Secondary Metabolites and Biological Activity of Endophytic Microorganisms

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Annotatsiya

Secondary natural bioactive compounds produced by endophytic microorganisms play a crucial role in the ecological relationships between plants and microorganisms. Their chemical diversity and biological activity significantly influence plant protection, growth, and development. Many novel compounds synthesized by endophytic microorganisms exhibit potent biological activities, including antibacterial, antifungal, cytotoxic, and antioxidant properties. Overall, these chemical compounds are regarded as a promising resource for the pharmaceutical industry, and ongoing research in this field is revealing their extensive pharmacological potential. This manuscript establishes a foundation for future scientific investigations and paves the way for the development of new natural drugs.

Keywords:

Endophytic microorganisms, secondary metabolites, antimicrobial activity, pathogenic microorganisms

Introduction.

Endophytic microorganisms produce a diverse array of biologically active compounds through their symbiotic relationships with plants. The secondary metabolites generated by these microorganisms not only provide protection to plants but also exhibit properties of significant pharmacological and biotechnological interest. In recent years, natural products derived from endophytic fungi and bacteria isolated from plants have garnered attention for their antimicrobial, cytotoxic, antifungal, antioxidant, and anti-inflammatory properties [1, 2]. The metabolites produced by these microorganisms can also be utilized as pesticides, antimalarial drugs, and agents that promote plant growth [3, 4]. Endophytic microorganisms interact with plants and play a crucial role in helping them adapt to environmental conditions. They are also regarded as an important source for the development of high-value pharmaceutical compounds. The relationship between plants and endophytes provides protection against pathogens and enhances stress tolerance, which, in turn, either eliminates pathogenic microorganisms or inhibits the production of toxins [3, 5-7]. As demonstrated in the examples above, endophytic microorganisms possess significant potential for the development of biological products. Secondary metabolites derived from fungi, such as *Stereum gausapatum*, have generated interest in pesticide development, while *Cladosporium oxysporum* has exhibited strong antibacterial activity. The biological diversity of endophytes and their metabolites remains largely unexplored. Researchers are increasingly focusing on studying endophytic microorganisms isolated from various plants to identify compounds that are pharmacologically and biotechnologically significant. This research could play a crucial role in the future development of new drugs and the creation of eco-friendly agricultural products [8, 9].

This manuscript presents information on 160 natural compounds derived from 31 species of endophytic microorganisms, which belong to 21 different taxonomic groups. Details regarding their taxonomy (Figures 1 and 2) and biological properties (Table 1) are included.

Figure 1: Distribution and proportion of endophytic microorganism collection sites

Figure 2: Number of species in different taxonomic groups of endophytic microorganisms

Table 1: Bioactive natural compounds isolated from endophytic microorganisms

Endophytic Microorganisms	Host plant	Collected place	Natural compounds	Biological Assays	References
Irpex lacteus	*Dendrobium devoninum*	Yunnan, China	**1-5 12-17**	Antifungal activity	[2]
Antrodia camphorata	*Cinnamomum kanehirai Hay (Lauraceae)*	China	**24-44**	Cytotoxic activity	[3]
Strasseria geniculate		New Zelandia	**45-48**	Cytotoxic activity	[4]
Periconia byssoides	*Periconia macrospinosa*	India	**49-61**	Cytotoxic activity, Antifungal activity	[6]
Setophoma sp		Thailand	**62-69**	Antifungal activity	[7]
Penicillium sp. KMU18029	*Aconitum brachypodum*	Yunnan, China	**70-71**	Cytotoxic activity	[10]
Penicillium nothofagi P-6	*Abies beshanzuensis*	Jejyan, China	**72**	Cytotoxic activity	[11]
Penicillium canescens	*Juniperus polycarpos*	Iran	**73-75**	Cytotoxic activity	[12]
Penicillium vulpinum	*Sophorae*	China	**76-78**	Inhibitory activity	[13]

