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REVIEW ARTICLE

Bioactive secondary metabolites produced by fungi of the genus *Diaporthe* (*Phomopsis*): Structures, biological activities, and biosynthesis

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Abstract *Diaporthe* and its anamorph *Phomopsis*, a genus of endophytic, saprotrophic, and plant pathogenic fungi, are found in many different ecosystems worldwide. *Diaporthe* (*Phomopsis*) fungi generate natural products such as pyrones, polyketides, alkaloids, and terpenoids. Most of these natural products show antibacterial, anti-inflammatory, and/or cytotoxic activity. In this review, we describe the 331 bioactive secondary metabolites isolated from 75 known species and various unidentified species of *Diaporthe* and *Phomopsis* from 2016 to 2021. These products comprise 143 bioactive compounds from *Diaporthe* and 188 from *Phomopsis*, including quinones, alkaloids, terpenoids, pyrones, polyketides, diphenyl ketones, diphenyl ethers, steroids, and fatty acids. The major activities of these compounds are as cytotoxic, antibacterial, and anti-inflammatory chemicals. All 21 fungi in the genus *Diaporthe* (*Phomopsis*) with available whole genome sequencing data contain several gene clusters for secondary metabolite biosynthesis. Such gene clusters and biosynthetic mechanisms have been identified for rugulosin A, terpestacin, and sch-642305. *Diaporthe* (*Phomopsis*) fungi produce abundant novel active natural products with great potential for drug development. In addition, these fungi provide important resources for research on the biosynthesis of secondary metabolites.

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1. Introduction

Diaporthe belongs to the family Diaporthaceae, which includes nearly 800 fungal species. Its asexual state is called *Phomopsis* (Dissanayake et al., 2020). *Diaporthe* is a common plant pathogenic fungus that produces natural products, including polyketides, alkaloids, peptides, terpenoids, and nucleosides (Tanney et al., 2016). These natural products possess antibacterial, anti-inflammatory, and cytotoxic properties. For example, the dimer anthraquinone compound *epi*-cytoskyrin A (Agusta et al., 2015a) has significant antibacterial activity; the terpenoids eupenifeldin and pycnidione have significant cytotoxic activity (Chen et al., 2020a, 2020b, 2020c, 2020d; Hsiao et al., 2012); terpestacin has angiogenic activity (Jung et al., 2010); sch-642305 has significant cytotoxic activity (Chu et al., 2003a); and libertellenone M has significant anti-inflammatory activity (Fan et al., 2020). To date, the genome sequences of 21 fungi from the *Diaporthe* (*Phomopsis*) genus have been published in the National Center for Biotechnological Information (NCBI) database. Among these fungi are *Diaporthe* sp. HANT25 (Tulsook et al., 2020), which produces mycoepoxydiene, and *Phomopsis* sp. CMU-LMA (Trenti et al., 2020), which produces the cytotoxic compound sch-642305. According to the genomic data, fungi of the genus *Diaporthe* (*Phomopsis*) represent important sources of abundant bioactive secondary metabolites.

Chepkirui et al. (Chepkirui and Stadler, 2017) reviewed our understanding of the structures and biological activities of natural products produced by fungi from the genus *Diaporthe* (*Phomopsis*) prior to 2015. Xu et al. (Xu et al., 2021a, 2021b) reviewed the progress made on the secondary metabolites of *Diaporthe* and *Phomopsis* fungi from 2010 to 2019 and their biological activities, and Nagarajan et al. (Nagarajan et al., 2020) reviewed research progress on the secondary metabolites of *Diaporthe* from 2015 to 2020 and their biological activities. However, these reviews do not discuss the biosynthesis of these important active compounds.

In the current review, we discuss the structures and biological activities of secondary metabolites isolated from *Diaporthe* (*Phomopsis*) fungi between 2016 and 2021. We also describe the biosynthetic pathways of important bioactive molecules produced by these fungi. This review will provide a reference for genome mining of novel active natural products derived from *Diaporthe* (*Phomopsis*) fungi as well as in-depth research on the biosynthesis and pharmacological mechanisms of known important active molecules.

2. Bioactive secondary metabolites from *Diaporthe* and *Phomopsis*

Diaporthe and *Phomopsis* fungi are valuable sources of bioactive chemicals for drug development, with several medical applications. In this review, we summarize the structures, biological activities, and biosynthesis of new natural products from the genus *Diaporthe* (*Phomopsis*). Between 2016 and 2021, 331 compounds isolated from the genus *Diaporthe* and its anamorph *Phomopsis* have been studied. The 143 compounds obtained from *Diaporthe* consisted of 50 pyrones (35%), 28 polyketides (19.6%), 27 alkaloids (18.9%), 21 fatty acids (14.7%), 6 terpenoids (4.2%), 4 diphenyl ketones (2.8%), 3 quinones (2.1%), 2 diphenyl ethers (1.4%), and 2 steroids (1.4%) (Fig. 1A). The primary sources of these chemicals include pyrones, polyketides, alkaloids, and fatty acids. *Phomopsis* produced 188 natural compounds, comprising 52 terpenoids (27.7%), 42 polyketides (22.3%), 41 alkaloids (21.8%), 29 pyrones (15.4%), 5 diphenyl ethers (2.7%), 4 diphenyl ketones (2.1%), 4 quinones (2.1%), 4 steroids (2.1%), and 7 others (3.7%) (Fig. 1B). The major sources of these chemicals are terpenoids, polyketides, alkaloids, and pyrones.

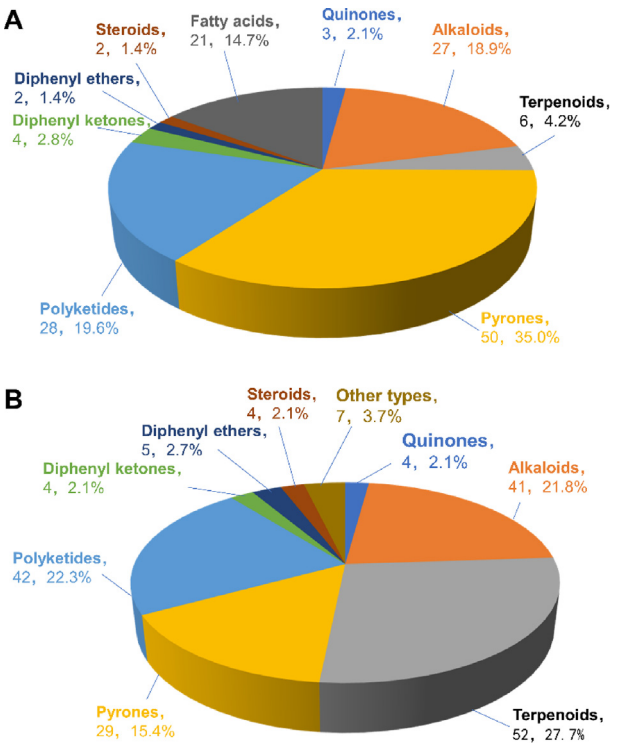

Fig. 1 Classes of bioactive secondary metabolites isolated from *Diaporthe* and *Phomopsis* from 2016 to 2021. (A) Distribution of 143 bioactive secondary metabolites isolated from *Diaporthe* from 2016 to 2021; (B) Distribution of 188 bioactive secondary metabolites isolated from *Phomopsis* from 2016 to 2021.

The bioactivities of the compounds identified from *Diaporthe* and *Phomopsis* are shown in Fig. 2. These bioactivities primarily include cytotoxic, anti-inflammatory, antibacterial, antiviral, antioxidant, neuroprotective, anti-α-glucosidase, anti-β-site amyloid precursor protein cleaving enzyme 1 (anti-BACE1), anti-acetylcholinesterase (anti-AchE), anti-pulmonary fibrosis, and anti-hyperlipidemic activities. As shown in Table 1, secondary metabolites of *Diaporthe* and *Phomopsis* primarily exhibit anti-inflammatory, antibacterial, and cytotoxic activities. Notably, a growing number of compounds with anti-inflammatory, antibacterial, and cytotoxic

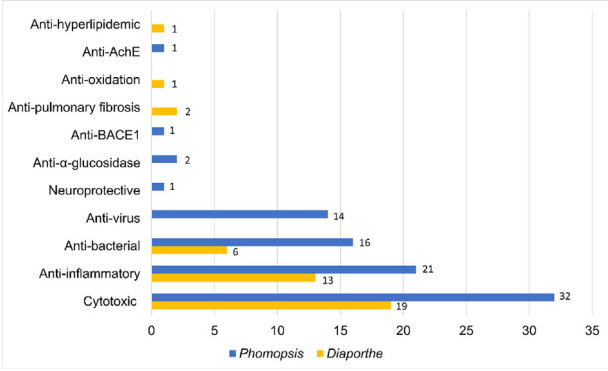

Fig. 2 Distribution of the major bioactivities of compounds isolated from *Diaporthe* and *Phomopsis* from 2016 to 2021.

Table 1 Bioactive secondary metabolites isolated from *Diaporthe* and *Phomopsis* (**1**–**331**).

Compound	Strain	Habitat	Activity	Refs.
epi-Cytoskyrin A (**1**)	*Diaporthe* sp. ARL-09	*Anoectochilus roxburghii*	Cytotoxic	(Tian et al., 2018)
Cytoskyrin C (**2**)	*Diaporthe* sp. ARL-09	*Anoectochilus roxburghii*	Cytotoxic	(Tian et al., 2018)
Biatriosporin N (**3**)	*Diaporthe vochysiae*	Red-clawed crab (*Chiromantes haematocheir*)	Anti-inflammatory	(Liu et al., 2019a)
Epoxyquinophomopsins A–B (**4–5**)	*Phomopsis* sp.	*Morus cathayana*	Cytotoxic	(Hermawati et al., 2021)
Compounds **6–7**	*Phomopsis* sp.	*Nicotiana tabacum* L.	Antibacterial	(Wu et al., 2021)
Diaporisoindoles A–E (**8–12**)	*Diaporthe* sp. SYSU-HQ3	*Excoecaria agallocha*	Antibacterial (**8**); Anti-inflammatory (**9–10**)	(Cui et al., 2017b, 2018)
Diaporphasines A–D (**13–16**)	*Diaporthe phaseolorum* SKS019	*Acanthus ilicifolius*	Cytotoxic	(Cui et al., 2017c)
Meyeroguillines C–D (**17–18**)	*Diaporthe phaseolorum* SKS019	*Acanthus ilicifolius*	Cytotoxic	(Cui et al., 2017c)
Compounds **19–20**	*Diaporthe* sp. GDG-118	*Sophora tonkinensis*	Antibacterial (**20**)	(Huang et al., 2019)
Diaporthichalasins A–C (**21** ~ **23**)	*Diaporthe* sp. GZU-1021	*Chiromantes haematocheir*	Cytotoxic (**22**)	(Liu et al., 2019b)
Diaporthichalasin D–H (**24–28**)	*Diaporthe* sp. SC-J0138	*Cyclosorus parasiticus*	Cytotoxic	(Yang et al., 2020a, 2020b)
Deacetyl-19-*epi*-cytochalasin P1 (**29–30**)	*Diaporthe* sp. RJ-47	*Dracaena cochinchinensis*	Antibacterial (**29**)	(Yan et al, 2021)
Vochysiamides A–B (**31–32**)	*Diaporthe vochysiae*	*Vochysia divergens*	Antibacterial (**32**)	(Noriler et al., 2019)
(±)-Diaporthin C (**33–34**)	*Diaporthe phragmitis*	*Actinidia chinensis*	–	(Yu et al., 2021a, 2021b)
Cytochalasins J1–J3 (**35–37**)	*Phomopsis* sp. CMB-M0042F	Marine sediment	Cytotoxic	(Shang et al., 2017)
Cytochalasins H1–H2 (**38– 39**)	*Phomopsis* sp. CMB-M0042F	Marine sediment	Cytotoxic	(Shang et al., 2017)
Phomopsichalasins D–E (**40–41**)	*Phomopsis* spp. xy21 and xy22	*Xylocarpus granatum*	Cytotoxic	(Luo et al., 2016)
Phomopsichalasins F–G (**42–43**)	*Phomopsis* spp. xy21 and xy22	*Xylocarpus granatum*	Cytotoxic (**43**)	(Luo et al., 2016)
Phomopchalasins A ~ C (**44–46**)	*Phomopsis* sp. shj2	*Isodon eriocalyx* var. laxiflora	Cytotoxic (**44–45**); Anti-inflammatory (**46**)	(Yan et al., 2016)
Phomocytochalasin (**47**)	*Phomopsis theicola* BCRC 09F0213	*Litsea hypophaea* Hayata	–	(Hsiao et al., 2016)
Phomopsisins A (**48–50**)	*Phomopsis* sp. sh917	*Isodon eriocalyx* var. laxiflora	Anti-inflammatory (**50**)	(Tang et al., 2020)
(±)-Farinomalein F (**51** ~ **52**)	*Phomopsis* sp. SYSU-QYP-23	Marine *Kandelia candel*	Anti-inflammatory	(Chen et al., 2020a, 2020b, 2020c, 2020d)
Farinomalein H (**53**)	*Phomopsis* sp. SYSU-QYP-23	Marine *Kandelia candel*	Anti-inflammatory	(Chen et al., 2020a, 2020b, 2020c, 2020d)
(±)-Farinomalein G (**54** ~ **55**)	*Phomopsis* sp. SYSU-QYP-23	Marine *Kandelia candel*	Anti-inflammatory	(Chen et al., 2020a, 2020b, 2020c, 2020d)
Phomoamide (**56**)	*Phomopsis* sp. SYSU-QYP-23	Marine *Kandelia candel*	Anti-inflammatory	(Chen et al., 2020a, 2020b, 2020c, 2020d)
Phochrodines A–B (**57–58**)	*Phomopsis* sp. 33#	*Rhizophora stylosa*	–	(Chen et al., 2018)
Phochrodines C–D (**59 –60**)	*Phomopsis* sp. 33#	*Rhizophora stylosa*	Anti-inflammatory	(Chen et al., 2018)
Phomopsol A (**61**)	*Phomopsis* sp. xy21	*Thai Xylocarpus granatum*	Neuroprotective	(Li et al., 2019)
(±)-Tersone A–E (**62 –71**)	*Phomopsis tersa* FS441	Sediment	Antibacterial (**70 –71**)	(Chen et al., 2019)
Tersone F–G (**72–73**)	*Phomopsis tersa* FS441	Sediment	–	(Chen et al., 2019)

(*continued on next page*)

Table 1 (*continued*)

Compound	Strain	Habitat	Activity	Refs.
Prenylcyclotryprostatin A (**74**)	*Phomopsis asparagi* CICC2706	China Center of Industrial Culture Collection	–	(Zhou et al., 2021)
7-hydroxy-*cis*-L(-)-3,6-dibenzyl-2,5-Dioxopiperazine (**75**)	*Phomopsis asparagi* CICC2706	China Center of Industrial Culture Collection	–	(Zhou et al., 2021a)
Lithocarins B–D (**76–78**)	*Diaporthe lithocarpus* A740	*Morinda officinalis*	Cytotoxic	(Liu et al., 2019)
Diaporpenoids A–C (**79–81**)	*Diaporthe* sp. QYM12	*Kandelia candel*	Anti-inflammatory (**79**)	(Yan et al, 2021)
Phomeroids A–B (**82–83**)	*Phomopsis tersa* FS441	Sediment	Cytotoxic	(Chen et al., 2020a, 2020b, 2020c, 2020d)
Eupenifeldin (**84**)	*Phomopsis tersa* FS441	Sediment	Cytotoxic	(Chen et al., 2020a, 2020b, 2020c, 2020d)
Pedinophyllols K–L (**85** ~ **86**)	*Phomopsis* sp. S12	*Illigera rhodantha*	–	(Xu et al., 2019a)
Libertellenone T (**87**)	*Phomopsis* sp. S12	*Illigera rhodantha*	Anti-inflammatory	(Xu et al., 2019b)
Photeroids A–B (**88–89**)	*Phomopsis tersa* FS441	Sediment sample	Cytotoxic	(Chen et al., 2020b)
Phomopoxides A–F (**90** ~ **96**)	*Phomopsis* sp. YE3250	*Paeonia delavayi*	Anti-α-glucosidase (**90** ~ **91**)	(Huang et al., 2018)
Phomophyllins A–K (**97–107**)	*Phomopsis* sp. TJ507A	*Phyllanthus glaucus*	Anti-β-site amyloid precursor protein cleaving enzyme 1 (**97**)	(Xie et al., 2018)
Phomophyllins L–N (**108–110**)	*Phomopsis* sp. TJ507A	*Phyllanthus glaucus*	–	(Xie et al., 2018)
Eremofortin G (**111**)	*Phomopsis* sp. SYSU-QYP-23	*Kandelia candel*	Anti-inflammatory	(Chen et al., 2021a, 2021b)
Eremofortins I–K (**112–114**)	*Phomopsis* sp. SYSU-QYP-23	*Kandelia candel*	Anti-inflammatory	(Chen et al., 2021a, 2021b)
Altiloxins C–E (**115–117**)	*Phomopsis* sp. SYSU-QYP-23	*Kandelia candel*	Anti-inflammatory	(Chen et al., 2021a, 2021b)
Phomomane (**118**)	*Phomopsis* sp. SYSU-QYP-23	*Kandelia candel*	Anti-inflammatory	(Chen et al., 2021a, 2021b)
Carneic acids C–O (**119–131**)	*Phomopsis* sp. SNB-LAP1-7–32	*Diospyros carbonaria*	Antiviral	(Peyrat et al., 2020)
Hydroxylithocarin A (**132**)	*Phomopsis asparagi* CICC 2706	China Center of Industrial Culture Collection	–	(Shi et al., 2020)
Lithocarin A (**133**)	*Phomopsis lithocarpus* FS508	Deep-sea sediment	Cytotoxic	(Xu et al., 2018a, 2018b)
Compounds **134–136**	*Diaporthe* sp. F2934	*Siparuna gesnerioides*	–	(Sousa et al., 2016)
Diaporchromanones A–D (**137–140**)	*Diaporthe phaseolorum* SKS019	*Acanthus ilicifolius*	Anti-inflammatory	(Cui et al., 2017a)
(±)-Phomopsichin A (**141–142**)	*Diaporthe phaseolorum* SKS019	*Acanthus ilicifolius*	Anti-inflammatory	(Cui et al., 2017a)
(±)-Diaporchromone A (**143**)	*Diaporthe phaseolorum* SKS019	*Acanthus ilicifolius*	Anti-inflammatory	(Cui et al., 2017a)
Phaseolorins A–H (**144–151**)	*Diaporthe phaseolorum* FS431	Marine sediment	–	(Guo et al., 2019)
Phomotide A (**152**)	*Phomopsis* sp. CFS42	*Cephalotaxus fortunei Hook*	–	(Ma et al., 2020)
Pestalotiopsone H (**153**)	*Diaporthe* sp. SCSIO 41011	Mangrove	–	(Luo et al., 2018b)
Methyl-Convolvulopyrone (**154**)	*Diaporthe* sp. SCSIO 41011	Mangrove	–	(Luo et al., 2018b)
Diaporpyranes A–C (**155** ~ **157**)	*Diaporthe* sp. QYM12	China Center of Industrial Culture Collection	Anti-inflammatory (**155**)	(Yan et al, 2021)

