Journal of Holistic Integrative Pharmacy 5 (2024) 257–261

Contents lists available at ScienceDirect

Journal of Holistic Integrative Pharmacy

journal homepage: www.keaipublishing.com/en/journals/journal-of-holistic-integrative-pharmacy

Secondary metabolites from the cold-seep-derived fungus *Penicillium* sp. SCSIO 41425 and their free radical scavenging activity

Yi Chen [a,b,1], Ying Liu [a,c,1], Jianglian She [a,b], Mengjing Cong [a,b], Junfeng Wang [a,b], Lalith Jayasinghe [a,d], Yonghong Liu [a,b], Xuefeng Zhou [a,b,*]

[a] *CAS Key Laboratory of Tropical Marine Bio-Resources and Ecology/Guangdong Key Laboratory of Marine Materia Medica, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou, 510301, China*
[b] *University of Chinese Academy of Sciences, Beijing, 100049, China*
[c] *Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang, 110016, China*
[d] *National Institute of Fundamental Studies, Hantana Road, Kandy, 200000, Sri Lanka*

ARTICLE INFO

Keywords:
Penicillium sp.
DPPH radical scavenging activity
Cold-seep

ABSTRACT

Objective: To study the chemical compositions from *Penicillium* sp. SCSIO 41425 and explore their DPPH radical scavenging activity.
Methods: Ethyl acetate extract of *Penicillium* sp. SCSIO 41425 was separated and purified by silica gel, Ostadecylsilane (ODS), semi-preparative HPLC, and thin layer chromatography, and their structures were determined by spectroscopic analysis and comparison with the reported literatures.
Results: A total of 18 compounds were isolated from *Penicillium* sp. SCSIO 41425, including one new compound, (2′*R*,3′*R*)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol (**1**) and seventeen known compounds (**2**–**18**). Their structures were elucidated by detailed NMR and ECD calculations. Compounds **4** and **5** exhibited potent DPPH radical scavenging activity, with EC_{50} values of 8.42 and 6.62 μg/mL, which were stronger than the positive control ascorbic acid (EC_{50}, 11.22 μg/mL).
Conclusion: This study expands the natural product library of marine cold-seep-derived fungus and provides marine-derived drug source molecules for potent antioxidants.

1. Introduction

Marine derived microorganisms can produce secondary metabolites with rich structures and activities.[1–3] Deep sea cold seeps are typical deep-sea chemical synthesis driven ecosystems, characterized by rich methane fluid emissions and unique sulfur redox reactions, which give rise to abundant cold spring microorganisms.[4,5] Deep sea fungi play an important role in deep-sea microorganisms, producing a series of secondary metabolites with rich structures and activities, such as alkaloids, polyketides, peptides, etc. They have anti-inflammatory, anti-tumor and other biological activities.[6–8] *Penicillium* sp., as the second most common species of marine fungi, are a rich source for discovering active compounds.[6,9] The novel structures penoxahydrazones A–C and penoxazolones A–B, isolated from the cold-seep-derived fungus *Penicillium oxalicum*, some of them exhibited inhibitory effects on some marine phytoplankton and marine-derived bacteria.[10] Poloncosidins A–F, isolated from the deep-sea-derived fungus *Penicillium polonicum* CS-252, showed inhibitory activities against several human and aquatic pathogens.[11]

In our study, eleven benzene derivatives (**1**–**11**), three polyketide compounds (**12**–**14**), two alkaloid compounds (**15**–**16**), one linear dipeptide derivative (**17**), and one fatty acid (**18**) (Fig. 1) were isolated from a cold-seep-derived fungus *Penicillium* sp. SCSIO 41425. Herein, the specifics of the isolation, structural elucidation, and antioxidant activity assessment of the isolated compounds were reported.

