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Terpenoids and other secondary metabolites produced by the *Eutypella* fungi and their bioactivities

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The fungi *Eutypella* could metabolize a myriad of natural products with unique structures and diverse bioactivities, which were deemed as key sources for lead compounds in drug discovery. Since the first research on the genus *Eutypella* in 2009, a myriad of secondary metabolites including terpenoids, alkaloids, and polyketides have been discovered in this genus, and most of them exhibited significant pharmacological activities. However, there are no systematic reviews that reported about the structures and bioactivities of *Eutypella* up to now. In this review, a total of 153 secondary metabolites and 42 references have been systematically summarized, and we found that the terpenoids (68.09%) and alkaloids (19.15%) were the new main components of this fungi, and the primary antiproliferative activity (64.89%) was mainly derived from the terpenoids and alkaloids. Thus, this review about the chemical diversity and biological activities of the metabolites from the fungus *Eutypella* provided a new perspective for the development of new drugs for pharmacologists.

KEYWORDS

fungi, *Eutypella* sp., terpenoids, bioactive metabolites, antiproliferative (cytotoxic) activity

1 Introduction

Eutypella are cosmopolite and diverse fungi, which are included in phylum *Diatrypaceae*, subclass *Xylariomycetidae*, and genus *Eutypella* (Acero et al., 2017). They are commonly isolated from various terrestrial and marine environments (Da Silva et al., 2008; Moyo et al., 2016; Zhang, 2019) and play an important ecological role as a decomposer (Lee et al., 2011; Deng et al., 2019; Brglez et al., 2020). Meanwhile, the fungi *Eutypella* are reported to be valuable biological resources due to their ability to produce bioactive secondary metabolites such as terpenoids, alkaloids, and polyketides (Sun et al., 2011; Liu et al., 2014b; Niu et al., 2017a; Zhang et al., 2020; Zhang et al., 2021b).

Accumulated reports suggest that the secondary metabolites represent a wide range of biological activities including antiproliferative, anti-inflammatory, antibacterial, and antiviral activities (Palem et al., 2015; Kuriakose et al., 2016; Liao et al., 2017; Niu et al., 2018; Mao et al., 2021). For example, libertellenone H (LH) (Zhang et al., 2021c) was isolated from the arctic fungus *Eutypella* sp. D-1 as antiproliferative against various cancer cells. Diaporthein B (Isaka et al., 2011), from the endophyte *Eutypella* sp. BCC 13199, displayed significant inhibitory activities against NCI-H187 human small-cell lung cancer cells with an IC_{50} value of 0.15 μM. Therefore, the fungi *Eutypella* can produce secondary metabolites with novel structures and have extensive pharmacological properties, which is of great research significance for drug discovery.

According to the previous literature reported, domestic and foreign researchers have studied 10 strains of this genus [*Eutypella* sp. BCC 13199 (Isaka et al., 2011), *E. scoparia* PSU-D44 (Pongcharoen et al., 2006), *E. scoparia* FS46 (Liu et al., 2017b), *E. scoparia* FS26 (Sun et al., 2012a), *E. scoparia* PSU-H267 (Kongprapan et al., 2015), *E.* sp. D-1 (Lu et al., 2014), *E. scoparia* ICB-OBX (Ciavatta et al., 2008), *E. scoparia* 1-15 (Qi et al., 2015), *E. scoparia* SCBG-8 (Zhang et al., 2020), and *E.* sp. MCCC 3A00281 (Niu et al., 2017a)] for their secondary metabolites. However, there is no systematic review on the structural diversity and biological activities for the fungi *Eutypella*. Therefore, in this review, we focused on the structural diversities and relevant biological activities of 153 metabolites from the fungi *Eutypella*, which provide new insights for chemists and pharmacologists in drug discovery.

2 Secondary metabolites

2.1 Terpenoids

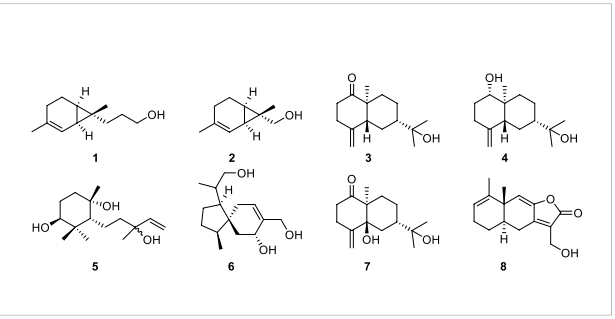
2.1.1 Monoterpenes and sesquiterpenes

Eutypellol A (**1**), the first norsesquiterpenoid of sesquicarene family, and a rare 7-methyl oxidized 2-carene derivative eutypellol B (**2**) (Liu et al., 2017b) were isolated from the marine-derived fungi *Eutypella scoparia* FS46, which was found to show potent anti-*Staphylococcus aureus* and cytotoxic activities. *Ent*-4(15)-eudesmen-11-ol-1-one (**3**) and *ent*-4(15)-eudesmen-1*R*, 11-diol (**4**) (Isaka et al., 2009) were enantiomers of known compounds, respectively, which were isolated from *Eutypella* sp. BCC 13199. Furthermore, **3** exhibited weak cytotoxicity towards NCI-H187, MCF-7, KB, and noncancerous Vero cells at concentrations ranging from 11 to 32 μM.

