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REVIEW

Marine-derived fungi as a source of bioactive indole alkaloids with diversified structures

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Abstract

Marine-derived fungi are well known as rich sources of bioactive natural products. Growing evidences indicated that indole alkaloids, isolated from a variety of marine-derived fungi, have attracted considerable attention for their diverse, challenging structural complexity and promising bioactivities, and therefore, indole alkaloids have potential to be pharmaceutical lead compounds. Systemic compilation of the relevant literature. In this review, we demonstrated a comprehensive overview of 431 new indole alkaloids from 21 genera of marine-derived fungi with an emphasis on their structures and bioactivities, covering literatures published during 1982–2019.

Keywords Indole alkaloid · Marine-derived fungus · Chemical diversity · Bioactivity

Introduction

Marine-derived fungi have been known to play a vital role in acquiring drug precursors with novel skeletons and bioactivities, whose metabolites have important application prospects in pharmaceutical research and development by virtue of their structural diversity, high multi-target activities and low toxic side effects (Cao et al. 2020; Liu et al. 2019; Molinski et al. 2009). In particular, fungal alkaloids, as one type of the nitrogen-containing natural products, are mainly derived from amino acid metabolism and the mevalonate pathway (Urban et al. 2000). As an unexploited treasure trove, alkaloids are usually present in a fungus as a mixture consisting of several major or a few minor compounds with the same biosynthetic origin (Dembitsky et al. 2005; Kita et al. 2005).

Marine-derived indole alkaloids have been by far the largest number of heterocyclic alkaloids, which have proven to be rich source of natural products with unique structures and abundant biological activities. Particularly, it has been proven that marine indole alkaloids may act on serotonin receptors to regulate neural activity, which suggested that this group of compounds might possess important research value in targeting neural receptors (Macedo et al. 2011). Notably, the majority of the antidepressant drugs on the market currently act on the amine neurotransmitter system. For instance, gelliusines A and B produced by marine *Orina* sp. significantly inhibit ligand binding (on neuropeptide Y receptor and human B2 bradykinin receptor sites) (Bifulco et al. 1995; Kochanowska-Karamyan and Hamann 2010). The structural similarity between endogenous indole alkaloids and 5-HT implicitly provided a material basis for exploring serotonin receptor function, which might be expected to be agonists of neurological disorders associated with 5-HT serotonin receptors.

Since 1960s, plenty of novel indole heterocyclic alkaloids have been continuously isolated from marine-derived fungi. Most of the marine-derived fungi perch on appendages, while a few live freely. According to the characteristics of their respective habitat, marine-derived fungi can be divided into woody, parasitic algal, mangrove-derived fungi, seaweed-associated fungi, parasitic animal fungi, etc. At the same time, indole alkaloids are isolated from various strains, which can be divided into indole diketopiperazine alkaloids

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(DKPs), indole diterpene alkaloids (IDTs), indolequinazoline alkaloids, cytochalasins and simple indole alkaloids on the basis of their chemical structure (Gul and Hamann 2005; Meyers and Hellring 1982; Rateb and Ebel 2011; Reddy et al. 2019). Given that different groups attach to the indole skeletons, these kinds of compounds have shown broad biological activities, such as lethality-toxicity, cytotoxic, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, as well as special protease enzyme inhibition activities (Norwood IV and Huigens III 2019; Sallam et al. 2014; Smetanina et al. 2007). As a consequence, many of these compounds show potential clinical application or have been used in clinical treatment. For example, halimide, a cytotoxic diketopiperazine phenylahistin isolated from a marine-derived *Aspergillus ustus* led to the synthesis of plinabulin (NPI-2358). As a novel tumor vascular inhibitor, plinabulin was active against tumor cells and restrained tubulin depolymerization (IC_{50} = 9.8–18.0 μmol/L), and has progressed to clinical stage phase III (Overy et al. 2014).

In this review, we provided information on current and potential pharmaceuticals, including the above subtype of indole alkaloids, their structure-based classification, bioactivity evaluation and producing strain of 431 reported indole alkaloids isolated from marine-derived fungi during 1982–2019 (Supplementary Table S1). In conclusion, the discovery of novel active indole alkaloids from marine-derived fungi is a feasible approach to find lead compounds.

Isolations, structures, and bioactivities of indole alkaloids from marine-derived fungi

Indole diketopiperazine alkaloids (DKPs)

Naturally occurring diketopiperazine alkaloids (DKPs) were a class of fungal secondary metabolites with diverse scaffolds, of which the spirocyclic DKPs were rarely found from nature. Phomazines A–C (**1–3**) (Fig. 1), associated with the mangrove plant *Kandelia candel*, were first isolated from the fermentation broth of an endophytic fungus, *Phoma* sp. OUCMDZ-1847. Compound **2** exhibited potent cytotoxicity against the MGC-803 (IC_{50} = 8.4 μmol/L) (Kong et al. 2014). Pseuboydone D (**4**) was isolated from the culture broth of the marine-derived fungus *Pseudallescheria boydii* F19-1 associated with the soft coral *Lobophytum crassum*. Compound **4** was devoid of antimicrobial and cytotoxic activities (Lan et al. 2016). Bioassay in association with the NMR/MS spectroscopic data guided fractionation of the solid fermentation of *Eutypella* sp. MCCC 3A00281, resulted in the isolation of eutypellazines A–R (**5–23**). Furthermore, compounds **5–16** showed inhibitory effects against pNL4.3.Env-.Luc co-transfected 293 T cells (HIV-1 model cells) with low cytotoxicity with the IC_{50} ranging from 3.2 to 18.2 μmol/L. In addition, compound **14** displayed reactivating effects toward latent HIV-1 in J-Lat A2 cells, while **20–22** exhibited inhibitory effects against vancomycin-resistant enterococci (VRE) with the MIC values of 32.0, 16.0, and 32.0 μmol/L, respectively, suggesting that they may be the potential inhibitors toward drug-resistant pathogenic bacteria (Niu et al. 2017a, b).

6-Acetylmonodethiogliotoxin (**24**) (Supplementary Fig. S1), isolated from a deep sea sediment derived fungus *Dichotomomyces cejpii*, dose-dependently down-regulated TNFα-induced NF-κB activity in human chronic myeloid leukemia cells with an IC_{50} value of 38.5 μmol/L (Harms et al. 2015). Bis(dethio)-10a-methylthio-3a-deoxy-3,3a-didehydrogliotoxin (**25**) and its analogue 6-deoxy-5a,6-didehydrogliotoxin (**26**) were obtained from the fungus *Penicillium* sp. JMF034, both of which exhibited cytotoxic activities against P388 murine leukemia cells with IC_{50} values of 3.4 μmol/L and 0.058 μmol/L, respectively (Sun et al. 2011). Neosartins A and B (**27** and **28**) and gliotoxin (**29**) were isolated from the marine-derived fungus *Neosartorya pseudofischeri*, of which, compound **29** showed potent inhibition against *Staphylococcus aureus* (ATCC29213), *S. aureus* (R3708) and *Escherichia coli* (ATCC25922) with MIC values of 12.2 μmol/L, 1.5 μmol/L and 24.5 μmol/L, respectively, and was screened for cytotoxic activities on the human embryonic kidney (HEK) 293 cell line and human colon cancer cell lines HCT-116 and RKO with IC_{50} values of 1.6, 1.2, and 0.8 μmol/L, respectively (Liang et al. 2014).

Graphiumins A–J (**30–39**) (Supplementary Fig. S2), bearing structurally rare DKPs with a phenylalanine-derived indolin substructure, were isolated from the culture broth of the marine-derived fungus *Graphium* sp. OPMF00224. Compounds **30**, **33**, **34**, **36–39** inhibited yellow pigment production by methicillin-resistant *Staphylococcus aureus* (MRSA) (Fukuda et al. 2015a, b). Quellenin (**40**) was isolated from the deep-sea fungus *Aspergillus* sp. YK-76, which was isolated from an *Osedax* sp. annelid, commonly called bone-eating worm, collected at the São Paulo Ridge off the Brazilian coastline (Takahashi et al. 2018). An analog of fellutanine A (**41**) was isolated from the ethyl acetate extract of a culture of the sponge-associated fungus *Neosartorya glabra* KUFA 0702 (May Zin et al. 2016).