* Corresponding author. CAS Key Laboratory of Tropical Marine Bio-Resources and Ecology/Guangdong Key Laboratory of Marine Materia Medica, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou, 510301, China.
E-mail address: xfzhou@scsio.ac.cn (X. Zhou).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jhip.2024.10.002
Received 25 September 2024; Received in revised form 23 October 2024; Accepted 24 October 2024

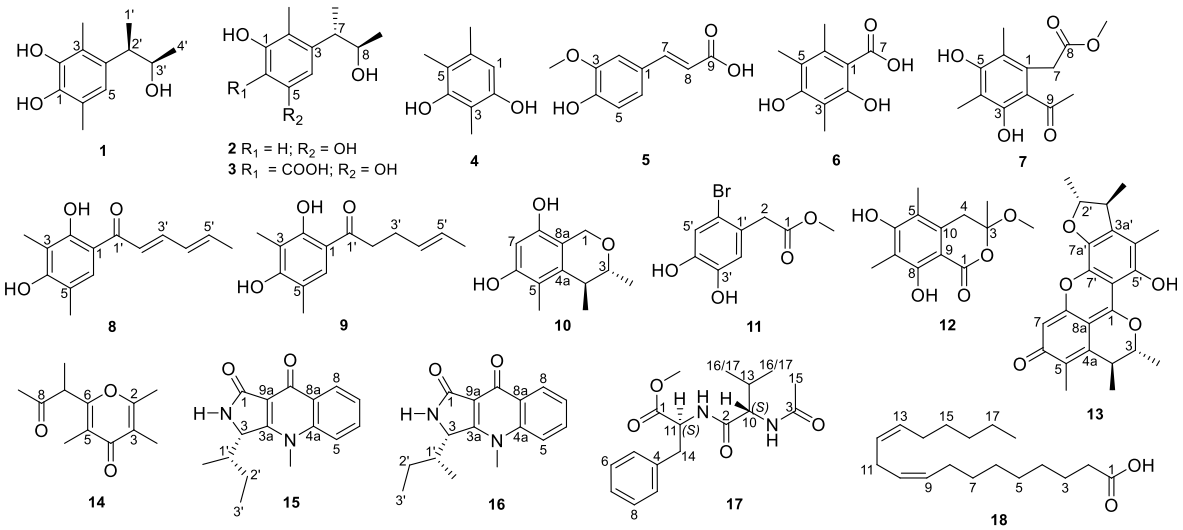

Fig. 1. Structures of compounds **1**–**18**.

2. Materials and methods

2.1. General experimental procedures

The Chirascan circular dichroism spectrometer (Applied Photophysics, Leatherhead Surrey, UK) was used to perform ECD spectra, while optical rotations were calculated using an Anton Paar MPC500 (Anton, Graz, Austria) polarimeter. A Shimadzu UV-2600 PC spectrometer (Shimadzu, Beijing, China) was used to record the UV spectra. The IR spectra were detected by an IR Affinity-1 spectrometer (Shimadzu). Using a Bruker maXis Q-TOF mass spectrometer (Bruker BioSpin International AG, Fällanden, Switzerland), high-resolution electrospray ionization mass spectroscopy (HRESIMS) spectra were acquired. The NMR spectra were tested on a Quantum-I Plus 500 MHz (Q-one Instrument Co., Ltd, Wuhan, China) operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR, and were collected on a AVANCE III HD 700 MHz (Bruker Switzerland AG, Fällanden, Switzerland) operating at 700 MHz for ^{1}H NMR and 175 MHz for ^{13}C NMR. Tetramethylsilane was used as an internal standard. ODS columns (ChromCore 120 C_{18}, 10 × 250 mm, 5 μm; COSMOSIL πNAP 10 × 250 mm; COSMOSIL 5C18-AR-II 10 × 250 mm) were used in semipreparative high-performance liquid chromatography (HPLC) which was performed on the Hitachi Primaide with a DAD detector (Hitachi, Tokyo, Japan). Silica gel (200–300 mesh) was used to perform the column chromatography and spots was detected on TLC (Qingdao Marine Chemical Factory, Qingdao, China) under 254 nm UV light, respectively. Tianjin Fuyu Chemical and Industry Factory, located in Tianjin, China, supplied all of the analytical-grade solvents that were used.

2.2. Fungal material

The strain *Penicillium* sp. SCSIO 41425 was isolated from a cold-seep sediment that was taken from the South China Sea in May 2022 at a depth of 1439 m. It was kept in storage at the Chinese Academy of Sciences (CAS) Key Laboratory of Tropical Marine Bioresources and Ecology, South China Sea Institute of Oceanology, CAS, Guangzhou, China. According to BLAST analysis of the ITS sequence (Supplementary Information), the strain was named *Penicillium* sp. SCSIO 41425 which revealed 90% of the strain's similarities to *Penicillium citrinum* (NR_121224.1). The sequence was finally added to GenBank and assigned the accession number PQ312694.