	tonkinensis				
Diaporthe sp. SC-J0138	*Cyclosorus parasiticus*	China	**79-88**	Cytotoxic activity	[5]
Phomopsis sp. CGMCC No.5416	*Achyranthes bidentata*	China	**89-93**	Cytotoxic activity	[14]
Phomopsis prunorum	*Hypericum ascyron*	China	**94-98**	Antimicrobial activity	[15]
Phomopsis stipata	*Styrax camporum Pohl*	Mycological Collections Department at the Federal University of Lavras	**99-100**	Antifungal activity	[16]
Chaetomium globosum	*Polygonatum sibiricum*	The city of Lin'an in Zhejiang Province, China.	**101**	Cytotoxic activity	[17]
Chaetomium globosum P2-2-2		China	**102-103**	Cytotoxic activity	[18]
Trichoderma koningiopsis QA-3	*Artemisia argyi*	China	**104-108**	Antimicrobial activity	[1]
Trichoderma atroviride	*Colquhounia coccinea var. mollis*	Kunming Botanical Garden, Yunnan, China.	**109-113**	Antimicrobial activity	[19]
Cladosporium oxysporum	*Avicennia marina mangrove*	Hainan Province, China.	**114-115**	Antimicrobial activity	[9]
Peniophora incarnata Z4	*Bruguiera gymnorrhiza*	South China Sea	**116-119**	Cytotoxic activity	[20]
Phellinus igniarius		Guizhou Province, China	**120-123**	Cytotoxic activity	[21]
Trichothecium crotocinigenum	*Solanum tuberosum* (Kartoshka)	Lincang County, Yunnan Province, China	**124-127**	Antifungal activity	[22]
Streptomyces fumigatiscleroticus HDN10255	-	China	**128-131**	Cytotoxic activity	[23]
Stereum gausapatum ATCC60954	-	In Yunnan Province, China	**132-134**	Antimicrobial activity	[8]
Aspergillus sp. GXNU-A9	-		**135**	Antifungal activity	[24]
Aspergillus terreus	*Hypericum perforatum*	Hubei Province, People's Republic of China	**136a-136b**	Cytotoxic activity	[25]
Aspergillus versicolor F210	*Lycoris radiata*	Yichang City, Hubei Province	**137**	Cytotoxic activity	[26]
Aplosporella javeedii	*Orychophragmus violaceus*	Beijing	**138, 138a, 138b, 138c**	Cytotoxic activity	[27]
Boeremia exigua	*Solanum tuberosum L.* (Kartoshka)	Lincang County, Yunnan Province, China	**139-140**	Cytotoxic activity	[28]
Fusarium chlamydosporum	*Anvillea garcinii* (*Asteraceae*)	Saudi Arabia	**141-143**	Antifungal activity	[29]
Epicoccum nigrum MK214079	*Salix* sp. (Salicaceae)	In the Caucasus Mountains of Russia	**144-145**	Antimicrobial activity	[30]
Actinomadura sp. RB99	*Macrotermes natalensis* (termit)	Korea	**146-160**	Antimicrobial activity	[31]

Discussion

Nigrospora genus

The chemical compounds released during the co-cultivation of phytopathogens and endophytic microorganisms can vary significantly due to their interactions. Studies indicate that such co-cultivation processes may lead to the production of new and unique metabolites. Phytotoxins, which are compounds synthesized by phytopathogens, can harm plants and have detrimental effects. For example, the co-incubation of the phytopathogen *Nigrospora oryzae* and the endophyte Irpex lacteus results in the release of phytotoxic azaphilone compounds, which are identified by the numbers (**1-5**) and (**12-17** Figure 3). Antifungal Compounds: Endophytic microorganisms frequently produce antifungal compounds to safeguard plants. For instance, tremulane sesquiterpenes isolated from *I. lacteus*

demonstrate antifungal activity, aiding in the protection of plants against pathogenic fungi. The interactions between phytopathogenic and endophytic microorganisms during co-cultivation present new opportunities for the development of biological products and environmentally friendly agricultural solutions. Ongoing research in this field continues to explore and reveal the potential of these interactions, necessitating further investigation for a comprehensive understanding. When the phytopathogenic fungi *Neonectria oryzae* and *Colletotrichum gloeosporioides* are co-cultivated, the production of new or enhanced phytotoxins is observed compared to when each pathogen is cultivated separately. In studying these interactions, an increase in azaphilone phytotoxins, including the formation of compounds such as nigbeauvin C and nigbeauvin D, has been identified (**6-10, 20-23**). Additionally, other classes of compounds, such as sesquiterpenes, polyketides, and phenolic compounds, can also be produced as a result of the interactions between these phytopathogens. The metabolites produced through the co-cultivation of the host plant, endophyte, and phytopathogen play a significant role in plant defense. These substances include phytotoxic compounds, sesquiterpenes such as syringaresinol and tremulane (**11, 12, 18, 19**). For example, the co-cultivation of the host plant *Dendrobium officinale*, the endophyte *Irpex lacteus*, and the phytopathogen *N. oryzae* has been shown to enhance the production of antifungal and pathogen-resistant metabolites [2].

Figure 3. The structures of natural compounds (**1-23**) isolated from *Nigrospora genus*.

Antrodia genus

Twenty-one bioactive compounds were isolated from the fungus *Antrodia camphorata*, including 11 new triterpenoids, designated as antcamphorol A−K (**24−34**), and 10 known triterpenoids (**35−44**). These compounds include antcamphorol A (**24**), antcamphorol B (**25**), antcamphorol C (**26**), antcamphorol D (**27**), antcamphorol E (**28**), antcamphorol F (**29**), antcamphorol G (**30**), antcamphorol H (**31**), antcamphorol I (**32**), antcamphorol J (**33**), and antcamphorol K **(34**, Figure 4), among others, which have been studied for their biological activity. Compounds **30, 32, 33, 39**, and **42** exhibited significant reactive oxygen species (ROS) scavenging activity in high-glucose-induced human umbilical vein endothelial cells (HUVECs), with percentages ranging from 63.9% to 70.5% at a concentration of 20 μM. Additionally, compounds **26** and **31** demonstrated moderate cytotoxic activity against the U251 (IC_{50} = 9.2 μM) and MCF-7 (IC_{50} = 8.1 μM) human cancer cell lines, respectively [3].

Figure 4. Triterpenoids isolated from the fungus *Antrodia camphorata*. Eleven of these are new triterpenoids (**24**−**34**), while ten are previously known triterpenoids (**35**−**44**).

