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records of natural products

# Bioactive Secondary Metabolites from the Endophytic *Aspergillus* Genus

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**Abstract:** A growing evidence indicates that the endophytic fungus *Aspergillus* is one of rich sources of natural products with a broad spectrum of biological activities. Up to now, 162 secondary metabolites had been structurally identified from 11 endophytic *Aspergillus* spp. and 67 of them were shown to have strong bioactivities with potential application in drug discovery. This review focuses on biology and chemistry of endophytic *Aspergilli*, especially their bioactive secondary metabolites. Covering: 2004 to 2014.

**Keywords:** *Aspergillus* genus; secondary metabolites; chemical constituent; bioactivity, progress. 

## 1. Introduction

*Aspergillus* has a long history of application in agriculture and industry, such as *A. niger*, *A. oryzae*, etc. The World of Microorganisms Information Center (WDCM) has recorded 378 *Aspergillus* spp. [1], which 299 species were deposited at the National Center of Biotechnology Information (NCBI) [2]. Endophyte, one special microbe associated with host plant without causing any obvious disease, has strongly attracted attention of microbiologists and natural product chemists because of its abundant biological and chemical diversity [3]. Up to now, 23 endophytic *Aspergillus* strains had been isolated and identified [4]. Chemical investigation suggested that the endophytic fungus *Aspergillus* is one of rich sources of bioactive natural products. This review mainly focuses on biology and chemistry of the endophytic *Aspergilli*, especially their bioactive secondary metabolites.

## 2. Biology of the endophytic *Aspergillus*

### *2.1. Ecology*

*Aspergilli* are prevalent on earth and distinguished between the good and the bad at all time [5]. The good *Aspergillus* strain is used to biologically synthesize raw materials, semi-finished products or finished products in food and drug industry [6]. While the bad always be found in patients with aspergillosis [7] or rotten plants [8]. However, *Aspergillus* can colonize in healthy plant, which is

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named as endophytic *Aspergillus* [9]. Previous studies indicated that endophytic *Aspergillus* has no specific host, which maybe ascribe to its strong adaptability and vitality. Since the first endophytic fungus *A. fumigatus* was isolated from *Cynodon dactylon* in 2004 [4], 23 endophytic *Aspergillus* strains had been characterized from 20 species of host plants, including *Acanthus ilicifolius* [10], *Artemisia annua* [11,12], *Colpomenia sinuosa* [13], *C. dactylon* [14,15], *Sargassum kjellmanianum* [16], *Erythrophloeum fordii* [17,18], *Eucommia ulmoides* [19], *Ficus carica* Linn. [20], *Ginkgo biloba* [21], *Gloriosa superba* [22], *Halimeda opuntia* [23], *Juniperus communis* [24], *Mammea siamensis* [25], *Melia azedarach* [26-28], *Paris polyphylla* [29], *Rosa rugosa* [30], *Silybum marianum* [31], *Stevia rebaudiana* [32], *Tribulus terrestris* [33], and *Coffea arabica* [34]. Environment and host plant are the main factors affect the distribution of the endophytic *Aspergillus* strain [35]. However, its colonization rule is still unclear [36].

### *2.2. Taxonomy*

*Aspergillus* spp. are very similar in their morphology and molecular characteristics [38]. Morphological classification is a traditional tool to divide *Aspergillus* genus into specie supplemented by physiological and biochemical feature. It includes morphology characteristics of colony, mycelium and spore, and pigmentation. Some cultivation conditions usually affect the identification results, such as culture medium component, pH, temperature. By comparison with other fungi, *Aspergillus* is still lack of undisputed sexual form and reproduction [39]. According to the study carried by Dyer and O'Gorman [5], many 'asexual' *Aspergilli* have the potential to undergo sexual reproduction. Another important way to identify *Aspergillus* strain is molecular technique, such as ribosomal DNA (rDNA) sequences analysis [40], random amplified polymorphic DNA (RAPD) and restriction fragment length polymorphism (RFLP) [41]. 11 endophytic *Aspergillus* spp. had been characterized from their host plants, including *A. fumigatus* [3,11,14,18,26,24,42,43], *A. niger* [13,25], *A. favipes* [10,32], *A. versicolor* [29,44], *A. clavatus* [27], *A. fumigatiaffnis* [33], *A. iizukae* [31], *A. ochraceus* [16], *A. oryzae* [34], *A. tamarii* [20], *A. terreus* [12].

## 3. Chemistry of Endophytic *Aspergillus* Genus

As we know, the chemical diversity of organism arises from its biological diversity. The chemical investigation of endophytic *Aspergilli* was carried out since 2004. To the end of 2014, a total of 162 metabolites had been isolated and identified from these endophytic *Aspergilli*. Some compounds have novel skeletons and/or potent bioactivities, which can be used as lead drugs and environment-friendly agrochemicals [45]. According their origin, these metabolites of the endophytic *Aspergillus* were summarized below.

### *3.1. Aspergillus flavipes*

Eleven small molecules (**1-11**, see Table 1 and Figure 1) had been isolated from an endophytic *A. favipes* colonized in *Acanthus ilicifolius* and *Stevia rebaudiana*. Among these compounds, flavipesin A (**2**) was shown to inhibit *Staphylococcus aureus* and *Bacillus subtillis* with MIC values of 8.0, 0.25 μg/mL, respectively [10]. 2-(((2-ethylhexyl)oxy)carbonyl)benzoic acid (**7**) had strong inhibitory effect on *Sclerotinia sclerotiorum*, which usually causes the damage of crop and vegetable [23].