(±)-Acrozines A–C (**42–47**) (Supplementary Fig. S3), three pairs of new *N*-methoxy-containing indole diketopiperazine enantiomers, were isolated from the culture extract of *Acrostalagmus luteoalbus* TK-43. In the bioassay, compound **45** showed activity against the plant pathogen *Fusarium solani* with the MIC value of 32.0 μg/ml, which was more potent than that of its enantiomer **44** and its epimers **42** and **43** (MIC > 64.0 μg/ml). Compounds **42** and **43** had modest anti-acetylcholinesterase (AChE) activity with an IC_{50} value of 9.5 μmol/L, and after chiral resolution, **42** (IC_{50} = 2.3 μmol/L) showed better activity than

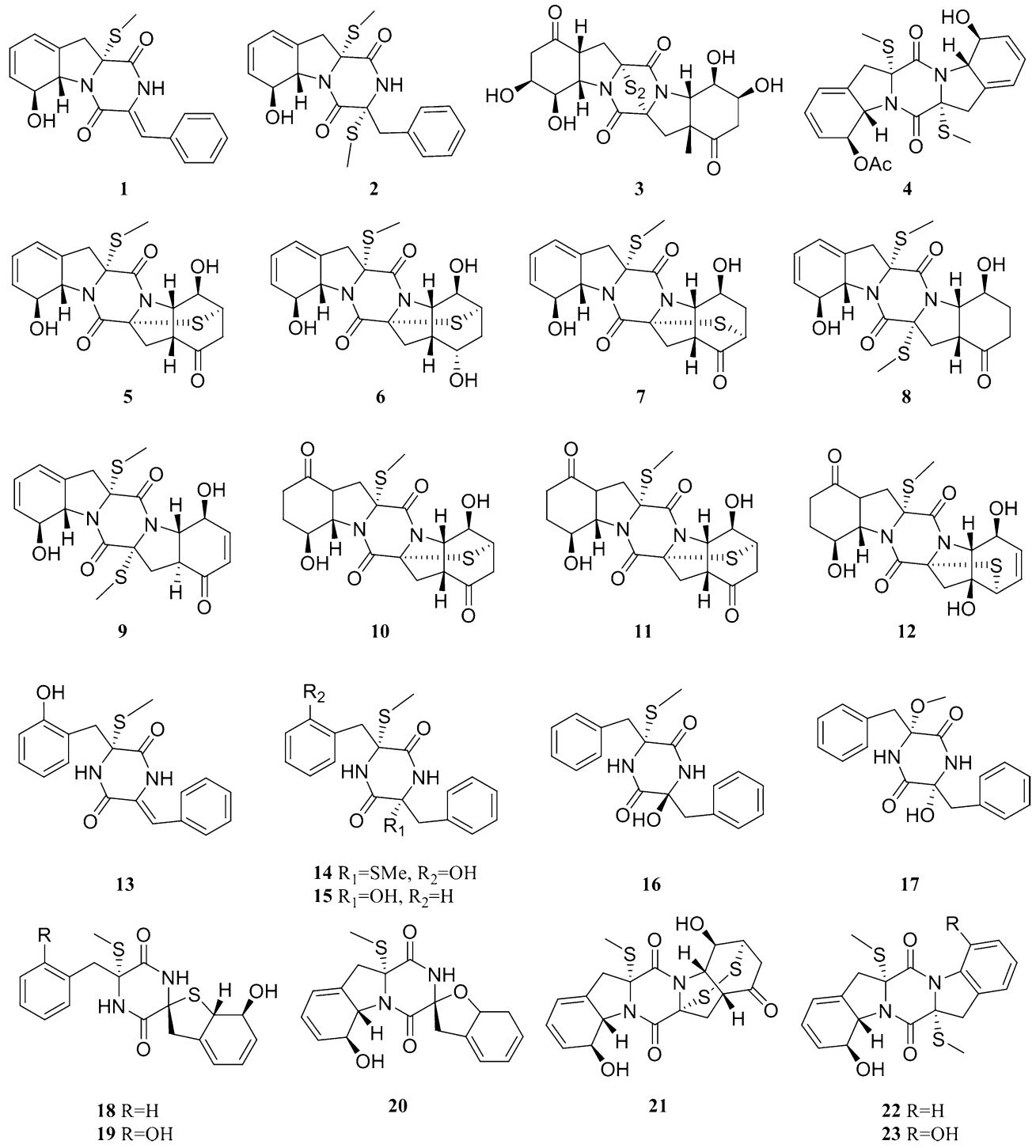

Fig. 1 The chemical structures of compounds **1**–**23**

that of **43** (IC_{50} = 13.8 μmol/L) (Cao et al. 2019). Pseudellones A–C (**48**–**50**) were isolated from the marine-derived fungus *Pseudallescheria ellipsoidea* F42-3. Compounds **48** and **49** were a pair of irregularly bridged epimonothiodiketopiperazine diastereomers constructed from unusual 3-indolylglycine and alanine residues, and compound **50** possessed an unique skeleton with a 2,2-di(3-indolyl)-1-propone fragment attached to a tryptophan derivative via an amide bond (Liu et al. 2015a).

Raistrickindole A (**51**) (Supplementary Fig. S4), a DKP containing an unusual pyrazino[1′,2′:2,3]-[1,2]oxazino[6,5-*b*]indole tetraheterocyclic ring system, was isolated from the marine-derived fungus *Penicillium raistrickii* IMB17-034. In the in vitro inhibitory assay against the hepatitis C virus (HCV) life cycle, compound **51** showed anti-HCV activity with an EC_{50} value of 5.7 μmol/L (Li et al. 2019a). Protubonines A and B (**52** and **53**) were isolated from the marine-derived fungus *Aspergillus* sp. SF-5044 (Lee et al. 2011). Takakiamide (**54**), a prenylated indole alkaloid, was isolated from the culture of the algicolous fungus *N. takakii* KUFC 7898 (May Zin et al. 2015). Another DPK, brevianamide X (**55**), was obtained from the marine-derived fungus *A. fumigatus* MR2012 (Wakefield et al. 2017).

Four alkaloids, including two meleagrin analogs, meleagrins B and C (**56** and **57**), and two DKPs, roquefortines F and G (**58** and **59**) (Supplementary Fig. S5), were isolated from a deep ocean sediment-derived fungus *Penicillium* sp., among which compound **56** showed moderate cytotoxicity against HL-60, A549, BEL-7402, and MOLT-4 cell lines with IC_{50} values of 6.7, 2.7, 1.8, and 2.9 μmol/L, respectively (Du et al. 2009). Chemical investigation of the deep-sea-derived fungus *P. granulatum* MCCC 3A00475 led to the isolation of roquefortine J (**60**) (Niu et al. 2018). New plant growth regulators, brevicompanines A and B (**61** and **62**), were purified from *P. brevicompactum*. Compounds **61** and **62** accelerated the root growth of the seedlings directly proportional to its concentration from 10.0 to 300.0 mg/L (Kusano et al. 1998).

9-Deoxy-PF1233 B (**63**), 9-deoxy-PF1233 A (**64**), *seco*-PF1233 B carboxylic acid (**65**), 9-deoxy-*seco*-PF1233 B carboxylic acid (**66**), and 4,9-dideoxy-*seco*-PF1233 B carboxylic acid (**67**) (Supplementary Fig. S6) were isolated from the marine-facultative *Aspergillus* sp. MEXU 27854. Compounds **65** and **67** inhibited P-glycoprotein-reversing doxorubicin-resistant cell line (Aparicio-Cuevas et al. 2017). Chemical analysis of an Australian marine sediment-derived *Aspergillus* sp. (CMB-M081F) yielded shornephine A (**68**), a diketomorpholine and 15b-*β*-methoxy-5-*N*-acetyladreemin (**69**). Compound **68** was a noncytotoxic inhibitor of P-glycoprotein-mediated drug efflux in multidrug-resistant human colon cancer cells at 20.0 μmol/L (Khalil et al. 2014).

Six new enantiomeric diketopiperazines, (±)-7,8-epoxy-brevianamide Q (**70** and **71**), (±)-8-hydroxy-brevianamide R (**72** and **73**), and (±)-8-epihydroxy-brevianamide R (**74** and **75**) (Supplementary Fig. S7) were isolated from the marine-derived fungus strain *A. versicolor* MF180151, which was recovered from a sediment sample collected from the Bohai Sea, China (Hu et al. 2019). Another analogue, 9ξ-*O*-2(2,3-dimethylbut-3-enyl) brevianamide Q (**76**), was obtained from the culture of *A. versicolor*, an endophytic fungus isolated from the marine brown alga *Sargassum thunbergii* (Miao et al. 2012). Tryprostatins A and B (**77** and **78**), new inhibitors of mammalian cell cycle, were obtained from the marine fungus *A. fumigatus*, which were isolated from a sea sediment sample collected in the sea bottom of the mouth of Oi river Sizuoka prefecture, Japan. In addition, they completely inhibited cell cycle progression of tsFT210 cells in the G2/M phase at final concentrations of 50.0 μg/ml of **77** and 12.5 μg/ml of **78** (Cui et al. 1995). 3,1′-Didehydro-3[2″(3‴,3‴-dimethyl-prop-2-enyl)-3″-indolylmethylene]-6-methyl pipera-zine-2,5-dione (**79**) was isolated from a mangrove endophytic fungus *P. chrysogenum* MTCC 5108, and exhibited significant activity against *Vibrio cholerae*, a pathogen causing cholera in humans, with an inhibition zone of 14–16 mm (Devi et al. 2012).

A class of prenylated DKPs, rubrumlines A–O (**80–94**) (Supplementary Fig. S8), were obtained from the marine-derived fungus *Eurotium rubrum*, which showed weak activity against H1N1 virus (Chen et al. 2015). Cristatumins A–D (**95–98**) were identified from the culture extract of *E. cristatum* EN-220, an endophytic fungus isolated from the marine alga *S. thunbergii*. Compound **96** exhibited moderate activity against brine shrimp lethality with the LD_{50} value of 74.4 μg/ml. Furthermore, **95** displayed potent inhibitory activity against *E. coli* and *S. aureus* with the MIC value of 64.0 μg/ml, while **98** showed weak activity against *S. aureus*, each giving the inhibition zone of 8.0 mm at 100.0 μg/disk (Du et al. 2015). Dihydroneochinulin B (**99**) was isolated from the mangrove rhizosphere soil-derived fungus, *A. effuses* H1-1, with cytotoxic activity against A-549 (IC_{50} = 30.5 μmol/L) (Gao et al. 2013). 12-Demethyl-12-oxo-eurotechinulin B (**100**), produced by the marine-derived fungus *E. rubrum*, exhibited cytotoxicity against SMMC-7721 with an IC_{50} value of 30.0 μg/ml (Yan et al. 2012).