Strasseria genus

From the endophytic fungus *Strasseria geniculata*, which belongs to the A*scomycetes* class, four compounds named strasseriolides A–D (**45–48**, Figure 5) have been isolated. The IC_{50} values of these compounds against the Plasmodium falciparum 3D7 parasites were 9.810 μM, 0.013 μM, 0.123 μM, and 0.128 μM, respectively, indicating strong antimalarial activity. Furthermore, these compounds exhibited no significant cytotoxicity against HepG2 cells (a human liver cancer cell line), suggesting their relative safety and therapeutic potential [4].

Figure 5. Structures of strasseriolides (**45**−**48**) isolated from the endophytic fungus *Strasseria geniculata***.**

Periconia genus

Peribysins are biologically significant compounds recognized for their unique properties in inhibiting cell adhesion. These compounds include peribysin A (**49**), peribysin B (**50**), peribysin C (**51**), peribysin D (**52**), peribysin E (**53**), peribysin F (**54**), peribysin G (**55**), peribysin H (**56**), peribysin I (**57**), peribysin J (**58**), peribysin O (**59**), peribysin P (**60**), and peribysin Q (**61**) (see Figure 6). Cell adhesion processes are crucial for cell-to-cell communication and the metastasis of tumor cells, making peribysins effective agents against tumor growth and metastasis. Furthermore, peribysins have been investigated in the context of diseases such as Sickle Cell Anemia, where the abnormal shape of red blood cells hinders their movement through blood vessels; this impairment could potentially be alleviated by inhibiting cell adhesion. The endophytic fungus *Periconia byssoides*, isolated from marine mollusks (*Aplysia*

kurodai), produces peribysins **49–59**, while *Periconia macrospinosa*, isolated from terrestrial plants, synthesizes peribysins **60–61** [6].

Figure 6. Structures of peribysins **49–59** isolated from the endophytic fungus *Periconia byssoides* and peribysins **60–61** isolated from the fungus *Periconia macrospinosa*.

***Penicillium* genus**

The production of perylenequinones, such as stemphyperylenol and its derivatives, by *Setophoma* sp. strain was observed to increase significantly when co-cultivated with the endophytic fungus *Penicillium brasilianum*. The induced stemphyperylenol was isolated based on its combined chromatographic and physicochemical properties and identified using spectroscopic methods. The compounds identified include stemphyperylenol (**62**), altertoxin I (**63**), alterlosin II (**64**), stemphytriol (**65**), alterlosin I (**66**), stemphyltoxin I (**67**), altertoxin II (**68**), alterperylenol, and alteichin (**69**) (see Figure 7). Stemphyperylenol exhibited not only antifungal activity against *P. brasilianum* but also demonstrated strong efficacy against *Penicillium digitatum*, a major postharvest pathogen of citrus fruits, and *Aspergillus fumigatus*, a ubiquitous soil fungus and significant human pathogen. Therefore, stemphyperylenol shows potential for agricultural applications as well as for use as a promising antifungal compound for human health [7].

Figure 7. Chemical structures of perylenequinones produced by the endophytic fungus *Setophoma* sp.

Endophytic *Penicillium* sp. KMU18029 has produced sesquiterpene coumarins, specifically Penisarins A (**70**) and B (**71**). Penisarins B (**71**, Figure 8) has demonstrated significant cytotoxicity against human cancer cell lines HL-60 and SMMC-7721, with IC_{50} values of 3.6 ± 0.2 μM and 3.7 ± 0.2 μM, respectively [10]. From the bark of *Abies beshanzuensis*, a new N-methoxy-1-pyridone alkaloid (**72**) was isolated from the endophytic fungus *Penicillium nothofagi* P-6. This compound demonstrated significant cytotoxic activity against human cancer cell lines A549 and HeLa, with IC_{50} values of 14.7 and 11.3 μM, respectively. Furthermore, the compound exhibited strong antibacterial activity against *Staphylococcus aureus*, with a minimum inhibitory concentration (MIC) value of 62.5 μg/ml [11].

Figure 8. Structures of Penisarins A (**70**) and B (**71**), isolated from *Penicillium* sp. KMU18029, and chromenopyridin **72**, isolated from *Penicillium nothofagi* P-6.

Currently, many individuals are affected by diabetes, with the majority being diagnosed with type 2 diabetes (T2D). The enzyme α-glucosidase, which is responsible for converting starch into monosaccharides, is a crucial therapeutic target in the management of T2D. A novel xanthone (**73**) and two known xanthones (**74** and **75**, as shown in Figure 9), isolated from the endophytic fungus *Penicillium canescens* found in the plant *Juniperus polycarpos*, have demonstrated inhibitory activity as α-glucosidase inhibitors. The three xanthones (**73, 74,** and **75**) inhibited α-glucosidase activity with IC_{50} values of 38.80 ± 1.01 μM, 32.32 ± 1.01 μM, and 75.20 ± 1.02 μM, respectively [12]. Three new compounds—10-formyl andrastin A **(76**), 10-demethyl andrastin A (**77**), and andrastin G (**78**)—were isolated from the endophytic fungus *Penicillium vulpinum*, and their bioactivities were investigated. Compound **77** demonstrated inhibitory activity against *Bacillus megaterium*, with a minimum inhibitory concentration (MIC) value of 6.25 mg/mL [13].