**Table 1.** Metabolites from endophyt*ic Aspergillus flavipes*.

| No. | Compound | Host Plant | Strain No. | Activity | Ref. |
|---|---|---|---|---|---|
| **1** | 3,4-diphenylfuran-2(5*H*)-one | *Acanthus ilicifolius* | AIL8 | | 10 |
| **2** | flavipesin A | | | antibacterial: *Bacillus subtilis, Staphylococcus aureus* | |
| **3** | flavipesin B | | | | |
| **4** | guignardic acid | | | | |
| **5** | phenguignardic acid methyl ester | | | | |
| **6** | 1-pentanamine, *N*-nitroso-*N*-pentyl | *Stevia rebaudiana* | | | 23 |

| | | | | | |
|---|---|---|---|---|---|
| **7** | 2-(((2-ethylhexyl)oxy) carbonyl)benzoic acid | | | antifungal: *Sclerotinia scleretiorum* | |
| **8** | 9-octadecenoic acid (*Z*)-methyl ester | | | | |
| **9** | 10,12-tricosadiynoic acid, methylester | | | | |
| **10** | dibutyl phthalate | | | | |
| **11** | hexadecanoic acid, methyl ester | | | | |

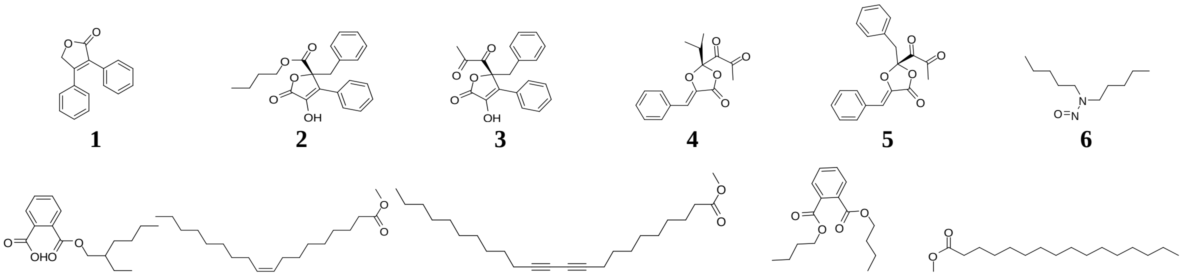


**Figure 1**. Chemical structures of compounds **1-11**.

### *3.2. Aspergillus fumigatus*

Generally, *Aspergillus fumigatus* is the most frequently isolated strain found in plants, such as *Artemisia annua*, *Cynodon dactylon*, *Eucommia ulmoides*, et al. Moreover, the chemical diversity of this endophtic fungus is the most abundant. To date, 90 secondary metabolites (**12-101**) have been isolated and identified (Table 2 and Figure 2). Biological assay indicated that some compounds had antimicrobial activities against *Canidia albicans*, *Peptostreptococcus anaerobius*, *Bacteroides distasonis* and other pathogens, such as **27**, **34**, **35**, **37**, **39**, **41**, **42**, **52-56**, **68**, **69**, **71** and **75**. And some metabolites exhibited antitumor, antivirus and brine shrimp toxicity, such as compounds **12-15**, **60**, **72-77**, **92-94**, **98**.