Rubrumazines A–C (**101–103**) (Supplementary Fig. S9), three DKPs of the isoechinulin type, were isolated from *E. rubrum* MA-150, a fungus obtained from mangrove-derived rhizospheric soil collected from the Andaman Sea coastline of Thailand. All of them displayed potent moderate lethality against brine shrimp with LD_{50} values of 29.8, 2.4, 1.7 μmol/L, respectively (Meng et al. 2015). Eurotiumins A–D (**104–107**) were isolated and characterized from the marine-derived fungus *Eurotium* sp. SCSIO F452. Among them, compounds **104** and **106** were screened for antioxidative activities against DPPH with IC_{50} values of 37.0 and 13.0 μmol/L, respectively (Zhong et al. 2018a). Noticeably, (+)-deoxyisoaustamide (**108**) and deoxydihydroisoaustamide (**109**), which are products of mixed biogenetic origins derived from the condensation of tryptophane, proline and isoprene units, were afforded from the methylethylketone extract of the *Penicillium* sp. JF-72 (Quang et al. 2013).

6-Methoxyspirotryprostatin B (**110**), 18-oxotryprostatin A (**111**), and 14-hydroxyterezine D (**112**) (Supplementary Fig. S10), were isolated from the ethyl acetate extract of

a marine-derived fungal strain, *A. sydowi* PFW1-13. Compounds **110–112** exhibited weak cytotoxicity against A-549 cells, with IC_{50} values of 8.3, 1.3, and 7.3 µmol/L, respectively; **110** also showed slight cytotoxicity against HL-60 cells, with an IC_{50} value of 9.7 µmol/L (Zhang et al. 2008). A tryptophan-derived alkaloid, 3-((1-hydroxy-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)methyl)-1-methyl-3,4-dihydrobenzo[e][1,4]diazepine-2,5-dione (**113**), was isolated from *Aspergillus* sp., selectively inhibiting *Vibrio* species (*V. proteolyticus*, *V. carchariae*) (MIC = 0.1 µg/ml), while showing no inhibition activities against other tested marine-derived bacteria (Zhou et al. 2014).

Brevianamides X and Y (**114** and **115**) (Supplementary Fig. S11) were isolated from the deep sea-derived fungus *P. brevicompactum* DFFSCS025 (Xu et al. 2017). Spirotryprostatin F (**116**) was isolated from the marine-derived fungus *A. fumigatus*, effectively stimulating the growth of sprout roots of soy [*Glycine max* (L.) *Merr.*], buckwheat (*Fagopyrum esculentum* Moench), and corn (*Zea mays* L.) (Afiyatullov et al. 2012). Another spirocyclic DKP, spirotryprostatin G (**117**), highly homologous to the biosynthetic gene clusters (BGCs) of DKP derivatives, was obtained by large-scale cultivation of the marine-derived fungus *P. brasilianum* HBU-136 using rice medium with 1.0% $MgCl_2$. In addition, cytotoxicity was observed for compound **117** against HL-60 cell line with an IC_{50} value of 6.0 µmol/L (Zhang et al. 2019). Using direct analysis in real time (DART) mass spectrometry, (–)-spiromalbramide (**118**), (+)-isomalbrancheamide B (**119**), (+)-malbrancheamide C (**120**), and (+)-isomalbrancheamide C (**121**) were initially detected from hyphae of the fungus *Malbranchea graminicola* (Watts et al. 2011).

Bioassay-guided fractionation led to the isolation of cyclotryprostatin E (**122**) (Supplementary Fig. S12) from the marine-derived fungus *A. sydowii* SCSIO 00305 (He et al. 2012). Prenylcyclotryprostatin B (**123**), 20-hydroxycyclotryprostatin B (**124**), 9-hydroxyfumitremorgin C (**125**), and 6-hydroxytryprostatin B (**126**) were isolated from the marine-derived fungus *A. fumigatus* YK-7. Furthermore, compounds **123** and **125** exhibited most potent activities against U937 cell lines with IC_{50} values of 25.3 and 18.2 µmol/L, respectively (Wang et al. 2012a). With the aid of genomic analysis, two DKPs, namely cyclotryprostatins F and G (**127** and **128**) were obtained from the marine-derived fungus *P. brasilianum*, with cytotoxicity against the MCF-7 cell line with IC_{50} values of 7.6 and 10.8 µmol/L, respectively (Zhang et al. 2019). Prenylated DKP peroxides, 24-hydroxyverruculogen (**129**), 26-hydroxyverruculogen (**130**), and 13-*O*-prenyl-26-hydroxyverruculogen (**131**) were isolated and identified from the culture extract of the marine sediment-derived fungus *P. brefeldianum* SD-273. Among them, compound **131** showed potent lethal activity against brine shrimp (*Artemia salina*), with the LD_{50} value of 9.4 µmol/L, while the positive control colchicine had the LD_{50} value of 99.0 µmol/L, and the activity was postulated to be related to the prenyl substitution at 13-OH (An et al. 2014).

It is noteworthy to mention that the marine-derived strains of *Aspergillus* and *Penicillium* exhibited an extensive co-metabolite profile representative of structurally diverse ring systems of this family of prenylated indole alkaloids. In addition, a wide range of biological activities, including insecticidal, antitumor, anthelmintic, calmodulin inhibitory, and antibacterial, have been reported within this structural family. Notoamides A–R (**132–149**) (Supplementary Fig. S13), a family of prenylated indole alkaloids that was hypothesized to be produce via biosynthetic intramolecular Diels–Alder reactions, were obtained from a fungus *Aspergillus* sp. Moreover, these compounds exhibited various activities. For instance, compounds **132–134** and **142** showed moderate cytotoxicity against HeLa and L1210 cells with IC_{50} values in the range of 21.0–52.0 µg/ml. Besides, compound **134** induced G2/M cell cycle arrest at a concentration of 6.3 µg/ml (Kato et al. 2007; Tsukamoto et al. 2008, 2009a, b, 2010). Coincidentally, 5-chlorosclerotiamide (**150**) and 10-*epi*-sclerotiamide (**151**) were isolated from the deep-sea-derived fungus *A. westerdijkiae* DFFSCS013. Furthermore, they showed cytotoxicity toward the K562 cell line with IC_{50} values of 44.0 µmol/L and 53.0 µmol/L (Peng et al. 2013), respectively. Biogenetically, 17-epinotoamides Q and M (**152** and **153**) were isolated from a marine-derived *Aspergillus* sp. fungus. Compounds **152** and **153** were the epimers of **144** and **148**, respectively (Chen et al. 2013).

Five prenylated indole alkaloids, 17-hydroxynotoamide D (**154**), 17-*O*-ethylnotoamide M (**155**), 10-*O*-acetylsclerotiamide (**156**), 10-*O*-ethylsclerotiamide (**157**), and 10-*O*-ethylnotoamide R (**158**) (Supplementary Fig. S14) were isolated from a co-culture of marine-derived fungi *A. sulphureus* KMM 4640 and *Isaria felina* KMM 4639. In particular, compound **155** inhibited the colony formation of human prostate cancer cells 22Rv1 at a non-cytotoxic (non-malignant cells, MRC-9 and HEK 293 T) concentration of 10 µmol/L (Afiyatullov et al. 2018). 6-*Epi*-stephacidin A (**159**), *N*-hydroxy-6-*epi*-stephacidin A (**160**), and 6-*epi*-avrainvillamide (**161**), were isolated from *A. taichungensis*. Simultaneously, biological evaluation showed that **160** and **161** exhibited significant cytotoxicity with IC_{50} values of 4.5 and 1.9 µmol/L against HL-60 and IC_{50} values of 3.0 and 1.9 µmol/L against A-549, respectively (Cai et al. 2013). Another stephacidin analogue, 21-hydroxystepahcidin (**162**) was isolated from the bromine-modified artificial seawater cultivation medium of the marine-derived fungus *A. ostianus* (Kito et al. 2009). Asperversiamides A–H (**163–170**), eight linearly fused prenylated indole alkaloids featuring an unusual pyrano[3,2-*f*]indole unit, were isolated from the marine-derived fungus *A. versicolor*. Compound **169** exhibited a potent inhibitory effect against iNOS with an IC_{50} value of

5.4 µmol/L (Li et al. 2018a). Dihydrocarneamide A (**171**) and *iso*-notoamide B (**172**) were isolated from the marine-derived endophytic fungus *Paecilomyces variotii* EN-291, which showed weak cytotoxic activity against NCI-H460 with IC_{50} values of 69.3 and 55.9 µmol/L, respectively (Zhang et al. 2015a).