Figure 9. Xanthones **73, 74**, and **75** were isolated from *Penicillium canescens*, and 10-formyl andrastin A (**76**), 10-demethyl andrastin A (**77**), and andrastin G (78) were isolated from *Penicillium vulpinum*.

***Diaporthe* genus**

The endophytic fungus *Diaporthe* sp. SC-J0138 was isolated from the leaves of *Cyclosorus parasiticus*. From this endophyte, five new cytochalasin compounds—diaporthichalasins D-H (**79–83**)—were identified, along with five known cytochalasins (**84–88**, see Figure 10). Compounds **79** and **83** exhibited significant cytotoxicity against human cancer cell lines A549, HeLa, and HepG2. Specifically, compound **83** demonstrated activity against these cancer cell lines with IC_{50} values ranging from 9.9 to 32.1 μM, while compounds **79, 86**, and **88** showed activity against A549 cells with IC_{50} values between 10.9 and 19.1 μM. All compounds (**79-88**), with the exception of compound **80**, displayed activity against HepG2 and HeLa cells, with IC_{50} values ranging from 8.8 to 38.1 μM [5].

Figure 10: Structures of cytochalasin compounds (**79-88**) isolated from the endophytic fungus *Diaporthe* sp. SC-J0138. These include new compounds, diaporthichalasins D-H (**79–83**), and known cytochalasins (**84–88**).

***Phomopsis* genus**

Three new azaphilones, phomopsones A-C (**89-91**), along with two known azaphilones (**92–93**), were isolated from *Phomopsis* sp. CGMCC No. 5416, an endophytic fungus associated with the medicinal plant *Achyranthes bidentata*. Compounds **90** and **91** demonstrated significant activity against human immunodeficiency virus type 1 (HIV-1), with IC_{50} values of 7.6 and 0.5 μmol/L, respectively. Additionally, these compounds exhibited moderate cytotoxicity against A549 (human lung adenocarcinoma), MDA-MB-231 (human breast cancer), and PANC-1 (human pancreatic adenocarcinoma) cell lines, with IC_{50} values ranging from 3.2 to 303 μmol/L. Furthermore, compound 91 induced apoptosis in PANC-1 cancer cells, resulting in an apoptosis rate of 28.54% [14].

Figure 11: Chemical structures of new azaphilones phomopsones A-C (**89-91**) and known azaphilones (**92–93**) isolated from *Phomopsis* sp. CGMCC No.5416.

From the endophytic fungus *Phomopsis prunorum*, isolated from the leaves of *Hypericum ascyron*, phomoterpene (**94**), two known analogs (**95** and **96**), and two new isocoumarins, phomoisocoumarins (**97-98**, Figure 12), were produced. Among these metabolites, phomoterpene **94** and phomoisocoumarin 98 exhibited moderate antibacterial activity against the plant pathogenic bacteria *Pseudomonas syringae* pv. and *Lachrymans*, with minimum inhibitory concentration (MIC) values of 15.6 μg/mL [15]. The fungus *Phomopsis stipata*, isolated from the plant *Styrax camporum* Pohl, produced two new polyketides: koninginin T (**99**) and koninginin U (**100**). These metabolites exhibited moderate antifungal activity against *Cladosporium cladosporioides* (Fresen.) de Vries SPC 140 and *Cladosporium sphaerospermum*, with nystatin serving as a positive control. Additionally, compound **99** demonstrated activity by inhibiting the enzyme acetylcholinesterase [16].

Figure 12: Structures of compounds **94-98** isolated from the endophytic fungus *Phomopsis prunorum* and compounds **99-100** isolated from the fungus *Phomopsis stipata*.

A new azaphilone, chaephilone C, was isolated from the ethyl acetate extract of *Chaetomium globosum*. The metabolite **101** was evaluated for cytotoxic activity against the human hepatoma cell line HepG-2 in vitro and demonstrated moderate cytotoxic activity, with an IC_{50} value of 38.6 µM [17]. Two new cytochalasins (**102−103**, see Figure 13) were isolated from the endophytic fungus *Chaetomium globosum* P2-2-2, and their biological activities were investigated. Among these compounds, only compound **103** exhibited significant cytotoxic activity against the tested cancer cell lines, with IC_{50} values ranging from 1.04 to 9.90 µM, while compound **102** demonstrated no cytotoxicity [18].

Figure 13. Structures of chaephilone C (**101**) isolated from the endophyte *Chaetomium globosum* and cytocalasins **102–103** isolated from the endophyte *Chaetomium globosum* P2-2-2.

***Trichoderma* genus**

Three polyketides, including trichodermaketone E (**104**), 4-epi-7-O-methylkoninginin D (**105**), and trichopyranone A (**106**), along with two new terpenoids (**107** and **108**, Figure 14), were isolated as secondary metabolites from the endophytic fungus *Trichoderma koningiopsis* QA-3, which was obtained from the plant *Artemisia argyi*. Metabolites **104-106** exhibited moderate antibacterial activity against *Escherichia coli*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, and *Vibrio anguillarum*, with minimum inhibitory concentration (MIC) values of 8 µg/mL. The compound 3-hydroxyharzianone (**107**) demonstrated strong activity against the human pathogen E. coli, with a MIC value of 0.5 µg/mL, while metabolite **108** exhibited activity against *E. coli*, M. luteus, and *Vibrio parahaemolyticus*, with MIC values of 2, 4, and 4 µg/mL, respectively [1].

