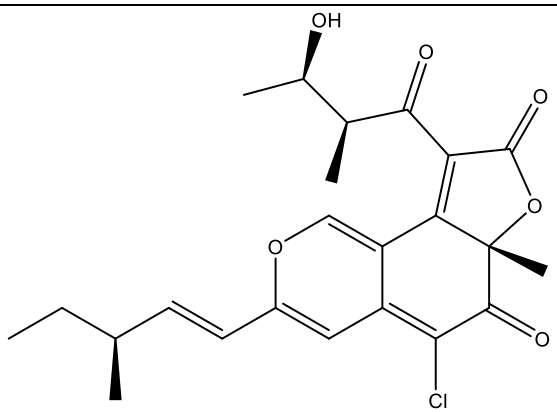
Various studies were carried by several investigators in Egypt, and they showed that the most common species of the genus *Chaetomium* is *C. globosum*. In their investigation of endophytic species in Egypt that produce anticancer products, **Salem and Abdel-Azeem (2014)** from eight medicinal plants in Saint Katherine Protectorate, South Sinai, Egypt, they were able to isolate *Chaetomium atrobrunneum, C. bostrychodes, C. brasiliense, C. arinthiacum, C. globosum, C. gracile, C. hamadae (Udagawa) Arx, C. iranianum, C. mareoticum, C. murorum, C. nigricolorwere* . They found *C. globosum* to be present among all studied plants with a high frequency rate.

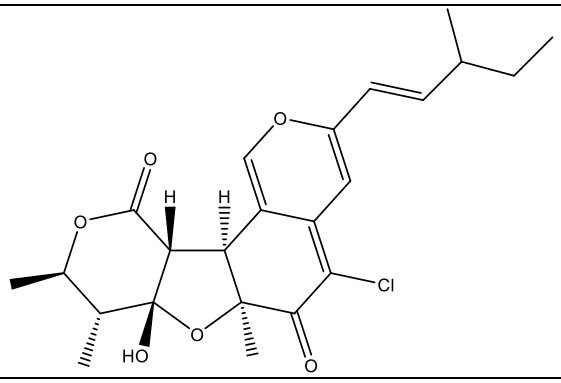
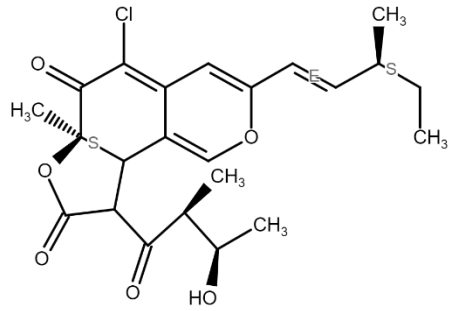
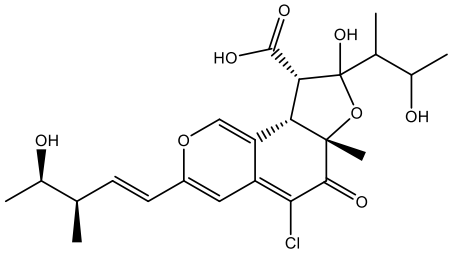
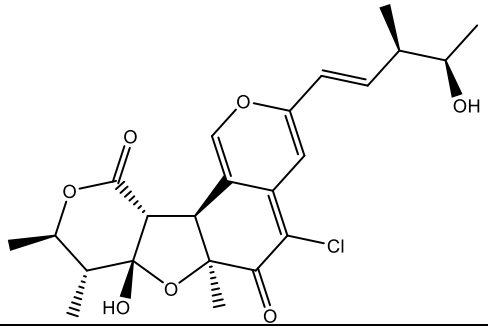
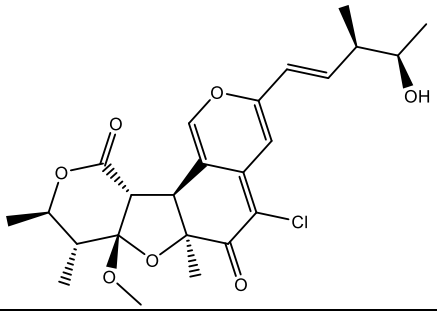
A study conducted as the first of its kind to be carried out in Egypt to produce antimicrobial pharmaceuticals from isolated native taxa of the fungal *Chaetomium*, followed by a chemical investigation of the existing bioactive metabolites **(Goda *et al.*, 2023).**

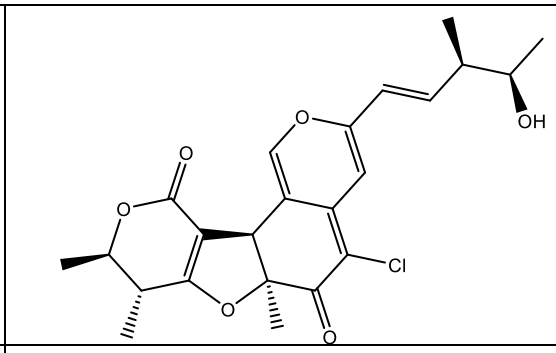
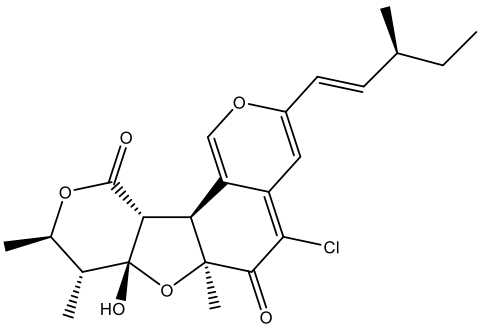
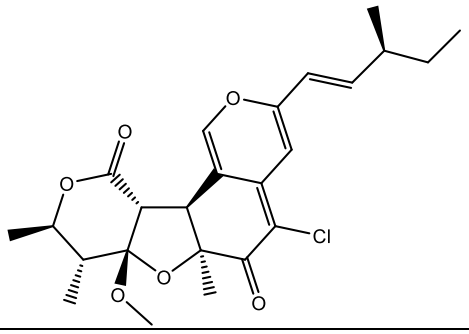
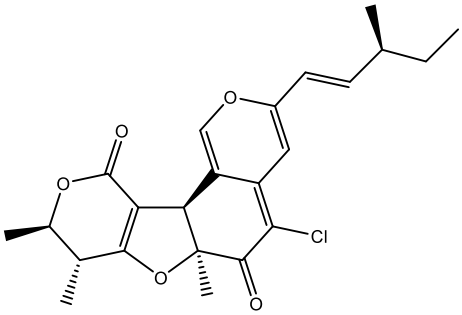
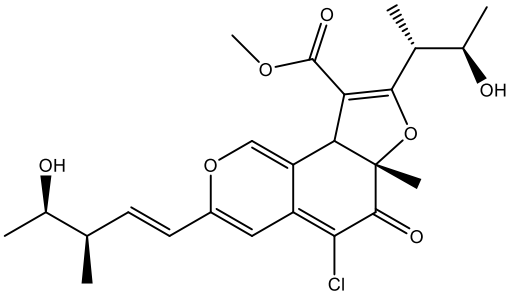
In this review we will shed light on the diversity of chemical constituents reported from genus *Chaetomium* with special reference to *C. globosum.*