Another DPK possessing a piperidine moiety, penioxamide A (**173**) (Supplementary Fig. S15), was isolated from *P. oxalicum* EN-201, an endophytic fungus obtained from the inner tissue of the fresh leaves of the marine mangrove plant *Rhizophora stylosa*. Compound **173** showed potent brine shrimp lethality with a LD_{50} value of 5.6 µmol/L (Zhang et al. 2015b). Two different culture media, soybean and rice solid, were used to ferment fungus *A. ruber* 1017 and afforded epoxyisoechinulin A (**174**) (Li et al. 2017a). Two minor metabolites, cycloexpansamines A and B (**175** and **176**) were isolated from the marine-derived fungus, *Penicillium* sp. SF-5292. Compound **175** moderately inhibited the activity of protein tyrosine phosphatase 1B, a promising and a validated therapeutic target to effectively treat type 2 diabetes mellitus and obesity, showing an IC_{50} value of 27.6 µmol/L (Lee et al. 2015).

Seven prenylated DKPs, versicamides A–H (**177–184**) (Supplementary Fig. S16), were obtained from the marine-derived fungus *A. versicolor* HDN08-60. Among them, compound **184** exhibited moderate activity against the HeLa, HCT-116, HL-60 and K562 cell lines, with IC_{50} values of 19.4, 17.7, 8.7, and 22.4 µmol/L, respectively. Target screening showed that **184** exhibited selective PTK inhibitory activity on c-Kit as one of the 18 PTKs tested, yielding an inhibitory rate of 60% at a final concentration of 10 µmol/L (Peng et al. 2014). Prenylated indole alkaloids, carneamides A–C (**185–187**), were isolated from the marine-derived fungus *A. carneus* KMM 4638 (Zhuravleva et al. 2012).

Three diprenylated indole alkaloids, mangrovamides A–C (**188–190**) (Supplementary Fig. S17), featured a bicyclo [2.2.2] diazaoctane core and possessed a γ-methyl proline and isoprene derived dimethyl γ-pyrone functionalities hitherto unknown among the family of paraherquamides, were isolated from the fungus *Penicillium* sp., which was separated from a mangrove soil sample. While for antiacetylcholinesterase activity, compound **190** showed moderate inhibitory effect with an IC_{50} value of 58.0 µmol/L (Yang et al. 2014). In addition, mangrovamides D–G (**191–194**) were also isolated from the same mangrove sediment-derived fungus *Penicillium* sp. SCSIO041218, cultured in the 1% NaCl PDB substrate (Yang et al. 2017).

N-(4′-hydroxyprenyl)-cyclo(alanyltryptophyl) (**195**), isovariecolorin I (**196**), 30-hydroxyechinulin (**197**), 29-hydroxyechinulin (**198**) (Supplementary Fig. S18) were isolated and identified from the culture extract of *E. cristatum* EN-220, an endophytic fungus obtained from the marine alga *S. thunbergii*. Compound **196** exhibited lethal activity against brine shrimp with a LD_{50} value of 19.4 µg/ml and showed moderate radical scavenging activity against DPPH with an IC_{50} value of 20.6 µg/ml (Du et al. 2017). 5-Prenyl-dihydrovariecolorin F (**199**) and 5-prenyl-dihydrorubrumazine A (**200**) were isolated from Antarctic marine-derived *Aspergillus* sp. SF-5976. As part of a further study, the compounds were selected to evaluate their effects on PGE2 production as well as on iNOS and COX-2 protein expression by ELISA and western blot analysis, respectively. In the case of LPS-stimulated RAW 264.7 cells, compound **200** decreased PGE2 production in a concentration-dependent manner, while both compounds **199** and **200** inhibited the production of PGE2 in LPS-stimulated BV2 cells. Furthermore, compound **200** inhibited iNOS and COX-2 protein expression in LPS-stimulated RAW 264.7 cells, while both **199** and **200** suppressed the expression of iNOS and COX-2 proteins in LPS-stimulated BV2 cells (Kwon et al. 2017).

Haenamindole (**201**) (Supplementary Fig. S19), which possessed benzyl-hydroxypiperazindione and phenyl-pyrimidoindole rings system in the molecule, was isolated from a culture of the marine-derived fungus *Penicillium* sp. KCB12F005 (Kim et al. 2015a). Penicimutanins A and B (**202** and **203**) and penicimutatin (**204**) were discovered by activating silent metabolite production in *P. purpurogenum* G59 through diethyl sulphate mutagenesis. All the compounds inhibited several human cancer cell lines (K562, HL-60, HeLa, BGC-823, and MCF-7) with IC_{50} values lower than 20.0 µmol/L while compound **204** moderately inhibited the cell lines (Fang et al. 2014).

The enantiomers of (+)-effusin A and (-)-effusin (**205** and **206**), two spirobicyclic *N*,*O*-acetal derivative with an unprecedented 3′,3a’,5′,6′-tetrahydrospiro-[piperazine-2,2′-pyrano[2,3,4-de]chromene] ring system, and two enantiomeric spiro-polyketide-DKP hybrid (+)-dihydrocryptoechinulin and (-)-dihydrocryptoechinulin D (**207** and **208**) (Supplementary Fig. S20) were isolated both as racemates (1:1) from a mangrove rhizosphere soil derived fungus, *A. effuses* H1-1. All isolated spirocyclic compounds showed potent activity on P388 cells with an IC_{50} value of 1.8 µmol/L. Compound **207** showed selectivity against topoisomerase I (Gao et al. 2012). Three pairs of spirocyclic alkaloids enantiomers (±)-eurotinoids A–C (**209–214**) were isolated from a marine-derived fungus *Eurotium* sp. SCSIO F452. Furthermore, these enantiomers exhibited antioxidative and cytotoxic activity against DPPH with IC_{50} values in the range of 3.7–24.9 µmol/L. To investigate their bioactive mechanism, five common types of antioxidative targets and six common types of cytotoxic targets were screened using molecular docking technique. The results showed that lipoxygenase (LOX) was the potential antioxidative target for compounds **209–214** (Zhong et al. 2019). (±)-Variecolortins A–C (**215–220**), three pairs of spirocyclic DKP enantiomers, were obtained from the marine-derived fungus

Eurotium sp. SCSIO F452. Compound **215** showed significant radical scavenging activity against DPPH with an IC_{50} value of 58.4 μmol/L, which was comparable to that of the positive control ascorbic acid (Vc) (IC_{50} = 45.8 μmol/L) and nearly three times stronger than **216** (IC_{50} = 159.2 μmol/L). Meanwhile, compound **217** showed moderate cytotoxicities against SF-268 and HepG2 cell lines with IC_{50} values of 12.5, 15.0 μmol/L, respectively, while those of **219** were 30.1, 37.3 μmol/L (Zhong et al. 2018b), respectively.

Laboratory cultures of the fungus *Plectosphaerella cucumerina* obtained from marine sediments collected in Barkley Sound, British Columbia, yielded the alkaloids plectosphaeroic acids A–C (**221–223**) (Supplementary Fig. S21). All them were inhibitors of indoleamine 2,3-dioxygenase (IDO) and exhibited an identical IC_{50} value of 2.0 μmol/L (Carr et al. 2009). Okaramines S–U (**224–226**), three indolic DKPs, were isolated from *A. taichungensis* ZHN-7-07. Compound **224** exhibited cytotoxic activity against HL-60 and K-562 cell lines with IC_{50} values 0.8 and 22.4 μmol/L, respectively (Cai et al. 2015).

Luteoalbusins A and B (**227** and **228**) (Supplementary Fig. S22) were isolated from the fungus *A. luteoalbus* SCSIO F457 originating from deep-sea sediment. In addition, both of them had significant cytotoxicities against SF-268, MCF-7, NCI-H460, and HepG-2 cell lines with IC_{50} values ranging from 0.2 to 1.3 μmol/L (Wang et al. 2012b). Gliocladins A–C (**229–231**) and glioperazine (**232**) were isolated from a strain of *Gliocladium* sp., obtained from a sea hare. All luteoalbusin congeners exhibited significant cytotoxicity against cultured P388 cells (ED_{50} = 6.5, 20.0, 2.4, 6.7 μg/ml, respectively) (Usami et al. 2004). Cristazine (**233**), a dioxopiperazine alkaloid, isolated from the mudflat-sediment-derived fungus *Chaetomium cristatum*, displayed potent radical-scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH), with an IC_{50} value of 19.0 μmol/L, which were similar to that of the positive control, ascorbic acid (IC_{50} = 20.0 μmol/L). Compound **233** also showed cytotoxic activity against human cervical carcinoma (HeLa) cells, with an IC_{50} value of 0.5 μmol/L (Yun et al. 2016).

Aspergilazine A (**234**) (Supplementary Fig. S23), dimerized by two DKP units via a rare N-1 to C-6 linkage, was isolated from the marine-derived fungus *A. taichungensis* ZHN-7-07. Compound **234** had a weak activity against influenza A (H1N1) virus with 34.1% inhibition at a concentration of 50.0 μg/ml (Cai et al. 2012). An *A. versicolor* obtained from sediment collected from Bohai Sea, China, yielded the dimeric DKP brevianamide S (**235**). Compound **235** exhibited selective antibacterial activity against Bacille Calmette-Guérin with a MIC value of 6.3 μg/ml. The result suggested a new mechanism of action that could inform the development of next-generation antitubercular drugs (Song et al. 2012). A DKP dimer (**236**) was isolated from the EtOAc extract of a sponge-derived fungus *A. violaceofuscus*. Compound **236** showed anti-inflammatory activity against IL-10 expression of the LPS-induced THP-1 cells with an inhibitory rate of 78.1% at a concentration of 10.0 μmol/L (Liu et al. 2018a). Asperazine (**237**) was a selective cytotoxic alkaloid from a sponge-derived culture of *Aspergillus niger*. Interesting selective activity was observed for **237** at 50.0 μg/disk in the primary in vitro assay which employs human leukemia murine colon 38 and human colon H116 or CX1 cell lines (Varoglu et al. 1997).