**Table 2.** Metabolites from endophyt*ic Aspergillus fumigatus*.

| No. | Compound | Host Plant | Strain No. | Activity | Ref. |
|---|---|---|---|---|---|
| **12** | 5-*N*-acetylardeemin | *Artemisia annua* | SPS-02 | | 11 |
| **13** | 5-*N*-acetyl-15b-β-hydroxyardeemin | | | anticancer: SK-OV-S/DDP | |
| **14** | 5-*N*-acetyl-15b-didehydroardeemin | | | anticancer: SK-OV-S/DDP | |
| **15** | 5-*N*-acetyl-16α-hydroxyardeemin | | | anticancer: K562/DOX, A549/DDP | |
| **16** | 5α,8α-epidioxy-ergosta-6,22-diene-3β-ol | *Cynodon dactylon* | CY018 | | 3,14,43 |
| **17** | 9-octadecenoic acid, (*E*)- | | | | |
| **18** | 9-octadecenoic acid, methyl ester | | | | |
| **19** | 9,12-octadecadienoic acid, ethyl ester | | | | |
| **20** | 9,12,15-octadecatrienoic acid | | | | |
| **21** | 9,12,15-octadecatrienoic acid, ethyl ester | | | | |
| **22** | 14-pentadecenoic acid | | | | |
| **23** | *n*-hexadecanoic acid | | | | |
| **24** | α-tocopherol | | | | |
| **25** | γ-tocopherol | | | | |
| **26** | asperfumin | | | | |
| **27** | asperfumoid | | | antifungal: *Candida Albicans* | |
| **28** | cyclo(Ala-Leu) | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **29** | cyclo(Ala-Ile) | | | | |
| **30** | dibutyl phthalate | | | | |
| **31** | ethyl Oleate | | | | |
| **32** | ethyl 9-hexadecenoate | | | | |
| **33** | ergosta-14,22-diene-3β-ol | | | | |
| **34** | fumigaclavine A | | | antibacterial: *Bacteroides distasonis, Bacteroides vulgatus, Peptostreptococcus anaerobius, Staphylococcus anaerobius, Veillonella parvula*, *Actinomyces israelii* | |
| **35** | fumigaclavine C | | | antifungal: *Candida Albicans* | |
| **36** | fumigaclavine D | | | | |
| **37** | fumigaclavine E | | | antibacterial: *Bacteroides distasonis, Bacteroides vulgatus, Peptostreptococcus anaerobius, Staphylococcus anaerobius, Veillonella parvula*, *Actinomyces israelii* | |
| **38** | fumigaclavine F | | | | |
| **39** | fumigaclavine G | | | antibacterial: *Bacteroides distasonis, Bacteroides vulgatus, Peptostreptococcus anaerobius, Staphylococcus anaerobius, Veillonella parvula*, *Actinomyces israelii* | |
| **40** | fumigaclavine H | | | | |
| **41** | festuclavine | | | antibacterial: *Bacteroides distasonis, Bacteroides vulgatus, Peptostreptococcus anaerobius, Staphylococcus anaerobius, Veillonella parvula*, *Actinomyces israelii* | |
| **42** | physcion | | | antifungal: *Candida Albicans* | |
| **43** | hexadecanoic acid, methyl ester | | | | |
| **44** | hexadecanoic acid, ethyl ester | | | | |
| **45** | heptadecanoic acid, methyl ester | | | | |
| **46** | hexadecenoic acid, Z-11- | | | | |
| **47** | heptadecanoic acid | | | | |
| **48** | linoleic acid | | | | |
| **49** | linoleic acid ethyl ester | | | | |
| **50** | octadecanoic acid | | | | |
| **51** | tetradecanoic acid, ethyl ester | | | | |
| **52** | 3b-hydroxy-5a,8a-epidioxy-ergosta-6,22-diene | *Cynodon dactylon* | CY725 | antibacterial: *Helicobacter pylori* | |
| **53** | monomethylsulochrin | *Cynodon dactylon*<br>*Eucommia ulmoides* | CY725<br>ER15 | antibacterial: *Escherichia coli, Helicobacter pylori*, *Staphylococcus aureus.* | 3,19 |
| **54** | ergosterol | *Cynodon dactylon*<br>*Eucommia ulmoides*<br>*Gloriosa superba* | CY018<br>FE-19<br>ER15 | antibacterial: *Bacillus subtilis, Escherichia coli, Helicobacter pylori*, *Peptostreptococcus anaerobius, Staphylococcus aureus, Salmonella typhimurium, streptococcus faecalis,* Antifungal: *Candida Albicans, andida krusei* | 3,19,22 |