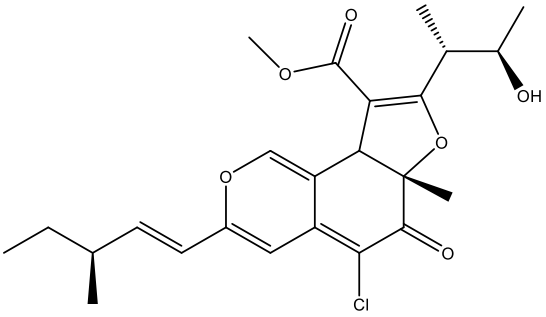
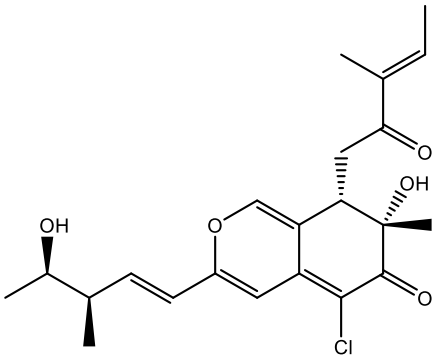
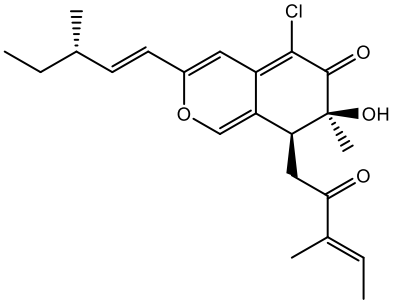
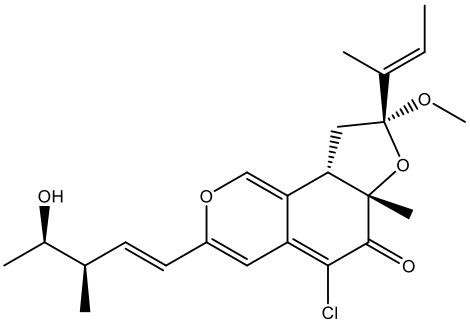
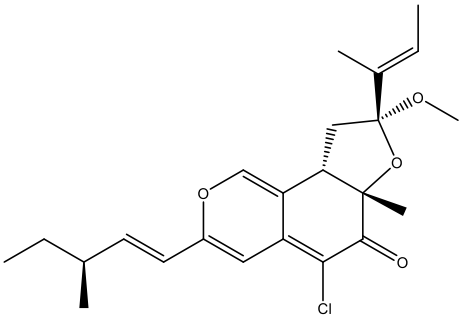
2. Chemical constituents reported from genus *Chaetomium*:

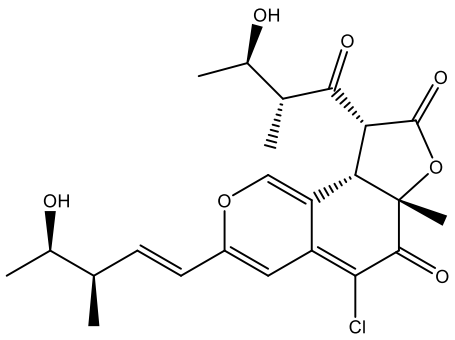
2.1 Azaphilones reported in genus *Chaetomium:*

Compound Name	Compound Structure	Biological use	Reference
Chaetoviridin A		Exhibited high *in vivo* and *in vitro* anti-fungal effect against *Magnaporthe grisea*	**(Takahashi *et al.*, 1990; Park *et al.*, 2005; Zhang *et al.*, 2012)**

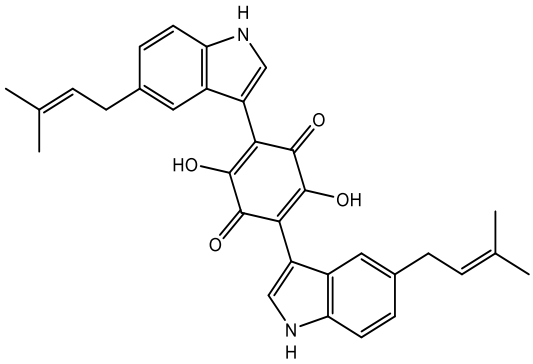
Chaetoviridin B		Exhibited high *in vivo* and *in vitro* anti-fungal effect against *Magnaporthe grisea* less than Chaetoviridin A	**(Takahashi *et al.*, 1990; Park *et al.*, 2005; Zhang *et al.*, 2012)**
Chaetoviridin C		Exhibited moderate cytotoxic activity against the murine P388 leukemia cell line, the human HL-60 leukemia cell line, the murine L1210 leukemia cell line and the human KB epidermoid carcinoma cell line.	**(Takahashi *et al.*, 1990; Yamada *et al.*, 2009; Zhang *et al.*, 2012)**
Chaetoviridin D		—	**(Takahashi *et al.*, 1990; Zhang *et al.*, 2012)**
Chaetomugilin A		- Showed cytotoxic activity against 39 human cancer cell lines in a selective manner. -Displayed marked toxicity against *Mucor miehei* and brine shrimp	**(Qin *et al.*, 2009; Zhang *et al.*, 2012)**
Chaetomugilin B		Tremendous growth inhibition against leukemia cell lines was shown (P388 and HL-60).	**(Zhang *et al.*, 2012)**