2.3. Fermentation and extraction

For 7 days, the fungus *Penicillium* sp. SCSIO 41425 was grown statically on MA media at 26 °C, then cut into small pieces and inoculated into the 1 L flask, which was incubated for 30 days using a rice medium (150 g rice, 3.2% sea salt, 150 mL H_2O) under static conditions. The entire fermented culture was extracted five times using Ethyl acetate (EtOAc) and eventually obtained the extract (317.7 g).

2.4. Isolation and purification

Using a step gradient elution of petroleum ether (PE)-dichloromethane (DCM) (*v*:*v* 1:0, 1:1, 0:1), DCM-methyl alcohol (CH_3OH) (*v*:*v* 100:1, 100:3, 20:1, 10:1, 5:1, 2:1, 0:1), yielded twelve fractions (Frs. 1–12) based on TLC characteristics. Fr. 2 was separated by semipreparative HPLC (80% CH_3OH/H_2O, 2.5 mL/min) to obtain compound **18** (7.2 mg, t_R 8.5 min). Fr. 3 to Fr. 6 were merged and was divided into 16 subfractions (Frs. 3-1–3-16) by ODS silica gel eluting with CH_3OH/H_2O (5%–100%). Fr. 3-6 was separated by semipreparative HPLC (35% CH_3OH/H_2O, 2.5 mL/min; 43% CH_3OH/H_2O, 0.04% formic acid, 2.5 mL/min) to obtain compound **4** (31.9 mg, t_R 17.0 min) and compound **5** (2.2 mg, t_R 12.5 min). Fr. 3-7 was separated by semipreparative HPLC (55% CH_3OH/H_2O, 2.5 mL/min) to obtain compound **12** (16.1 mg, t_R 20.5 min). Fr. 3-9 was divided into 14 subfractions (Frs. 3-9-1–3-9-14) by ODS silica gel eluting with CH_3OH/H_2O (10%–100%). Compound **13** (10.4 mg, t_R 13.8 min) was purified from Fr. 3-9-10 by semipreparative HPLC (76% CH_3OH/H_2O, 3.0 mL/min). Fr. 3-11 was separated by semipreparative HPLC (70% CH_3OH/H_2O, 3.0 mL/min) to obtain compound **8** (9.6 mg, t_R 24.3 min) and **9** (5.1 mg, t_R 27.8 min). Fr. 7 to Fr. 9 were merged and was divided into 13 subfractions (Frs. 7-1–7-13) by ODS silica gel eluting with CH_3OH/H_2O (20%–100%). Fr. 7-4 was separated into five components (Frs. 7-4-1–7-4-5) by semipreparative HPLC (40% CH_3OH/H_2O, 3.0 mL/min). Compound **1** (5.1 mg, t_R 19.4 min) was purified from Fr. 7-4-1 by semipreparative HPLC (38% CH_3OH/H_2O, 2.5 mL/min). Compound **14** (2.7 mg, t_R 32.7 min) was purified from Fr. 7-4-2 by semipreparative HPLC (33% CH_3OH/H_2O, 2.5 mL/min). Fr. 7-4-3 was separated by semipreparative HPLC (35% CH_3CN/H_2O, 0.04% formic acid, 3.0 mL/min) to obtain compound **7** (6.1 mg, t_R 9.4 min). Compound **6** (6.4 mg, t_R 31.2 min) and compound **10** (3.1 mg, t_R 33.6 min) were purified from Fr. 7-4-5 by semipreparative HPLC (30% CH_3OH/H_2O, 3.0 mL/min). Fr. 7-5 to Fr. 7-6 were merged once more and divided into 10 subfractions (Frs. 7-5-1–7-5-10) by ODS silica gel eluting with CH_3OH/H_2O (5%–100%). Compound **17** (5.5 mg, t_R 36.2 min) was purified from

Table 1
^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data for compound **1** in DMSO-d_6.