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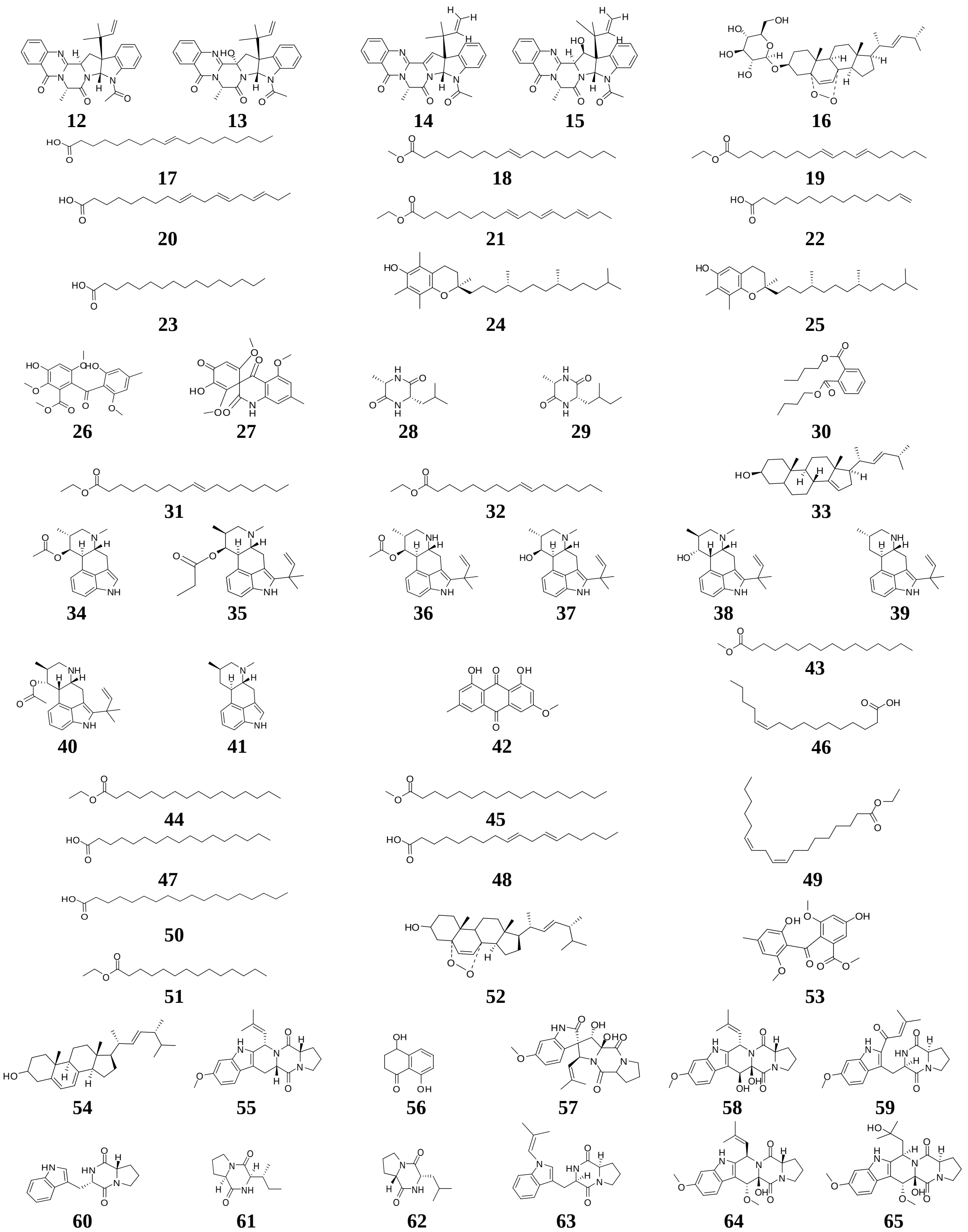
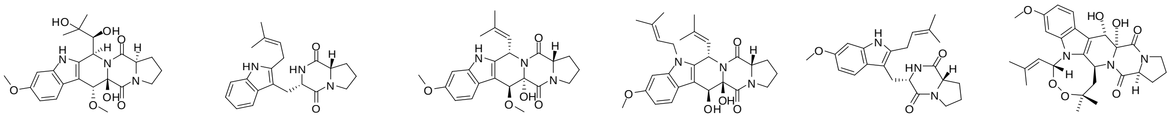
|---|---|---|---|---|---|
| **55** | fumitremorgin C | *Cynodon dactylon*<br>*Ficus carica*<br>*Melia azedarach* | CY018<br>FL06<br>CY725 | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activity: armyworm larvae<br>Inhibitory effect on β-glucuronidase | 26,17,23 |
| **56** | helvolic acid | *Cynodon dactylon*<br>*Melia azedarach* | CY018<br>LN-4 | toxicity: brine shrimp<br>Antifungal: *Alternaria alternata*, *Alternaria solani*, *Candida albicans*, *Botrytis cinerea*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>inhibitory effect on β-glucuronidase | 3,26 |
| **57** | (3*S*,8*S*,9*S*,18*S*)-8,9-dihydroxyspirotryprostatin A | | | | |
| **58** | 8,9-dihydroxyfumitremorgin C | | | | |
| **59** | 18-oxotryprostatin A | | | | |
| **60** | brevianamide F | | | inhibitory effect on β-glucuronidase | |
| **61** | cyclo(L-isoleucyl-L-prolyl) | | | | |
| **62** | cyclo(L-leucyl-L-prolyl) | | | inhibitory effect on β-glucuronidase | |
| **63** | cyclo(*N*'-prenyl-*L*-tryptophyl-*L*-prolyl) | *Erythrophloeum fordii* | | | 17 |
| **64** | rel-(8*R*)-9-hydroxy-8-methoxy-18-epi-fumitremorgin C | | | | |
| **65** | rel-(8*S*)-19,20-dihydro-9,20-dihydroxy-8-methoxy-9,18-di-epi-fumitremorgin C | | | | |
| **66** | rel-(8*S*,19*S*)-19,20-dihydro-9,19*S*,20-trihydroxy-8-methoxy-9-epi-fumitre-morgin C | | | | |
| **67** | tryprostatin B | *Erythrophloeum fordii*<br>*Ficus carica* | | inhibitory effect on β-glucuronidase | 17,20 |
| **68** | cyclotryprostatin B | *Ficus carica*<br>*Melia azedarach* | FL06<br>LN-4 | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii* | 20,26 |
| **69** | fumitremorgin B | | | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activity: armyworm larvae | |

| | | | | | |
|---|---|---|---|---|---|
| **70** | tryprostatin A | | | | |
| **71** | verruculogen | | | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Botrytis cinerea*, *Candida albicans*, *Alternaria solani*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activitie: armyworm larvae | |
| **72** | 3-hydroxyfumiquinazoline A | | | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activitie: armyworm larvae | |
| **73** | 4,8-dihydroxy-1-tetralone | | | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii* | |
| **74** | 12β-hydroxyverruculogen TR-2 | *Melia azedarach* | LN-4 | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii* | 26 |
| **75** | 12β-hydroxy-13α-methoxy-verruculogen TR-2 | | | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii* | |
| **76** | tryptoquivaline O | | | toxicity: brine shrimp<br>Antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activity: armyworm larvae | |
| **77** | bisdethiobis(methylthio)gliotoxin | | | toxicity: brine shrimp | |
| **78** | *cis*-3,4-dihydro-3,4,8-trihydroxynaphthalen-1(2*H*)-one | | | | |
| **79** | (3*S*,8a*S*)-7-hydroxy-3- | | | | |