Figure 14. Structures of compounds (**104-108**) isolated from the endophytic fungus *Trichoderma koningiopsis* QA-3.

The endophytic fungus *Trichoderma atroviride* was isolated from the healthy flowers of *Colquhounia coccinea* var. mollis (Schlecht.). From this endophytic fungus, secondary metabolites, specifically diterpenes—harzianol (**109-113**, Figure 15)—were extracted. Among these metabolites, compound **112** demonstrated significant antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis, and Micrococcus luteus*, with IC_{50} values of 7.7 ± 0.8, 7.7 ± 1.0, and 9.9 ± 1.5 μg/mL, respectively [19].

Figure 15. Harzianol structures (**109-113**) isolated from the endophytic fungus *Trichoderma atroviride*.

Cladosporium genus

The endophytic fungus *Cladosporium oxysporum*, isolated from the roots of the mangrove plant *Avicennia marina*, produced thiocladospolides (structures **114-115**, see Figure 16) when cultured in a liquid nutrient medium consisting of soluble starch (4.0%), yeast extract (0.1%), sodium glutamate (0.2%), sucrose (4.0%), maltose (3.0%), soybean meal (0.05%), peptone (0.2%), $MgSO_4 \cdot 7H_2O$ (0.03%), and KH_2PO_4 (0.05%). Compound **115** demonstrated the highest antimicrobial activity against the aquatic pathogen *Edwardsiella tarda*, with a minimum inhibitory concentration (MIC) value of 4 μg/ml [9].

Figure 16. Structures of thiocladospolides (**114-115**) isolated from the endophytic fungus *Cladosporium oxysporum*.

Peniophora genus

The endophytic fungus *Peniophora incarnata* Z4, isolated from the plant *Bruguiera gymnorrhiza*, produced novel natural metabolites known as tetrahydroxanthones (structures **116-119**, see Figure 17). Among these, compound **117** exhibited significant activity against three human cancer cell lines: A375, MCF-7, and HL-60. The cytotoxic activity of this metabolite was characterized by IC_{50} values of 8.6 ± 0.2 μM, 6.5 ± 0.4 μM, and 4.9 ± 0.2 μM, respectively [20].

Figure 17. Structures of tetrahydroxanthones (**116-119**) isolated from the endophytic fungus *Peniophora incarnata* Z4.

***Phellinus* genus**

Phellinus igniarius was cultured in a fermentation medium consisting of 5% glucose, 0.15% pork peptone, 0.5% yeast powder, 0.05% KH_2PO_4, and 0.05% $MgSO_4$, resulting in the production of phellinignins A-D (structures **120-123**, see Figure 18). Phellinignin A (**120**) was evaluated for its cytotoxic activity against three human cancer cell lines—HL-60, SMMC-7721, and SW480—using the MTT assay. The metabolite phellinignin A (**120**) exhibited significant cytotoxic activity, with IC_{50} values of 3.8, 12.1, and 0.7 μM, respectively [21].

Figure 18. Structures of phellinignins A-D (**120-123**) isolated from the endophytic fungus *Phellinus igniarius*.

***Trichothecium* genus**

New meroterpenoids D-G (structures **124-127**, Figure 19) were isolated from the endophytic fungus *Trichothecium crotocinigenum*, which is associated with potatoes. Compounds **124-127** are rare meroterpenoids that contain a seco-phenyl group, and compounds **124** and **125** feature a distinctive 6-6/5 fused ring system. Compounds **124-127** demonstrated antifungal activity against four plant pathogens, with minimum inhibitory concentration (MIC) values ranging from 8 to 128 μg/mL [22].

Figure 19. Structures of meroterpenoids D-G (**124-127**) isolated from the endophytic fungus *Trichothecium crotocinigenum*.

***Streptomyces* genus**

Four new tetrahydroanthracene derivatives (structures **128, 129, 130,** and **131**, as shown in Figure 20) were identified from *Streptomyces fumigatiscleroticus* HDN10255. These compounds include 4-epi-Julichrome Q10 (**128**), 4-epi-Julichrome Q10.10 A (**129**), 4-epi-Julichrome Q10.10 B (**130**), and 4-epi-Julichrome Q10.10 C (**131**). Compound **130** demonstrated significant cytotoxicity, exhibiting the highest activity against HeLa (cervical cancer) cells, with an IC_{50} value of 1.8 μM [23].

Figure 20. Structures of tetrahydroanthracene derivatives (**128-131**) isolated from the endophytic fungus *Streptomyces fumigatiscleroticus* HDN10255.

***Stereum* genus**

Three new compounds have been isolated from the fungus *Stereum gausapatum* ATCC60954. These compounds are designated as strobilol N (**132**), strobilol O (**133**), and strobilol P (**134**). Compound **132** demonstrated activity against the nematode Caenorhabditis elegans, exhibiting 75.8% mortality at a concentration of 200 μg/ml within 36 hours [8].

Figure 21. Structures of strobilols (**132-134**) isolated from the fungus *Stereum gausapatum* ATCC60954.