Table 1 (*continued*)

Compound	Strain	Habitat	Activity	Refs.
Compounds (**158–162**)	*Diaporthe foeniculina* BZM-15	*Leptospermum brachyandrum*	–	(Yu et al., 2021a, 2021b)
Ellagic acid B (**163**)	*Diaporthe* sp. CB10100	*Sinomenium acutum* (Thunb.)	–	(Pu et al., 2021)
Diaporpyrones A–D (**164–167**)	*Diaporthe* sp. CB10100	*Sinomenium acutum* (Thunb.)	–	(Pu et al., 2021)
Compounds **168–169**	*Diaporthe phaseolorum* FS459	Deep-sea sediment	–	(Hu et al., 2021)
Compounds **170–172**	*Diaporthe phaseolorum* FS459	Deep-sea sediment	–	(Hu et al., 2021)
Foeniculins A–K (**173–183**)	*Diaporthe foeniculina* SCBG-15	Leptospermum brachyandrum	–	(Lu et al., 2021)
Phomaspyrones A–E (**184–188**)	*Phomopsis asparagi* SWUKJ5.2020	*Kadsura angustifolia*	Cytotoxic (**186**)	(Song et al., 2017)
Phomopsichins A–D (**189–192**)	*Phomopsis* sp. 33#	*Rhizophora stylosa*	–	(Huang et al., 2016)
(10S)-10-O-b-D-40-Methoxymanno-pyranosyldiaporthin (**193**)	*Phomopsis* sp. sh917	*Isodon eriocalyx* var. laxiflora	–	(Tang et al., 2017)
Clearanol H (**194**)	*Phomopsis* sp. sh917	*Isodon eriocalyx* var. laxiflora	–	(Tang et al., 2017)
Phomochromenones A –K (**195–203**)	*Phomopsis* sp. HNY29-2B	*Acanthus ilicifolius* Linn	–	(Ding et al., 2017)
Phomoisocoumarins C–D (**204 – 205**)	*Phomopsis prunorum*	*Hypericum ascyron*	Antibacterial (**205**)	(Qu et al., 2020)
Phomotide A (**206**)	*Phomopsis* sp. CFS42	*Cephalotaxus fortunei Hook*	–	(Ma et al., 2020)
Phomopsinins B–C (**207–208**)	*Phomopsis* sp. CAM212	*Garcinia xanthochymus*	–	(Jouda et al., 2020)
Phomochromenones D –G (**209–212**)	*Phomopsis asparagi* DHS-48	*Rhizophora mangle*	–	(Wei et al., 2021)
Acetoxydothiorelone B (**213**)	*Diaporthe pseudomangiferaea*	*Tylophora ouata*	Anti-pulmonary fibrosis	(Liu et al., 2018)
(15S)-acetoxydothio relone A (**214**)	*Diaporthe pseudomangiferaea*	*Tylophora ouata*	–	(Liu et al., 2018)
Dothiorelones K–N (**215** ~ **218**)	*Diaporthe pseudomangiferaea*	*Tylophora ouata*	Anti-pulmonary fibrosis (**216**)	(Liu et al., 2018)
5-Hydroxy-7-methoxy-4,6-dimethyl-2-Phenyliso in doline-1,3-dione (**219**)	*Diaporthe pseudomangiferaea*	*Tylophora ouata*	–	(Liu et al., 2018)
(13R)-diaporphthalide A (**220**)	*Diaporthe pseudomangiferaea*	*Tylophora ouata*	–	(Liu et al., 2018)
(9S, 17R, 19S, 6Z, 10E, 14E)-diaporlactone A (**221**)	*Diaporthe pseudomangiferaea*	*Tylophora ouata*	–	(Liu et al., 2018)
Isochromophilones A–F (**222** ~ **227**)	*Diaporthe* sp. SCSIO 41011	Mangrove plant	Cytotoxic (**225**)	(Luo et al., 2018a)
Isochromophilone G (**228**)	*Diaporthe perseae* sp.	*Pongamia pinnata* (L.)	Antibacterial/Antioxidation	(Niaz et al., 2020)
11-Hydrochermesinone B (**229**)	*Diaporthe phaseolorum* FS459	deep-sea sediment	–	(Hu et al., 2021)
Diaportones A–C (**230–232**)	*Diaporthe foeniculina* BZM-15	*Leptospermum brachyandrum*	–	(Kang et al., 2021)
(15R)-Acetoxydothiorelone A (**233**)	*Diaporthe* sp. SCSIO 41011	Mangrove	–	(Luo et al., 2018b)
(±)-Microsphaerophthalides H~I (**234–235**)	*Diaporthe* sp. SCSIO 41011	Mangrove	–	(Luo et al., 2018b)

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Table 1 (*continued*)

Compound	Strain	Habitat	Activity	Refs.
Diaporindenes A–D (**236–239**)	*Diaporthe* sp. SYSU-HQ3	Mangrove	Anti-inflammatory	(Cui et al., 2018)
Isoprenylisobenzofuran A (**240**)	*Diaporthe* sp. SYSU-HQ3	Mangrove	–	(Cui et al., 2018)
Phomopsiketones A–C (**241–243**)	*Phomopsis* sp. sh917	*Isodon eriocalyx* var. laxiflora	Cytotoxic (**241** ~ **242**)	(Tang et al., 2017)
Compounds **244–245**	*Phomopsis* sp. PSU-H188	*Hevea brasiliensis*	–	(Kongprapan et al., 2017)
Phomopones A–C (**246** –**248**)	*Phomopsis* sp. D15a2a	*Alternanthera bettzickiana*	–	(Yu et al., 2019)
Koninginins T–U (**249** –**250**)	*Phomopsis stipata*	*Styrax camporum Pohl*	Antibacterial/anti-acetylcholinesterase (**249**); Antibacterial (**250**)	(Biasetto et al., 2020)
Compounds **251–253**	*Phomopsis* sp.	–	Antiviral (**251**)	(Du et al., 2017)
Compounds **254–258**	*Phomopsis fukushii*	*Nicotiana tabacum*	Antibacterial	(Yang et al., 2017), (Li et al., 2021)
Phomopsol B (**259**)	*Phomopsis* sp. xy21	*Xylocarpus granatum*	–	(Li et al., 2019)
Compound **260**	*Phomopsis* sp. xy21	*Xylocarpus granatum*	–	(Li et al., 2019)
(±)-Phomopsisin A (**261** ~ **262**)	*Phomopsis asparagi* CICC 2706	China Center of Industrial Culture Collection	–	(Zhou et al., 2021)
Lithocaldehydes A–B (**263** ~ **264**)	*Phomopsis lithocarpus* FS508	Marine sediment	Antibacterial	(Liu et al., 2020)
Phomopsones A–C (**265** ~ **267**)	*Phomopsis* sp. CGMCC No.5416	*Achyranthes bidentata*	Antiviral/Cytotoxic (**266** ~ **267**)	(Yang et al., 2020a, 2020b)
Tersaphilones B–D (**268** ~ **271**)	*Phomopsis tersa* FS441	Sediment	Cytotoxic (**270**)	(Chen et al., 2021a, 2021b)
Diaporindenes E–I (**272–276**)	*Phomopsis lithocarpus* FS508	Deep-sea sediment sample	–	(Liu et al., 2021a, 2021b)
Tenellones J–M (**277–280**)	*Phomopsis lithocarpus* FS508	Deep-sea sediment sample	Cytotoxic (**278**)	(Liu et al., 2021a, 2021b)
Lithocarpinols A–B (**281** ~ **282**)	*Phomopsis lithocarpus* FS508		Cytotoxic (**281**)	(Xu et al., 2019a, 2019b)
Tenellones C–D (**283–284**)	*Diaporthe* sp. SYSU-HQ3	*Excoecaria agallocha*	Anti-inflammatory (**283**)	(Cui et al., 2018)
Tenllone I (**285**)	*Diaporthe lithocarpus* A740	*Morinda officinalis*	–	(Liu et al., 2019)
Tenellones D–H (**286–290**)	*Phomopsis lithocarpus* FS508	Deep-sea sediment sample	Cytotoxic (**290**)	(Xu et al., 2018a, 2018b)
Diaporthols A–B (**291** –**292**)	*Diaporthe* sp. ECN-137	*Phellodendron amurense*	Cytotoxic	(Nakashima et al., 2018)
Phomopsinin A (**293**)	*Phomopsis* sp. CAM212	*Garcinia xanthochymus*	–	(Jouda et al., 2020)
Compound **294**	*Phomopsis* sp. CAM212	*Garcinia xanthochymus*	Anti-inflammatory	(Jouda et al., 2020)
Compounds **295–297**	*Phomopsis fukushii*	*Paris polyphylla* var. *yunnanensis*	Antibacterial	(Gao et al., 2019)
Diapolic acids A–B (**304–305**)	*Diaporthe terebinthifolii*	*G. glabra*	–	(Yedukondalu et al., 2017)
Eucalyptacid A (**306**)	*Diaporthe eucalyptorum*	*Melia azedarach*	Antibacterial	(Gao et al., 2020a)
Eucalactam B (**307**)	*Diaporthe eucalyptorum*	*Melia azedarach*	–	(Gao et al., 2020b)
Diaporthsins A–K (**308** –**318**)	*Diaporthe* sp. JC-J7	*Dendrobium nobile Lindl*	Antihyperlipidemic (**312**)	(Hu et al., 2018a, 2018b)
Diaporthesters A–D (**319–322**)	*Diaporthe* sp. T24	*Ligularia fischeri*	Cytotoxic (**319**)	(He et al., 2021)
Diaportheolides A–B (**323** –**324**)	*Diaporthe* sp. SXZ-19	*Camptotheca acuminata*	–	(Liu et al., 2021a, 2021b)
Lithocarpins A–G (**325** –**331**)	*Phomopsis lithocarpus* FS508	Marine sediment	Cytotoxic (**327–329**)	(Xu et al., 2018a, 2018b), (Xu et al., 2021a, 2021b)

properties were recently investigated for their effects on significant human disorders.

2.1. Quinones

Quinones and anthraquinones are widely found in nature, primarily in microorganisms and plants. Their pharmacological activities include antitumor, anti-inflammatory, anti-HIV (human immunodeficiency virus), antioxidant, antiviral, antibacterial, and other related activities. The drugs on the market with a quinone structure with antitumor effects include mitomycin and adriamycin.

A novel anthraquinone dimer derivative with a cage skeleton known as *epi*-cytoskyrin A (**1**) and its derivative, cytoskyrin C (**2**) were isolated from *Diaporthe* sp. ARL-09, an endophytic fungus of the Jewel orchid (*Anoectochilus roxburghii*) (Tian et al., 2018) (Fig. 3). Biatriosporin N (**3**), a new quinone derivative isolated from the endophytic fungus *Diaporthe vochysiae*, inhibited nitric oxide (NO) production by RAW 264.7 cells exposed to lipopolysaccharide (LPS) with an IC_{50} (the concentration at which NO production is repressed by 50%) value of 11.5 μM (positive control drug indomethacin, IC_{50} = 29.7 μM) (Liu et al., 2019a). Two new benzoquinone compounds, epoxyquinophomopsin A and B (**4** and **5**), were isolated from the fermentation products of the deciduous tree *Morus cathayana* infected by the endophytic fungus *Phomopsis* sp. Compound **4** significantly inhibited Bruton's tyrosine kinase (BTK) activity (Hermawati et al., 2021). New anthraquinone derivatives **6** and **7** were identified in the fermentation products of rice (*Oryza sativa*) infected by *Phomopsis* sp. This endophytic fungus is found in tobacco (*Nicotiana tabacum*) (Wu et al., 2021). These two compounds showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). (See Figs. 4-7)

2.2. Alkaloids

Alkaloids are a class of nitrogen-containing organic compounds that widely exist in plants, microorganisms, and animals (Mishra et al., 2017). A total of 68 alkaloids was isolated from fungi of the genus *Diaporthe* (*Phomopsis*) (Fig. 1), accounting for 20.5% of the total compounds recently identified. Their major activities include antibacterial, anti-inflammatory, and cytotoxic properties.

2.2.1. Alkaloids isolated from Diaporthe

Diaporisoindoles A–E (**8**–**12**) were discovered among the metabolites of the endophytic fungus *Diaporthe* sp. SYSU-HQ3, which originated from mangroves (Cui et al., 2017b, 2018). Compounds **8** and **9** are novel isoprene isoindole alkaloids, and compound **10** is a unique dimer of an isoprene isoindole alkaloid. Compound **8** showed significant inhibitory activity against protein tyrosine phosphatase B of *Mycobacterium tuberculosis*, with IC_{50} values of 4.2 μM, whereas compounds **9** and **10** showed inhibitory activity against NO production, with IC_{50} values of 22.7 μM and 18.2 μM, respectively. Diaporphasines A–D (**13**–**16**) and two new isoindolinones, meyeroguillines C–D (**17**, **18**), were discovered in the metabolites of *Diaporthe phaseolorum* SKS019 (Cui et al., 2017c), which was originally derived from holy mangrove (*Acanthus ilicifolius*). These compounds were tested on five tumor cell lines and showed no significant inhibitory effects. Two new cytorelaxin derivatives (**19**, **20**) were identified in the metabolites of the endophytic fungus *Diaporthe* sp. GDG-118 from the traditional Chinese medicine herb *Sophora tonkinensis* (Huang et al., 2019). Compound **20** showed significant activity against *Bacillus anthracis* and *Escherichia coli*, with a MIC (minimum inhibitory concentration, allowing complete inhibition of bacterial growth) value of 12.5 μg/mL. Three novel cytosolasin alkaloid derivatives, diaporthichalasins A–C (**21**–**23**), were identified in the metabolites of the endophytic fungus *Diaporthe* sp. GZU-1021 (Liu et al., 2019a). These compounds inhibited NO production in LPS-induced RAW 264.7 cells.

Five novel cytoflasin derivatives, diaporthichalasins D–H (**24**–**28**), were identified in the fermentation metabolites of the endophytic fungus *Diaporthe* sp. SC-J0138 (Yang et al., 2020a, 2020b), which was derived from parasitic maiden fern (*Cyclosorus parasiticus*). Compounds **24**–**28** demonstrated varying degrees of cytotoxicity against A549, HeLa, HepG2, and MCF-7 tumor cells. Surprisingly, compounds **24** and **28** showed strong cytotoxic activity against HepG2 cells, with IC_{50} values of 8.8 ± 1.7 μM and 9.9 ± 1.6 μM, respectively.