3,7,10-Trihydroxy-6,11-cyclofarnes-1-ene (**5**) and 8-(hydroxymethyl)-1-(2-hydroxy-1-methylethyl)-4-methylspiro [4.5]-dec-8-en-7-ol (**6**) (Sun et al., 2012a), which were identified as monocyclofarnesane-type and acorane-type sesquiterpene, respectively, were constituents of *Eutypella scoparia* FS26. In the bioassays, both of them showed weak inhibitory activities against the MCF-7 cell line at the concentration of 100 μM by the MTT method.

Scopararane C (**7**), a new β-eudesmol sesquiterpene, was produced by a fungal strain, *Eutypella scoparia* 1-15, which was isolated from mangrove rhizosphere soil of Jimei, Fujian Province, China (Qi et al., 2015). *Eutypella* sp. D-1 yielded a minor fermentation product, *eut*-guaiane sesquiterpene (**8**) (Zhou et al., 2017). When 50 μg of sesquiterpene (**8**) acted on the antibacterial paper (Φ = 6 mm), the results showed that **8** had strong antibacterial activities against *Bacillus subtilis*, *S. aureus*, and *Escherichia coli* such as the positive control ampicillin. Moreover, **8** also exhibited *in vitro* weak cytotoxicity towards the SGC7901 cell line.

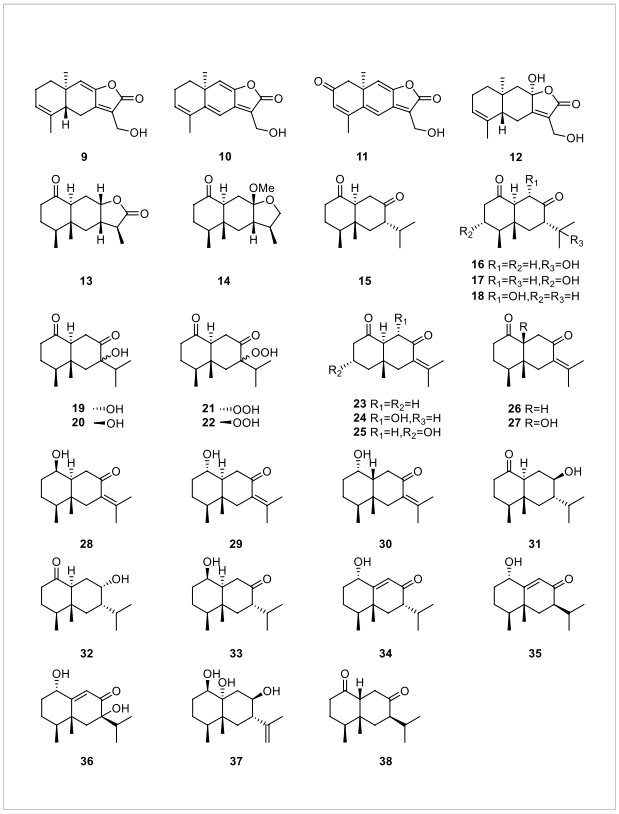
To investigate the bioactive metabolites, isolation of four new eudesmanolides of a subgroup of 12,8-eudesmanolides (**9**–**12**)



from soil-related mangrove fungus *Eutypella* sp. 1-15 had been performed (Wang et al., 2017). Notably, compound **9** displayed cytotoxic activities towards liver cancer cells HepG2 and human sleeve lymphoma cancer cells JEKO-1 with IC_{50} values of 28.5 and 8.4 μM, respectively. Moreover, compound **9** also showed moderate antibacterial activity against *Bacillus pumilus* CMCC63202 and *B. subtilis* CMCC63501 with IC_{50} values of 23.8 and 18.1 μM, respectively.