SF5280-415 (**238**) (Supplementary Fig. S24) was isolated from an EtOAc extract of the marine-derived fungus *Aspergillus* sp. SF-5280. Compound **238** showed inhibitory effects against protein tyrosine phosphatase 1B (PTP1B) activity with an IC_{50} value of 14.2 μmol/L (Cho et al. 2017). A DKP, WIN 64821 (**239**) along with its asymmetric stereoisomers (**240–242**), were isolated from the culture broth of a marine gut fungus *Aspergillus* sp. DX4H, all of which showed weak cytotoxicity against the prostate cancer PC3 cell line at 20.0 μg/ml (Xu et al. 2018). A DKP dimer (**243**) and brevianamide J (**244**) were isolated from a culture of *A. niger* and *A. versicolor* (Li et al. 2017b; Ovenden et al. 2004). Two epipolythiodioxopiperazines, chetracins E and F (**245** and **246**), were isolated from the fungus *A. luteoalbus* HDN13-530. Both chetracins exhibited potent cytotoxicity against five cancer lines (A549, HCT116, K562, H1975, HL-60) in low-micromolar or nanomolar IC_{50} values. Compound **245** showed the strongest cytotoxicity on H1975 cells with an IC_{50} value of 0.2 μmol/L. Meanwhile, computational docking study indicated that both congeners could bind to the C-terminal of heat shock protein 90 (Hsp90), which was in line with the experimental observation of decrease in levels and active forms of Hsp90 client proteins (Yu et al. 2018).

Chaetocin derivatives, leptosins A–F (**247–252**), I and J (**253** and **254**), M (**255**), M1 (**256**), N (**257**) and N1 (**258**), and O–S (**259–263**) (Supplementary Fig. S25), were isolated from the mycelium of a strain of *Leptosphaeria* sp. associated with the alga *S. tortile*. All derivatives showed potent or moderate cytotoxicity against cultured P388 cells. Compounds **247** and **249** exhibited significant antitumour activity against Sarcoma 180 ascites, while **255** was proved to significantly inhibit specifically two protein kinases, PTK and CaMKIII, and human topoisomerase II (Takahashi et al. 1994a, b; Yamada et al. 2002, 2004). A DKP dimer, eurocristatine (**264**), was isolated from the culture of the sponge-associated fungus *E. cristatum* KUFC 7356 (Gomes et al. 2012). Another pair of enantiomeric DKP dimers [(–)- and (+)-asperginulin A (**265** and **266**)] with an unprecedented 6/5/4/5/6 pentacyclic skeleton were isolated from the mangrove endophytic fungus *Aspergillus* sp. SK-28. Among them, compound **266** exhibited antifouling activity against the barnacle *Balanus reticulatus* (Cai et al. 2019).

Indole diterpenoid alkaloids (IDTs)

An IDT, penicindopene A (**267**) (Supplementary Fig. S26) was isolated from the deep-sea fungus *Penicillium* sp. YPCMAC1. Compound **267** represented the first example of IDTs possessing a 3-hydroxyl-2-indolone moiety, and it exhibited moderate cytotoxicities against A549 and HeLa cell lines with IC_{50} values of 15.2 and 20.5 μmol/L, respectively (Liu et al. 2018b). Anthcolorins A–F (**268–273**), unique tetrahydropyrane IDT metabolites with oxoindoline at C-3, were isolated from a strain of *A. versicolor* originally isolated from the sea urchin *Anthocidaris crassispina*. Compounds **269–271** exhibited significant growth inhibition against cultured P388 cells with IC_{50} values in the range of 2.2–8.5 μmol/L (Nakanishi et al. 2013). Three IDTs, penicilindoles A–C (**274–276**), were isolated from the mangrove-derived fungus *Eupenicillium* sp. HJ002. It is worth noting that compound **274** showed cytotoxic activity against human A549 and HepG2 cell lines with IC_{50} values of 5.5 and 1.5 μmol/L, respectively (Zheng et al. 2018).

Three IDT derivatives asporyzin A–C (**277–279**) (Supplementary Fig. S27) were isolated from an endophytic fungus *A. oryzae*, obtained from the marine red alga *Herosiphonia japonica*. Notably, compound **279** exhibited potent activity against *E. coli* with an inhibition diameter of 8.3 mm at 30.0 μg/disk (Qiao et al. 2010). A marine-derived strain of *D. cejpii* produced the compounds emindole SB betamannoside (**280**) and 27-*O*-methylasporyzin C (**281**). Indole derivative **280** was found to be a CB2 antagonist with a K_i value of 10.6 μmol/L, while **281** was identified as the first selective GPR18 antagonist with an indole structure (IC_{50} = 13.4 μmol/L), which suggested that they might serve as lead structures for the development of GPR18- and CB receptor-blocking drugs (Harms et al. 2014). A systematic chemical exploration of the marine-derived fungus *P. janthinellum* led to the isolation of two IDT derivatives, penijanthines C and D (**282** and **283**). All of them displayed significant anti-*Vibrio* activity (MIC values ranging from 3.1 to 12.5 μmol/L) against three pathogenic *Vibrio* sp. (*V. anguillarum*, *V. parahemolyticus*, and *V. alginolyticus*) (Guo et al. 2019). Asperindoles A–D (**284–287**) were isolated from the marine-derived strain of the fungus *Aspergillus* sp. KMM 4676, associated with an unidentified colonial ascidian. Of note, compounds **286** and **287** contained a 2-hydroxyisobutyric acid (2-HIBA) residue, which was rarely found in natural compounds. Furthermore, compound **284** exhibited cytotoxic activities against hormone therapy-resistant PC-3 and 22Rv1, as well as hormone therapy-sensitive human prostate cancer cells, and induced apoptosis in these cells with IC_{50} values of 69.4, 4.9, and 47.8 μmol/L, respectively (Ivanets et al. 2018).

Four unusual IDTs, penerpenes A–D (**288–291**) (Supplementary Fig. S28), were isolated from the marine-derived fungus *Penicillium* sp. KFD28. Meanwhile, compounds **288** and **289** showed potent inhibitory activities toward protein tyrosine phosphatases (PTP1B and TCPTP) with IC_{50} values in the range of 1.7–5.0 μmol/L (Kong et al. 2019a). Further research led to the isolation of penerpenes E–I (**292–296**) from the above fungus. Compound **294** contained an additional oxygen atom between C-21 and C-22 compared to paxilline to form an unusual 6/5/5/6/6/7 hexacyclic ring system bearing a 1,3-dioxepane ring, which was rarely encountered in natural products. Compounds **292**, **293** and **295** showed inhibitory activities against PTP1B with IC_{50} values of 14.0, 27.0, 23.0 μmol/L, respectively (Zhou et al. 2019). Two IDTs, (2*R*,4b*R*,6a*S*,12b*S*,12c*S*,14a*S*)-4b-deoxy-*β*-aflatrem (**297**), (2*R*,4b*S*,6a*S*,12b*S*,12c*R*)-9-isopentenyl paxilline D (**298**), were isolated from the fermentation broth of the marine-derived fungus, *A. flavus* OUCMDZ-2205. In addition, compound **297** exhibited antibacterial activity against *S. aureus* with a MIC value of 20.5 μmol/L and showed PKC-beta inhibition with an IC_{50} value of 15.6 μmol/L. Both of them could arrest the A549 cell cycle in the S phase at a concentration of 10.0 μmol/L (Sun et al. 2014). Three IDTs, namely, 22-hydroxylshearinine F (**299**), 6-hydroxylpaspalinine (**300**), and 7-*O*-acetylemindole SB (**301**), were isolated from the sea-anemone-derived fungus *Penicillium* sp. AS-79 (Hu et al. 2017).

Shearinines A–C (**302–304**) (Supplementary Fig. S29) were isolated from the ascostromata of *Eupenicillium shearii*, displaying activity in dietary assays against the corn earworm *Helicoverpa zea* and the dried fruit beetle *Carpophilus hemipterus*. Compound **302** exhibited activity in a topical assay against *H. zea*, and **303** caused significant mortality in a leaf disk assay against the fall armyworm *Spodoptera frugiperda* (Belofsky et al. 1995). Another series of IDTs, shearinines D–K (**305–312**), were isolated from an endophytic *Penicillium* sp. HKI0459. Biologically, compounds **305**, **306**, and (with reduced potency) **308** exhibited significant in vitro blocking activity on large-conductance calcium-activated potassium channels (Xu et al. 2007). Two compounds, including a chlorinated IDT 19-hydroxypenitrem A (**313**) and its dechlorinated derivative 19-hydroxypenitrem E (**314**) were isolated and identified from the cultures of *A. nidulans* EN-330. Furthermore, compounds **313** and **314** exhibited cytotoxic activity against brine shrimp with the LD_{50} values of 3.2 and 4.6 μmol/L, respectively. Besides, the chlorinated **313** showed antimicrobial activity against human-(*E. coli and S. aureus*) and aqua-pathogens (*Edwardsiella tarda* and *V. anguillarum*). Preliminary SAR study revealed that the Cl substitution at C-6 enhanced the cytotoxic activity against brine shrimp and antimicrobial activity, while the 19-OH substitution suppressed the activity (Zhang et al. 2015c).