***Aspergillus* genus**

A new tetracyclic depsidone derivative, guanxidone (structure **135**, Figure 22), was isolated from the endophytic fungus Aspergillus sp. GXNU-A9. This compound significantly reduced nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated cells, with an IC_{50} value of 8.22 mM [24]. Two new butenolide derivatives, (±)-aspertereton (**136a/136b**), were isolated from the endophytic fungus *Aspergillus terreus* found in the plant *Hypericum perforatum*. The isolated compounds **136a** and **136b** demonstrated cytotoxic activity against human pancreatic cancer cell lines, including AsPC-1, SW1990, and PANC-1, with IC_{50} values ranging from 1.2 to 15.6 μM [25].

Figure 22. Structures of guanxidone A (**135**) isolated from the endophytic fungus *Aspergillus* sp. GXNU-A9, and aspertereton F (**136a/136b**) isolated from the endophytic fungus *Aspergillus terreus*.

(±)-Versicolin A ((±)-**137**) was isolated from the endophytic fungus *Aspergillus versicolor* F210, found in the bulbs of *Lycoris radiata*. (±)-**137** exists as two pairs of keto-enol tautomers ((+)-**137a/(+)-137b** and (−)-**137a/(−)-137b**, Figure 23). Compound **137** exhibited moderate cytotoxicity against HL-60 cells, with an IC_{50} value of 5.6 μM [26].

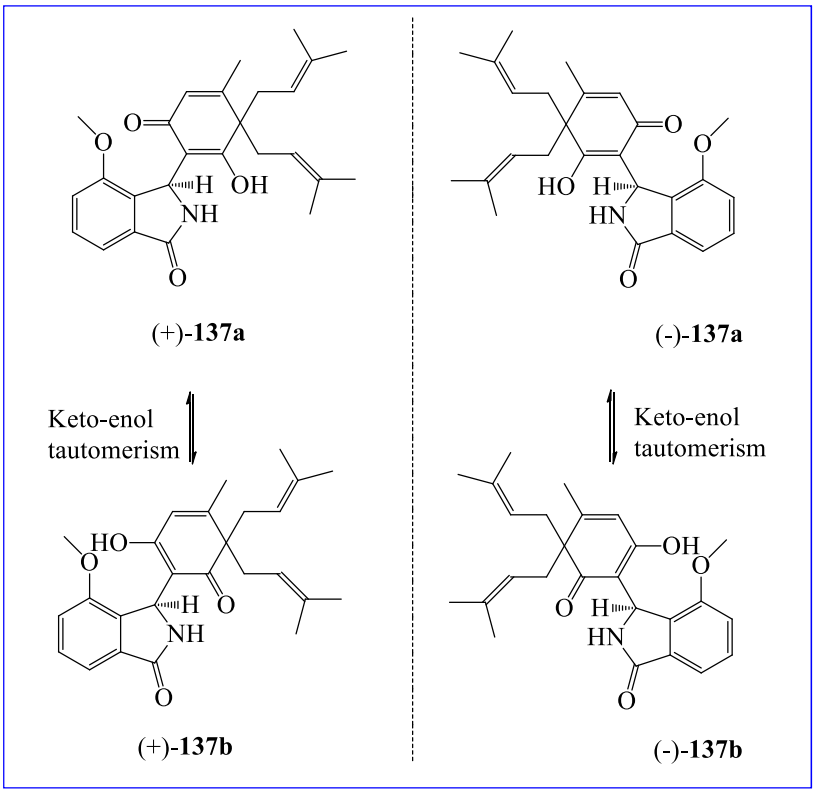

Figure 23. Structures of (±)-versicolin A ((±)-**137**) isolated from the endophytic fungus *Aspergillus versicolor* F210.

Aplosporella genus

A sesterterpene (**138**) was isolated from the endophytic fungus *Aplosporella javeedii*. This compound, along with its acetyl derivatives (**138a**, **138b, 138c**; see Figure 24), exhibited moderate cytotoxicity against the mouse lymphoma cell line L5178Y, with IC_{50} values ranging from 6.2 to 12.8 μM. Furthermore, compounds **138a** and **138c** demonstrated cytotoxic effects against human leukemia (Jurkat J16) and lymphoma (Ramos) cells [27].

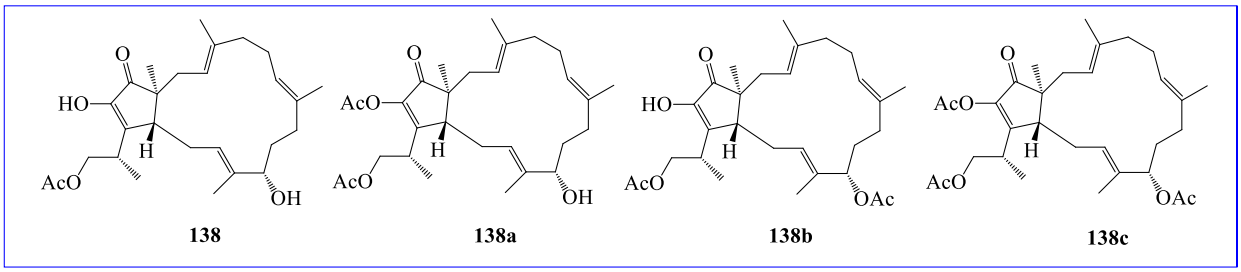

Figure 24. Structures of the sesterterpene (**138**) and its derivatives (**138a, 138b, 138c**) isolated from the endophytic fungus *Aplosporella javeedii*.