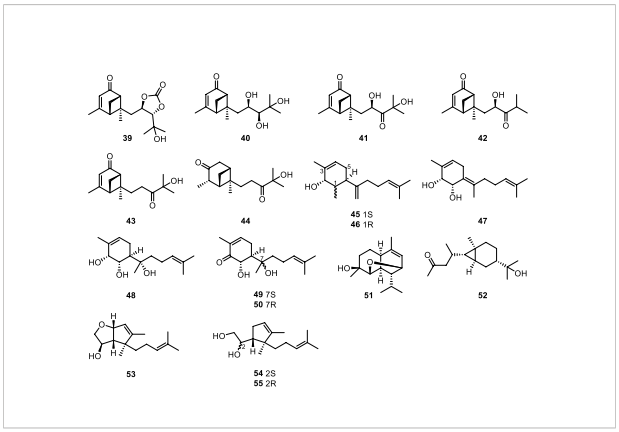
Cultivation of fungus *Eutypella* sp. MCCC 3A00281 using two chemical epigenetic manipulation reagents suberohydroxamic acid (SBHA) and histone deacetylase inhibitor (HDI) led to the isolation of a variety of novel eremophilane-type sesquiterpenoids eutyperemophilanes A-Z (**13**–**38**) (Niu et al., 2018). Among them, eutyperemophilane B (**14**), eutyperemophilane I (**21**), and eutyperemophilane J (**22**) showed weak cytotoxic activity with CC_{50} > 100 μM on RAW264.7 cells. In particular, eutyperemophilane I (**21**) and eutyperemophilane J (**22**) were further evaluated as anti-inflammatory agents with IC_{50} values of 8.6 and 13 μM, respectively.

As part of an ongoing investigation into fungus *Eutypella* sp. MCCC 3A00281, a suberohydroxamic acid (SBHA) and a DNA methyltransferase inhibitor (5-azacytidine) were co-treated with the fungus, which led to the isolation of 17 sesquiterpenes eutypeterpenes A–Q (**39**–**55**) (Niu et al., 2021). They are classified into bergamotane-type (**39**–**44**),



bisabolane-type (**45**–**50**), cadinene-type (**51**), carabrane-type (**52**), and an undescribed subtype of sesquiterpenes with a cyclopentane ring (**53**–**55**). Except for eutypeterpene K (**49**) and eutypeterpene L (**50**), all these metabolites inhibited the production of NO in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages. Among them, eutypeterpene N (**52**) was the most effective sesquiterpene to inhibit the NO production, with an IC_{50} of 8.6 μM, which has the potential to treat inflammatory diseases.

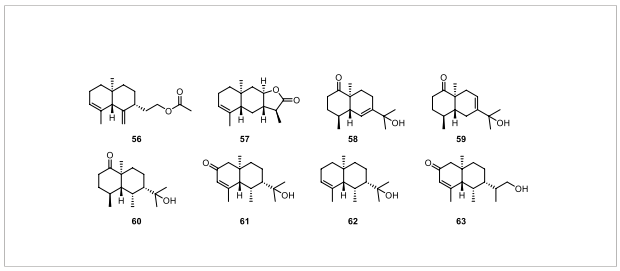
Chromatographic separation of the bioactive extract (anti-MRSA) of the endophytic fungus *Eutypella scoparia* SCBG-8 resulted in the isolation of a group of new sesquiterpenes, named eutyscoparins A–H (**56**–**63**) (Zhang et al., 2021a). Eutyscoparin G (**63**) exhibited antibacterial activity against MRSA



(methicillin-resistant *S. aureus*) and *S. aureus* with MIC values of 6.3 μg/ml.

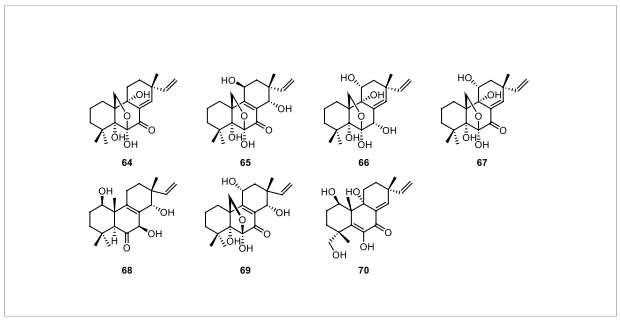
2.1.2 Diterpenes

Scopararanes A and B (**64** and **65**), as well as two known



diterpenes diaportheins A and B (**66** and **67**) (Pongcharoen et al., 2006), were isolated from the *Eutypella* sp. PSU-D44. Of note, all of them showed weak antibacterial activities against *Microsporum gypseum* SH-MU-4 and *S. aureus* ATCC 25923. Investigation on the endophyte *Eutypella scoparia* BCC 13199, which was fermented in a bioreactor containing malt extract broth after shake incubation in PDB, resulted in the isolation of two novel γ-lactones diterpenes eutypellones A and B (**68** and **69**) and three known diterpenes scopararane A (**64**), diaportheim B (**67**), and libertellenone C (**70**) (Isaka et al., 2011). Meanwhile, antiproliferative activity demonstrated that scopararane A (**64**) and diaportheim B (**67**) displayed significant inhibitory activities against human small-cell lung cancer cells NCI-H187 with IC_{50} values of 0.024 and 0.15 μM, respectively.