Position	δ_H (ppm), *J* (Hz)	δ_C (ppm)
1	–	153.2
2	–	153.0
3	–	113.6
4	–	140.3
5	6.28, s	105.1
6	–	108.3
1′	1.04, d, (7.0)	15.2
2′	2.93, m	41.1
3′	3.66, m	69.1
4′	0.93, d, (6.2)	19.1
3-CH_3	1.94, s	11.5
6-CH_3	2.02, s	9.1

Fr. 7-5-2 by semipreparative HPLC (65% CH_3OH/H_2O, 0.04 % formic acid, 2.8 mL/min). Fr. 10 was separated by semipreparative HPLC (85% CH_3OH/H_2O, 3.0 mL/min) to offer four subfractions (Frs. 10-1–10-4). Compound **2** (10.0 mg, t_R 14.2 min) and compound **11** (3.8 mg, t_R 13.4 min) were purified from Fr. 10-1 by semipreparative HPLC (45% CH_3OH/H_2O, 2.5 mL/min). Fr. 10-3 was separated by semipreparative HPLC (50% CH_3OH/H_2O, 2.2 mL/min) to obtain compound **3** (8.5 mg, t_R 9.2 min). Compound **15** (15.6 mg, t_R 10.5 min) and compound **16** (11.5 mg, t_R 12.0 min) were purified from Fr. 10-4 by semipreparative HPLC (68% CH_3OH/H_2O, 3.0 mL/min).

(2′*R*,3′*R*)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol (**1**): Red brown oil; $[\alpha]^{25}_D$ –9.7 (*c* 0.1, CH_3OH); UV (CH_3OH): λ_{max} (log ε): 206 (4.52); ECD (0.48 mM, CH_3OH) λ_{max} 201 (–6.81), 216 (–1.05), 232 (–2.93), 264 (+0.29); IR (film) ν_{max} 3348, 1645, 1634, 1101 cm^{-1}; ^{1}H and ^{13}C NMR data see Table 1; HRESIMS *m/z* 211.1330 $[M+H]^+$ (calcd. for $C_{12}H_{19}O_3^+$, 211.1329).

2.5. Computational methods

Optimized the four conformational structures of compound **1** using MM2 molecular force field in ChemBio3D Ultra 14.0, and conducted random conformational searches for optimized structures using MMFF molecular force field in Spartan'14 software. Selected reasonable conformations beyond 5% Boltzmann distribution from the results. Then, Gaussian 09W software density functional DFT was used for further optimization at the B3LYP/6-31+G (d) level. The optimized stable conformation was subjected to energy calculation at the B3LYP/6-311+G (d, p) level, and the calculated results were weighted averaged using the Boltzmann distribution. Next, Gaussian View 6.0 software was used to adjust the half width parameter (0.3–0.4 eV) and exported the ECD curve data. Ultimately, ECD spectra were drawn using Origin 2021 software.[12,13]

In the meanwhile, MMFF was used to calculate the ^{13}C NMR chemical shift in Spartan'14 software, selecting conformers of **1** with a Boltzmann population of greater than 5%. The Gaussian 09W software density functional DFT was used to re-optimize the conformers at the B3LYP/6-31G (d) level. GIAO was used to compute the chemical shifts of the NMR data at the PCM/mPW1PW91/6-311G (d, p) level in dimethylsulfoxide. The Boltzmann distribution theory was used to average the simulated spectra of the conformers in order to obtain the final spectra. The DP4+ probability analysis was carried out using shielding constants. The Excel spreadsheet, which was freely accessible at sarotti-NMR.weebly.com, was used to perform the DP4+ computations.[12]

2.6. Antioxidant activity assay

The effect of compounds on DPPH radicals was estimated referring to the previous methods.[14,15] Generally, the compounds were dissolved in DPPH methanol solution to get a final concentration of 2.5–250 μg/mL. The mixture was thoroughly shaken before being allowed to stand at room temperature in the dark for 30 mins, measured the OD_{517} values