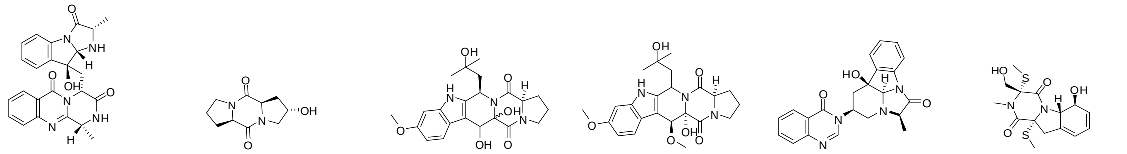
| | | |
|---|---|---|
| | methylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione | |
| **80** | cyclo-(Pro-Ala) | |
| **81** | cyclo-(Pro-Gly) | |
| **82** | cyclo-(Pro-Ser) | |
| **83** | cyclo-(Gly-Ala) | |
| **84** | cyclo-(Gly-Phe) | |
| **85** | cyclo-(Leu-4-OH-Pro) | |
| **86** | cyclo-(*cis*-OH-*D*-Pro-*L*-Phe) | |
| **87** | cyclo-(Ser-trans-4-OH-Pro) | |
| **88** | cyclo-(Pro-trans-4-OH-Pro) | |
| **89** | cyclotryprostatin A | |
| **90** | (*D*-Pro-*L*-Ala) | |
| **91** | fumigaclavine B | |
| **92** | fumiquinazoline D | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activity: armyworm larvae |
| **93** | fumiquinazoline F | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii*<br>antifeedant activity: armyworm larvae |
| **94** | fumiquinazoline G | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp. Vasinfectum*, *Gibberella saubinettii* |
| **95** | methoxyl spirotryprostatin B | |
| **96** | pseurotin A | |
| **97** | pseurotin $A_1$ | |
| **98** | phytotoxic nordammarane triterpenoid helvolic acid | toxicity: brine shrimp<br>antifungal: *Alternaria alternata*, *Alternaria solani*, *Botrytis cinerea*, *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium solani*, *Fusarium oxysporum f. sp. Niveum*, *Fusarium oxysporum f. sp.* |

| | | |
|---|---|---|
| | | *Vasinfectum, Gibberella saubinettii* antifeedant activity: armyworm larvae |
| **99** | terezine D | |
| **100** | trans-3,4-dihydro-3,4,8-trihydroxynaphthalen-1(2*H*)-one | |
| **101** | uracil | |



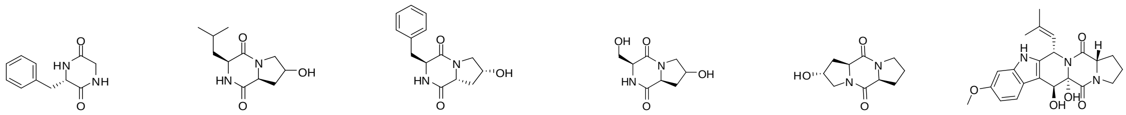


**66** **67** **68** **69** **70** **71**

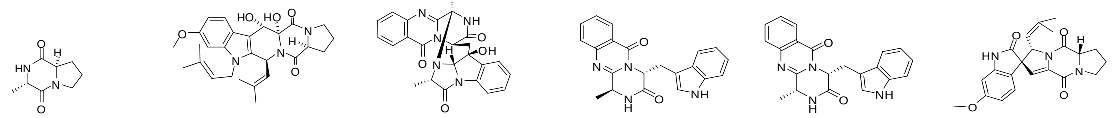


**72** **73** **74** **75** **76** **77**

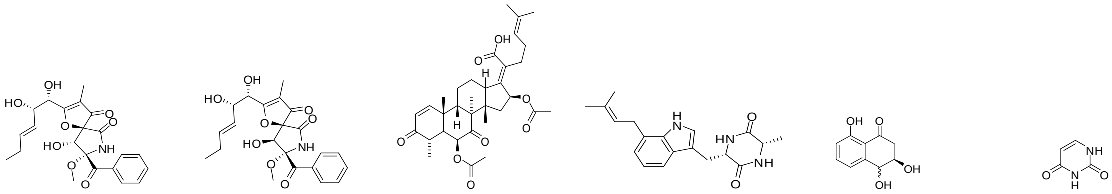
**78** **79** **80** **81** **82** **83**



**84** **85** **86** **87** **88** **89**



**90** **91** **92** **93** **94** **95**

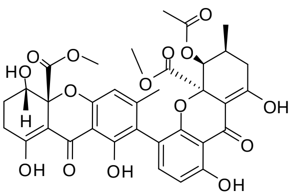


**96** **97** **98** **99** **100** **101**

**Figure 2**. Chemical structures of compounds **12-101**.

### *3.3. Aspergillus fumigatiaffinis*

Till 2014, only one *Aspergillus fumigatiaffnis* strain had been isolated from *Tribulus terrestris* [33]. Chemical investigation indicated that this endophytic *Aspergillus* strain metabolized an antibiotic, Neosartorin (**102**) (Figure 3). This compound exhibited strong antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, and *Bacillus subtilis* with MIC values in the range of 4-8 μg/mL. Moreover, this compound also had moderate cytotoxicity against eukaryotic cell THP-1 with an IC50 value of 12 μg/mL.