Boeremia genus

Five new compounds were isolated from the endophytic fungus *Boeremia exigua* found in potatoes, and their bioactivity was investigated. Among these compounds, boremexin B (**139**) and boremexin E (**140**, Figure 25) demonstrated cytotoxic activity against human breast cancer cells (MCF-7), with IC_{50} values of 33.1 μM and 4.0 μM, respectively [28].

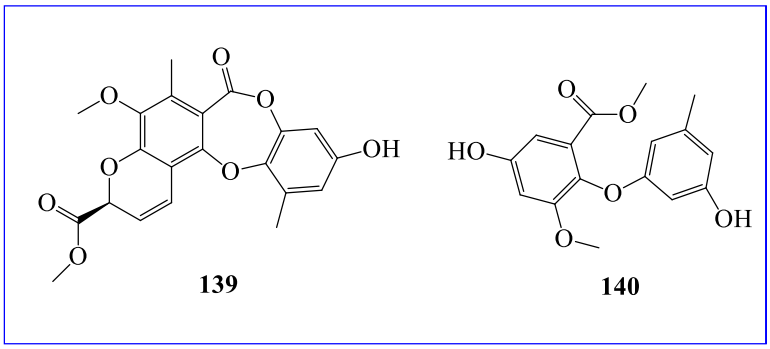

Figure 25. Structures of boremexin B (**139**) and boremexin E (**140**) isolated from the endophytic fungus *Boeremia exigua*.

Fusarium genus

New ergosterol derivatives, chlamydosterol A (**141**) and chlamydosterol B (**143**) (see Figure 26), along with the previously known ergosterol (ergosta-5,7,22-trien-3β-ol) (**142**), were isolated from the endophytic fungus *Fusarium chlamydosporum*, which was obtained from the leaves of *Anvillea garcinii* (*Asteraceae*) growing in Saudi Arabia. Compounds **141** and **142** demonstrated activity as 5-LOX (5-lipoxygenase) inhibitors, with IC_{50} values of 3.06 mM and 3.57 mM, respectively. This enzyme plays a crucial role in the production of biologically active substances known as leukotrienes from arachidonic acid. Leukotrienes are essential in the inflammatory process and are generated during conditions such as asthma, allergies, arthritis, and other inflammatory diseases [29].

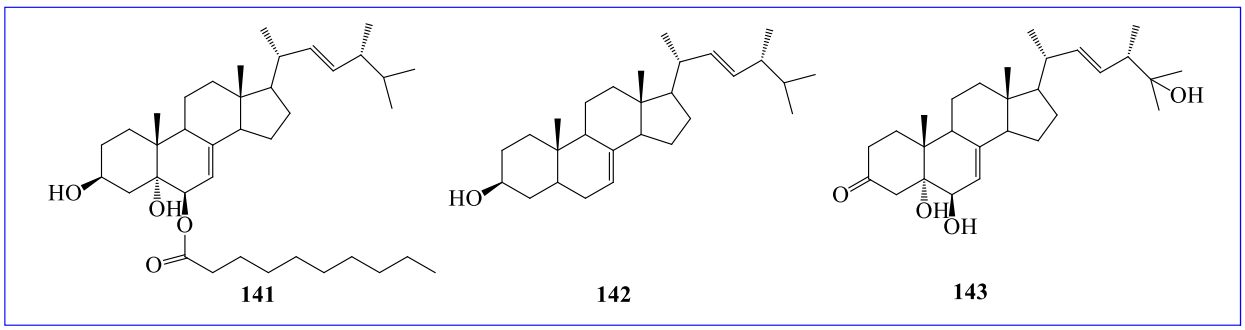

Figure 26. Structures of ergosterol derivatives (**141, 142, 143**) isolated from the endophytic fungus *Fusarium chlamydosporum*.

Epicoccum genus

The compounds epipyrone (**144**) and epicoccamide (**145**, Figure 27) were isolated from the endophytic fungus *Epicoccum nigrum* MK214079, and their bioactivity was investigated. Compounds **144** and **145** demonstrated activity against the fungus *Ustilago maydis* AB33, with minimum inhibitory concentration (MIC) values of 1.6 mM and 1.8 mM, respectively [30].