Chaetomugilin C		Shown cytotoxic activity against 39 human cancer cell lines in a selective manner.	**(Zhang *et al.*, 2012)**
Chaetomugilin D		Displayed marked toxicity against *Mucor miehei* and brine shrimp	**(Qin *et al.*, 2009; Zhang *et al.*, 2012)**
Chaetomugilin E		Tremendous growth inhibition against leukemia cell lines was shown (P388 and HL-60).	**(Zhang *et al.*, 2012)**
Chaetomugilin F		Shown cytotoxic activity against 39 human cancer cell lines in a selective manner.	**(Zhang *et al.*, 2012)**
Chaetomugilin G		Shown a growth-inhibitory effect on P388, HL-60, L1210, and KB cells in culture.	**(Zhang *et al.*, 2012)**

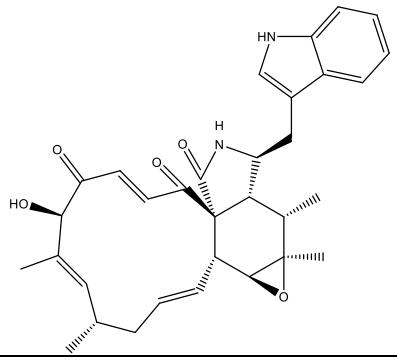
Chaetomugilin H		Shown a growth-inhibitory effect on P388, HL-60, L1210, and KB cells in culture.	**(Zhang *et al.*, 2012)**
Chaetomugilin I		-Exerted pronounced growth inhibition of P388, HL-60, L1210, and KB cell lines. **-S**howed selectively cytotoxic activity against 39 human cancer cell lines.	**(Zhang *et al.*, 2012)**
Chaetomugilin J		Used to significantly suppress the growth of the P388, HL-60, L1210, and KB cell lines.	**(Zhang *et al.*, 2012)**
Chaetomugilin K		Used to significantly suppress the growth of the P388, HL-60, L1210, and KB cell lines.	**(Zhang *et al.*, 2012)**
Chaetomugilin L		Used to significantly suppress the growth of the P388, HL-60, L1210, and KB cell lines.	**(Zhang *et al.*, 2012)**

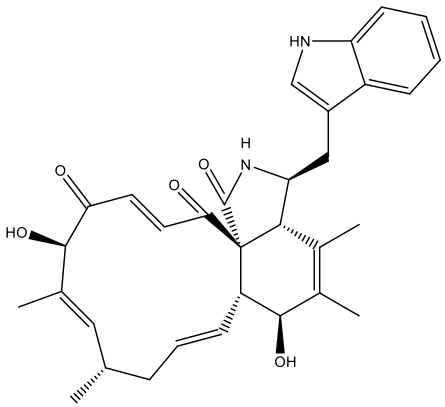
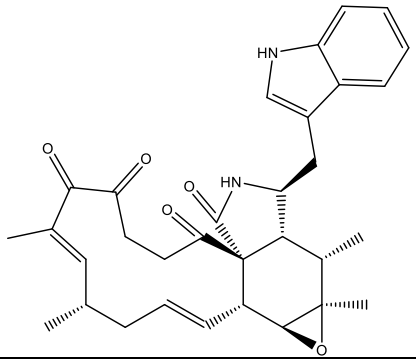
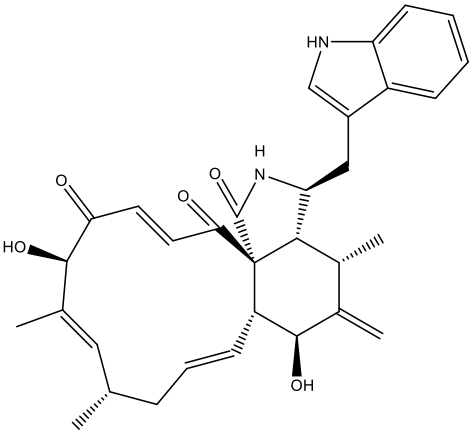
Chaetomugilin M		Used to significantly suppress the growth of the P388, HL-60, L1210, and KB cell lines.	**(Zhang *et al.*, 2012)**

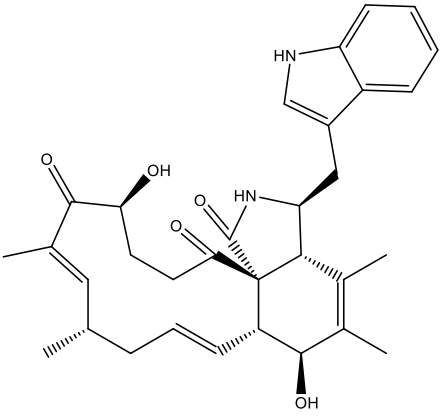
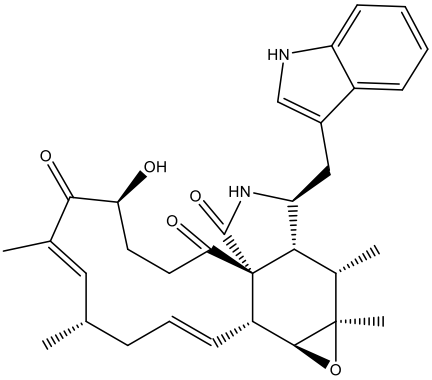
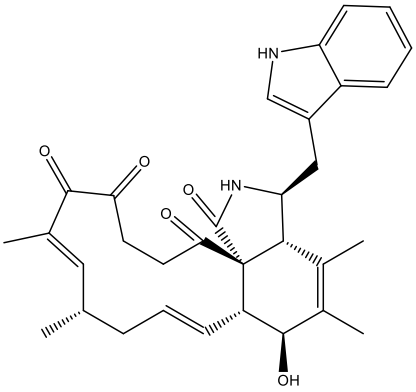
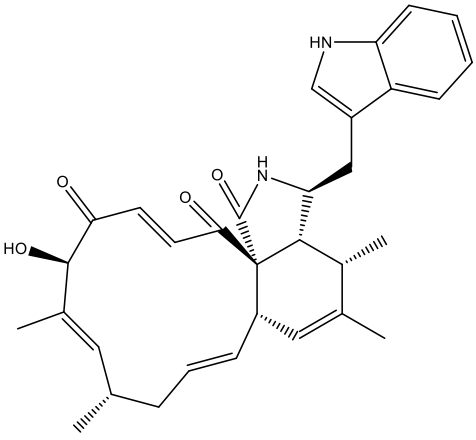
2.2 Bis(3-indolyl)-benzoquinones:

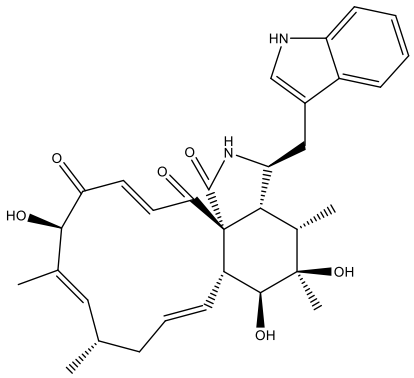
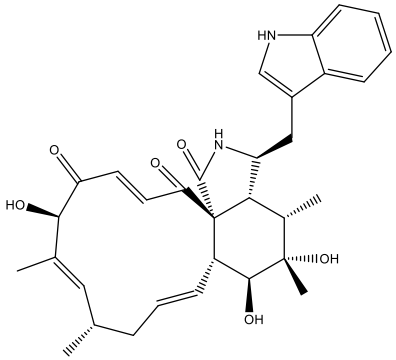
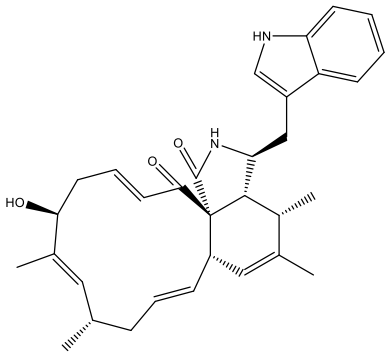
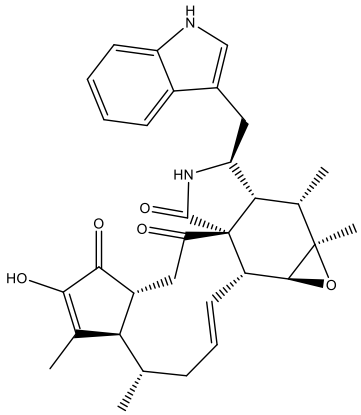
Compound Name	**Chemical Structure**	**Biological use**	**Reference**
Cochliodinol		In addition to preventing some species of microfungi from growing, it also prevented the germination of spores from *Fusarium moniliforme* and *Botrytis allii* at concentrations of 1 to 10 g/ml. At 30 g/ml, numerous strains of *Pseudomonas aeruginosa* had their growth suppressed.	**(Brewer *et al.*, 1970; Zhang *et al.*, 2012)**

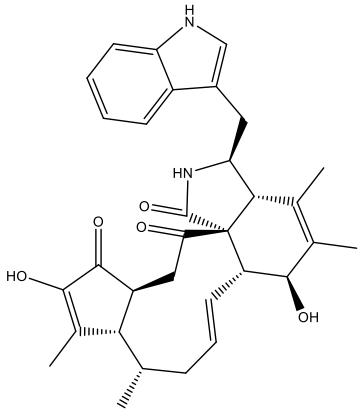
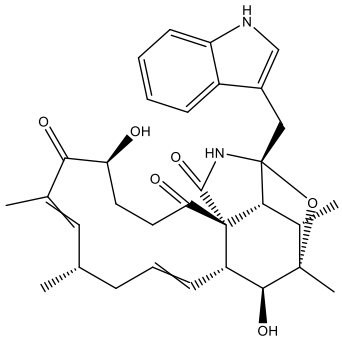
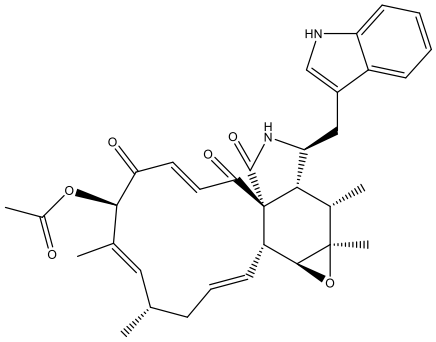
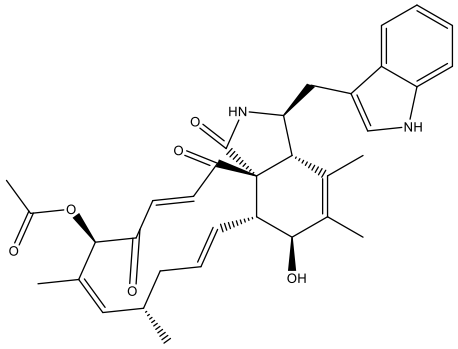
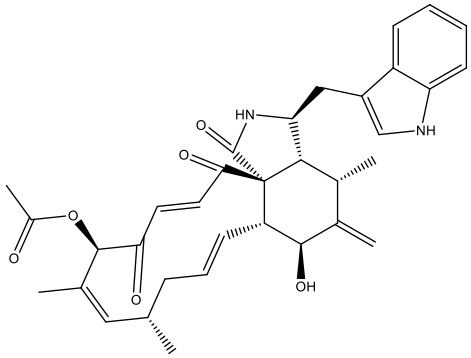
2.3 Chaetoglobosins:

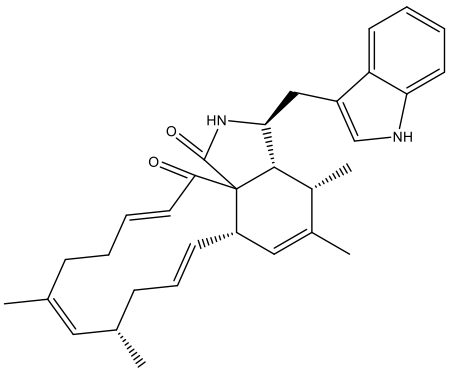
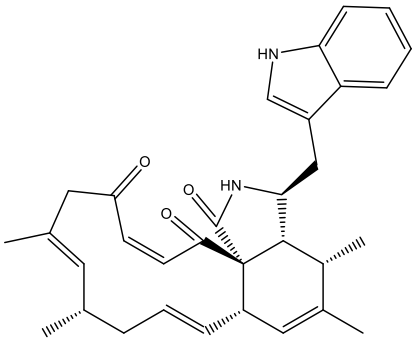
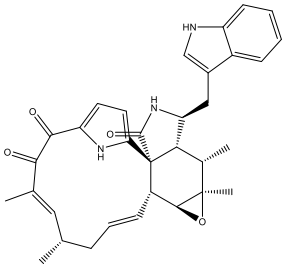
Compound Name	**Chemical Structure**	**Biological use**	**Reference**
Chaetoglobosin A		- High cytotoxicity when tested against several human cancer cell lines - Increase the urokinase-induced fibrinolytic activity of bovine aortic endothelial cells at 3-100 μM.	**(Ko *et al.*, 1998; Shinohara *et al.*, 2000; Zhang *et al.*, 2012**)

Chaetoglobosin B		- Effective against the tumour cells Jurkat (leukemia) and B16F10 (melanoma) -Displayed significant cytotoxicity against the P388 murine leukemia cell line (IC50 = 1.58-4.90 μg/ml). -Shown to be antimicrobial against *Bacillus subtilis*, *Cladosporium resinae*, and *Trichophyton mentagrophytes*. -Showed cytotoxicity against the human breast cancer BC1 cell lines (IC50 = 2.54-21.29 μM) and cholangiocarcinoma cell lines (IC50=3.41-86.95 μM).	**(Momesso *et al.*, 2008; Zhang *et al.*, 2012)**
Chaetoglobosin C		-Showed cytotoxicity against the human breast cancer BC1 cell lines (IC50 = 2.54-21.29 μM) and cholangiocarcinoma cell lines (IC50=3.41-86.95 μM).	**(Umeda *et al.*, 1975; Sekita *et al.*, 1976, 1977, 1982; Zhang *et al.*, 2012)**
Chaetoglobosin D		- Shown effective cytotoxicity over P388 murine leukemia cell line (IC50 = 1.58-4.90 μg/ml). - Shown to have antimicrobial effect against *Cladosporium resinae*, *Trichophyton mentagrophytes* and *Bacillus subtilis*. - Shown cytotoxicity toward the human breast cancer BC1 cell lines (IC50 = 2.54-21.29μM) as well as the cholangiocarcinoma cell lines (IC50=3.41-86.95 μM).	**(Umeda *et al.*, 1975; Sekita *et al.*, 1976, 1977, 1982; Zhang *et al.*, 2012)**

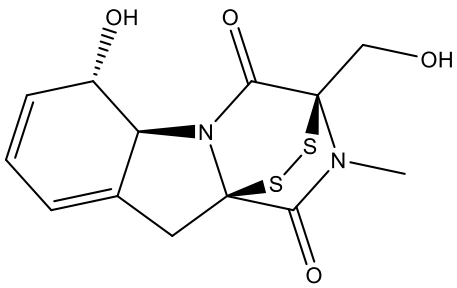
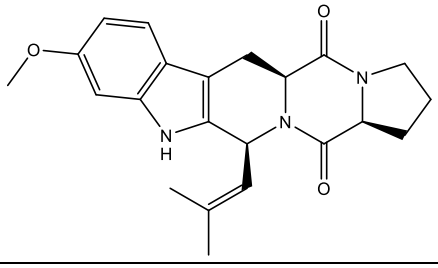
Chaetoglobosin E		-Anti-fungal -Phytotoxicity -Anti-tumor	**(Umeda *et al.*, 1975; Sekita *et al.*, 1976, 1977, 1982; Zhang *et al.*, 2012, 2013; Li *et al.*, 2014; Chen *et al.*, 2015)**
Chaetoglobosin F		Showed cytotoxicity against the human breast cancer BC1 cell lines (IC50 = 2.54-21.29 μM) and cholangiocarcinoma cell lines (IC50=3.41-86.95 μM).	**(Umeda *et al.*, 1975; Sekita *et al.*, 1976, 1977, 1982; Zhang *et al.*, 2012)**
Chaetoglobosin G		Showed cytotoxicity against the human breast cancer BC1 cell lines (IC50 = 2.54-21.29 μM) and cholangiocarcinoma cell lines (IC50=3.41-86.95 μM).	**(Umeda *et al.*, 1975; Sekita *et al.*, 1976, 1977, 1982; Zhang *et al.*, 2012)**
Chaetoglobosin J		- Shown effective cytotoxicity over P388 murine leukemia cell line (IC50 = 1.58-4.90 μg/ml). -Shown to have antimicrobial effect against *Cladosporium resinae*, *Trichophyton mentagrophytes* and *Bacillus subtilis*.	**(Umeda *et al.*, 1975; Sekita *et al.*, 1976, 1977, 1982; Zhang *et al.*, 2012)**