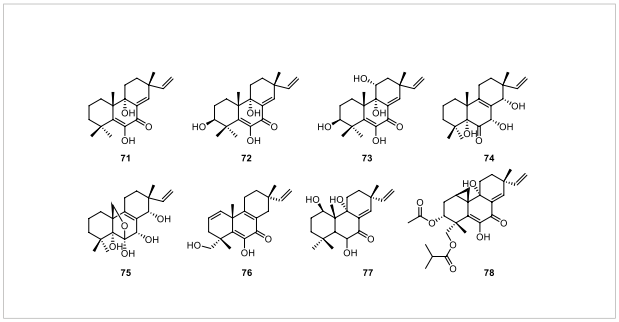
A strain of *Eutypella scoparia* FS26 yielded a series of oxygenated pimarane diterpenes scopararanes C–G (**71**–**75**)



(Sun et al., 2012b). Among them, scopararanes C (**71**) and D (**72**) exhibited moderate cytotoxic activities with IC_{50} values of 35.9 μM and 25.6 μM in the tumor cell line MCF-7. Furthermore, the MTT method was subjected to two known compounds diaporthein B (**67**) and libertellenone A (**76**), and both of them exhibited strong cytotoxicity against NCI-H460, SF-268, and MCT-7 ranging from 4.4 to 9.9 μM and from 12.0 to 40.2 μM, respectively. Bioassay-guided separation of the EtOAc extract of the fungus *Eutypella* sp. D-1 resulted in the isolation of two novel diterpenes libertellenones G (**77**) and H (**78**), along with two known ones libertellenone C (**70**) and libertellenone A

(**76**) (Lu et al., 2014). Meanwhile, libertellenone G (**77**) displayed moderate antibacterial activities against *B. subtilis*, *S. aureus*, and *E. coli*. In addition, LH (**78**) showed significant cytotoxic activities with IC_{50} values in the range of 3.31 to 44.1 μM in an array of cancer cell lines (U251 cells, MCF-7 cells, SG7901 cells, H460 cells, Huh-7 cells, Hela cells, and SW-1990 cells).

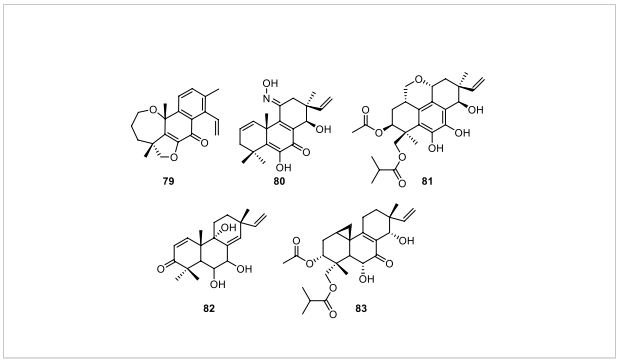
Investigation on the *E.* sp. D-1 obtained from soil of the high-latitude Arctic led to the isolation of three special



pimarane-type diterpenes eutypenoids A–C (**79**–**81**) (Zhang et al., 2016). Among them, **79** and **81** are ring A rearranged pimarane diterpenes. The NMR data suggested that **79** is a diterpenoid with a new carbon skeleton, which possessed a tetracyclic system consisting of two hexatomic rings, the furan ring and the oxepane skeleton of ring A. Eutypenoid C (**81**) is a disubstituted tetracyclic pimarane diterpenoid with an additional pyranoid ring compared to the typical pimarane diterpenoid. Moreover, eutypenoid B (**80**) is a nitrogenous diterpene, which showed strong antiproliferative activity of splenocyte under concanavalin A induction within the concentration from 0.16 to 40 μM.

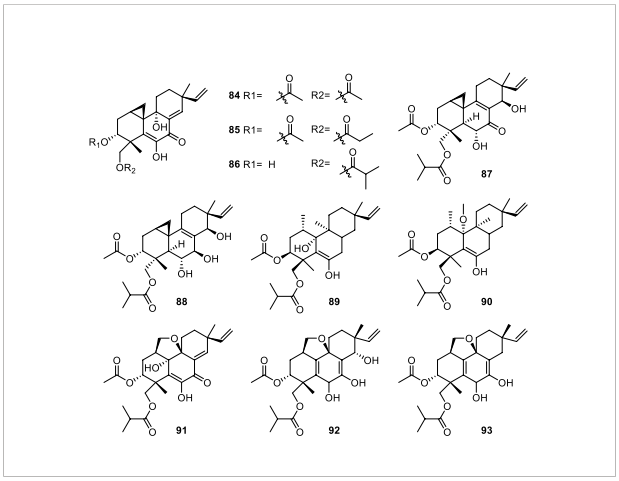
Scopararanes H and I (**82** and **83**) (Liu et al., 2017a), identified as new pimarane diterpenes, were isolated from fungus *Eutypella* sp. FS46. Furthermore, scopararane I (**82**) exhibited inhibitory activities against NCI-H460 (human non-small cell lung cancer cell line), MCF-7 (human breast adenocarcinoma cell line), and SF-268 (human glioma cell line) with IC_{50} values of 13.5, 25.3, and 83.9 μM, respectively.