**102**

**Figure 3**. Chemical structure of compound **102**.

### *3.4. Aspergillus iizukae*

El-Elimat et al. firstly isolated 7 secondary metabolites from *Aspergillus iizukae* endophytic on *Silybum marianum*, including silybin A (**103**), silybin B (**104**), silydianin

(**105**), silychristin (**106**), isosilybin A (**107**), isosilybin B (**108**) and isosilychristin (**109**) (Figure 4) [31]. These compounds were found to have anti-inflammatory effects [46], antitumor [47] and cytoprotective activities [48].

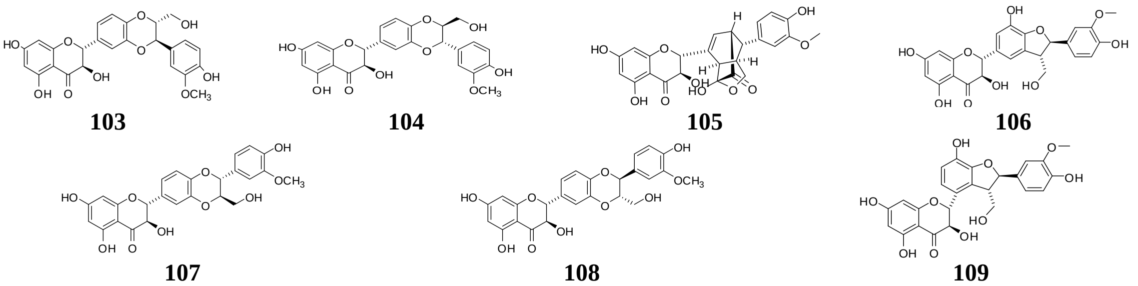
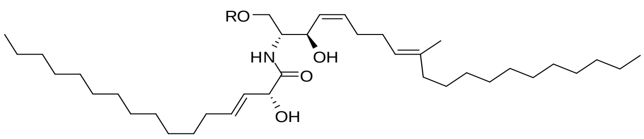


**Figure 4**. Chemical structures of compounds **103-109**.

### *3.5. Aspergillus niger*

An endophytic *Aspergillus niger* from *Colpomenia sinuosa* was found to produce asperamides A (**110**) and B (**111**) (Figure 5) [13]. Their corresponding glycosphingolipid possessed an unreported 9-methyl-C20-sphingosine moiety. In biological assay, compound **111** displayed moderate antimicrobial activity against *Candida albicans*.



**110** R=H；**111** R=β-D-glucopyranoside

**Figure 5**. Chemical structures of compounds **110** and **111**.

### *3.6. Aspergillus versicolor*

Endophytic *Aspergillus versicolor* had been isolated from *Halimeda opuntia* and *Paris polyphylla*. Chemical investigation showed that this endophytic fungus can produce antimicrobial and toxic compounds, such as 1-methyl emodin (**113**), emodin (**116**), isorhodoptilometrin-*L*-methyl ether (**118**), siderin (**119**), and asperphenol B (**124**). Compounds **113** and **116** exhibited more strong activity against HCV NS3/4A with IC50 values of 22.5, 40.2 μg/mL, respectively [44]. **118** and **119** showed moderate inhibitory effect on *Bacillus subtilis*, *B. cereus*, and *Staphylococcus aureus* at the concentration of 50 μg/disk [44]. Compound **124** had high anti-TMV (Tobacco Mosaic Virus) activity with an inhibition rate of 46.7% [29] (Table 3 and Figure 6).

**Table 3.** Metabolites from endophytic *Aspergillus versicolor*.

| No. | Compound | Host Plant | Acitivity | Ref. |
|---|---|---|---|---|
| **113** | 1-methyl emodin | | | |
| **114** | 7-hydroxyemodin 6,8-methyl ether | | | |
| **115** | arugosin C | | | |
| **116** | emodin | *Halimeda opuntia* | toxicity: normal cell CFU-GM<br>anticancer: colon cancer HCT-116, lung cancer H-125 | 44 |
| **117** | evariquinone | | | |
| **118** | isorhodoptilometrin-methyl ether | | antibacterial: *Bacillus cereus*, *Bacillus subtilis, Staphylococcus aureus* | |

| | | | | |
|---|---|---|---|---|
| | | | toxicity: normal cell CFU-GM<br>anticancer: Leukemia L1210, CCRF-CEM, Colon cancer HCT-116, Colon 38, Lung cancer H-125, Liver cancer HEP-G2 | |
| **119** | siderin | | antibacterial: *Bacillus cereus*, *Bacillus subtilis, Staphylococcus aureus* | |
| **120** | variculanol | | | |
| **121** | 4-(4-hydroxyphenyl)-5-(4-hydroxyphenylmethyl)-2-hydroxyfurane-2-one | *Paris polyphylla* | TMV infection inhibition | 29 |
| **122** | aspernolide B | | | |
| **123** | asperphenol A | | | |
| **124** | asperphenol B | | | |
| **125** | aspernolide E | | | |
| **126** | butyrolactone I | | | |