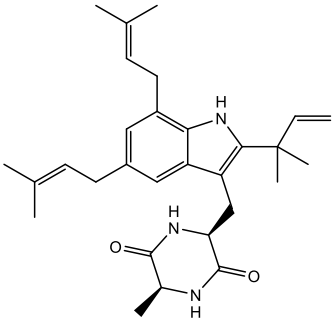
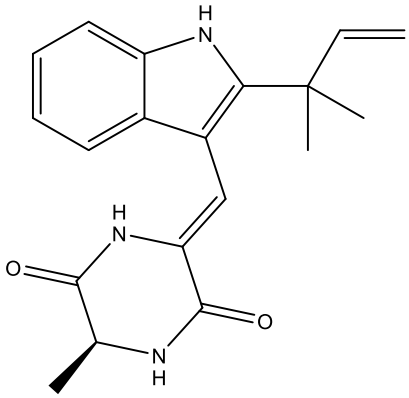
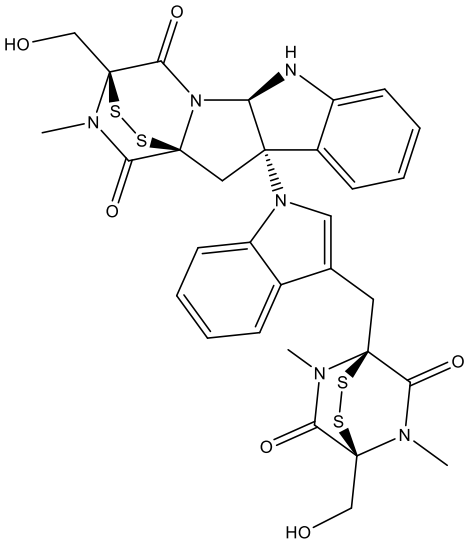
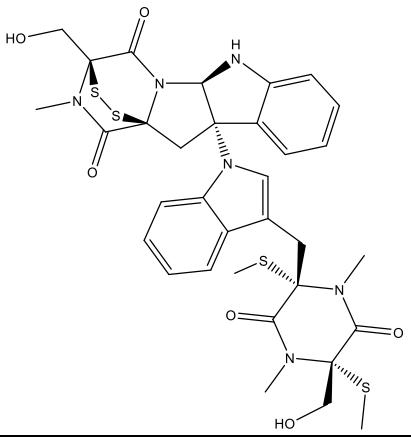
Chaetoglobosin Q		-Shown effective cytotoxicity over P388 murine leukemia cell line (IC50 = 1.58-4.90 µg/ml).	**(Zhang *et al.*, 2012)**
Chaetoglobosin R		Anti-fungal	**(Zhang *et al.*, 2012, 2013; Yan *et al.*, 2018)**
Chaetoglobosin T		-Shown effective cytotoxicity over P388 murine leukemia cell line (IC50 = 1.58-4.90 µg/ml).	**(Zhang *et al.*, 2012)**
Chaetoglobosin U		Shown to exhibit cytotoxic activity against the human nasopharyngeal epidermoid tumor KB cell line	**(Ding *et al.*, 2006)**

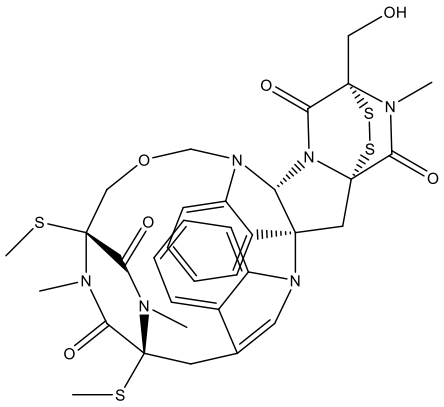
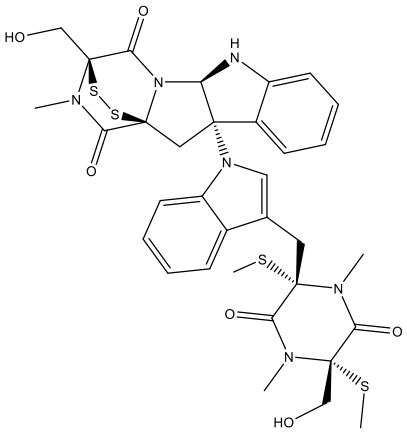
Chaetoglobosin V		-Anti-fungal -Phytotoxicity -Anti-tumor -Anti-bacterial	**(Zhang *et al.*, 2012; Li *et al.*, 2014; Gao *et al.*, 2019)**
Chaetoglobosin W		Anti-tumor	**(Zhang *et al.*, 2010, 2012)**
Acetylchaetoglobosin A		Anti-tumor Nematicidal	**(Zhang *et al.*, 2012; Ashrafi *et al.*, 2017)**
Acetylchaetoglobosin B		—	**(Zhang *et al.*, 2012)**
Acetylchaetoglobosin D		—	**(Zhang *et al.*, 2012)**

Prochaetoglobosin I		-Shown to have antimicrobial effect against *Cladosporium resinae, Trichophyton mentagrophytes* and *Bacillus subtilis*.	**(Zhang *et al.*, 2012)**
Prochaetoglobosin II		-Shown to have antimicrobial effect against *Cladosporium resinae, Trichophyton mentagrophytes* and *Bacillus subtilis*.	**(Zhang *et al.*, 2012)**
Penochalasin A		Shown to have a moderate effect on the KB cell line	**(Numata *et al.*, 1996; Ding *et al.*, 2006)**

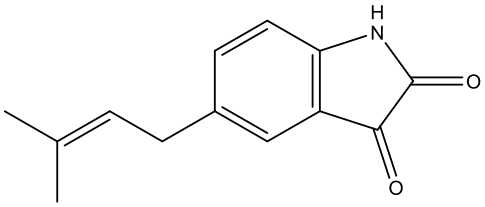
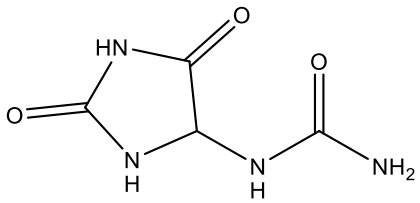
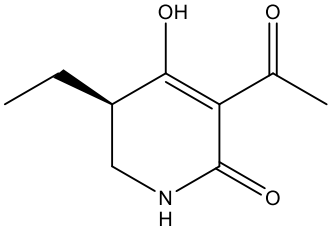
2.4 Diketopiperazines:

Compound name	**Compound Structure**	**Biological Use**	**Reference**
Gliotoxin		Had good antifungal action against pathogenic fungus that affect plants, such as *Cercospora sorghi, Fusarium oxysporum f. sp. vasinfectum, Fusarium graminearum, Fusarium sulphureum,* and *Alternaria alternate*.	**(Zhang *et al.*, 2012)**
Fumitremorgin C		—	**(Zhang *et al.*, 2012)**

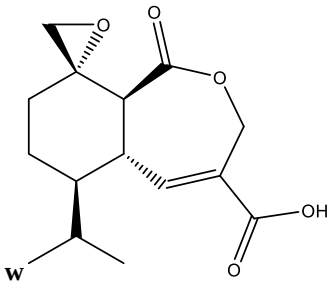
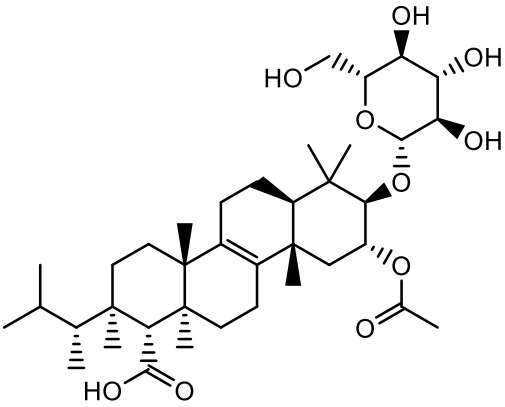
Echinuline		Exhibited inhibitory activity on *M. tuberculosis*	**(Kanokmedhakul *et al.*, 2002; Zhang *et al.*, 2012)**
Neoechinulin A		—	**(Wang *et al.*, 2006; Zhang *et al.*, 2012)**
Chaetomin		It was found to has potential for the treatment of cancer by stopping the communication between HIF-alpha and the transcriptional coactivator p300 by zinc ejection mechanism	**(Cook *et al.*, 2009; Zhang *et al.*, 2012)**
Chaetocochin A		Cytotoxicity against cancer cell lines *in vitro* N-04, Bre-04 (MDA-MB-231), and Lu-04 (NCIH460) (SF-268)	**(Li *et al.*, 2006; Zhang *et al.*, 2012)**

Chaetocochin B		—	**(Li *et al.*, 2006; Zhang *et al.*, 2012)**
Chaetocochin C		Cytotoxicity against cancer cell lines *in vitro* N-04, Bre-04 (MDA-MB-231), and Lu-04 (NCIH460) (SF-268)	**(Li *et al.*, 2006; Zhang *et al.*, 2012)**

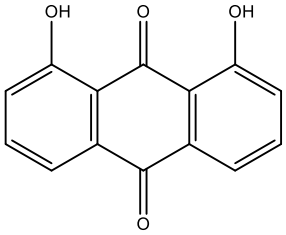
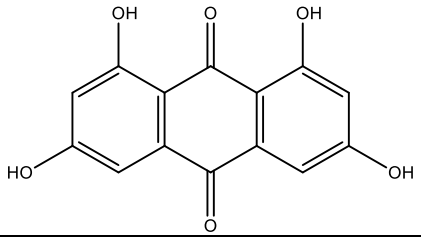
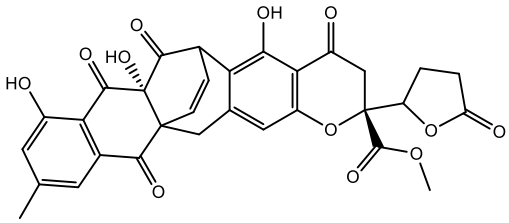
2.5 Other N-Compounds:

Compound Name	**Compound Structure**	**Biological use**	**Reference**
Prenisatin		Inhibited the *in vitro* growth of *Botrytis cinerea*	**(Zhang *et al.*, 2012)**
Allantoin		—	**(Qin *et al.*, 2009; Zhang *et al.*, 2012)**
Chaetoglocin D		—	**(Ge *et al.*, 2011)**

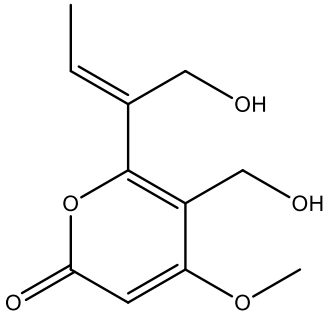
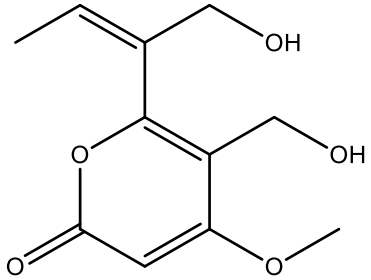
2.6 Terpenoids:

Compound Name	Compound Structure	Biological use	Reference
Heptelidic acid		- Especially effective against the anaerobic bacterium *Bacteroides fragilis*. - After 8 hours of etoposide administration, it may inhibit caspase-3 production in human leukemia U937 cells (IC_{50} = 40 μM). - It may, in a dose-dependent way, prevent DNA fragmentation and caspase-3 activation, which are biological indicators of apoptosis. This suggests that it prevents etoposide-induced apoptosis by downregulating caspases.	**(Kim & Lee, 2009; Zhang *et al.*, 2012)**
Fuscoatroside		It presented *in vitro* and *in vivo* antifungal activity against both *Aspergillus fumigatus* and *Aspergillus flavus*	**(Kobayashi *et al.*, 2005; Zhang *et al.*, 2012)**