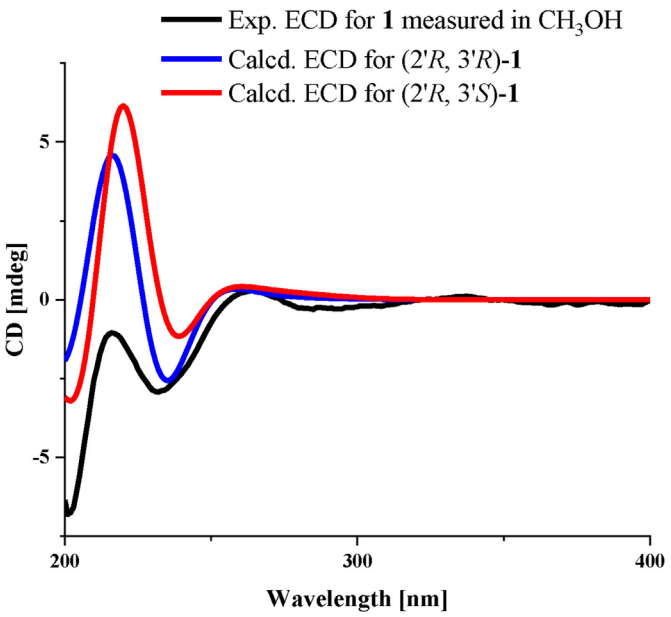

Fig. 2. Experimental and calculated ECD spectrum of **1**.

using the PerkinElmer Enspire Multi-mode micro-orifice detector and enzyme labeling instrument (PerkinElmer, Waltham, MA, USA). This experiment used ascorbic acid as a positive control. Then, used the formula to calculate the free radical scavenging rate K (%) based on the obtained OD_{517} value, and determined the EC_{50} value using Origin 2021.

3. Results and discussion

Compound **1** was obtained as a red brown oil and was determined to have the molecular formula $C_{12}H_{18}O_3$ from the HRESIMS data at *m/z* 211.1330 $[M+H]^+$. The 1D NMR data of **1** (Table 1) showed signals of five unsaturated carbon signals (δ_C 153.2, 153.0, 113.6, 140.3, 108.3), one aromatic methine ($\delta_{H/C}$ 6.28/105.1), one oxygen-containing saturated methine ($\delta_{H/C}$ 3.66/69.1), one saturated methine ($\delta_{H/C}$ 2.93/41.1), and four methyls ($\delta_{H/C}$ 1.94/11.5, 2.02/9.1, 1.04/15.2, and 0.93/19.1). The NMR data of **1** was carefully analyzed and found to be comparable to 4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol with its planar structure.[16] By calculating the CD, the measured curve of compound **1** was fitted with the theoretical curves of (2′*R*,3′*R*)-**1**, (2′*R*,3′*S*)-**1**, (2′*S*, 3′*R*)-**1**, and (2′*S*,3′*S*)-**1**. The results showed that the trend of the curve of (2′*R*,3′*R*)-**1** and (2′*R*,3′*S*)-**1** were basically consistent with the measured curve (Fig. 2). This resulted in two unassigned chiral centers (CH-2′ and CH-3′) with two probable diastereoisomers, 3′*R* and 3′*S*. The PCM solvent continuum model with dimethylsulfoxide as a solvent was then studied using the gauge independent atomic orbital (GIAO) strategy at the mPW1PW91/6-311G (d, p) level of theory. With a 99.77% confidence level, the DP4+ probability analysis revealed that the configuration (2′*R*, 3′*R*)-**1** was the most likely stereoisomer. Therefore, it was confirmed that the compound **1** was a new configuration compound, and the final structure of **1** was determined to be (2′*R*,3′*R*)-4-(3-hydroxybutan-2-yl)-3, 6-dimethylbenzene-1,2-diol.

The structures of the seventeen known compounds were identified as phenol A (**2**)[17,18], phenol A acid (**3**)[17,19], 2,4-dihydroxy-3,5,6-trimethylbenzene (**4**)[20], ferulic acid (**5**)[21], 2,4-dihydroxy-3,5,6-trimethylbenzoic acid (**6**)[22], methyl 2-(2-acetyl-3,5-dihydroxy-4,6-dimethylphenyl)acetate (**7**)[23], sorbicillin (**8**)[24,25], 2′,3′-dihydrosorbicillin (**9**)[24,26], decarboxydihydrocitrinin (**10**)[27], methyl 2-(6-bromo-3,4-dihydroxyphenyl) acetate (**11**)[28], stoloniferol A (**12**)[29], penicitrinone A (**13**)[27], 2,3,5-trimethyl-6-(3-oxobutan-2-yl)-4*H*-pyran-4-one (**14**)[30], quinolactacin A2 (**15**)[31], quinolactacin A1 (**16**)[31], *N*-acetyl-L-valyl-L-phenylalanine methyl ester (**17**)[32] and α-linoleic acid (**18**)[33–35] by contrasting the spectroscopic

Table 2
DPPH radical scavenging activity assay.