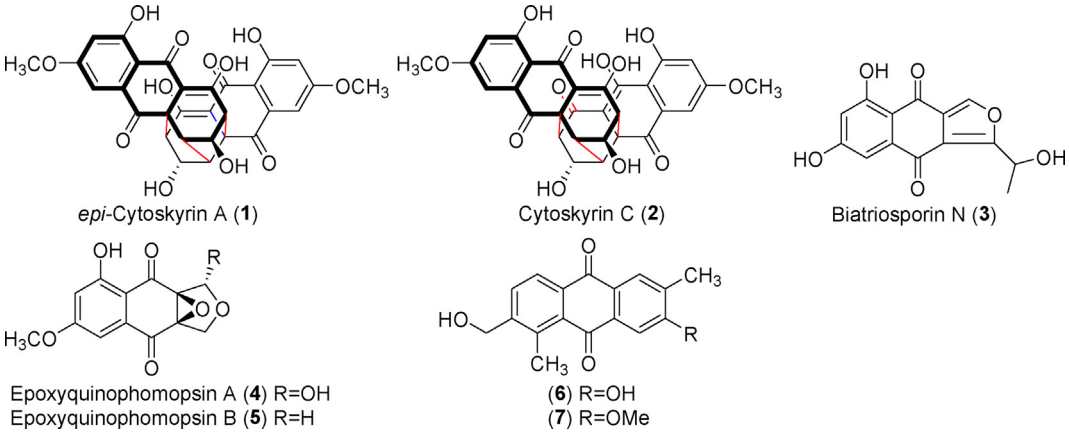

Fig. 3 Anthraquinones isolated from *Diaporthe* and *Phomopsis* (**1**–**7**).

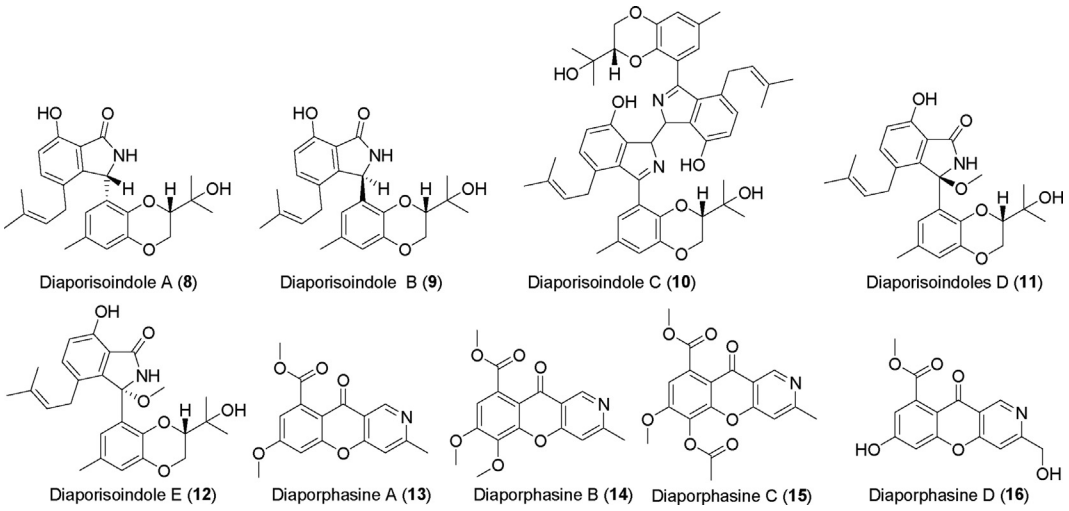

Fig. 4 Alkaloids isolated from fungi of the genus *Diaporthe* (**8–16**).

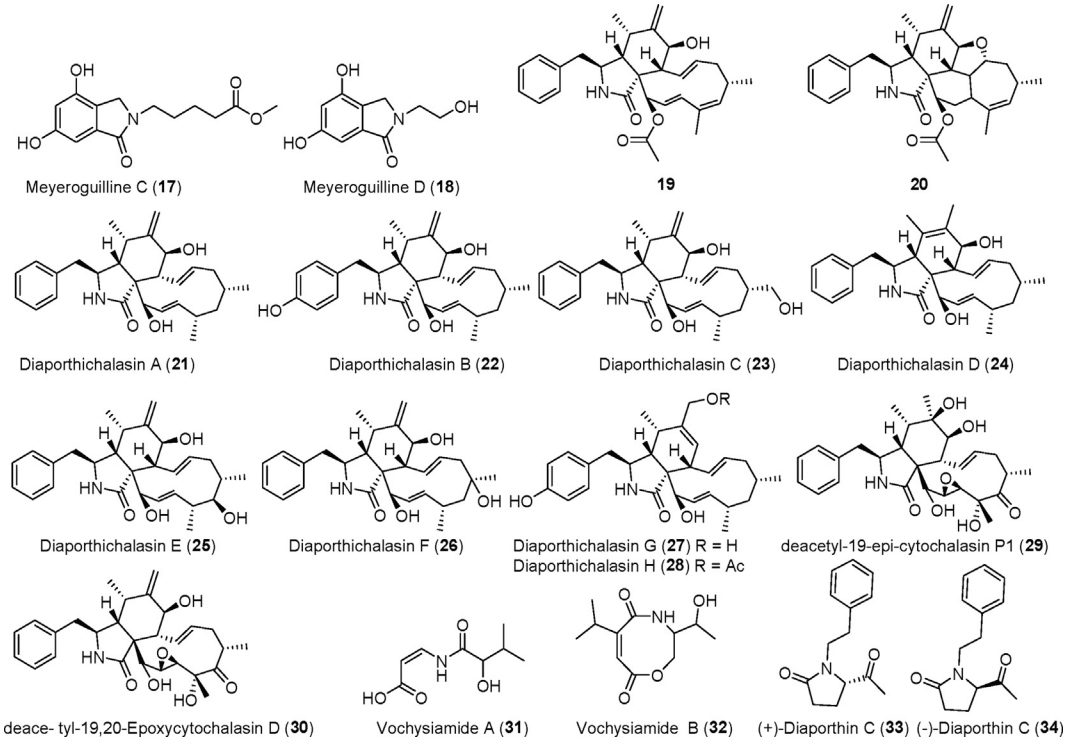

Fig. 5 Alkaloids isolated from fungi of the genus *Diaporthe* (**17–34**).

Two new cytochalasin alkaloids, deacetyl-19-*epi*-cytochalasin P1 (**29**) and deacetyl-19, 20-epoxycytochalasin D (**30**), were identified in the fermentation metabolites of the endophytic fungus *Diaporthe* sp. RJ-47 (Yan et al, 2021); compound **29** showed antibacterial activity. Two new alkaloid derivatives, vochysiamides A and B (**31**, **32**), were identified in the metabolites of the newly identified endophytic fungus *Diaporthe vochysiae* (Noriler et al., 2019). Compound **32** showed certain activity against *Klebsiella pneumoniae*. A new pair of pyrrolidone derivatives (±), diaporthin C (**33, 34**), were identified in the fermentation products of the endophytic fungus *Diaporthe phragmitis* from kiwi (*Actinidia chinensis*) (Yu et al., 2021a, 2021b); these compounds did not show any significant antibacterial activity.

2.2.2. Alkaloids isolated from Phomopsis

Five cytochalasins, J1–J3 (**35–37**) and H1–H2 (**38**, **39**), were identified in the metabolites of *Phomopsis* sp. CMB-M0042F (Shang et al., 2017), which originated from marine sediments. Compounds **35** and **36** have rare 5/6/6/7/5 four-ring fused skeletons, and compounds **37** and **39** have rare 5/6/5/8 ring systems. Compounds **35–39** exhibited significant cytotoxic activity against the human cell lines SW620, NCI-H460, HepG2, and HEK, with IC_{50} values of 0.1 μM to 12.9 μM.

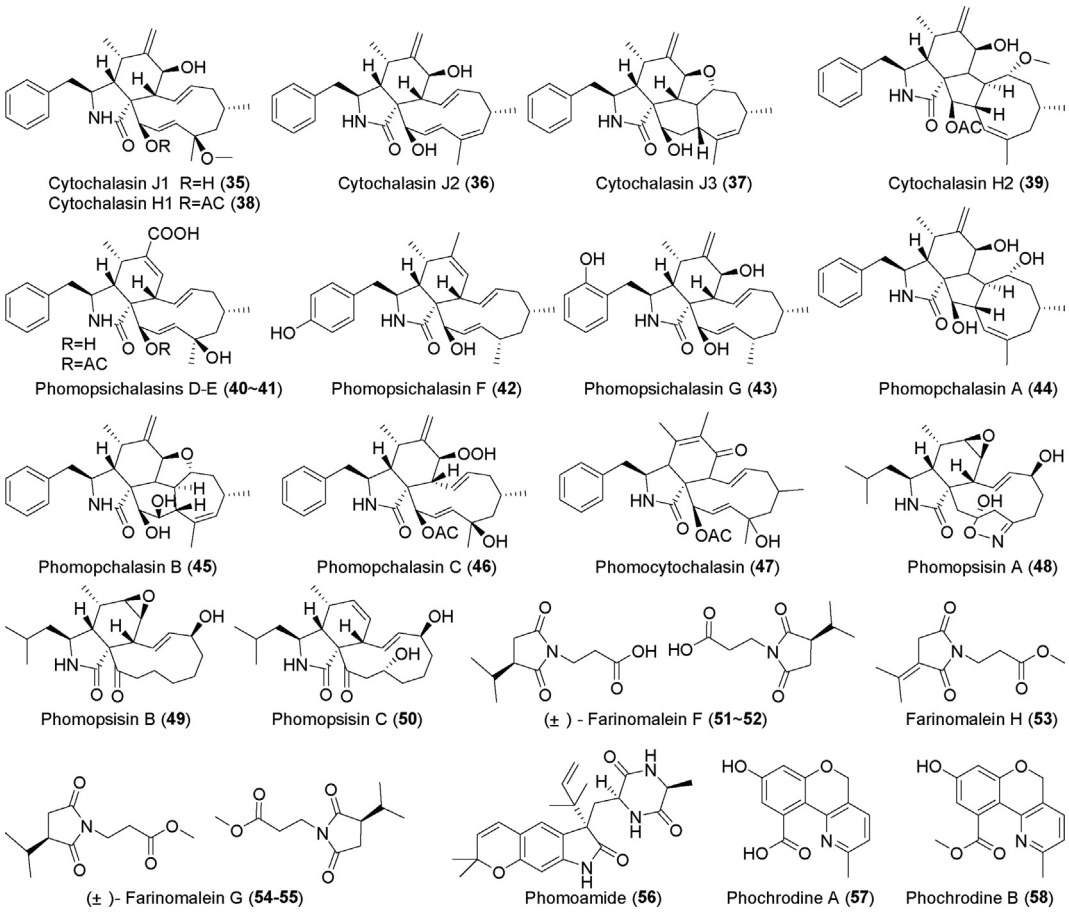

Fig. 6 Alkaloids isolated from fungi of the genus *Phomopsis* (**35–58**).

Four new alkaloid cytochalasin derivatives, phomopsichalasins D–G (**40–43**), were identified in the metabolites of the endophytic fungi *Phomopsis* sp. xy21 and xy22 originating from mangrove plants (Luo et al., 2016). These compounds showed significant cytotoxic activity against five tumor cell lines, HCT-8, HCT-8/T, A549, MDA-MB-231, and A2780, with IC_{50} values of 7.5 μM, 8.6 μM, 6.4 μM, 3.4 μM, and 7.1 μM, respectively. Three new alkaloid derivatives, phomopchalasins B–D (**44–46**), were identified in the metabolites of the endophytic fungus *Phomopsis* sp. shj2 derived from the medicinal plant *Isodon eriocalyx* var. laxiflora (Yan et al., 2016); compound **44** has a unique 5/6/5/8 tetracyclic thickened skeleton, whereas compound **45** has a novel 5/6/6/7/5 pentacyclic thickened skeleton. Compound **45** showed moderate cytotoxic activity against HL-60, SMMC-7721, and A-549 cells, with IC_{50} values of 14.9 μM, 22.7 μM, and 21.1 μM, respectively. Compound **46** showed inhibitory activity against NO production by LPS-induced RAW 264.7 cells, with an IC_{50} value of 11.2 μM.

Phomocytochalasin (**47**), a novel alkaloid, was discovered in the metabolites of *Phomopsis theicola* BCRC 09F0213 (Hsiao et al., 2016). Three novel leucine-derived cytochalasin alkaloids, phomopsisins A–C (**48–50**), were identified in the fermentation metabolites of the endophytic fungus *Phomopsis* sp. sh917 derived from *Isodon eriocalyx* var. laxiflora (Tang et al., 2020); compound **48** is a cytochalasin compound with a rare 2H–*iso*-xazole group, and compound **50** was shown to inhibit NO production. Maleamide derivatives (±)-farinomalein F (**51–52**), (±)-farinomalein G (**53–54**), farinomalein H (**55**), and one new linearly fused prenylated indole alkaloid phomoamide (**56**) were found in the metabolites of the endophytic fungus *Phomopsis* sp. SYSU-QYP-23, which originated from the mangrove plant *Kandelia candel*. (±)-farinomalein G (**53–54**), farinomalein H (**55**), and phomoamide (**56**) showed no significant anti-inflammatory activity (Y. Chen et al., 2020a, 2020b, 2020c, 2020d).

Four new tryptopyridine derivatives, phochrodines A–D (**57 –60**), were identified in the metabolites of *Phomopsis* sp.33#, an endophytic fungus found in mangrove forests (Chen et al., 2018). There was no evidence of significant anti-inflammatory, antioxidant, or cytotoxic activities. Phomopsol A (**61**), a highly oxidized alkaloid polyketide, was found in the metabolites of *Phomopsis* sp. xy21 (Li et al., 2019), but there are no reports of its activity. Seven new pyridinone derivatives, (±)-tersones A–E (**62–71**) and tersones F-G (**72–73**), were discovered in the metabolites of the deep-sea fungus *Phomopsis tersa* FS441 (Chen et al., 2019). Compounds **62–65** have a rare 6/6/5/5 ring system. Neither antibacterial nor cytotoxic activities were detected for these compounds. Prenylcyclotryprostatin A (**74**) and 7-hydroxy-*cis*-L(-)-3,6-dibenzyl-2,5-dioxopiperazine (**75**), two new diketopiperazine alkaloids isolated from the fermentation metabolites of *Phomopsis asparagi* CICC2706, showed no significant inhibitory activity against glucosidase (Zhou et al., 2021).

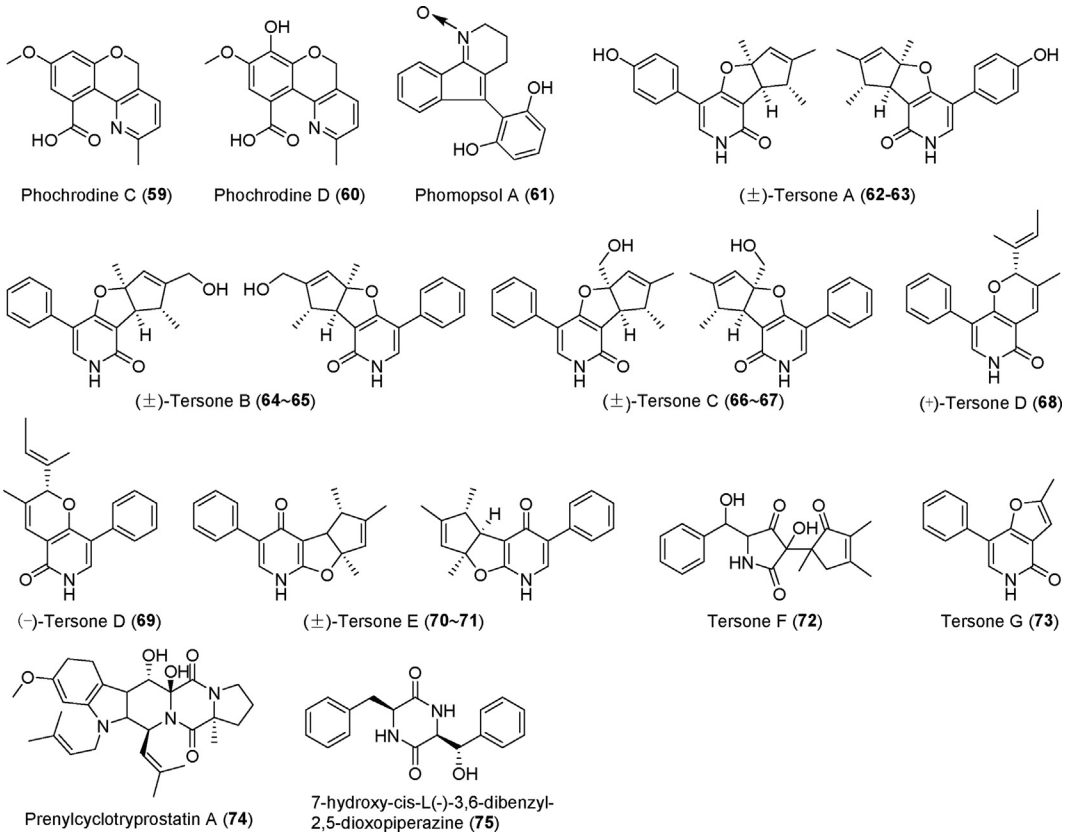

Fig. 7 Alkaloids isolated from fungi of the genus *Phomopsis* (**59**–**75**).

2.3. Terpenoids

Terpenoids, the most abundant natural organic compounds based on isoprene, are found in plants, fungi, and other organisms. Monoterpenes, sesquiterpenes, diterpenes, and triterpenes are the most common types of terpenoids. Fifty-eight terpenoids were isolated from fungi of the genus *Diaporthe* (*Phomopsis*) between 2016 and 2021, accounting for 17.5% of all metabolites (Figs. 8–11). Terpenoids have significant cytotoxic activity, α-glycosidase inhibitory activity, and an anti-inflammatory effects.