Quinazoline-containing indole alkaloids

Aspertoryadins A–G (**315–321**) (Supplementary Fig. S30) were isolated from the marine-derived fungus *Aspergillus* sp. HNMF114 from the bivalve mollusk *Sanguinolaria chinensis*. Notably, compounds **320** and **321** exhibited quorum sensing inhibitory activity against *Chromobacterium violaceum* CV026 with the MICs of 32.0, 32.0 μg/well, respectively (Kong et al. 2019b). Another two analogs, tryptoquivalines R and S (**322** and **323**), were isolated from a marine-derived fungus *Neosartorya* sp. HN-M-3, separated from mud in the intertidal zone of Hainan Province of China (Xu et al. 2013). A comparative study on the metabolic profile of the sponge-associated fungus *A. carneus* using the OSMAC approach was conducted. As a result, isopropylchaetominine (**324**) was isolated, which showed strong cytotoxicity against the mouse lymphoma cell line L5178Y with an IC_{50} value of 0.4 μmol/L (Özkaya et al. 2018). Fumiquinazoline Q (**325**), isolated from the marine-derived fungus *P. expansum* Y32, exhibited potent vasculogenetic activity in vasculogenesis experiments, which suggested that it could be a promising candidate for cardiovascular disease lead compound (Fan et al. 2015).

Versiquinazolines A–K (**326–336**) (Supplementary Fig. S31), 11 fumiquinazoline-type alkaloids, were isolated from the gorgonian-derived fungus *A. versicolor* LZD-14-1. Compounds **326**, **327**, **332**, and **336** exhibited inhibitory activities against thioredoxinreductase with IC_{50} values ranging from 12.0 to 20.0 μmol/L (Cheng et al. 2016). Further chemical examination of the above fungus by the HPLC–DAD detection resulted in the isolation of six polycyclic alkaloids, namely versiquinazolines L–Q (**337–342**). In addition, compounds **341** and **342** exhibited significant inhibition against thioredoxin reductase (TrxR) with IC_{50} values of 13.6 and 12.2 μmol/L, which suggested that both of them were potential for micro-environmental regulation of tumor progression and metastasis (Cheng et al. 2018). Fumigatosides B–D (**343–345**), the first examples of glycosidated fumiquinzoline-type alkaloids, were isolated from the fungus *A. fumigatus* derived from the jellyfish *Nemopilema nomurai* (Liu et al. 2015b).

Cytochalasin

Flavichalasines N and O (**346** and **347**) (Supplementary Fig. S32) were isolated from *A. flavipes* PJ03-11 through the application of OSMAC strategy. Compounds **346** and **347** exhibited significant cytotoxic activities against three human cancer cell lines (THP1, HL-60 and PC3) with IC_{50} values ranging from 3.0 to 15.1 μmol/L (Si et al. 2018). Two aspochalasins, tricochalasin A (**348**) and aspochalasin A2 (**349**), were isolated from the different culture broth of *Aspergillus* sp., which was found in the gut of a marine isopod *Ligia oceanica*. All of them showed weak activity against PC3 cell line ($IC_{50} > 36.0$ μmol/L) (Li et al. 2018b). Four cytochalasin derivatives, cytochalasins B_3–B_6 (**350–353**), were isolated from a jellyfish-derived fungus *Phoma* sp. All of them showed moderate cytotoxicity against a small panel of human solid tumor cell lines (A549, KB, and HCT116) with IC_{50} values in the range of 19.9–45.0 μmol/L (Kim et al. 2015b). Cytoglobosins A–G (**354–360**) were isolated and identified from the cultures of *C. globosum* QEN-14. Among them, compounds **359** and **360** displayed cytotoxic activity against the A549 tumor cell line with IC_{50} values of 2.3 and 2.6 μmol/L, respectively (Cui et al. 2010).

Another analogue, chaetoglobosin A (**361**) (Supplementary Fig. S33) was isolated from the broth filtrate of a strain assigned to *Chaetomium* sp., which was isolated from the green alga, *Halimeda discoidea* by bating method. In the bioassay, compound **361** showed weak inhibitory activity to the assembly of microtubule proteins, and also showed acute toxicity and teratogenic activity to mice (Kobayashi et al. 1996). Chaetoglobosin-510 (**362**), chaetoglobosin-540 (**363**), and chaetoglobosin-542 (**364**) were produced by cultures of the marine-derived fungus *Phomopsis asparagi*, challenged with the known F-actin inhibitor jasplakinolide. Compound **364** displayed antimicrofilament activity at 1.0 μg/ml with eventual cell loss at 10.0 μg/ml and was cytotoxic toward murine colon (C38) and leukemia (L1210) cancer cell lines (Christian et al. 2005).

A class of cytochalasans, penochalasins A–K (**365–375**) (Supplementary Fig. S34), were isolated from a strain of *Penicillium* sp. In addition, compounds **365–372** exhibited potent cytotoxicity against cultured P388 cells with the ED_{50} values of 0.3 and 3.2 μg/ml. Compound **373** exhibited marked cytotoxicity against MDA-MB-435 and SGC-7901 cells ($IC_{50} < 9.0$ μmol/L), while **374** greatly inhibited *Colletotrichum gloeosporioides* (MIC = 25.1 μmol/L), and showed an antifungal activity higher than that of carbendazim. Compound **375** displayed significant inhibitory activities against *C. gloeosporioides* and *Rhizoctonia solani* (MICs = 6.1 and 12.3 μmol/L, respectively), which was better than those of carbendazim, and exhibited potent cytotoxicity against MDA-MB-435, SGC-7901 and A549 cells ($IC_{50} < 10.0$ μmol/L) (Huang et al. 2016; Iwamoto et al. 2001; Numata et al. 1996; Zhu et al. 2017).

The simple indole alkaloids

A melatonin analogue 6-hydroxy-*N*-acetyl-*β*-oxotryptamine (**376**) (Supplementary Fig. S35) was isolated from the marine-derived fungus *Penicillium* sp. KMM 4672. Furthermore, **376** protected Neuro2a cells against the damaging influence of 6-OHDA. Compound **376** was more effective in the PQ-induced model, and increased cell viability

by 40%, whereas in the 6-OHDA-induced model, it could increase cell viability by 23% only (Yurchenko et al. 2018). 1-(3-indolyl)-2*R*,3-Dihydroxypropan-1-one (**377**) was isolated from the EtOAc extract of the marine-associated fungus, *Daldinia eschscholzii* (Hu et al. 2014a). Brocaeloid C (**378**), containing C-2 reversed prenylation, was isolated from cultures of *P. brocae* MA-192, an endophytic fungus obtained from the fresh leaves of the marine mangrove plant *Avicennia marina* (Zhang et al. 2014). Two prenylated indole 3-carbaldehyde derivatives, 2-(2-methyl-3-en-2-yl)-1*H*-indole-3-carbaldehyde (**379**) and 2-(2,2-dimethylcyclopropyl)-1*H*-indole-3-carbaldehyde (**380**), were isolated from the culture of the endophytic fungus *E. chevalieri* KUFA 0006. Simultaneously, compounds **379** and **380** showed inhibition of biofilm production in *S. aureus* ATCC 25923. Interestingly, **380** was the most effective in inhibiting biofilm formation in *E. coli* ATCC 25922, which also caused nearly 80% reduction of the biofilm production in *S. aureus* ATCC 25923 (May Zin et al. 2017).

Luteoride D (**381**) (Supplementary Fig. S36), featuring an oxazino[6,5-*b*]indole nucleus, was obtained by dual induction of microbial secondary metabolites by fungal bacterial co-cultivation of *A. fumigatus* MR2012 and *Streptomyces leeuwenhoekii* C34 (Wakefield et al. 2017). Luteoride E (**382**), a prenylated tryptophan derivative, isolated and identified from a coral-associated fungus *A. terreus*, showed significant inhibitory potency against LPS-induced NO production with an IC_{50} value of 24.6 μmol/L (Liu et al. 2018c). Another indole alkaloid, nigrospin A (**383**) was isolated from a culture broth of the marine-derived fungal strain *Nigrospora oryzae* SCSGAF 0111 (Dong et al. 2014).

Two *β*-carboline alkaloids, aspergillspins A and B (**384** and **385**) (Supplementary Fig. S37), were isolated from the gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501 (Ma et al. 2019). Another two *β*-carbolines, penipalines A and B (**386** and **387**), and one indole carbaldehyde derivative, penipaline C (**388**), were isolated from the deep-sea-sediment derived fungus *P. paneum* SD-44. Compounds **387** and **388** showed respective potent cytotoxic activities with IC_{50} values of 20.4 and 21.5 μmol/L against A549 and 14.9 and 18.5 μmol/L against HCT-116 (Li et al. 2015). A pyrazine derivative, trypilepyrazinol (**389**), was isolated from the marine-derived fungus *Penicillium* sp. IMB17-046. Notably, compound **389** exhibited broad-spectrum antiviral activities against different types of viruses, including HIV, HCV, and IAV, with IC_{50} values ranging from 0.5 to 7.7 μmol/L. Compound **389** also showed antibacterial activities against a causative pathogen of various gastric diseases, *Helicobacter pylori* G27 and 159 with the MIC values of 4.0 and 16.0 μg/ml, respectively (Li et al. 2019b).