Compounds	1	2	3	4	5	7	10	13	Ascorbic acid
EC_{50} (μg/mL)	41.37	41.07	32.59	8.42	6.62	55.95	19.74	53.83	11.22

data with those documented in the literature.

Free radicals mediate the occurrence and development of many diseases *in vivo*, such as cancer, diabetes, etc.[36,37] In order to investigate the free radical scavenging activity of the isolated compounds, the DPPH radical scavenging activity of the isolated compounds was tested using a 96 well plate method. The results in Table 2 indicated that compounds **4** (EC_{50}, 8.42 μg/mL) and **5** (EC_{50}, 6.62 μg/mL) demonstrated potent radical scavenging capacity, which were superior to the positive control (ascorbic acid, EC_{50}, 11.22 μg/mL). In addition, compounds **1**–**3** and **10** also exhibited strong DPPH scavenging activity. Comparing the activities of compounds **1**, **2**, and **3**, it could be observed that their activities were stronger when a carboxyl group was attached to the benzene ring than when a hydroxyl group was attached, indicating that attaching a carboxyl group to the benzene ring could enhance free radical scavenging activity. Comparing the activities of compounds **5** and **7**, it was found that their activities decreased when the carboxyl group on the chain was esterified. The above analysis indicated that carboxyl groups had a significant impact on the resistance of compounds to free radicals. It was speculated that this was due to the reaction between carboxyl groups (•COOH) and free radicals (•OH), which enhanced their free radical scavenging ability. Research had shown that excessive production of free radicals in the body was considered a trigger for various damages in biological species and a deactivator of enzymes, leading to the occurrence of many diseases.[38] Therefore, compounds **4** and **5** had good potential in anti-tumor and other diseases, which may develop into tiny therapeutic molecules derived from marine cold-seep.

4. Conclusion

A new benzene derivative, (2′*R*,3′*R*)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol (**1**), together with seventeen known compounds (**2**–**18**) were isolated from the secondary metabolites of rice fermentation by *Penicillium* sp. SCSIO 41425, a fungus derived from deep-sea cold-seep. Compound **1** was a new compound reported for its configuration for the first time, and compound **17** was a linear dipeptide isolated from a deep-sea cold-seep strain for the first time, which had good antibacterial activity of its similar chemicals.[39,40] Compounds **4** (EC_{50}, 8.42 μg/mL) and **5** (EC_{50}, 6.62 μg/mL) had strong free radical scavenging ability, which were stronger than the positive control (ascorbic acid, EC_{50}, 11.22 μg/mL), which had the potential to become potent antioxidants. In summary, the active and diverse compounds isolated in this study further expand the pool of active natural products from marine cold-seep.

CRediT authorship contribution statement

Yi Chen: Writing – original draft, Investigation, Data curation. **Ying Liu:** Investigation, Data curation. **Jianglian She:** Data curation. **Mengjing Cong:** Investigation. **Junfeng Wang:** Data curation. **Lalith Jayasinghe:** Data curation. **Yonghong Liu:** Project administration. **Xuefeng Zhou:** Writing – review & editing, Project administration, Funding acquisition.

Conflicts of interest

These authors have no conflict of interest to declare.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Zhou xuefeng reports financial support was provided by The Special Project for Marine Economic Development of the Department of Natural Resources of Guangdong Province, and the International Partnership Program of Chinese Academy of Sciences. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was funded by the Special Project for Marine Economic Development of the Department of Natural Resources of Guangdong Province (GDNRC[2024]25), and the International Partnership Program of Chinese Academy of Sciences (059GJHZ2023104MI).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhip.2024.10.002.