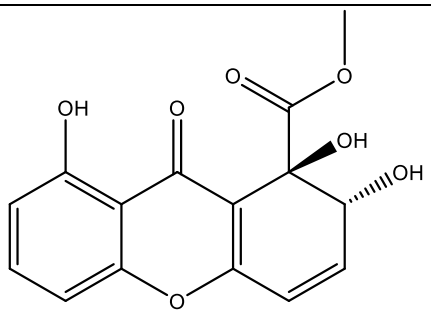
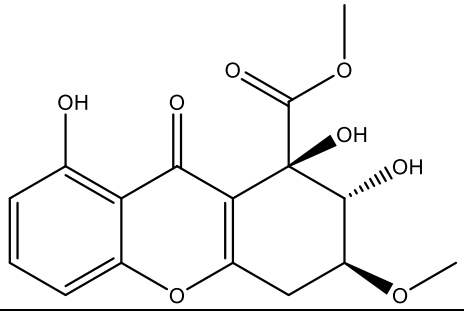
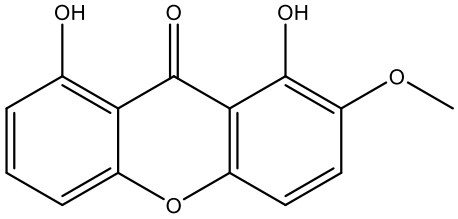
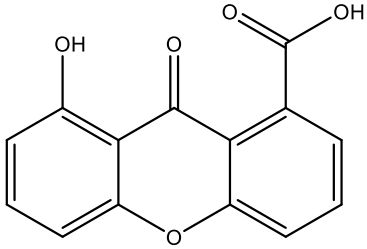
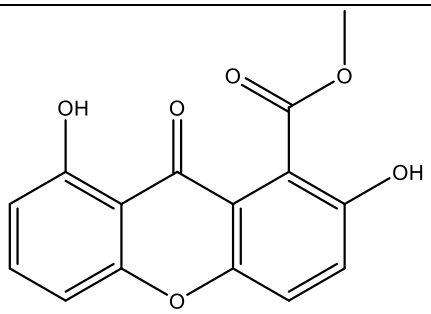
2.7 Anthraquinones & Anthraquinone-chromanones:

Compound Name	Compound Structure	Biological use	Reference
Chrysazin		—	**(Zhang *et al.*, 2012)**
Rheoemodin (1,3,6,8-tetrahydroxyanthraquinone)		—	**(Zhang *et al.*, 2012)**
Chaetomanone		Shown inhibition of *M. tuberculosis*	**(Kanokmedhakul *et al.*, 2002; Zhang *et al.*, 2012)**

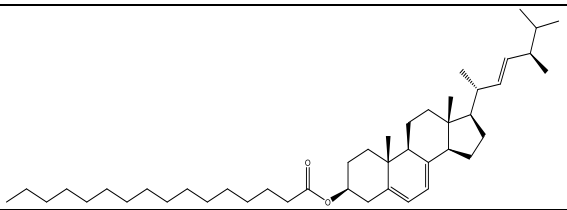
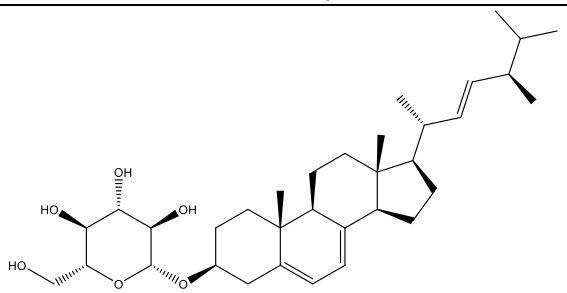
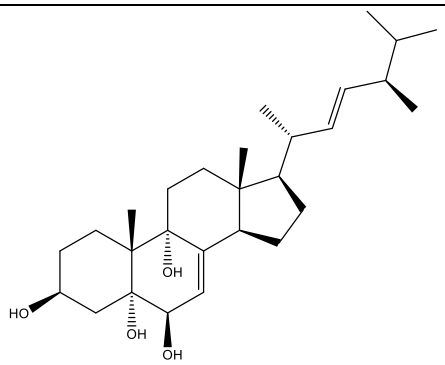
2.8 Pyranones:

Compound Name	Compound Structure	Biological use	Reference
Chaetoglocin A		Displayed antimicrobial activity against the gram +ve bacteria with minimum inhibitory concentrations between 8 & 32 µg/mL	**(Ge *et al.*, 2011; Zhang *et al.*, 2012)**
Chaetoglocin B		Displayed antimicrobial activity against the gram +ve bacteria with minimum inhibitory concentrations between 8 & 32 µg/mL	**(Ge *et al.*, 2011; Zhang *et al.*, 2012)**

2.9. Xanthones:

Compound Name	Compound Structure	Biological use	Reference
Globosuxanthone A		High cytotoxicity against a spectrum of seven human solid human cancer cell lines (MCF-7, SF-268, NCIH460, PC-3, PC-3M, LNCaP, and DU-145), disruption of the cell cycle resulting in an accumulation of cells in the G2/M or S phase, and induction of cell death.	**(Wijeratne *et al.*, 2006; Zhang *et al.*, 2012)**
Globosuxanthone B		—	**(Wijeratne *et al.*, 2006; Zhang *et al.*, 2012)**
Globosuxanthone C		—	**(Wijeratne *et al.*, 2006; Zhang *et al.*, 2012)**
Globosuxanthone D		—	**(Wijeratne *et al.*, 2006; Zhang *et al.*, 2012)**
2-hydroxyvertixanthone		—	**(Zhang *et al.*, 2012)**

2.10 Steroids:

Compound Name	Compound Structure	Biological use	Reference
Ergosteryl palmitate		—	**(Kanokmedhakul *et al.*, 2002; Phonkerd *et al.*, 2008)**
Ergosterol-β-D-glucoside		—	**(Kanokmedhakul *et al.*, 2002; Phonkerd *et al.*, 2008)**
9-hydroxycerevisterol		Showed *in vitro* marked cytotoxic activity against the HeLa cells	**(Qin *et al.*, 2009; Zhang *et al.*, 2012)**

3. Conclusion:

The fungal genus *Cheatomium* showed the existence of a broad range of bioactive compounds, which include chaetoglobosins, sterols, xanthones, terpenoids along with many other compounds. This review study covered the secondary metabolites reported in *chaetomium* genus. More research involving the isolation of bioactive compounds, safety profile, nanoformulation, and clinical trials of native fungi in Egypt should be conducted in order to discover new drugs for medical, industrial, and nanotechnology applications.

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