Large-scale fermentation of the fungus *Eutypella* sp. D-1 resulted in the characterization of seven new pimarane-type diterpenes, libertellenones O–S (**84**–**88**), eutypellenone A (**89**), and eutypellenone B (**90**) (Yu et al., 2018b). Most importantly, all



of them showed different levels of cytotoxic activities towards SW1990, MCF-7, PANC-1, HCT-116, and HeLa cells, with IC_{50} values in the range of 0.8 to 29.4 μM. Furthermore, eutypellenones A (**89**) and B (**90**) could inhibit the activity of NF-κB in a dose-dependent manner and exerted significant inhibitory effects to reduce NO production induced by LPS with IC_{50} < 10 μM. A further study on *Eutypella* sp. D-1 resulted in the discovery of three pimarane-type diterpenes eutypellenoids A–C (**91**–**93**) (Yu et al., 2018a), which possessed an infrequent tetrahydrofuran-fused pimarane diterpene skeleton. Significantly, antifungal tests demonstrated that eutypellenoid B (**92**) showed strong inhibitory activities on *Candida albicans*, *Candida parapsilosis, Candida glabrata*, and *Candida tropicalis* with MIC values of 8.0, 8.0, 16.0, and 32.0 μg/ml, respectively, and also displayed antibacterial activity against *E. coli* and *S. aureus* with an MIC value of 8 μg/ml for both. Meanwhile, eutypellenoid B (**92**), which was assessed for its cytotoxic activity, could reduce the proliferation of the HCT-116 cell line with an IC_{50} value of 3.7 μM.

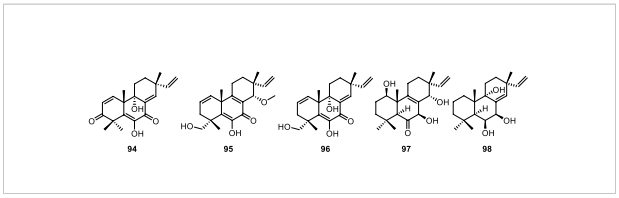
In-depth investigation on the CH_2Cl_2 extract of *Eutypella* sp. D-1 led to the identification of two new pimarane-type diterpenes, libertellenone M (**94**) and libertellenone N (**95**), and five known



compounds, libertellenones A–C (**76, 96, 70**), eutypellone A (**97**), and kaempulchraol W (**98**) (Wang et al., 2018). Among them, libertellenone M (**94**) exhibited antibacterial activity against *V. vulnificus*, *S. aureus*, and *E. coli*, while libertellenone A (**76**) showed extra antibacterial activity against *B. subtilis*. Moreover, cytotoxicity assay indicated that libertellenone N (**95**) showed excellent antiproliferative activity with an IC_{50} value of 7.67 μM in the K562 cell line. Apart from the reported MCF-7 (Lu et al., 2014), libertellenone A (**76**) also exhibited moderate cytotoxicity against four human cancer cells SW1990, HCT-116, K562, and HeLa with IC_{50} values of 17.31, 15.39, 14.81, and 14.31 μM, respectively.

2.1.3 Meroterpenoids

Four unusual meroterpenoids eutypellacytosporins A–D (**99**–**102**) (Zhang et al., 2019), structurally related to

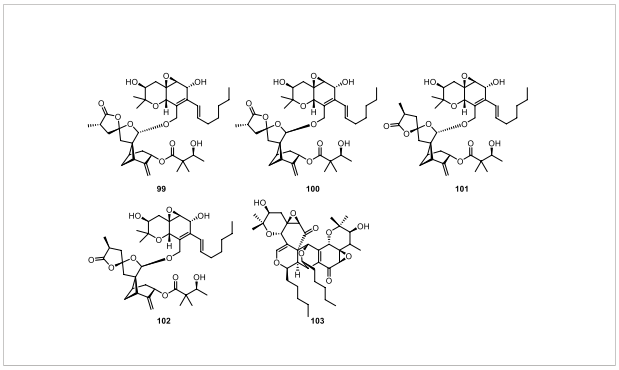


cytosporins and decipienolides, were acquired from an Arctic stain of *Eutypella* sp. D-1. In particular, the research proposed **99**–**102** may be constructed by two moieties cytosporin D and decipienolide A or decipienolide B through a 12,32-ester linkage. Bioactivity evaluation suggested that all the compounds possessed cytotoxic activity against PANC-1, Huh7, DU145, and SW1990 cell lines with IC_{50} values in the range of 4.9 to 17.1 μM.