References

1. Chen SH, Cai RL, Liu ZM, et al. Secondary metabolites from mangrove-associated fungi: source, chemistry and bioactivities. *Nat Prod Rep*. 2022;39(3):560–595.
2. She JL, Zhou XF. New insights into the antitumor potential of natural piericidins. *J Holistic Integr Pharm*. 2021;2(3):153–162.
3. Zhou XF. Mangrove soil-derived *Streptomyces*: an important resource of pharmaceutical active natural products. *J Holistic Integr Pharm*. 2022;3(3):300–314.
4. Chi LP, Li XM, Wan YP, et al. Two new phenol derivatives from the cold seep-derived fungus *Aspergillus insuetus* SD-512. *Chem Biodivers*. 2021;18(10):e2100512.
5. Cong MJ, Pang XY, Zhao K, et al. Deep-sea natural products from extreme environments: cold seeps and hydrothermal vents. *Mar Drugs*. 2022;20(6):404.
6. Cai SY, He JL, Bai KK, et al. Secondary metabolites of deep-sea fungi and their biological activities: research advances. *J Int Pharm Res*. 2020;47(12):1033–1046, 1056.
7. He LM, Zhao ZF, Zhang MK, et al. Peniciisoquinoline A: a new tetrahydroisoquinoline from mangrove-derived fungus *Penicillium sp.* DM27. *J Holistic Integr Pharm*. 2022;3(3):248–254.
8. Xu JL, Liu HX, Chen YC, et al. Highly substituted benzophenone aldehydes and eremophilane derivatives from the deep-sea derived fungus *Phomopsis lithocarpus* FS508. *Mar Drugs*. 2018;16(9):329.
9. Wang JW, Liu YY, Chen GY, et al. Alkaloid-metabolites from the mangrove-derived fungus *Penicillium robsamsonii* HNNU0006. *Fitoterapia*. 2024;175(2024):105906.
10. Liu YP, Fang ST, Shi ZZ, et al. Phenylhydrazone and quinazoline derivatives from the cold-seep-derived fungus *Penicillium oxalicum*. *Mar Drugs*. 2020;19(1):9.
11. Li YH, Li XM, Li X, et al. Verrucosidin derivatives from the deep sea cold-seep-derived fungus *Penicillium polonicum* CS-252. *Int J Mol Sci*. 2022;23(10):5567.
12. Cai J, Gao L, Wang Y, et al. Discovery of a novel anti-osteoporotic agent from marine fungus-derived structurally diverse sirenins. *Eur J Med Chem*. 2024;265(2024):116068.
13. Luo XW, Lin XP, Tao HM, et al. Isochromophilones A-F, cytotoxic chloroazaphilones from the marine mangrove endophytic fungus *Diaporthe* sp. SCSIO 41011. *J Nat Prod*. 2018;81(4):934–941.
14. Hatano T, Kagawa H, Yasuhara T, et al. Two new flavonoids and other constituents in licorice root: their relative astringency and radical scavenging effects. *Chem Pharm Bull*. 1988;36(6):2090–2097.
15. Yen GC, Chen HY. Antioxidant activity of various tea extracts in relation to their antimutagenicity. *J Agric Food Chem*. 1995;43(1):27–32.
16. Han Z, Mei WL, Cui HB, et al. Antibacterial constituents from the endophytic fungus *Penicillium* sp. of mangrove plant *Cerbera manghas*. *Chem J Chin Univ*. 2008;29(4):749–752.
17. Rödel T, Gerlach H. Enantioselective synthesis of the polyketide antibiotic (3*R*,4*S*)-(−)-citrinin. *Liebigs Ann*. 1995;5(5):885–888.
18. Song TF, Chen MX, Ge ZW, et al. Bioactive penicipyrrodiether A, an adduct of GKK1032 analogue and phenol a derivative, from a marine-sourced fungus *Penicillium* sp. ZZ380. *J Org Chem*. 2018;83(21):13395–13401.
19. Anh NM, Huyen VTT, Quyen VT, et al. Antimicrobial and cytotoxic secondary metabolites from a marine-derived fungus *Penicillium Citrinum* VM6. *Curr Microbiol*. 2023;81(1):32.