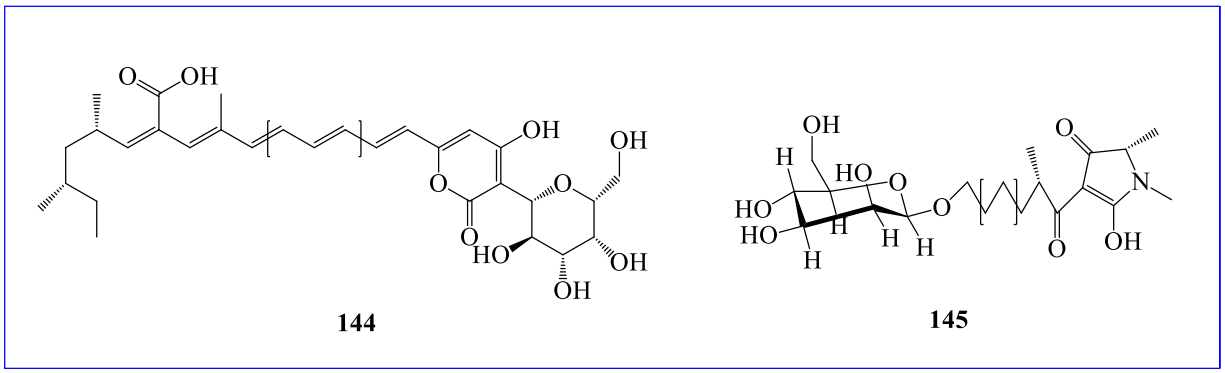

Figure 27. Structures of epipyrone (**144**) and epicoccamide (**145**) isolated from the endophytic fungus *Epicoccum nigrum* MK214079.

Actinomadura species

Fifteen bioactive compounds were synthesized by the termite-associated bacterium *Actinomadura* sp. RB99. These compounds, designated as maduractermol A (**146**), maduractermol B (**147**), maduractermol C (**148**), maduractermol D (**149**), maduractermol E (**150**), maduractermol F (**151**), maduractermol G (**152**), maduractermol I (**155**), maduractermol J (**156**), maduractermol K (**157**), maduractermol L (**158**), maduractermol M (**159**), and maduractermol N (**160**) (see Figure 28), were isolated in pure form, and their chemical and biological properties were investigated. The compounds' activity against pathogenic microorganisms was assessed, revealing that

compounds **152** and **156** exhibited activity against the pathogenic bacterium H. pylori, with MIC_{50} values of 6.9 µg/mL (9) and 14.5 µg/mL (13), respectively [31].

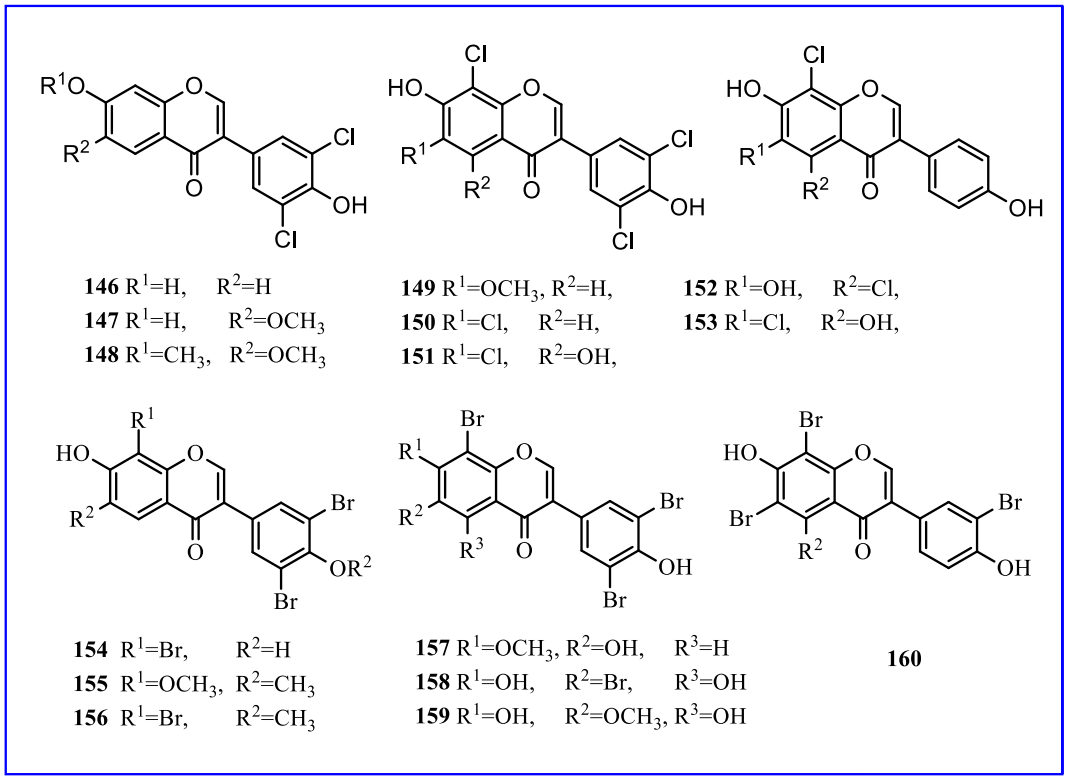

Figure 28. Structures of maduractermol compounds (**146-160**) synthesized by *Actinomadura* sp. RB99 bacterium.

Conclusion

In summary, a total of 160 natural compounds have been isolated from 31 endophytic microorganisms, and their biological activities have been thoroughly investigated. Among these microorganisms, species from the genera *Penicillium*, *Phomopsis*, *Aspergillus*, and *Chaetomium* exhibit the highest levels of bioactivity. The substances produced by these microorganisms demonstrate significant antimicrobial, antifungal, cytotoxic, and antioxidant effects, underscoring their potential as novel sources for drug discovery. These chemical compounds serve as promising leads for the pharmaceutical industry and reveal a wide range of pharmacological potential. The findings of this study establish a foundation for future research and may pave the way for the development of new natural drug candidates.

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