Marine-derived fungus *Eutypella scoparia* SCBG-8 extract was subjected to a chemical research, yielding a unique meroterpenoid eutyscoparol J (**103**) (Zhang et al., 2021b). Interestingly, **103** was endowed with an unusual 6/6/6/6/6/6/6 polycyclic ring system based on the dimeric isoprenylated epoxyquinol skeleton. Meanwhile, eutyscoparol J (**103**) exhibited a moderate antiproliferative effect.

2.2 Alkaloids

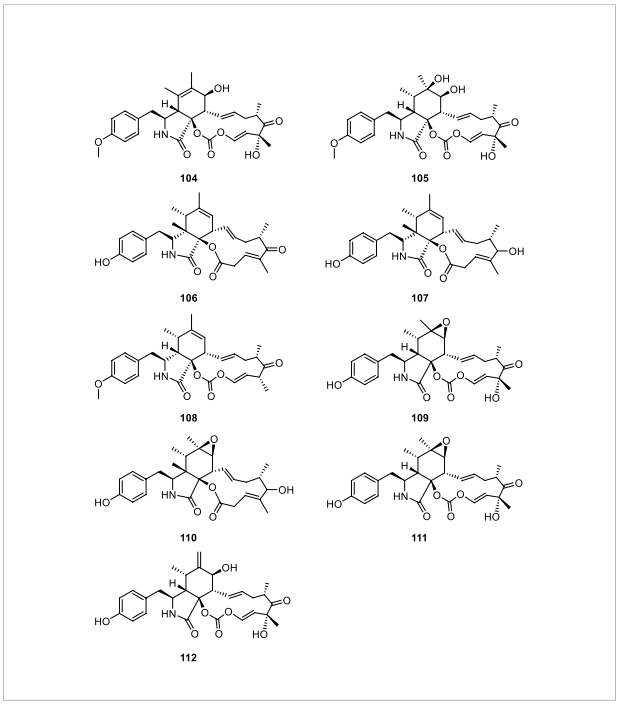
Antimicrobial activity-guided fractionation of fungus *Eutypella scoparia* PSU-D44 produced two new alkaloids scoparasin A (**104**) and scoparasin B (**105**) (Pongcharoen et al., 2006). Interestingly, scoparasin B (**105**) displayed sensible inhibitory activity against *M. gypseum* SH-MU-4 with an MIC value of 30.3 μM.



Chromatographic separation of a crude extract obtained from the fungus *Eutypella* sp. D-1 yielded three new alkaloids Z_{24}–Z_{26} (**106**–**108**) and a known one alkaloid scoparasin B (**105**) (Liu et al., 2014a). Furthermore, cytochalasin Z_{24} (**106**) exhibited strong cytotoxicity against the MCF-7 human breast cancer cell line with an IC_{50} value of 9.33 μM. Moreover, scoparasin B (**105**) was selective for the H460 lung cell line with an IC_{50} of 3.9 μM.

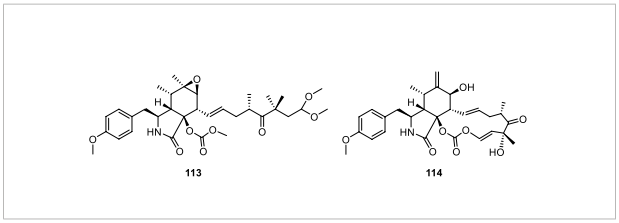
A new alkaloid, scoparasin C (**109**), and four known alkaloid derivatives, [12]-Cytochalasin (**110**), phenochalasin B (**111**), isomer of 5,6-dehydro-7-hydroxy-29-methoxycytochalasin E (**112**), and scoparasin A (**104**) (Kongprapan et al., 2015), were isolated from *Eutypella* sp. PSU–H267. Of note, phenochalasin B (**111**), the methyl ether derivative of **109**, was remarkable against KB cell lines with an IC_{50} value of 2.46 μM. Meanwhile, scoparasin C (**109**), phenochalasin B (**111**), and isomer of 5,6-dehydro-7-hydroxy-29-methoxycytochalasin E (**112**) displayed substantial cytotoxic activity toward Vero cell lines with IC_{50} values of 1.19, 0.04, and 1.01 μM, respectively. [12]-Cytochalasin (**110**) (Sun et al., 2013) exhibited mild cytotoxic activities on MCF-7 and SF-268 with IC_{50} values of 47.2 and 35.4 mM, respectively.