20. Wang L, Qin D, Zhang K, et al. Metabolites from the co-culture of nigranoic acid and *Umbelopsis dimorpha* SWUKD3.1410, an endophytic fungus from *Kadsura angustifolia*. *Nat Prod Res*. 2017;31(12):1414–1421.
21. Choi BR, Hong SS, Han XH, et al. Antioxidant constituents from *Portulaca oleracea*. *Nat Prod Sci*. 2005;11(4):229–232.
22. Cui XQ, Zhu GL, Liu HS, et al. Diversity and function of the Antarctic krill microorganisms from *Euphausia superba*. *Sci Rep*. 2016;6:36496.
23. Chen L, Huang K, Zhong P, et al. Tumonoic acids K and L, novel metabolites from the marine-derived fungus *Penicillium citrinum*. *Heterocycles*. 2012;85(2):413–419.
24. Trifonov LS, Bieri JH, Prewo R, et al. Isolation and structure elucidation of three metabolites from *Verticillium intertextum*: sorbicillin, dihydrosorbicillin and bisvertinoquinol. *Tetrahedron*. 1983;39(24):4243–4256.
25. Zhao PJ, Li GH, Shen YM. New chemical constituents from the endophyte *Streptomyces* species LR4612 cultivated on *Maytenus hookeri*. *Chem Biodiversity*. 2006; 3(3):337–342.
26. Maskey RP, Grün-Wollny I, Laatsch H. Sorbicillin analogues and related dimeric compounds from *Penicillium notatum*. *J Nat Prod*. 2005;68(6):865–870.
27. Wakana D, Hosoe T, Itabashi T, et al. New citrinin derivatives isolated from *Penicillium citrinum*. *J Nat Med*. 2006;60(4):279–284.
28. Leutou AS, Yun K, Kang JS, et al. Induced production of methyl bromodihydroxyphenyl acetates by the marine-derived fungus *Aspergillus* sp. *Chem Pharm Bull*. 2013;61(4):483–485.
29. Xin ZH, Tian L, Zhu TJ, et al. Isocoumarin derivatives from the sea squirt-derived fungus *Penicillium stoloniferum* QY2-10 and the halotolerant fungus *Penicillium notatum* B-52. *Arch Pharm Res (Seoul)*. 2007;30(7):816–819.
30. Li DH, Cai SX, Tian L, et al. Two new metabolites with cytotoxicities from deep-sea fungus, *Aspergillus sydowi* YH11-2. *Arch Pharm Res (Seoul)*. 2007;30(9):1051–1054.
31. Kim WG, Song NK, Yoo ID. Quinolactacins A1 and A2, new acetylcholinesterase inhibitors from *Penicillium citrinum*. *J Antibiot*. 2001;54(10):831–835.
32. Lu LW, Bao SS, Tan MH, et al. Research on alkaloid metabolites from endophytic fungus *Penicillium* sp. *J China Three Gorges Univ (Nat Sci)*. 2018;40(1):97–99.
33. Zeng JX, Xu BB, Bi Y, et al. Chemical constitutes from *plantaginis semen* (II). *Chin J Exp Tradit Med Formulae*. 2017;23(4):81–84.
34. Alamsjah MA, Hirao S, Ishibashi F, et al. Algicidal activity of polyunsaturated fatty acids derived from *Ulva fasciata* and *U. pertusa* (Ulvaceae, Chlorophyta) on phytoplankton. *J Appl Phycol*. 2007;20(5):713–720.
35. Song ZW, Sun YJ, Xu SY, et al. Secondary metabolites from the endophytic fungi *Fusarium decemcellulare* F25 and their antifungal activities. *Front Microbiol*. 2023;14: 1127971.
36. Gupta N, Verma K, Nalla S, et al. Free radicals as a double-edged sword: the cancer preventive and therapeutic roles of curcumin. *Molecules*. 2020;25(22):5390.
37. Zaric BL, Macvanin MT, Isenovic ER. Free radicals: relationship to human diseases and potential therapeutic applications. *Int J Biochem Cell Biol*. 2023;154:106346.
38. Liu ZQ. Bridging free radical chemistry with drug discovery: a promising way for finding novel drugs efficiently. *Eur J Med Chem*. 2020;189:112020.
39. Dai Y, Lin Y, Pang XY, et al. Peptides from the soft coral-associated fungus *Simplicillium* sp. SCSIO41209. *Phytochemistry*. 2018;154(2018):56–62.
40. Liang X, Yang JF, Huang ZH, et al. New antibacterial peptaibiotics against plant and fish pathogens from the deep-sea-derived fungus *Simplicillium obclavatum* EIODSF 020. *J Agric Food Chem*. 2024;72(12):6402–6413.