2.3.1. Terpenoids isolated from fungi of the genus Diaporthe

Two new eremophilane derivatives, lithocarins B–C (**76**, **77**), and the new monoterpenoid lithocarin D (**78**) were isolated from the endophytic fungus *Diaporthe lithocarpus* A740 (Liu et al., 2019), which originated from the medicinal plant Indian mulberry (*Morinda officinalis*). Compounds **76**–**78** showed weak inhibitory activity against HepG-2, MCF-7, SF-268, and A549 tumor cells. The new diterpenoid diaporpenoid A (**79**) and two new sesquiterpenoids B–C (**80**, **81**) were discovered in the fermentation products of *Diaporthe* sp. QYM12 (Yan et al, 2021). Compound **79** inhibited NO production

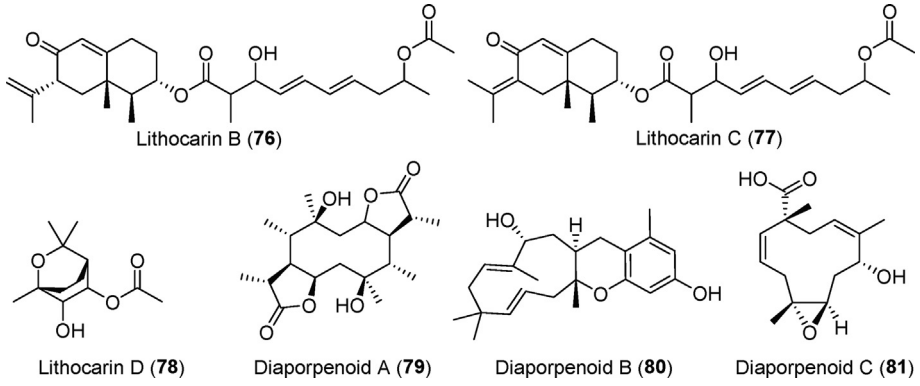

Fig. 8 Terpenoids isolated from fungi of the genus *Diaporthe* (**76**–**81**).

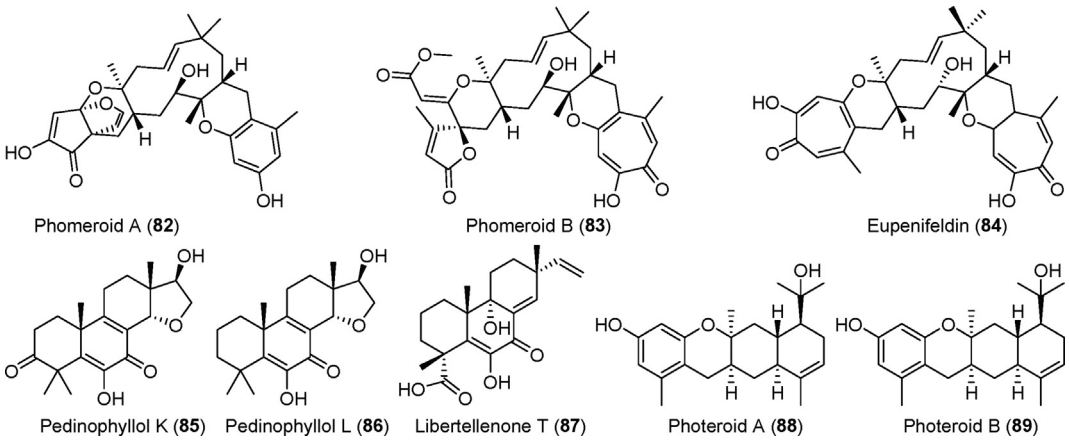

Fig. 9 Terpenoid derivatives isolated from fungi of the genus *Phomopsis* (**82–89**).

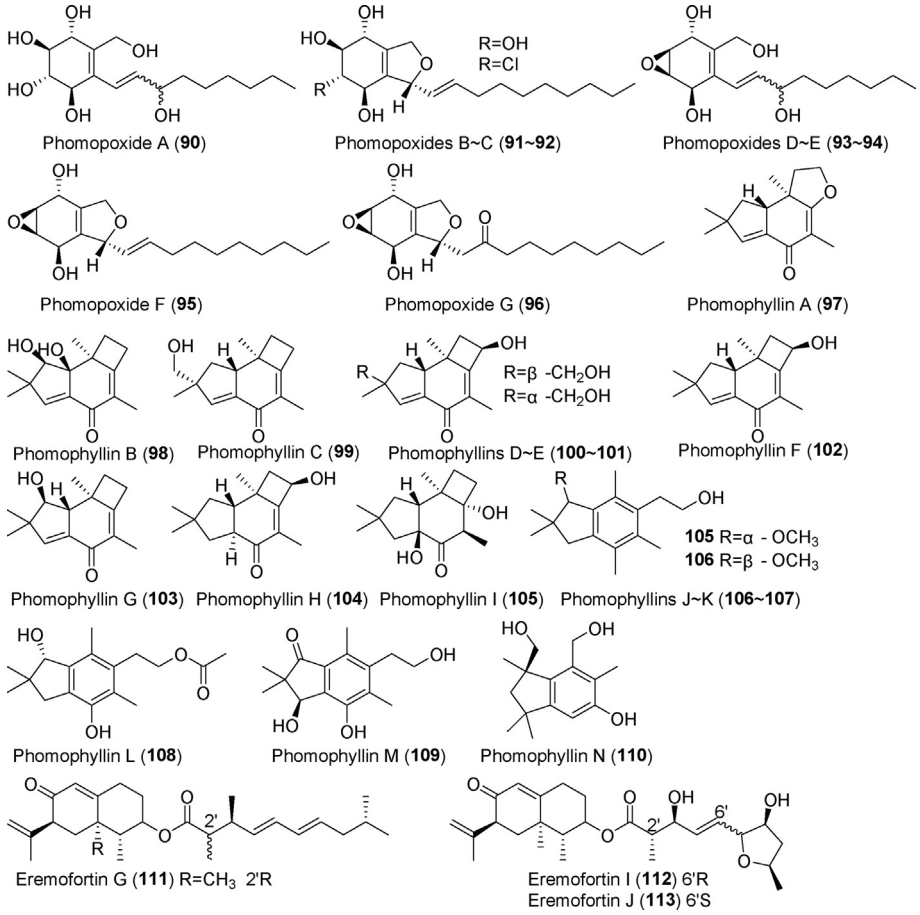

Fig. 10 Terpenoid derivatives isolated from fungi of the genus *Phomopsis* (**90–113**).

from LPS-induced RAW264.7 cells, with an IC_{50} value of 21.5 μM.

2.3.2. Terpenoids from Phomopsis fungi

Two terpenoids with new types of skeletons, phomeroid A and B (**82–83**), were isolated from the deep-sea-derived fungus *Phomosis tersa* FS441, along with one known terpenoid, eupenifeldin (**84**) (Chen et al., 2020a, 2020b, 2020c, 2020d). Compound **82** is a sesquiterpenoid derivative with a 6/6/11/6/5/5 ring; compound **83** is a sesquiterpenoid derivative with a unique 7/6/11/6–5 screw ring. Compound **83** showed significant inhibitory activity against HepG-2, MCF-7, SF-268, and A549 tumor cells, with IC_{50} values of 0.5 μM, 0.3 μM, 1.0 μM, and 1.1 μM, respectively. A study of three new diterpenoids, pedinophyllol K (**85**), pedinophyllol L (**86**), and libertellenone T (**87**), and two known compounds from metabolites of the

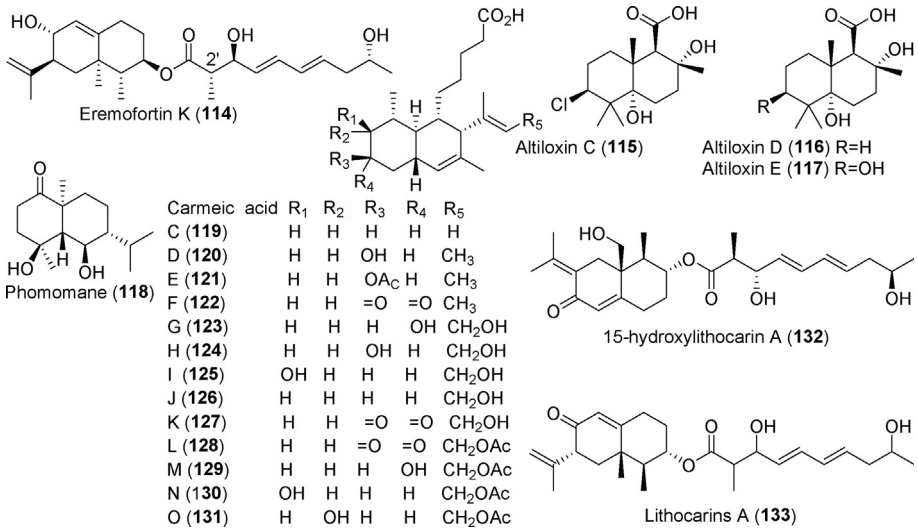

Fig. 11 Terpenoid derivatives isolated from fungi of the genus *Phomopsis* (**114**–**133**).

endophytic fungus *Phomopsis* sp. S12 (Xu et al., 2019a, 2019b) showed that compound **87** had anti-inflammatory activity against RAW 264.7 cells incubated with LPS. Two photeroids, A–B (**88**, **89**), with a 6/6/6/6 tetracyclic highly dense skeleton, were isolated from the deep-sea fungus *Phomopsis tersa* FS441 (Chen et al., 2020b). These compounds had inhibitory activity against SF-268, MCF-7, HepG-2, and A549 tumor cells, with IC_{50} values between 20 μM and 26 μM.

Seven new polyoxygenated cyclohexenoids, phomopoxides A–G (**90**–**96**), were isolated from the fermentation broth extract of the endophytic fungus *Phomopsis* sp. YE3250 from the medicinal plant Delavay's tree peony (*Paeonia delavayi* Franch) (Huang et al., 2018). Phomopoxides A–C (**90**–**92**) inhibited glucosidase activity in a manner similar to that of acarbose. Thirteen new sesquiterpenoids, phomophyllins A–N (**97**–**110**), were discovered in the metabolites of the endophytic fungus *Phomopsis* sp. TJ507 from *Phyllanthus glaucus* (Xie et al., 2018). Compound **97** showed an excellent inhibitory effect on β-site amyloid precursor protein lyase 1 (BACE1) and no hepatotoxicity. Eight new sesquiterpenoids, eremofortin G (**111**), eremofortins I–K (**112**–**114**), altiloxins C–E (**115**–**117**), and phomomane (**118**), were obtained from the fermentation metabolites of *Phomopsis* sp. SYSU-QYP-23, which was derived from the mangrove species *Kandelia candel* (Chen et al., 2021a, 2021b). These compounds showed a potent inhibitory effect on NO production by LPS-induced RAW 264.7 cells, with an IC_{50} value of 8.6–14.5 μM. Thirteen new sesquiterpenoid acid derivatives, carneic acids C—O (**119**–**131**), were isolated from the fermentation metabolites of *Phomopsis* sp. SNB-LAP1-7–32 (Peyrat et al., 2020), an endophytic fungus derived from *Diospyros carbonaria*. Five of these compounds significantly inhibited dengue polymerase activity, with IC_{50} values ranging from 10 μM to 20 μM with no cytotoxicity. The novel sesquiterpenoid 15-hydroxylithocarin A (**132**) was identified in the fermentation metabolites of *Phomopsis asparagi* CICC 2706 (Shi et al., 2020); this compound did not inhibit glucosidase activity. Lithocarin A (**133**) is a new sesquiterpenoid isolated from metabolites of *Phomopsis lithocarpus* FS508, a fungus isolated from deep-sea sediment (Xu et al., 2018a, 2018b). This compound showed weak inhibitory activity against HepG-2, MCF-7, SF-268, and A549 cells.

2.4. Pyrones

Pyrone, an active group present in some drugs, is divided into two types: α-pyrone and γ-pyrone. Between 2016 and 2021 (Figs. 12–14), 79 compounds were discovered in this genus of fungi, accounting for 23.9% of the total identified compounds.

2.4.1. Pyrones isolated from fungi of the genus Diaporthe

Three pyrone derivatives (**134**–**136**) were identified from metabolites of the endophytic fungus *Diaporthe* sp. F2934 (Sousa et al., 2016). No obvious antibacterial activity was found. Seven novel chromogenone derivatives, diaporchromanones A–D (**137**–**140**), (–)-phomopsichin A (**141**), (+)-phomopsichin B (**142**), and (±)-diaporchromone A (**143**), were found in the metabolites of the endophytic fungus *Diaporthe phaseolorum* SKS019 (Cui et al., 2017a). These compounds moderately inhibited NF-kappaB (NF-κB) activity in RANKL (receptor activator of NF-κB ligand)-induced RAW 264.7 cells. Five new chromogenone derivatives, phaseolorins A–F (**144**–**149**), were identified in the metabolites of the deep-sea fungus *Diaporthe phaseolorum* FS431 (Guo et al., 2019), but they displayed weak cytotoxic activity. Two pyrone derivatives, phaseolorin G and H (**150**–**151**), were isolated from the metabolites of the deep-sea fungus *Diaporthe phaseolorum* FS431 (Niu et al., 2019). These compounds showed weak inhibitory activity against MCF-7, HepG-2, and A549 tumor cells. Phomolide A (**152**), a compound discovered in the metabolites of *Phomopsis* sp. CFS42 (Ma et al., 2020), showed no biological activity. Pestalotiopsone H (**153**) and methyl convolvulopyrone (**154**), two previously unreported chrogenic ketone derivatives, were identified in the metabolites of *Diaporthe* sp. SCSIO 41011 (Luo et al., 2018b). No obvious inhibitory effect against the influenza A virus was detected.

Three previously unknown diaporpyran derivatives (**155**–**157**) were identified in the fermentation metabolites of *Diaporthe* sp. QYM12 (Yan et al, 2021). Compound **155** showed

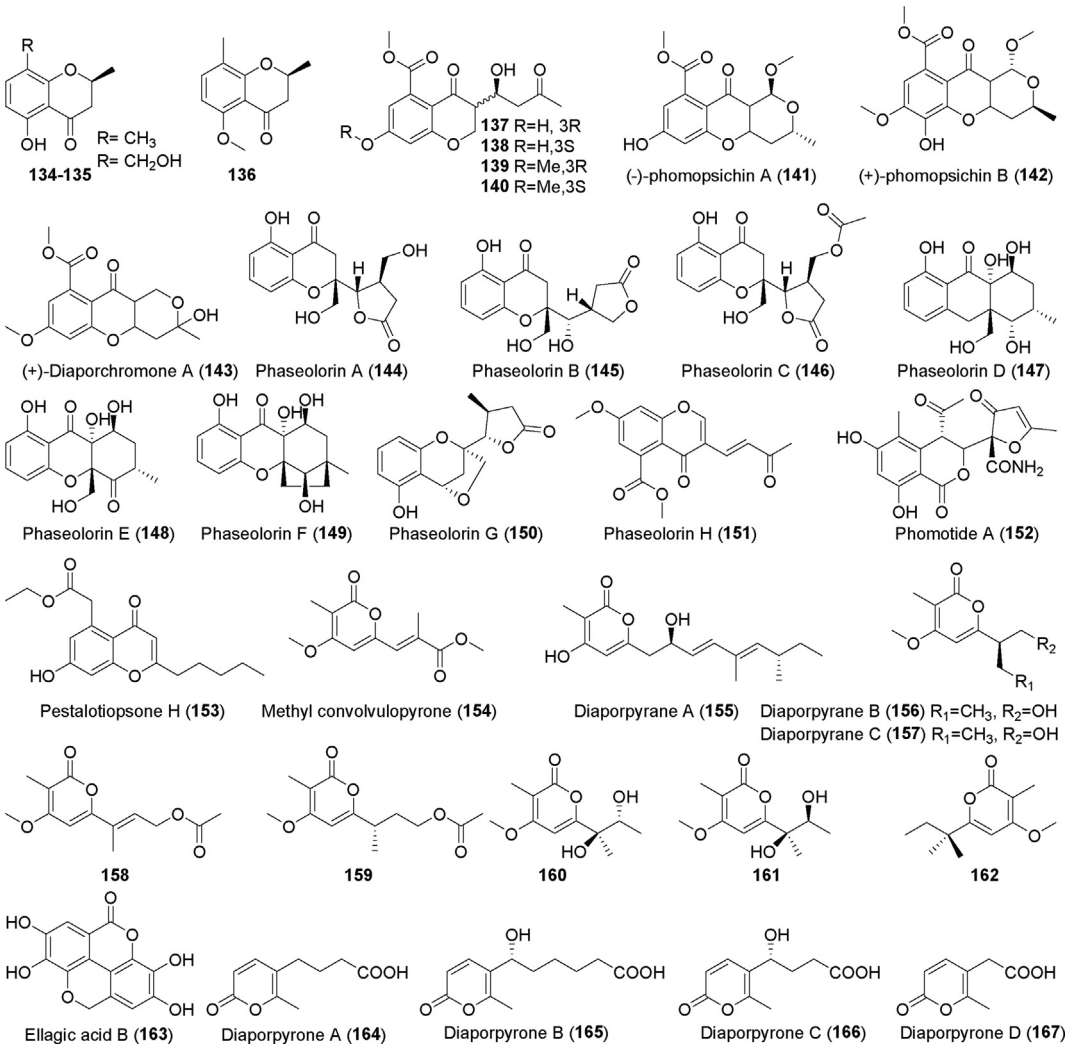

Fig. 12 Pyrone derivatives isolated from fungi of the genus *Diaporthe* (**134–167**).

anti-inflammatory activity, with an IC_{50} value of 12.5 μM. Four derivatives of 2-pyrone (**158–162**), including a pair of enantiomers (**160** and **161**), were isolated from rice fermentation products of the endophytic fungus *Diaporthe foeniculina* BZM-15, which was derived from the weeping tea tree (*Leptospermum brachyandrum*) (Yu et al., 2021a, 2021b). These compounds showed no significant cytotoxic activity against SF-268, MCF-7, or HepG-2 tumor cells. Five new pyrone derivatives are produced by the endophytic fungus *Diaporthe* sp. CB10100, which was derived from *Sinomenium acutum* (Thunb.) (Pu et al., 2021). Among these, the novel dibenzo α-pyrone derivative ellagic acid B (**163**) and four α-pyrones, diaporpyrones A–D (**164–167**) showed no obvious inhibitory activity against cyclooxygenase (COX-2) or inducible nitric oxide synthase (iNOS). Three new tryptophan derivatives (**168**, **169,** and **172**) and a pair of new heteroisomer mixtures (**170** and **171**) were obtained from rice fermentation products of the deep-sea-derived fungus *Diaporthe phaseolorum* FS459 (Hu et al., 2021). Compounds **168–171** have rare 2′,3′-dime thyl-dioxopentyl structures. No significant activity was observed *in vitro*. Eight novel cyclohexanone derivatives, foeniculins A–H (**173–183**), were identified from rice fermentation products of the endophytic fungus *Diaporthe foeniculina* SCBG-15, which was derived from *Leptospermum brachyandrum* (Lu et al., 2021). Three novel phenolic acid derivatives, foeniculins I–K (**181–183**), showed moderate cytotoxic activity against SF-268, MCF-7, and HepG-2 tumor cells, with IC_{50} values of 27.73 μM, 42.54 μM, and 25.12 μM, respectively.