Extraction of a stain of fungus *Eutypella scoparia* 1-15 yielded two new alkaloids, including an open-chain alkaloid



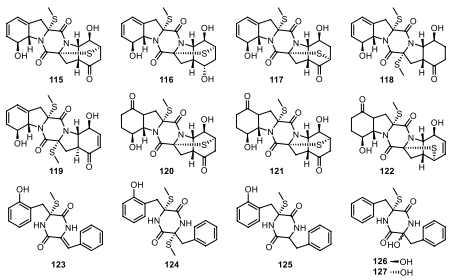
scoparasin C (**113**) and a pyrichalasan scoparasin D (**114**) (Qi et al., 2015). Scoparasin D (**114**) had potent inhibitory activities against A375, A549, MCF-7, and HepG2 cancer cell lines with very low IC_{50} values of 1.08, 2.25, 3.40, and 3.51 μM, respectively.

In the ongoing search for bioactive thiodiketopiperazine-type alkaloids, a class of new congeners named eutypellazines A–M (**115**–**127**) were disclosed from fungus *Eutypella* sp. MCCC 3A00281 based on bioassay and the NMR/MS spectroscopic data



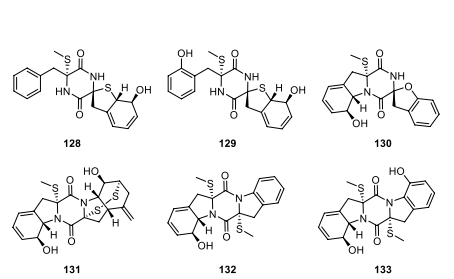
(Niu et al., 2017a). Significantly, eutypellazine E (**115**) exhibited the strongest anti-HIV activity with an IC_{50} value of 3.2 μM, while other alkaloids caused HIV-1 inhibition with IC_{50} values from 5.0 to 20 μM.

Eutypellazines N–S (**128**–**133**) (Niu et al., 2017b), six thiodiketopiperazine-type alkaloids, were isolated from fungus



Eutypella sp. MCCC 3A00281. Among them, eutypellazines N–P (**128**–**130**) contained a special ring structure, while eutypellazines N–O (**128**–**129**) possessing a spirocyclic tetrahydrobenzothiophene motif were a new case of fungus. Furthermore, the inhibitory effects of eutypellazines P–S (**130**–**133**) against vancomycin-resistant enterococci indicated them as potential drug-resistant pathogens with MIC values of 32, 16, and 32 μM, respectively.

2.3 Polyketides



The marine-derived fungus *Eutypella scoparia* FS26, from the South China Sea, yielded two polyketides 7,8-dihydroxy-3 5,7-trimethyl-8,8a-dihydro-1*H*-isochromen-6 (7*H*)-one (**134**) and 6-(hydroxymethyl)-2,2-dimethyl-3,4-dihydro-2*H*-chromene-3,4-diol (**135**) (Sun et al., 2013). Three benzo[c]oxhepteng polyketides were isolated from *Eutypella* sp. D-1 and identified as cladoacetal C (**136**), benzophomopsin A (**137**), and peastalospirane B (**138**) (Yu et al., 2020). Among them, cladoacetal C (**136**) was a new compound and peastalospirane B (**138**) exerted moderate cytotoxicity towards PANC-1 and SW1990 cells with IC_{50} values of 13.4 and 10.3 μM, respectively. Subsequent fractionation of the leaves of *Leptospermum brachuandrum* endophytic fungus *Eutypella scoparia* SCBG-8 led to the identification of six new polyketides eutyscoparols A–F (**139**–**144**), together with a new natural product eutyscoparol G (**145**) (Zhang et al., 2020).

2.4 Others

In addition to the three types of metabolites summarized above, many scholars discovered some other types of compounds from the genus *Eutypella*, including three benzopyran derivatives (**146**–**148**) (Ciavatta et al., 2008; Liao et al., 2017), four lactones (**149**–**152**) (Isaka et al., 2009; Zhang et al., 2021b), and a steroid (**153**) (Zhang et al., 2021a).

Research on a strain of *Eutypella* sp. ICB-OBX resulted in the discovery of novel benzopyran derivatives cytosporin D (**146**) and cytosporin E (**147**) (Ciavatta et al., 2008) from the marine pulmonate mollusc *Onchidium* sp. Most significantly, cytosporin E (**147**) was identified as containing an unusual cyclic carbonate functionality by an analysis of 2D-NMR techniques and modified Mosher's method. Investigation on the fungus *Eutypella* sp. originated from gorgonian corals; one novel enzopyran derivative cytosporin L (**148**) and two known derivatives cytosporin D (**103**) and cytosporin E (**147**) (Liao et al., 2017) were separated and purified. Furthermore, all of them were evaluated for their antiviral activities; the research showed that cytosporin D (**103**) and cytosporin L (**148**) were able to obviously inhibit the respiratory virus (RSV) with IC_{50} values of 30.2 and 72.0 μM, respectively.