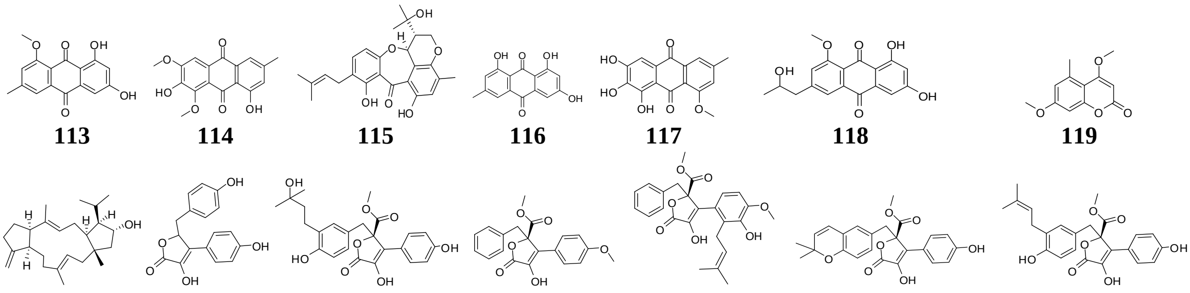


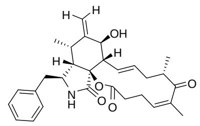

**Figure 6**. Chemical structures of compounds **113** and **126**.

## *3.7. Aspergillus terreus*

One *Aspergillus terreus* strain from *Artemisia annua*, a traditional Chinese herb, was found to produce bioactive alkaloids **12-14**, **127-132** (Table 4 and Figure 7) [12]. Biological assays suggested that cytochalasin Z17 (**131**) had moderate cytotoxicity against human nasopharyngeal epidermoid tumor KB cell line with an $IC_{50}$ value of 26.2 μM.

**Table 4.** Metabolites from endophyt*ic Aspergillus terreus*.

| No. | Compound | Host Plant | Strain No. | Acitivity | Ref. |
|---|---|---|---|---|---|
| **12** | 5-*N*-acetylardeemin | | | | |
| **13** | 5-*N*-acetyl-15b-β-hydroxyardeemin | | | anticancer: SK-OV-S/DDP | |
| **14** | 5-*N*-acetyl-15b-didehydroardeemin | *Artemisia annua* | IFB-E030 | anticancer: SK-OV-S/DDP | 12 |
| **127** | 10-phenyl-[12]-cytochalasin Z16 | | | | |
| **128** | cytochalasin E | | | | |
| **129** | cytochalasin Z11 | | | | |
| **130** | cytochalasin Z13 | | | | |
| **131** | cytochalasin Z17 | | | anticancer: KB | |
| **132** | rosellichalasin | | | | |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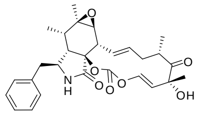
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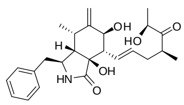
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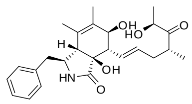
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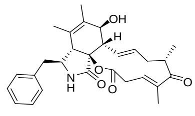
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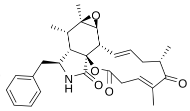

**132**

**Figure 7**. Chemical structures of compounds **127** and **132**.

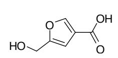
### 3.8. *Other Aspergillus* spp.

Several unidentified endophytic *Aspergillus* strains were isolated from *Eucommia ulmoides* [19], *Ginkgo biloba* [21], *Gloriosa superba* [22] and *Melia azedarach* [28]. These fungal endophytes had ability to produce bioactive metabolites **133-162** (Table 5 and Figure 8). For example, **138-140** and **151** exhibited inhibitory effect on neuraminidase [21]. **153** was shown to have antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Saccharomyces cerevisiae*, *Canidia albicans*, and *Cryptococcus gastricus* [22]. Compounds **153** and **154** had moderate cytotoxicity against THP-1 [22].