2.4.2. Pyrones isolated from fungi of the genus Phomopsis

Five new pyranoid ketone derivatives, phomaspyrones A–E (**184–188**), were found in the metabolic products of the endophytic fungus *Phomopsis asparagi* SWUKJ5.2020 (Song et al., 2017), which was derived from the evergreen shrub *Kadsura angustifolia*. Compound **186** showed significant cytotoxic activity against various cancer cell lines, which include A549, Raji, HepG2, MCF-7, HL-60 and K562, with IC_{50} values of 1.2, 2.0, 1.6, 2.2, 1.0, and 1.2 μg/mL. Four previously unreported pyrone derivatives, phomopsichins A–D (**189–192**), were identified in the metabolites of the endophytic fungus *Phomopsis* sp. 33# from mangrove forests (Huang et al., 2016). These four compounds failed to inhibit α-glucosidase and showed no antibacterial or cytotoxic properties. Two new pyranone derivatives, (10S)-10-O-B-D-40-methoxy

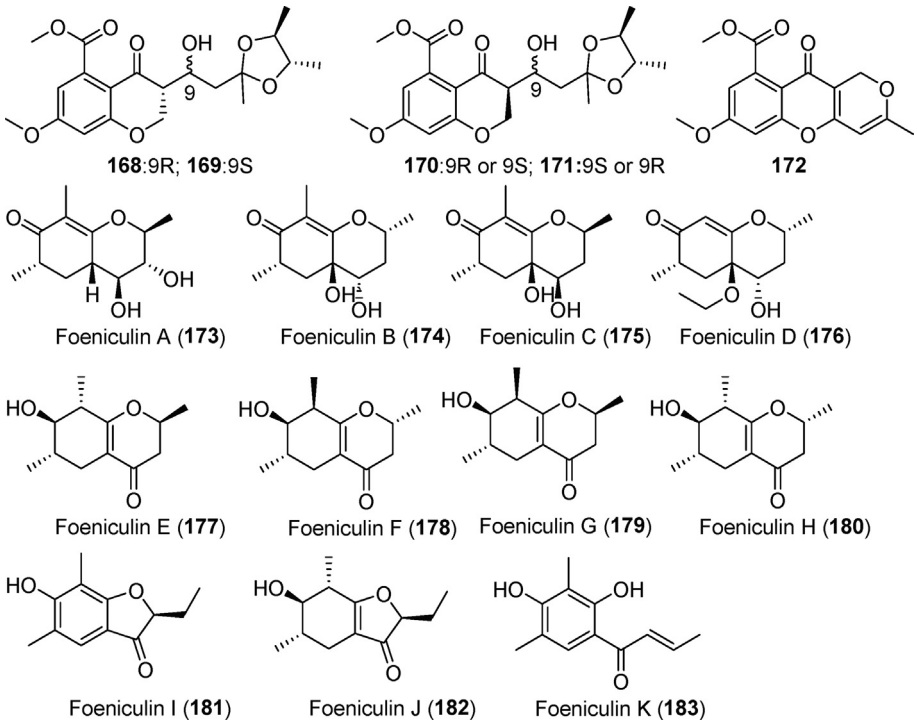

Fig. 13 Pyrone derivatives isolated from fungi of the genus *Diaporthe* (**168**–**183**).

manno-pyranosyldiaporthin (**193**) and clearanol H (**194**), were identified in the metabolites of the endophytic fungus *Phomopsis* sp. sh917, which was derived from *Isodon eriocalyx* var. laxiflora. These compounds showed no significant antiangiogenic activity (Tang et al., 2017). Three pyrone derivatives, phomochromenones A–C (**195**–**197**), were isolated from metabolites of the endophytic fungus *Phomopsis* sp. HNY29-2b, which was derived from the mangrove plant *Acanthus ilicifolius* Linn (Ding et al., 2017). Six new pyrone derivatives, phomoxanthones F–K (**198**–**203**), were identified in the metabolites of the endophytic fungus *Phomopsis* sp. xy21 (Hu et al., 2018a, 2018b). Among these, compounds **199** and **200** are highly oxidized xanthones. No cytotoxic activity was detected against tumor cell lines.

Two previously undescribed pyrone derivatives, phomoisocoumarins C and D (**204**–**205**), are metabolites of the endophytic fungus *Phomopsis prunorum* (Qu et al., 2020); phomoisocoumarin D (**205**) showed antibacterial activity. Phomotide A (**206**) is a previously unreported pyranone derivative from the metabolites of the endophytic fungus *Phomopsis* sp. CFS42 of Chinese plum yew (*Cephalotaxus fortunei* Hook) (Ma et al., 2020); this compound showed no significant antimicrobial activity. Phomopsinin B and C (**207**, **208**) are novel pyrone natural products derived from fermentation metabolites of *Phomopsis* sp. CAM212. These compounds showed no anti-inflammatory properties.

Two novel pyrone natural products, phomopsinin B and C (**207**, **208**), were identified in the fermentation metabolites of the endophytic fungus *Phomopsis* sp. CAM212 (Jouda et al., 2020), which originated from the medicinal plant gamboge (*Garcinia xanthochymus*). These compounds did not appear to have any anti-inflammatory properties. Four new chromenones, phomochromenones D–G (**209**–**212**), were obtained from rice fermentation products of *Phomopsis asparagi* DHS-48, which was derived from the Chinese mangrove plant *Rhizophora mangle* (Wei et al., 2021). These compounds showed no obvious immunosuppressive activity.

2.5. Polyketides

2.5.1. Polyketides isolated from fungi of the genus Diaporthe

Nine new polyketide compounds, acetoxydothiorelone B (**213**), (15S)-acetoxydothiorelone A (**214**), dothiorelone K–N (**215**–**218**), 5-hydroxy-7-methoxy-4,6-dimethyl-2-phenyliso in doline-1,3-dione (**219**), (13R)-diaporphthalide A (**220**), and (9S, 17R, 19S, 6Z, 10E, 14E)-diaporlactone A (**221**) were identified in the metabolites of the endophytic fungus *Diaporthe pseudomangiferaea* from the medicinal plant Indian Sarsaparilla (*Tylophora ouata*) (Liu et al., 2018) (Fig. 15). These compounds showed no significant cytotoxicity against tumor cell lines. Six new highly oxidized isochromophilones, A–F (**222**–**227**), were identified in the metabolites of the endophytic fungus *Diaporthe* sp. SCSIO 41011 (Luo et al., 2018a), which was derived from mangrove. Compound **225** inhibited 786-O tumor cell growth, with an IC_{50} value of 8.9 μM.

Isochromophilone G (**228**) is an azaphilone derivative isolated from the endophytic fungus *Diaporthe perseae* of the mangrove plant *Pongamia pinnata* (Niaz et al., 2020). This compound exhibited antibacterial and antioxidant properties. A new azaphilone (**229**) was identified in rice fermentation products of the deep-sea fungus *Diaporthe phaseolorum* FS459 (Hu et al., 2021). No significant cytotoxicity, antibacterial activity, or inhibitory effect on NO production was detected for this compound. Diaportone A (**230**) is a novel γ-butyrolactone derivative isolated from rice fermentation products of *Diaporthe foeniculina* BZM-15, an endophytic fun-

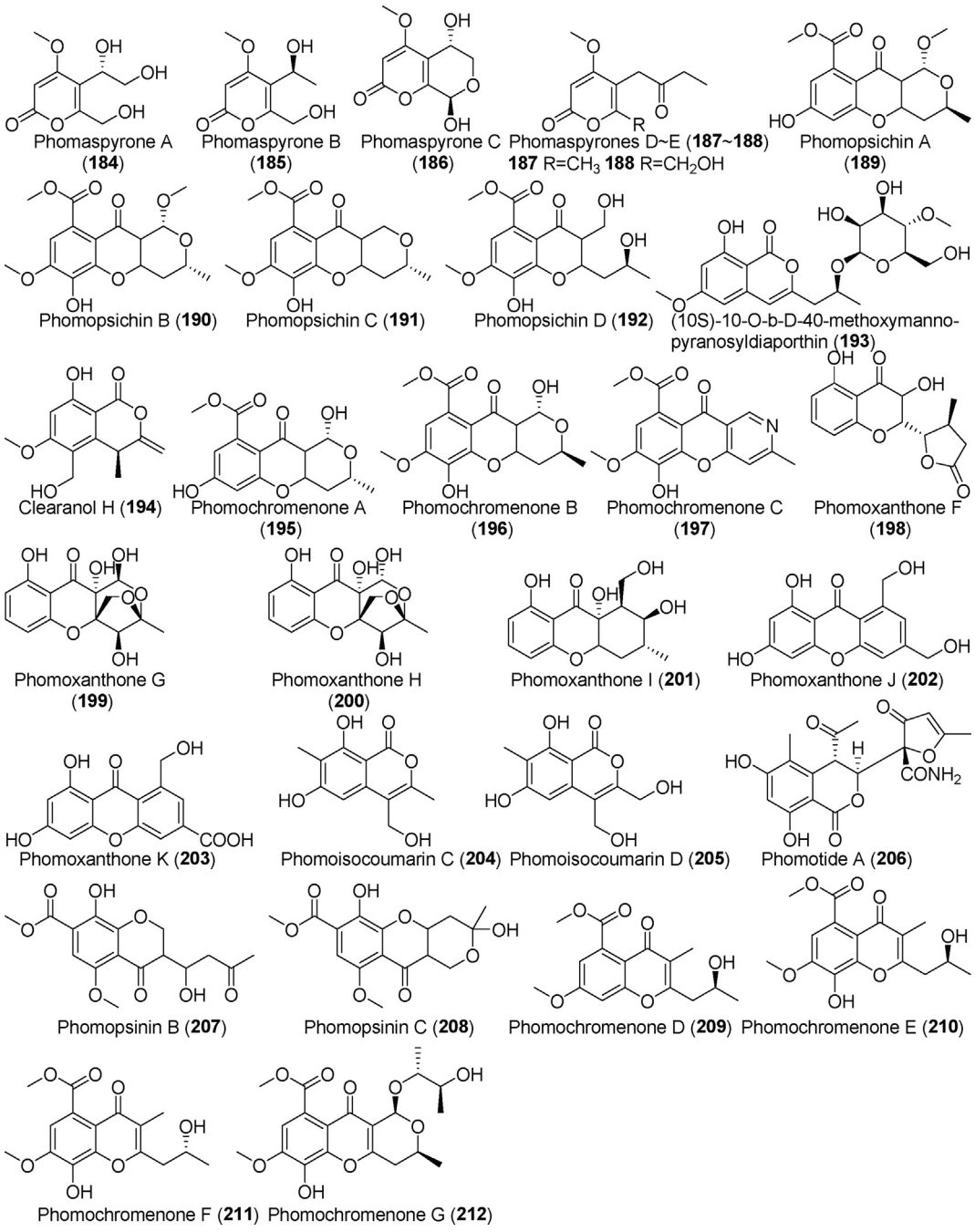

Fig. 14 Pyrone derivatives isolated from fungi of the genus *Phomopsis* (**184**–**212**).

gus derived from *Leptospermum brachyandrum* (Kang et al., 2021).

The novel cyclopentenone derivative diaportone B (**231**) showed no significant antibacterial or cytotoxic properties. Four novel polyketides, dothiorelone O (**232**), (15R)-acetoxydothiorelone A (**233**), microsphaerophthalide H (**234**), and microsphaerophthalide I (**235**) were identified in metabolites of the mangrove fungus *Diaporthe* sp. SCSIO 41011 (Fig. 16) (Luo et al., 2018b). No significant inhibitory effects were detected against influenza A virus. Diaporindenes A–D (**236**–**239**), four new polyketide derivatives with 2,3-dihydro-1H–indene chemical structures, were isolated from the metabolites of *Diaporthe* sp. SYSU-HQ3 (Cui et al., 2018). All four compounds significantly inhibited NO production, with IC_{50} values ranging from 4.2 μM to 9.0 μM.

2.5.2. Polyketides isolated from Phomopsis

Three new polyketides, phomopsiketones A–C (**241**–**243**), were isolated from the metabolites of the endophytic fungus *Phomopsis* sp. sh917 from *Isodon eriocalyx* var. laxiflora (Fig. 17) (Tang et al., 2017). Compounds **241** and **242** showed certain antiangiogenic activities. Two previously unreported polyketides, **244** and **245**, were found in the metabolites of the endophytic fungus *Phomopsis* sp. PSU-H188 from rubber

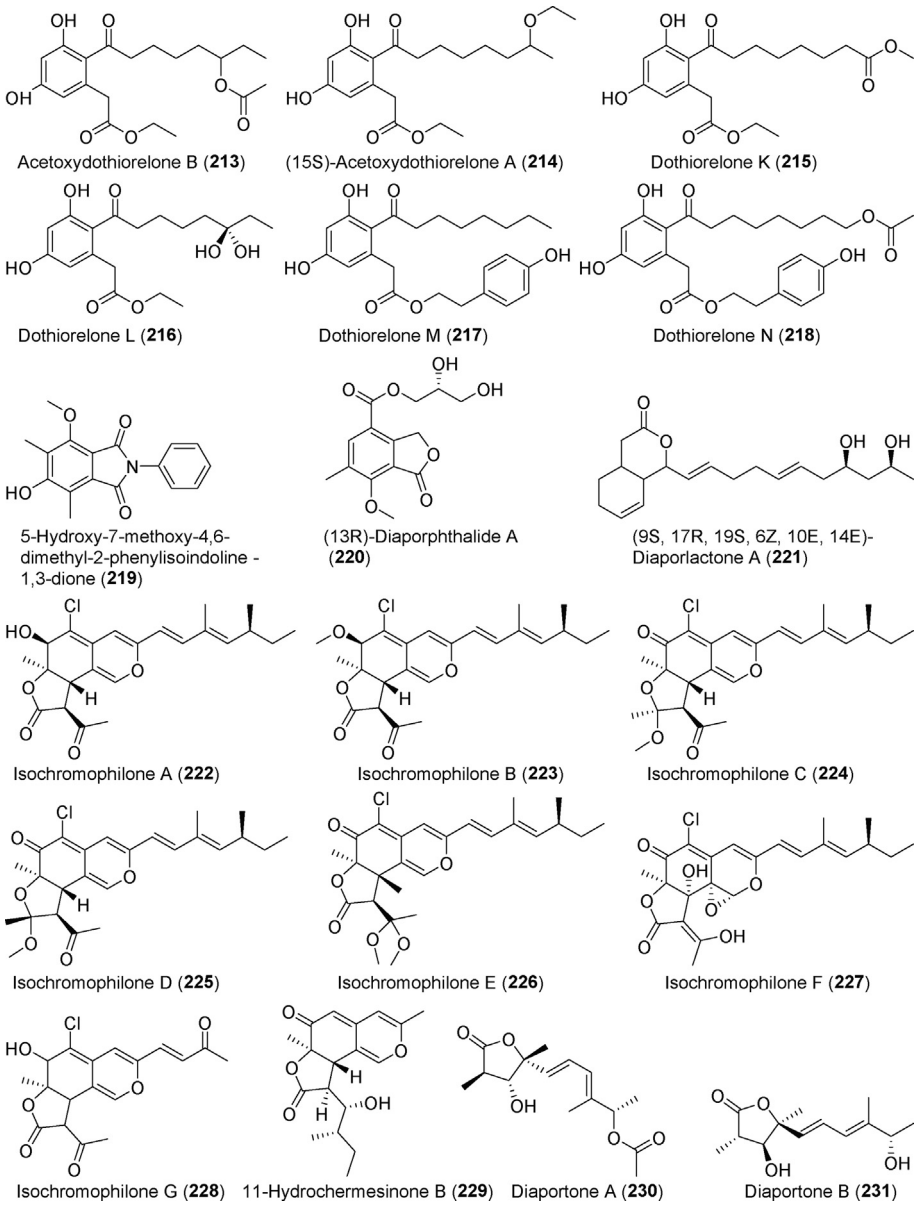

Fig. 15 Polyketides isolated from fungi of the genus *Diaporthe* (**213**–**231**).