Two lactones, eutypellins A and B (**149** and **150**) (Isaka et al., 2009), were separated from the endophyte *Eutypella* sp. BCC 13199, of which eutypellin A (**149**) was able to inhibit proliferation of human small-cell lung cancer cells NCI-H187 with an IC_{50} value of 12 μM. *Eutypella scoparia* SCBG-8 produced two lactones eutyscoparols H–I (**151**–**152**) (Zhang et al., 2021b). In addition, both showed weak activities against HeLa, MDA-MB-231, and MCF-7 tumor cells.

Based on the antibacterial activity, 11 compounds were isolated from *Eutypella* sp. SCBG-8. Among them, eutyscoparene A (**153**) (Zhang et al., 2021a) was identified as a new steroid.

3 Discussion

This review provides a comprehensive overview of the diverse chemical structures and bioactive properties of new metabolites that have been isolated from the fungi *Eutypella* in the last 20 years. Up to 141 new compounds have been discovered and 12 known compounds were first isolated from the 10 *Eutypella* fungal strains. Among 141 new compounds, terpenoids accounted for 68.09%, which were further divided into monoterpenes (2, 1.42%), sesquiterpenes (61, 43.26%), diterpenes (28, 19.86%), and meroterpenoids (5, 3.55%), and the rest were composed of alkaloids (19.15%),

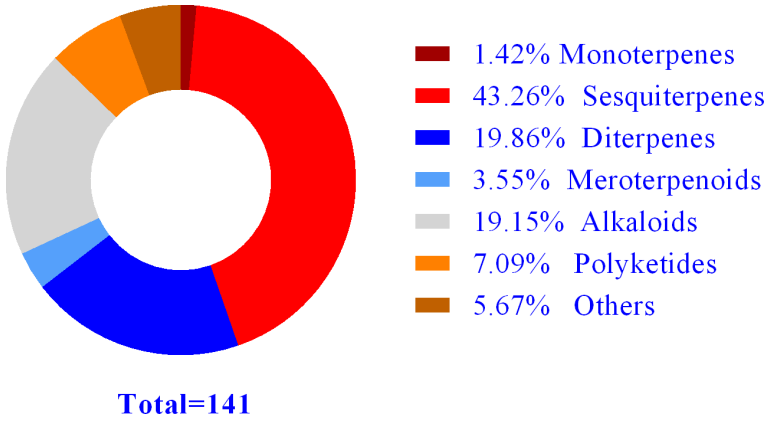


FIGURE 1
The distribution of total new metabolites in *Eutypella* fungi.

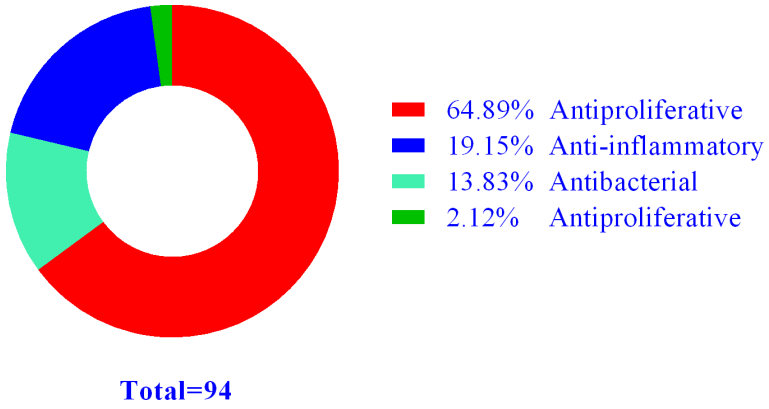


FIGURE 2
Biological activity distribution of active metabolites in *Eutypella* fungi.

polyketides (7.09%), and others (5.67%) (Figure 1). According to the data above, terpenoids comprised the highest proportion of all metabolites. Simultaneously, the antiproliferative (64.89%), anti-inflammatory (19.15%), and antibacterial activities (13.83%) were the top three ranked in biological activity, followed by antiviral (2.13%) activity (Figure 2). In particular, the antiproliferative activity might be the main pharmacological value for the genus *Eutypella*, and we also found that the alkaloids and diterpenes contributed to the antiproliferative activity (37.7% and 31.1%, respectively). Secondly, the sesquiterpenes played a key role in the anti-inflammatory activity. Thus, due to the chemical diversity and medicinal values of the metabolites from the fungi *Eutypella*, it is worth studying the fungi further to find the promising lead compounds for the development of future drug discovery.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. YZ was responsible for designing, searching and writing literature, and JH was responsible for statistics and writing literature.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmars.2022.1074135/full#supplementary-material

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