Two indole alkaloids, 2-(3,3-dimethylprop-1-ene)-costaclavine (**390**) and 2-(3,3-dimethylprop-1-ene)-epicostaclavine (**391**) (Supplementary Fig. S38) were isolated from the marine-derived fungus *A. fumigatus*. They showed weak cytotoxicity against a mouse leukemia cell line (P388) with IC_{50} values of 64.9 and 259.7 μmol/L, respectively (Zhang et al. 2013).

Preliminary research on the marine fungus *Fusarium* sp. XBB-9 resulted in a pair of bisindole alkaloid enantiomers, (+)- and (–)-fusaspoid A (**392** and **393**) (Supplementary Fig. S39) (Shaker et al. 2019). The composition of the culture medium had great influence on the metabolite production of the marine fungus *P. boydii* F44-1. By adding amino acids to GPY culture medium, two bisindole alkaloids, pseudboindoles A and B (**394** and **395**), were isolated from the culture broth (Yuan et al. 2019). Another unreported *bis*-indolyl benzenoid, candidusin D (**396**) was isolated from the cultures of the sponge-associated fungus *A. candidus* KUFA 0062, and was also tested for cytotoxic effect against eight cancer cell lines (HepG2, HT29, HCT116, A549, A375, MCF-7 and U-251) with cell viability values in the range of 39.8–69.3% (Buttachon et al. 2018). Varioloids A and B (**397** and **398**) were isolated from the alga-derived endophytic fungus *P. variotii* EN-291. Both exhibited cytotoxicity against A549, HCT116, and HepG2 cell lines with IC_{50} values ranging from 2.6 to 8.2 μg/ml (Zhang et al. 2016).

Asperginine (**399**) (Supplementary Fig. S40), an alkaloid possessing a rare skeleton, was isolated from the fungus *Aspergillus* sp. Z-4 isolated from the gut of the marine isopod *L. oceanica* (Wang et al. 2015). By adding L-tryptophan and L-phenylalanine to GPY medium, dichotomocej D (**400**) was discovered from the marine-derived fungus *D. cejpii* F31-1 (Chen et al. 2017). A Papua New Guinea collection of the marine cyanobacterium *Lyngbya majuscula* yielded hermitamide B (**401**), which exhibited the LD_{50} value of 18.0 μmol/L in the brine shrimp bioassay and an IC_{50} value of 5.5 μmol/L to Neuro-2a neuroblastoma cells in tissue culture (Tan et al. 2000). JBIR-81 and JBIR-82 (**402** and **403**), two terpeptin analogs, from the marine-derived *Aspergillus* sp. SpD081030G1f1, showed stronger protective activity against L-glutamate toxicity in cells with EC_{50} values of 0.7 and 1.5 μmol/L, respectively (Izumikawa et al. 2010). Misszrtine A (**404**) was isolated from sponge-derived fungus *Aspergillus* sp. SCSIO XWS03F03. Compound **404** represented the first example of an *N*-isopentenyl tryptophan methyl ester with a phenylpropanoic amide arm, which exhibited a potent antagonistic activity on HL60 (IC_{50} = 3.1 μmol/L) and LNCaP (IC_{50} = 4.9 μmol/L) cell lines (Zhou et al. 2018). Two isomeric linear peptides, (±)-aspergillamides A and B (**405–407**), were isolated from the mycelium of a cultured marine fungus of the genus *Aspergillus* sp. CNC-120. Among them, compound **405** showed modest in vitro cytotoxicity (IC_{50} = 16.0 μg/ml) toward the HCT-116 cell line (Toske et al. 2010).

Communesin I (**408**) (Supplementary Fig. S41) was obtained from the marine-derived fungus *P. expansum*

Y32. Compound **408** showed a significant mitigative effect on bradycardia caused by astemizole in heart rate experiments (Fan et al. 2015). Two highly oxygenated hexacyclic cyclopiazonic acid alkaloids, speradines B and C (**409** and **410**), together with one related tetracyclic oxindole alkaloid, speradine D (**411**), were isolated from the sponge-derived fungus *A. flavus* MXH-X104. Among them, compound **410** possessed an unprecedented 6/5/6/5/5/6 hexacyclic ring system and a 4-oxo-1, 3-oxazinane ring (Ma et al. 2015). Four tetracyclic oxindole alkaloids, speradines B–E (**412–415**), were isolated from the marine-derived fungus *A. oryzae*. Among these compounds, compounds **412** and **415** showed weak cytotoxic effects on the HeLa cell line with IC_{50} values of 0.2 and 0.2 μmol/L, respectively (Hu et al. 2014b). Further investigation resulted in the discovery of a rare hexacyclic oxindole alkaloid, speradine F (**416**), together with two tetracyclic oxindole alkaloids, speradines G and H (**417** and **418**), isolated from the same fungus *A. oryzae* (Hu et al. 2015).

Iso-α-cyclopiazonic acid (**419**) (Supplementary Fig. S42), together with its isomer α-cyclopiazonic acid (**420**) were isolated from the marine-derived fungus *A. flavus*. Meanwhile, the cytotoxicities of **419** and **420** were studied using HL-60, MOLT-4, A549, and BEL-7402 cell lines, **419** with IC_{50} values of 90.0, 68.6, 42.2, 100.0 μmol/L, respectively, and **420** with IC_{50} values of 2.4, 12.3, 21.5, 17.5 μmol/L, respectively (Lin et al. 2009). Another pentacyclic oxindole alkaloid, speradine A (**421**), was isolated from the cultured broth of a fungus *A. tamarii.* In addition, it exhibited inhibitory activity against Ca^{2+}-ATPase (IC_{50} = 8.0 μmol/L), inhibitory activity against histone deacetylase (IC_{50} = 100.0 μg/ml), and antibacterial activity against *Mycrococcus luteus* (MIC = 16.7 μg/ml) (Tsuda et al. 2003). Bioassay-guided fractionation led to the isolation of 3-hydroxysperadine A (**422**). It was produced by *A. oryzae* HMP-F28 induced significant extracellular alkalinization coupled with augmented H_2O_2 production in tobacco cell suspensions (Cao et al. 2018). Cyclopiamides B–J (**423–431**), oxindole alkaloids, were isolated from the deep-sea-derived fungus *P. commune* DFFSCS026. Compound **426** contained a rare 2*H*-pyrrole[2,1-*b*]pyridine unit, and **430** and **431** were complex polycyclic and polyhydroxy alkaloids (Xu et al. 2015).

Summary of indole alkaloids from marine-derived fungi

The genera of marine-derived fungi for indole alkaloids

Marine-derived fungi have demonstrated to be an important source of structurally new and biologically active indole alkaloids. Among the 21 types of marine-derived fungi, the genus *Aspergillus* (42.0%) was one of the main sources of bioactive secondary metabolites with diverse structures in addition to the genus *Penicillium* (21.3%) and the genus *Eurotium* (10.7%) (Fig. 2). The distribution of different substructures of indole alkaloids in each genus was listed in Fig. 3 (the number corresponds to the number of indole alkaloids in different kinds of fungi genera). Results showed that marine-derived fungi produce significant classes of indole alkaloids, including DKPs [(61.7%, mainly from *Aspergillus* (24.1%), *Penicillium* (10.2%), and *Eurotium* (8.12%)], IDTs [(11.1%, mainly from *Penicillium* (6.7%), and *Aspergillus* (3.9%)], quinazoline-containing indole alkaloids [(7.2%, mostly from *Aspergillus* (6.5%)], cytochalasans [(7.0%, from *Penicillium* (2.6%), and *Aspergillus* (1.0%)], and simple indole alkaloids [(13.0%, from *Aspergillus* (6.5%), and *Penicillium* (3.7%)].