**Table 5.** Metabolites from other endophytic *Aspergillus* genus.

| No. | Compound | *Host Plant* | Strain No. | Acitivity | Ref. |
|---|---|---|---|---|---|
| **133** | 5-hydroxymethylfuran-3-carboxylic acid | *Eucommia ulmoides* | ER-15 | antibacterial: *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, Streptococcus faecalis* antifungal: *Aspergillus niger, Candida albicans, Candida krusei, Fusarium solani, Penicillium chrysogenum,* | 19 |
| **134** | 5-methoxymethylfuran-3-carboxylic acid | | | antibacterial: *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Streptococcus faecalis, Staphylococcus aureus* antifungal: *Aspergillus niger, Candida albicans, Candida krusei, Fusarium solani, Penicillium chrysogenum* | |
| **135** | allantoin | | | antibacterial: *Escherichia coli, Staphylococcus aureus,* antifungal: *Aspergillus niger, Candida albicans, Candida krusei, Fusarium solani, Penicillium chrysogenum* | |
| **136** | cerevisterol | | | antibacterial: *Bacillus subtilis, , Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus faecalis, Salmonella typhimurium* antifungal: *Candida albicans, Candida krusei* | |
| **137** | trypacidin | | | antibacterial: *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, Streptococcus faecalis* antifungal: *Candida albicans, Candida krusei, Fusarium solani, Penicillium chrysogenum* | |
| **138** | 3-hydroxyter-phenyllin | *Ginkgo biloba* | YXf3 | inhibitory activity against neuraminidase | 21 |
| **139** | 4″-deoxycandidusin A | | | inhibitory activity against neuraminidase | |
| **140** | 4″-deoxyterphenyllin | | | | |
| **141** | 4″-deoxy-3-hydroxyterphenyllin | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **142** | 4″-deoxy-5’-hydroxyterphenyllin | | | | |
| **143** | 4,5-dimethoxycandidusin A | | | | |
| **144** | 5′-desmethylterphenyllin | | | | |
| **145** | aspergiloid A | | | | |
| **146** | aspergiloid B | | | | |
| **147** | aspergiloid C | | | | |
| **148** | aspergiloid D | | | | |
| **149** | candidusin A | | | | |
| **150** | candidusin C | | | | |
| **151** | terphenolide | | | inhibitory activity against neuraminidase | |
| **152** | terphenyllin | | | | |
| **153** | 4-hydroxy-phthalic acid-dimethyl ester | | | | |
| **154** | 6-methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide | *Gloriosa superba* | FE-19 | antibacterial: *Bacillus subtilis, Cryptococcus gastricus, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* Antifungal: *Candida albicans, Saccharomyces cerevisiae* | 22 |
| **155** | 5-(hydroxymethyl) furan-2-carbaldehyde | | | antibacterial: *Bacillus subtilis, Escherichia coli, Staphylococcus aureus* antifungal: *Saccharomyces cerevisiae* | |
| **156** | (*R*)-3-hydroxybutanonitrile | | | antifungal: *Alternaria solani, Colletotrichum gloeosporioides, Gibberella saubinetti, Magnaporthe grisea* | |
| **157** | asperazine | | | antifungal: *Alternaria solani, Botrytis cinerea, Gibberella saubinetti* | |
| **158** | asperpyrone A | | | antifungal: *Alternaria solani, Gibberella saubinetti* | |
| **159** | dianhydro-aurasperone C | *Melia azedarach* | KJ-9 | | 28 |
| **160** | fonsecinone A | | | antifungal: *Alternaria solani, Botrytis cinerea, Gibberella saubinetti, Magnaporthe grisea* | |
| **161** | isoaurasperone A | | | antifungal: *Alternaria solani,Colletotrichum gloeosporioides, Gibberella saubinetti,* | |
| **162** | rubrofusarin B | | | antifungal: *Alternaria solani* | |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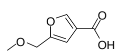
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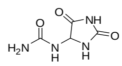
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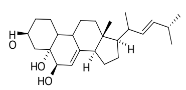
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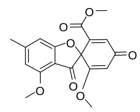
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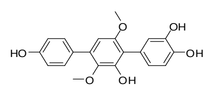
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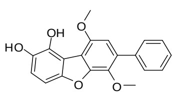
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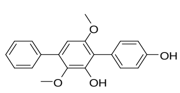
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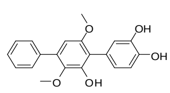
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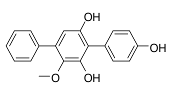
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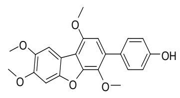
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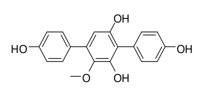
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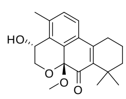
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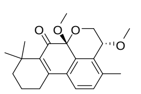
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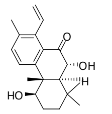
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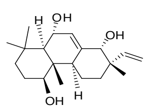
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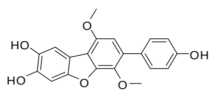
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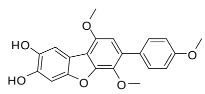
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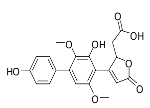
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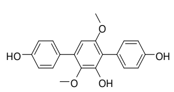
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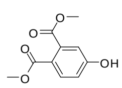
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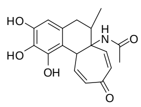
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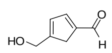
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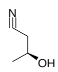
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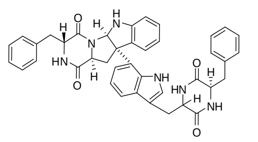
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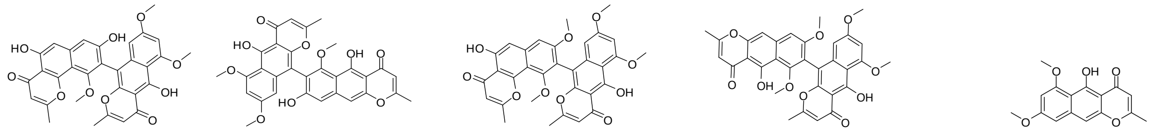

**158** **159** **160** **161** **162**

**Figure 8**. Chemical structures of compounds **133-162**.

## 4. Concluding Remarks

*Aspergillus* strain has strong adaptability in healthy plants. Endophytic *Aspergillus* and its host had formed a symbiont during the long co-evolution. In this micro-environment, host plant provides nutrients for the growth and reproduction of endophytic *Aspergillus* strain. As a reward, endophytic *Aspergillus* metabolites bioactive compounds to protect its host against adverse biotic factors, such as pathogen invasion, virus infection, and herbivore feeding. A growing evidence suggests that the endophytic *Aspergillus* is one of rich sources of natural products with new structures and/or potent bioactivities. And these bioactive compounds would have a great possibility to be applied in medicine and agrochemical industry.

## Acknowledgments

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