tree (*Hevea brasiliensis*) (Kongprapan et al., 2017). These compounds showed no significant antibacterial activity or tumor cytotoxicity. Three new polyketides, phomopones A–C (**246**–**248**), were identified in the metabolites of the endophytic fungus *Phomopsis* sp. D15a2a (Yu et al., 2019), which originated from calico-plant (*Alternanthera bettzickiana*). The polyketide derivatives koninginin T and U (**249**, **250**) were isolated from the endophytic fungus *Phomopsis stipata* from the shrub *Styrax camporum* Pohl (Biasetto et al., 2020). Compounds **249** and **250** showed moderate antifungal activity, and compound **249** also inhibited acetylcholinesterase activity. (See Fig. 18)

Three new arylbenzofuran derivatives, **251–253,** were isolated from the metabolites of the endophytic fungus *Phomopsis* sp. (Du et al., 2017). Compound **251** displayed anti-tobacco mosaic virus (TMV) activity, with an inhibition rate of 35.2%. The polyketide derivatives **254–256** were found in the metabolites of the endophytic fungus *Phomopsis fukushii* (Yang et al., 2017), which originated from Zhonglu, Yunnan Province. Compound **254** displayed excellent antimicrobial activity against MRSA. Two new naphthalene derivatives (**257–258**) were isolated from the fermentation products of the endophytic fungus *Phomopsis fukushii* from the roots of tobacco (*Nicotiana tabacum*) (Li et al., 2021). These compounds showed certain inhibitory effects on *Staphylococcus aureus*. Two polyketides, phomopsol B (**259**) and **260**, were found in the metabolites from *Phomopsis* sp. xy21 (Li et al., 2019), but no activity was reported.

Two new polyketides, (±)-phomopsisin A (**261, 262**), were isolated from the fermentation metabolites of *Phomopsis asparagi* CICC 2706 (Zhou et al., 2021). These compounds did not exhibit significant inhibitory activity against glycosidase. Two new polyketoids with a 6/6/5/5/6 highly fused ring skeleton, lithocaldehydes A and B (**263, 264**), were detected

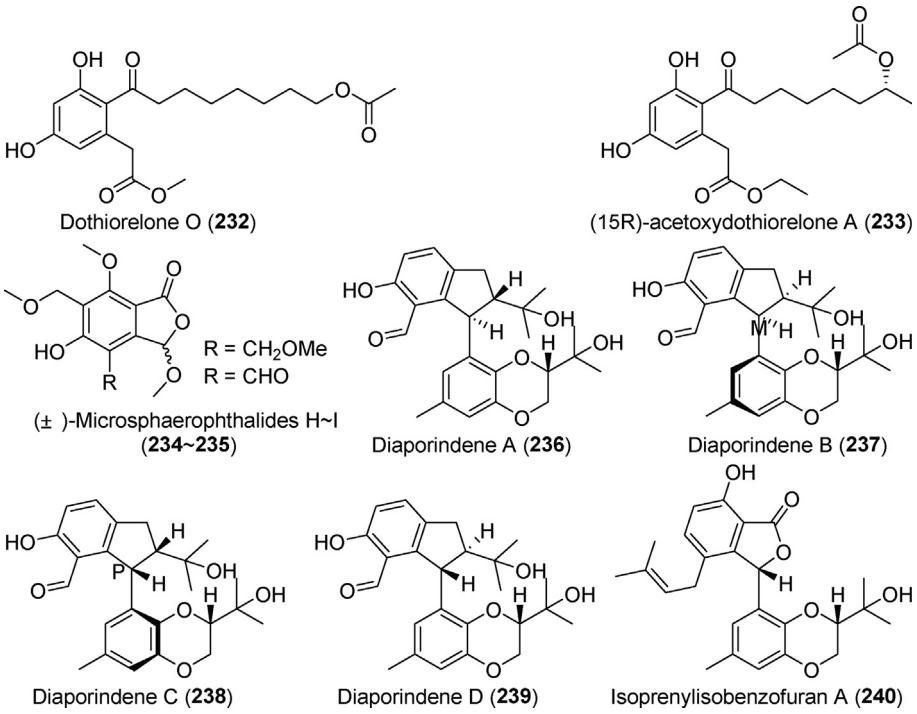

Fig. 16 Polyketides isolated from fungi of the genus *Diaporthe* (**232**–**240**).

in the fermentation metabolites of the deep-sea fungus *Phomopsis asparagi* FS508 (Liu et al., 2020). These compounds showed antifungal activity. Three new azaphilone-like compounds, phomopsones (**265–267**), were isolated from the fermentation metabolites of the endophytic fungus *Phomopsis* sp. CGMCC No.5416 from ox knee (*Achyranthes bidentata*) (Yang et al., 2020a, 2020b). Compounds **266** and **267** displayed significant anti-HIV activity, with IC_{50} values of 7.6 μM and 0.5 μM, respectively. In addition, compounds **266** and **267** showed moderate cytotoxic effects against A549, MDA-MB-231, and PANC-1 cells, with IC_{50} values ranging from 3.2 μM to 303 μM. Compound **267** induced early apoptosis in PANC-1 cancer cells, with an apoptosis rate of 28.54%.

The novel chlorine-containing azaphilone derivatives tersaphilones A–D (**268**–**271**) were found in the fermentation metabolites of the deep-sea fungus *Phomopsis tersa* FS441 (Chen et al., 2021a, 2021b). Among these compounds, compound **269** has a unique 6/6/6 carbon skeleton and a cleaved tetrahydrofuran ring, and compounds **270** and **271** are diastereomers with epoxide ring groups, which are rarely found in azaphilones. Compound **270** showed significant inhibitory activity against tumor cell lines MCF-7, SF-268, and A549, with IC_{50} values ranging from 5.4 μM to 8.3 μM. Five new 2,3-dihydro-1H–ninhydrin derivatives, diaporindenes E–I (**272**–**276**), and four new benzophenone derivatives, tenellones J–M (**277**–**280**), were isolated from the rice fermentation products of the deep-sea fungus *Phomopsis lithocarpus* FS508 (Liu et al, 2021a, 2021b). Compound **278** showed cytotoxicity against SF-268 cells, with an IC_{50} value of 11.36 μM. Two new polyketide derivatives, lithocarpinol A and B (**281**, **282**), were isolated from metabolites of the deep-sea fungus *Phomopsis lithocarpus* FS508 (Xu et al., 2019a, 2019b). Compound **281** had good inhibitory effects on HepG-2 and A549 tumor cell lines, with IC_{50} values of 9.4 μM and 10.9 μM, respectively.

2.6. Phenyl ketones

Two novel benzophenone derivatives, tenellones C–D (**283**, **284**), were found in the metabolites of *Diaporthe* sp. SYSU-HQ3 (Cui et al., 2018). Tenellone C (**283**) inhibited NO production (Fig. 19). The new benzophenone derivative tenellone I (**285**) was isolated from the metabolites of the endophytic fungus *Diaporthe lithocarpus* A740 from *Morinda officinalis* (Liu et al., 2019); this compound showed no significant cytotoxic activity against tumor cells. Five new benzone derivatives, tenellones D–H (**286**–**290**), were found in the metabolites of the deep-sea fungus *Phomopsis lithocarpus* FS508 (Xu et al., 2018a, 2018b). Tenellone H (**290**) exhibited cytotoxic activity against cell lines HepG-2 and A549, with IC_{50} values of 16.0 μM and 17.6 μM, respectively.(See Fig. 20)

2.7. Diphenyl ethers

The new diphenyl ether compounds Diaporthols A and B (**291**–**292**) are produced by the endophytic fungus *Diaporthe* sp. ECN-137 of Amur cork tree (*Phellodendron amurense*) (Nakashima et al., 2018) (Fig. 19). Compounds **291** and **292** exhibited an anti-migration effect against TGF-1 (transforming growth factor beta-1)-induced MDA-MB-231 breast cancer cells at 20 μM. Phomopsinin A (**293**), a new diphenyl ether natural product, was discovered in the metabolites of *Phomopsis* sp. CAM212, an endophytic fungus of the medicinal plant *Garcinia xanthochymus* (Jouda et al., 2020). These chemicals did not show anti-inflammatory properties. However, compound **294** considerably suppressed NO generation once its chemical structure was acetylated, with an IC_{50} value of 14.80 μM. The association between the structure and activity of this compound indicates that the anti-inflammatory

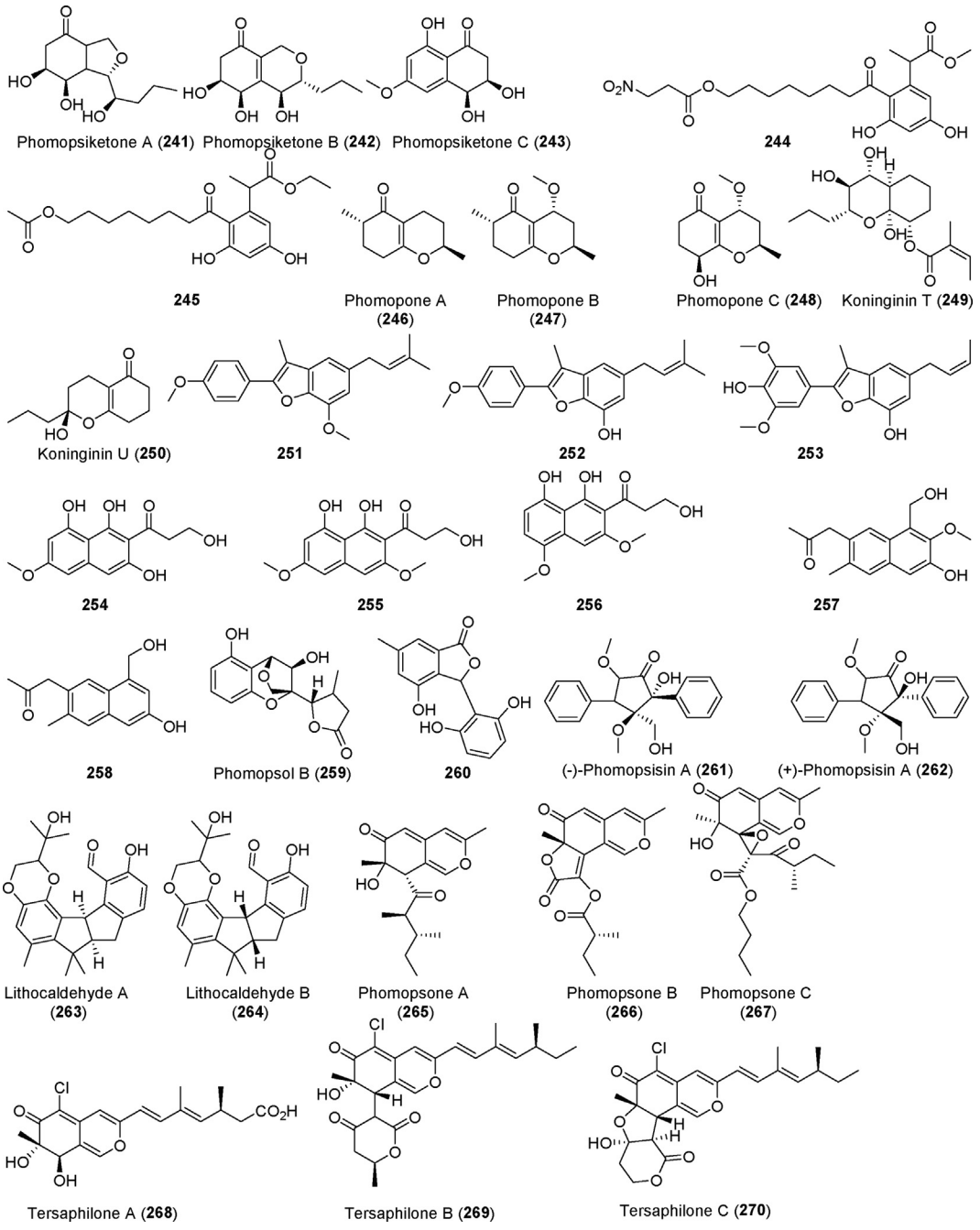

Fig. 17 Polyketides isolated from fungi of the genus *Phomopsis* (**241**–**270**).

effects of **294** are significantly influenced by acetyl groups. Compound **294** inhibited the expression of iNOS, COX-2, and IL-6 but had no effect on the expression of IL-1. The novel diphenyl ether derivatives **295**–**297** were isolated from the metabolites of the endophytic fungus *Phomopsis fukushii*, which was derived from *Paris polyphylla* var. yunnanensis (Gao et al., 2019). Both **295** and **297** showed potent anti-MRSA activity.

2.8. Nonsteroidal compounds

Two novel steroid derivatives, diaporthins A and B (**298** and **299**), were detected in *Diaporthe phragmitis*, an endophytic fungus isolated from *Actinidia chinensis* (Yu et al., 2021a, 2021b) (Fig. 21). These two compounds failed to exhibit any appreciable antibacterial activity. A novel steroid derivative (**300**), as well as five known steroid derivatives, were produced from the rice fermentation products of *Phomopsis* sp. MGF222, which was discovered in mangrove plants (Zhu et al., 2021). These compounds showed no substantial antibacterial activity.

Homopsterones A and B (**301**, **302**) were found in the metabolites of the endophytic fungus *Phomopsis* sp. TJ507A from the medicinal plant *Phyllanthus glaucus* (Hu et al., 2017). Compound **301** is a distinct ergosteroid with a skeleton made of rearranged bicyclic nonane components. iNOS pro-

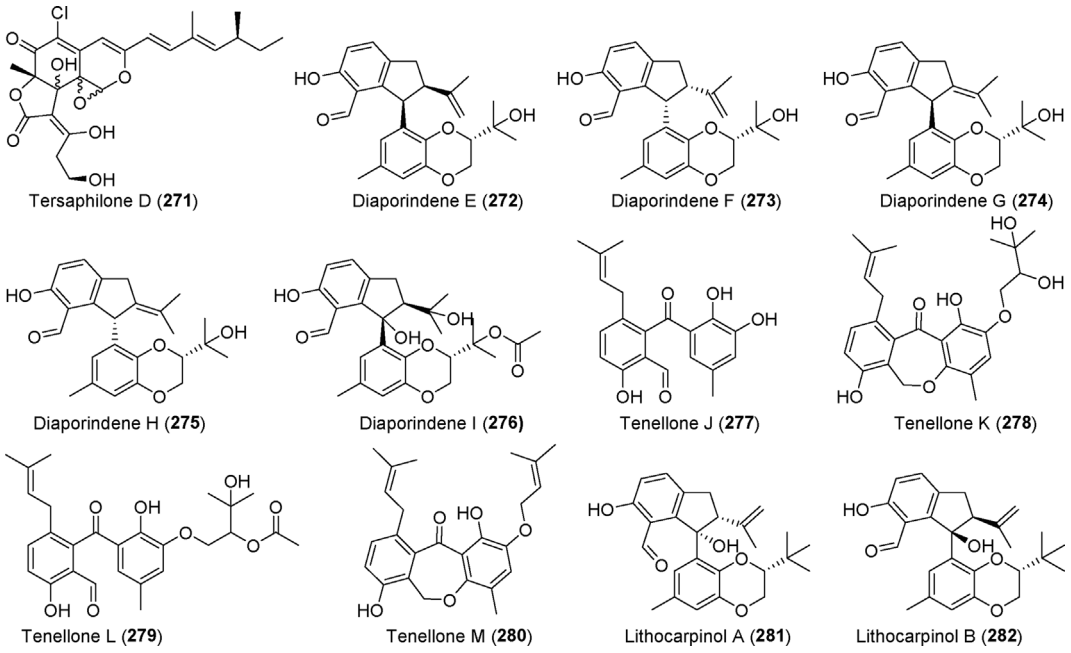

Fig. 18 Polyketides isolated from fungi of the genus *Phomopsis* (**271**–**282**).