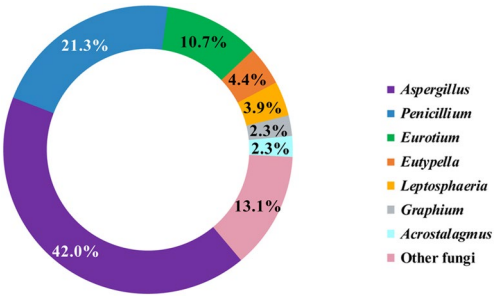

Fig. 2 The indole alkaloids from different fungi genera in this review

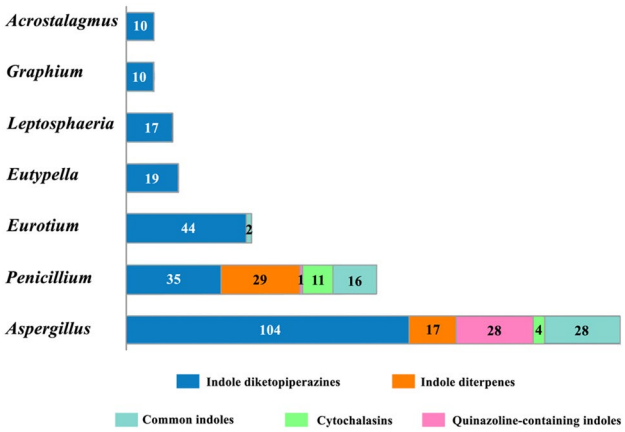

Fig. 3 The relationship between different chemical groups of indole alkaloids and their producers (marine fungi)

Chemical structures

Indole alkaloids are widely present in fungal metabolites, and many of the compounds have various physiological activities with novel structures and various types. In this

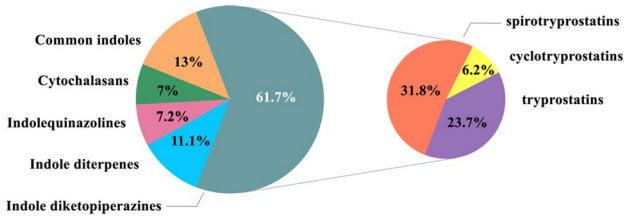

Fig. 4 The distribution of indole alkaloids in five different subtypes

paper, the structures, activities and fungi genera of 431 indole alkaloids isolated from marine-derived fungi from 1984 to 2019 were reviewed, including 266 DKPs (61.7%), 48 indole diterpene alkaloids (11.1%), 31 indolequinazoline alkaloids (7.2%), 30 cytochalasins (7.0%), and 56 simple indole alkaloids (13.0%) (Fig. 4).

DKPs with an indole group, structurally characterized by a diketopiperazine ring, were natural products mainly isolated from fungi and exhibited various biological activities. DKPs should be divided into open-loop compounds tryprostatins, closed-loop compounds cyclotryprostatins and spirocyclic compounds spirotryprostatins through the connection between the indole unit C-2 and the diketoperazine N-8. For example, a pair of enantiomeric DKP dimers [(–)- and (+)-asperginulin A (**265** and **266**)] with an unprecedented 6/5/4/5/6 pentacyclic skeleton were isolated from the mangrove endophytic fungus *Aspergillus* sp. in November 2019, and compound **265** exhibited antifouling activity against the barnacle *B. reticulatus* (Cai et al. 2019).

IDTs represent a class of fungal metabolites with a common core structure consisting of a cyclic diterpene fusing with an indole moiety skeleton derived from geranylgeranyl diphosphate and indole-3-glycerol phosphate. Most natural indole-diterpenes have an invariable framework. Usually, C-7, C-13, and C-27 are oxidized. The oxygenation of C-27 is often followed by the formation of an ether bridge between C-27 and C-7 with inversion of the stereoconfiguration at C-7. In May 2019, penerpenes A (**288**), a unique spiro indole-diterpene bearing a 1,4-dihydro-2H-benzo[*d*][1,3]oxazine motif, was isolated from the marine-derived fungus *Penicillium* sp. KFD28, and showed potent inhibitory activity toward protein tyrosine phosphatases (Kong et al. 2019a).

The quinazoline-containing indole alkaloids, including tryptoquivalines, tryptoquialanines, neosartoryadins, and fiscalins, are one of the largest classes of fungal alkaloids, which contain a common core structure consisting of quinazolin-4(3*H*)-one and indoline moieties. Since fumiquinazolines A–G were isolated from marine fish associated *A. fumigatus* in early 1990, a certain numbers of analogues were separated from diverse marine fungi. For example, isopropylchaetominine (**324**), an induction from sponge-associated fungus *A. carneus* by OSMAC approach, showed strong cytotoxicity against the mouse lymphoma cell line L5178Y with an IC_{50} value of 0.4 μmol/L (Özkaya et al. 2018).

Cytochalasans are one class of alkaloids characterized by a polysubstituted perhydroisoindolone moiety to which typically a macrocyclic ring is fused. Among them, the macrocyclic ring of most cytochalasans are 9-, 11-, or 13-membered, up to now, more than 100 chaetoglobosins have been isolated from various microorganisms, mainly from the fungal genus *Chaetomium*. For example, penochalasin I (**373**), a chaetoglobosin with an unprecedented six-cyclic 6/5/6/5/6/13 fused ring system, exhibited marked cytotoxicity against MDA-MB-435 and SGC-7901 cells ($IC_{50} < 10.0$ μmol/L) (Zhu et al. 2017).

In addition to the above several representative substructures, indole alkaloids also include peptides and other alkaloids containing indole moiety, that is, simple indole alkaloids. For example, two *β*-carboline alkaloids, aspergillspins A and B (**384** and **385**) were isolated from the gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501 (Ma et al. 2019). JBIR-81 (**402**) and JBIR-82 (**403**), two terpeptin analogs, from the culture of a marine-derived *Aspergillus* sp. SpD081030G1f1, showed stronger protective activity against L-glutamate toxicity in cells with the EC_{50} values of 0.7 and 1.5 μmol/L, respectively (Izumikawa et al. 2010).

Bioactivities

Across various bioassays, 229 indole alkaloids showed various activities, including nine biological activities (antibacterial, antifungal, antiviral, lethality-toxicity, protease inhibition, anti-inflammatory, antioxidant and cytotoxicity). Cytotoxicity was the most significant pharmacological activity, accounting for 49.8% of the total number of active molecules, among which chetracin E (**245**), a epipolythiodioxopiperazine isolated from the fungus *Acrostalagmus luteoalbus* HDN13-530, showed strong cytotoxicity on H1975 cells with an IC_{50} value of 0.2 μmol/L (Yu et al. 2018). Furthermore, the distribution of biological activity of different sub-types of compounds was further investigated. On this base, the bioactivities of the compounds were evaluated for different targets, ranging from a specific cellular mechanism to the entire organism. For example, the inhibitory activity of special protease was shown to target enzymatic processes when lethality-toxicity, phytotoxicity, and antimicrobial activity were tested against whole organisms. In addition, cytotoxicity was based on the cell line level, and some research was related to their specific cellular and molecular mechanisms; anti-inflammatory and antioxidant activities were mainly assessed on the basis of specific cellular mechanisms, which might also be included in cytotoxicity and other activities. Laterally, it was found that some activities might be only show for certain subtypes, such as antiviral activity only for DKPs, distinctly. The number of

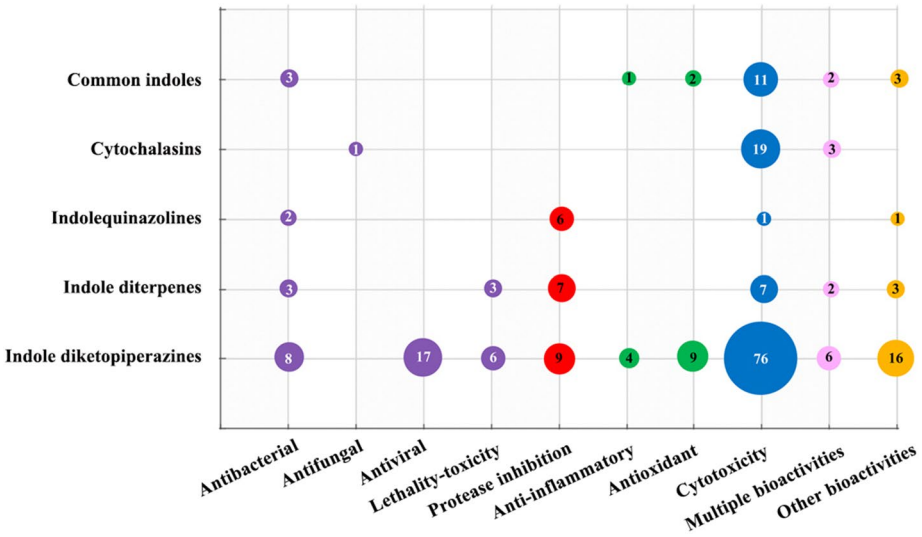

Fig. 5 Classification of 229 bioactive indole alkaloids based on activities and chemical classes

compounds was symbolized by the disc diameters for each bioactivity and each chemical class (Fig. 5). The colors correspond to the different categories of the activity targets. Purple represented the entire organism target, red represented the enzyme target, green primarily represented the specific cellular mechanism, blue represented a cell line target, pink represented mix targets, and yellow represented other targets.

Conclusions and outlooks

We provided a comprehensive overview of the structures, bioactivities, and sources of the 431 indole alkaloids from marine-derived fungi described over the years 1984–2019.

Marine indole alkaloids represented a rich group of natural compounds and have tremendous potential to become precursor compounds. Nevertheless, the reported bioactivities were limited by many factors and they were not comprehensive, which suggested that these natural compounds should be screened on a wider variety of bioassays in order to unveil their full potential. Another noteworthy fact was that the comprehensive and intensive understanding of biochemical pathways concerning both production and metabolism of these fungal metabolites was still essential. Hence, more efforts should be made to explore the pharmacodynamic relationships and pharmacological effects of promising compounds and conduct clinical trials to complete the drug-like evaluation of these molecules.

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Author contributions ZHM and TTS wrote the paper. GZZ and YFY collected the data. QHC analyzed the data. FC and HJZ designed, directed and revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and human rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

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