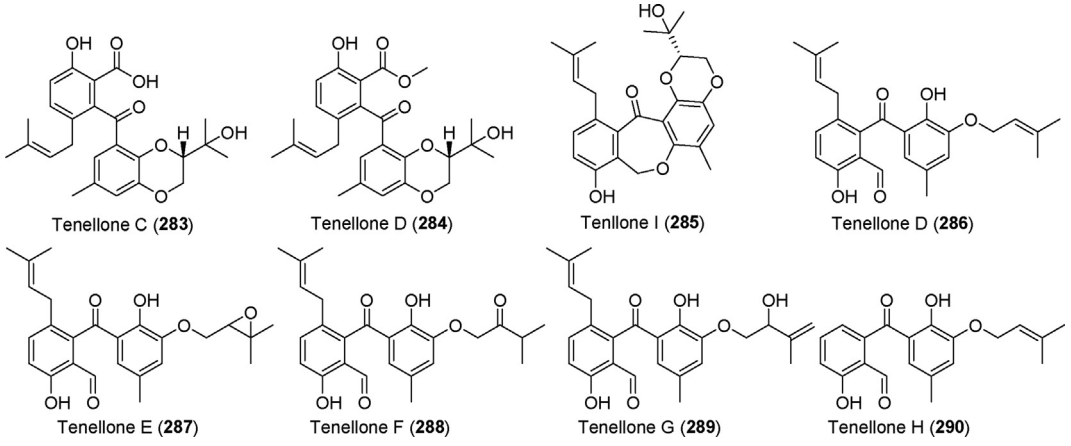

Fig. 19 Diphenyl ketone derivatives isolated from fungi of the genus *Diaporthe* (*Phomopsis*) (**283**–**290**).

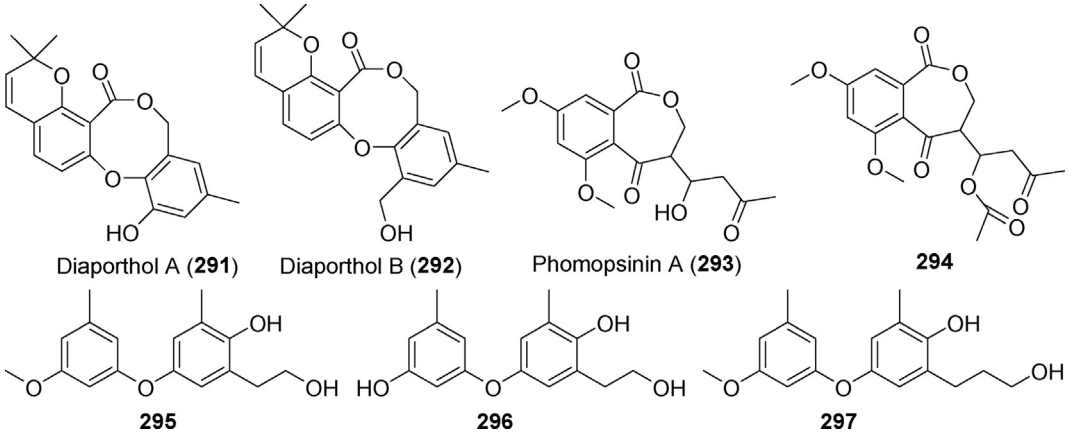

Fig. 20 Diphenyl ethers isolated from fungi of the genus *Diaporthe* (*Phomopsis*) (**291**–**297**).

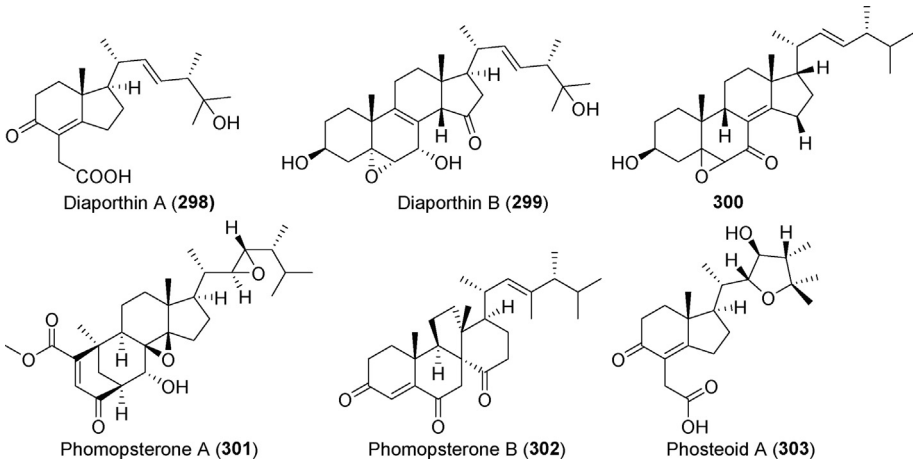

Fig. 21 Steroids isolated from fungi of the genus *Diaporthe* (*Phomopsis*) (**298**–**303**).

tein abundance and NO production were both suppressed by compounds **302,** with IC_{50} values of 4.65 μM and 1.49 μM, respectively. The metabolites of *Phomopsis tersa* FS441 (Chen et al., 2020a), which were tested for cytotoxic and anti-inflammatory activities, contained a highly oxidized steroid derivative named phosteoid A (**303**) with a distinctive 6/5/5 tricyclic structure. This compound clearly demonstrated inhibitory activity at a concentration of 100 μM.

2.9. Fatty acids

The new fatty acid derivatives diapolic acids A and B (**304, 305**) were isolated from metabolites of the endophytic fungus *Diaporthe terebinthifolii* (Yedukondalu et al., 2017) (Fig. 22). These two compounds showed no significant cytotoxic activity. Eucalactam B (**307**) and eucalyptacid A (**306**), two novel compounds isolated from the metabolites of the fungus *Diaporthe eucalyptorum* (Gao et al., 2020a), showed specific antifungal activity.

Diaporthsins A–K (**308–318**) were identified as alternate derivatives of fatty acids from metabolites of the endophytic fungus *Diaporthe* sp. JC-J7 from *Dendrobium nobile* (Hu et al., 2018a, 2018b). Compound **312** had antilipemic (lipid limiting) effects comparable to lovastatin. Diaporthesters A–D (**319**–**322**) are four novel fatty acid derivatives isolated from the fermentation products of the endophytic fungus *Diaporthe* sp. T24. This fungus was obtained from the stems of the medicinal plant *Ligularia fischeri* (He et al., 2021). Compound **319** showed cytotoxicity against HCT-8 and MCF-7 cells, with IC_{50} values of 0.06 μM and 0.65 μM, respectively. Diaportheolides A and B (**323, 324**) were isolated from the fermentation metabolites of the endophytic fungus *Diaporthe* sp. SXZ-19 from Happy tree (*Camptotheca acuminata*) (Liu et al., 2021a, 2021b). These compounds showed no antibacterial activity.

2.10. Other types of compounds

Four new macrolide derivatives, lithocarpins A–D (**325**–**328**), were extracted from the metabolites of the deep-sea fungus *Phomopsis lithocarpus* FS508 (Xu et al., 2018a, 2018b) (Fig. 23). Compounds **327** and **328** showed antitumor effects against the HepG-2, MCF-7, and SF-268 cell lines, with IC_{50} values ranging from 17.0 μM to 21.6 μM. Three novel macrolide skeleton derivatives, lithocarpins E–G (**329**–**331**), were identified from the secondary metabolites of the deep-sea fungus *Phomopsis lithocarpus* FS508 (Xu et al., 2021a, 2021b). Compound **329** considerably inhibited HepG-2 cell growth, with an IC_{50} of 6.30 μM. The activation of p-Erk, Bax, and Caspase-3 gene expression by this chemical induced apoptosis in HepG2 cells.

3. Biosynthesis of important compounds

Based on all genomes deposited in the NCBI database as of December 2021, the full genome sequences of 21 *Diaporthe* fungi had been published. The genome size of members of this genus typically ranges from 50 Mb to 65 Mb (Table 2). This information paves the way for investigating secondary metabolites and their biosynthesis in these species.

3.1. epi-cytoskyrin a and its analogs

epi-cytoskyrin A (**1**) is a dimeric anthraquinone derivative with a unique cage-like skeleton that was first isolated by Agusta et al. (Agusta, 2006; Agusta et al., 2015b) from the metabolites of the endophytic fungus *Diaporthe phaseolorum* SW-93–13 in tea plants (Fig. 24). This compound exhibited considerable anti-MRSA (MIC = 0.25 g/mL) and anti-*E. coli* activity (MIC = 1.00 g/mL). Brady et al. (Brady et al., 2000) isolated cytoskyrins A and B (**332** and **333**) from the endophytic fungus *Cytospora* sp. CR200 in 2000. Tian et al. (Tian et al., 2018) isolated *epi*-cytoskyrin A (**1**) and cytoskyrin C (**334**) from the metabolites of the endophytic fungus *Diaporthe* sp. in 2018. Rugulosins A–C (**335**–**337**) were identified from *Penicillium radicum* FKI-3765–2 metabolites in 2010 (Yamazaki et al., 2010).(See Figs. 25 and 26)

Rugulosin A (**335**) is an analog of *epi*-cytokyrin A (**1**) with anti-MRSA activity, with MIC values as low as 0.125 g/mL. The gene cluster that controls the simultaneous biosynthesis of rugulosin A (**335**) in *Talaromyces* sp. YE3016 was first described by Han et al. in 2021 (Han et al., 2021). The discovery of the gene functions, biosynthetic precursors, and enzymes involved in the creation of their molecular architecture was made possible using a combination of genome sequencing,

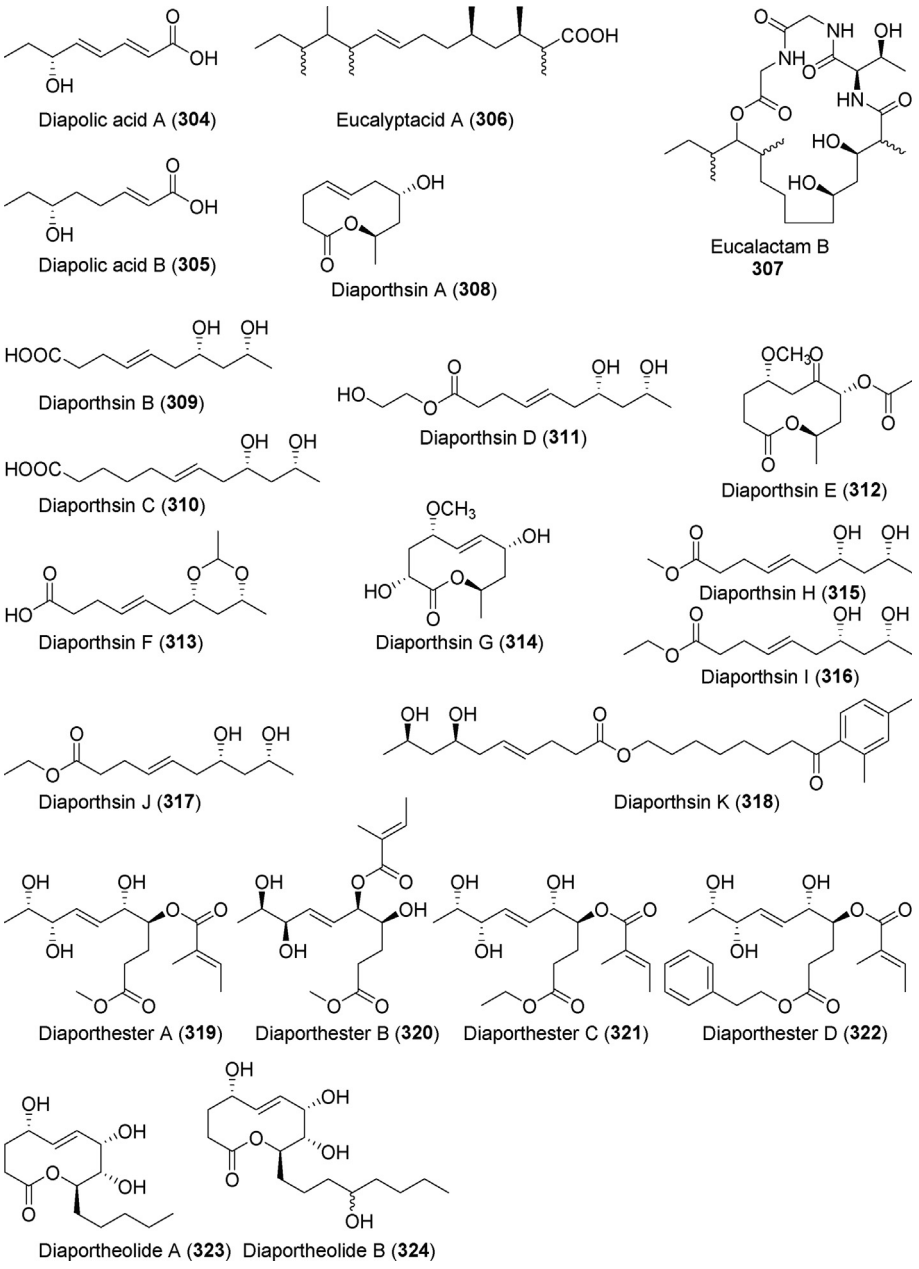

Fig. 22 Fatty acids isolated from fungi of the genus *Diaporthe* (**304–324**).

gene inactivation, heterologous expression, and biotransformation assays. Skyrin is formed via the 5,5′-dimerization of emodin radicals, which is catalyzed by RugG. Dimeric polyphenols can be created (chemo)enzymatically by cytochrome P450 monooxygenases. The fungal aldo–keto reductase RugH hijacks the closest skyrin precursor (CSP) immediately following emodin radical coupling and catalyze CSP ketone reduction to inactivate its tautomerization into skyrin, thus allowing a spontaneous intramolecular Michael addition to cyclize the ketone-reduced form of CSP into rugulosin A (**335**). *Penicillium islandicum* Sopp. produces luteoskyrin, a hepatotoxic anthraquinone. Long-term feeding of mice (*Mus musculus*) with *P. islandicum* Sopp-infected rice and isolated luteoskyrin elicited pathological changes in the liver, including adenoma and hepatoma (Ueno and Ishikawa, 1969). These findings could facilitate the manufacturing of *epi*-cytokyrin A (**1**) and its analogs.

3.2. Terpestacin

Terpetacin (**341**), a disesquiterpenoid that exhibits HIV-inhibitory and anti-angiogenic activity by binding to the 13.4-kDa subunit of mitochondrial complex III (ubiquinol-cytochrome *c* reductase binding protein, UQCRB), was discovered in 1993 from metabolites of the fungus *Arthrinium* sp. SF1744 (Iimura et al., 1993; Narita et al., 2018; Oka et al., 1993). The metabolites of the fungi *Fusarium culmorum* (Schlegel et al., 2001), *Arthrinium* sp. (Ye et al., 2019), *Mariannaea humicola* IG100 (Schlegel et al., 2001), and *Aplosporella javeedii* (Gao et al., 2020b) were subsequently obtained. In

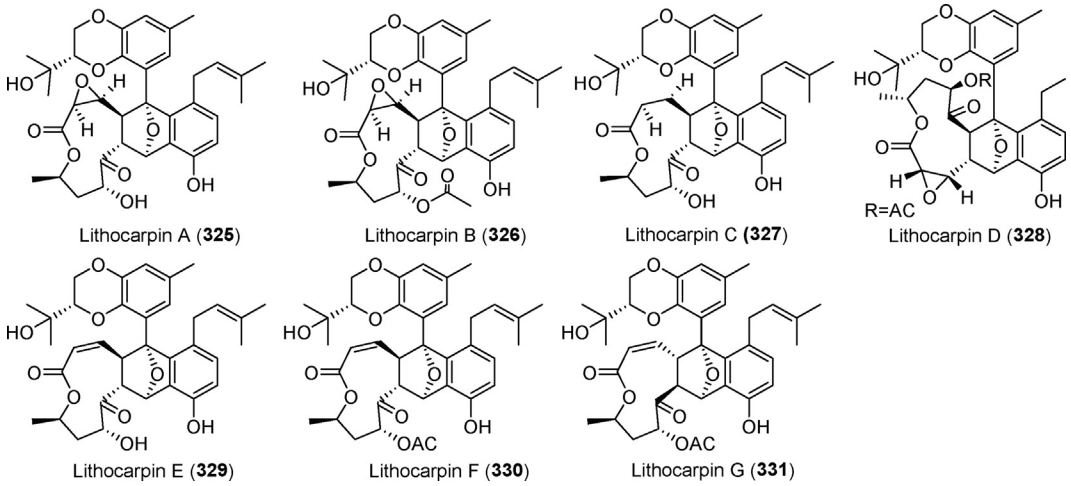

Fig. 23 Diphenyl ethers isolated from fungi of the genus *Phomopsis* (**325**–**331**).

Table 2 Members of the genus *Diaporthe* whose whole genomes have been sequenced as of December 2021.

No.	Strain	Genome size (Mb)	Year	GenBank acc. number	Reference
1	*Diaporthe longicolla* TWH P74	64.71	2014	GCA_000800745.1	(Li et al., 2015)
2	*Diaporthe longicolla* MSPL 10–6	129.0	2014	GCA_000498855.2	(Li et al., 2015)
3	*Diaporthe ampelina* DA912	47.3	2015	GCA_001006365.1	(Morales-Cruz et al., 2015)
4	*Diaporthe ampelina* I2T2	59.9	2015	GCA_001006365.1	(Savitha et al., 2016)
5	*Diaporthe aspalathi* MS-SSC91	55.03	2015	GCA_001447215.1	(Li et al., 2016)
6	*Diaporthe ampelin* S3MP	59.50	2016	GCA_001630405.1	(Savitha et al., 2016)
7	*Diaporthe helianthin* 7/96	63.67	2018	GCA_001702395.2	NA
8	*Diaporthe* sp. HANT25	55.34	2020	GCA_013435955.1	(Tulsook et al., 2020)
9	*Diaporthe* sp. NJD1	58.33	2020	GCA_013842865.1	NA
10	*Diaporthe capsica* GY-Z16	57.56	2020	GCA_013364905.1	(Fang et al., 2020)
11	*Diaporthe citri* NFHF-8–4	63.69	2020	GCA_014595645.1	(Gai et al., 2021)
12	*Diaporthe citr* ZJUD2	60.38	2020	GCA_014872965.1	(Gai et al., 2021)
13	*Diaporthe citr* ZJUD14	53.97	2020	GCA_014872985.1	(Gai et al., 2021)
14	*Diaporthe citr* Q7	63.64	2020	GCA_014873005.1	(Gai et al., 2021)
15	*Diaporthe citriasiana* ZJUD30	53.41	2020	GCA_014872975.1	(Gai et al., 2021)
16	*Diaporthe citriasiana* ZJUD30	50.67	2020	GCA_016432825.1	(Gai et al., 2021)
17	*Diaporthe citrichinensis* ZJUD34	54.5	2020	GCA_014872995.1	(Gai et al., 2021)
18	*Diaporthe destruens* CRI305-2	56.11	2021	GCA_016859255.1	NA
19	*Diaporthe batatas* CRI 302–4	54.2	2021	GCA_019321695.1	NA
20	*Diaporthe* sp. DP-2020a	57.82	2021	GCA_018137895.1	NA
21	*Diaporthe vexans* PV4	59.77	2021	GCA_021188095.1	NA

NA, not available.

2020, our research team also discovered this compound in the metabolites of *Diaporthe* sp. CB10100 (publication in preparation). Related derivatives reported thus far include terpetacins B and C (**342**, **343**) (Gao et al., 2020b), fusaproliferin (**344**) (Santini et al., 1996), fusaproliferin A and B (**345**, **346**) (Liu et al., 2013), and 24-α-d-glucosyl-terpestacin (**347**) (Liu et al., 2013). The structure of these compounds includes a unique binary ring architecture of 5/15 rings, which may be valuable for future development in addition to their remarkable biological activity.

In 2018, Narita et al. (Narita et al., 2018) verified the biosynthetic gene cluster of terpestacin (**341**) in *Aspergillus oryzae* by heterologous gene expression (*tpcA–D*) (Fig. 27). Two cytochrome P450s (tpcBC) catalyze the biosynthesis of three hydroxyl groups at the A-ring in a stereoscopic and spatially selective manner in the presence of bifunctional terpenoid synthase (tpcA). Subsequently, a flavin-dependent oxidase (TpcD) catalyzes the oxidation of the vicinal diol molecule to generate α-diketone, which is then enolized to yield terpstacin (**341**).

3.3. Sch-642305

Sch-642305 (**354**) is a distinctive bicyclic 10-membered macrolide produced by *Phomopsis* sp. CMU-LMA and other fungi (Trenti et al., 2020). Chu et al. (Chu et al., 2003b) isolated sch-642305 (**354**) from the metabolites of *Penicillium verrucosum* for the first time in 2003. In 2005, Jayasuriya et al. (Jayasuriya et al., 2005) discovered that this compound exhibited anti-HIV activity, with an IC_{50} value of 1 μM. Dermenci

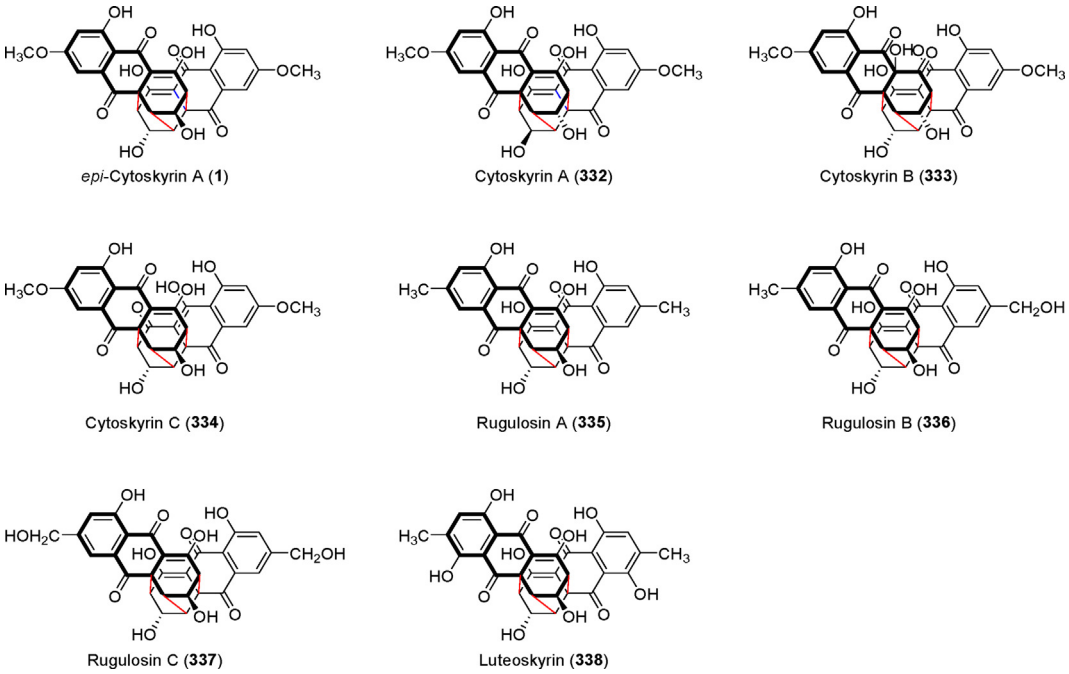

Fig. 24 Derivatives of the cytoskyrins series containing unique cage dimer anthraquinone skeletons (**1**, **332**–**338**).

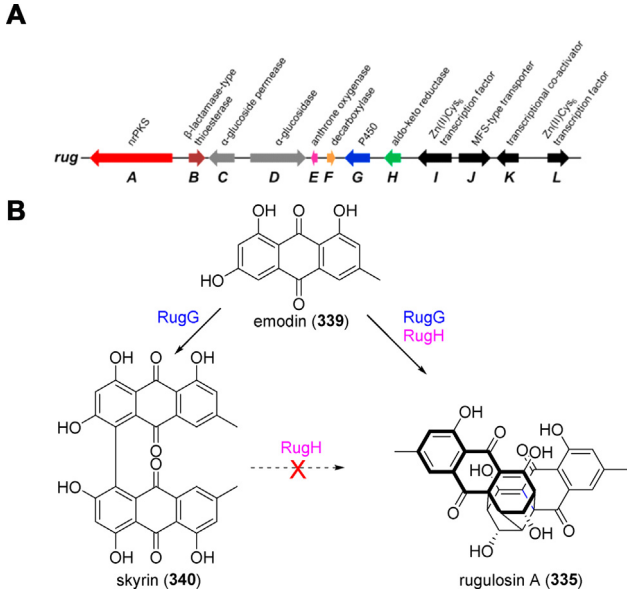

Fig. 25 rug gene cluster governing the intertwined biosynthesis of rugulosin A (335) (Han et al., 2021).

et al. (Dermenci et al., 2011) discovered in 2018 that sch-642305 (**354**) inhibits glioma cell proliferation, which has significant development and application potential. Trenti et al. (Trenti et al., 2020) used heterologous expression, gene knockdown, and precursor feeding to identify the biosynthetic gene cluster responsible for sch-642305 (**354**) production in *Phomopsis* sp. CMU-LMA in 2020. An analysis using targeted gene disruption and pathway reconstruction revealed the crucial chemical steps and a succession of redox activities that occur in this pathway (Fig. 28).

4. Conclusions and future prospects

In this review, we summarized the structures, biological activities, and biosynthesis of new natural products from the genus *Diaporthe* and its anamorph *Phomopsis*. The 331 compounds isolated from *Diaporthe* and *Phomopsis* between 2016 and 2021, comprising 143 compounds from *Diaporthe* and 188 from *Phomopsis*, have diverse chemical structures and bioactivities. The major categories of these compounds include alkaloids, terpenoids, pyrones, and polyketides. These chemicals have a wide range of biological effects, including anti-inflammatory, antibacterial, and anticancer properties. These findings pave the way for future pharmaceutical research.

In addition, we described the biosynthesis of three compounds generated by *Diaporthe* (*Phomopsis*) and listed the 21 strains of *Diaporthe* (*Phomopsis*) fungi whose full genome sequences are available in the NCBI database. Many novel substances may be created by activating the expression of suppressed gene clusters using advanced molecular techniques including heterologous expression, gene deletion, and other approaches. We also described the biosynthesis of rugulosin A (**335**), terpestacin (**341**), sch-642305 (**354**), and other chemicals with anticancer effects. By studying the biosynthesis of these chemicals, fascinating biosynthetic enzymes have been revealed, expanding the pool of biological elements for synthetic biology. Furthermore, in light of the growing interest in the biosynthetic routes of natural products originating from fungi, identifying certain unique catalytic enzymes from *Diaporthe* (*Phomopsis*) is of particular interest. The literature on secondary metabolites of *Diaporthe* (*Phomopsis*) fungi greatly expanded between 2016 and 2021. These investigations have substantially aided in the identification of novel active natural products derived from these fungi, as well as the development and use of existing active natural products.

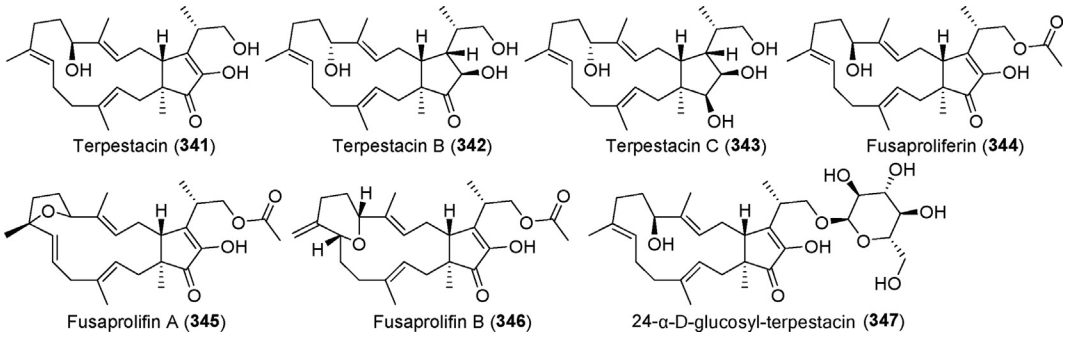

Fig. 26 Terpestacin and its related derivatives (**341**–**347**).

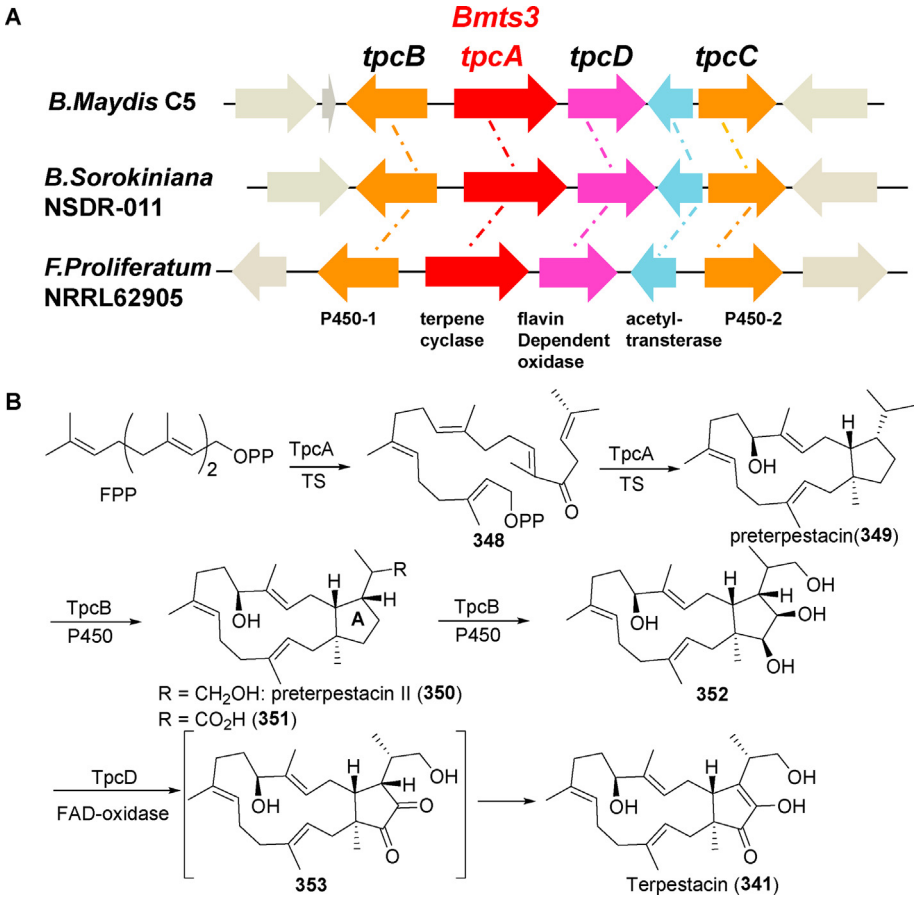

Fig. 27 (A) Biosynthetic gene clusters of terpestacin in fungi such as Bipolaris maydis, Bipolaris sorokiniana, and Fusarium proliferatum; (B) A possible biosynthetic pathway for terpestacin (Narita et al., 2018).

Therefore, *Diaporthe* (*Phomopsis*) fungi represent important resources for the discovery of novel natural active substances and research on natural compound biosynthesis. To date, research on *Diaporthe* (*Phomopsis*) fungi has mainly focused on the isolation and identification of novel natural products and preliminary biological activity screening, whereas only a few studies have focused on the key biosynthetic genes and enzymes involved in their production. In addition, the bioactivities of most of these compounds have only been studied *in vitro*. To fully develop and exploit *Diaporthe* (*Phomopsis*) fungi, further investigations are needed on the biosynthesis and pharmacological mechanisms of highly active compounds from this genus.

CRediT authorship contribution statement

Lin Jiang: Conceptualization, Writing – original draft. **Qingxian Ma:** Writing – original draft. **Aijie Li:** Writing – review & editing. **Runze Sun:** Writing – review & editing. **Genyun Tang:** Writing – review & editing. **Xueshuang Huang:** . **Hong Pu:** Conceptualization, Writing – original draft.

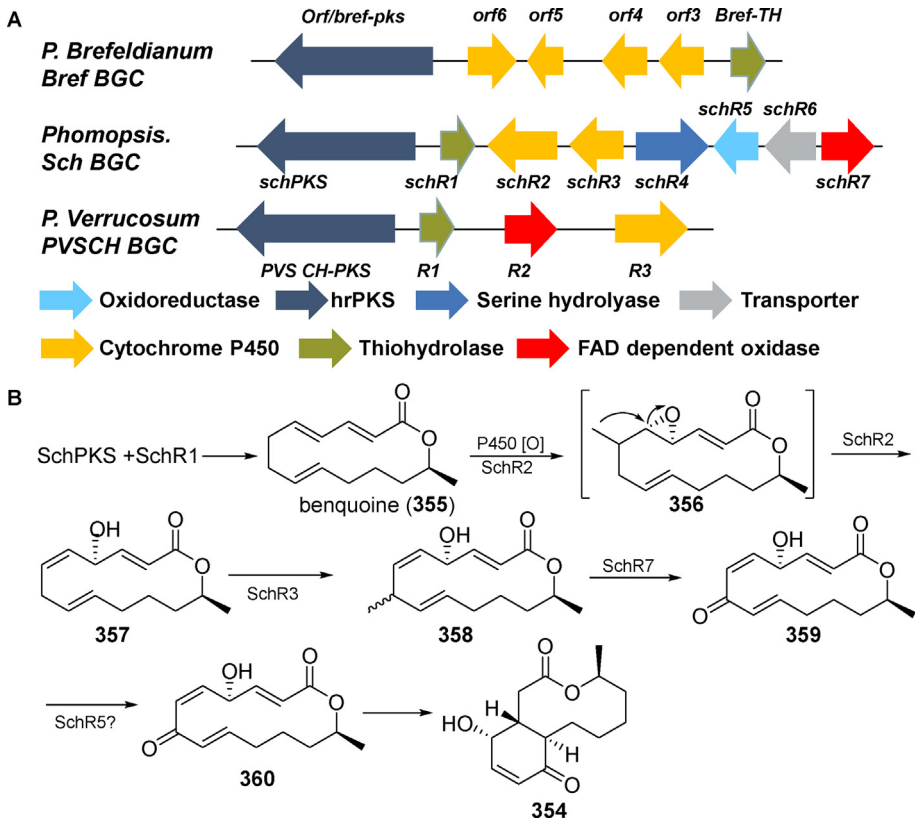

Fig. 28 Gene cluster and biosynthetic pathway of sch-642305 (354) (Trenti et al., 2020).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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