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# A Systematic Review on Secondary Metabolites of *Paecilomyces* Species: Chemical Diversity and Biological Activity

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## ABSTRACT

Fungi are well known for their ability to synthesize secondary metabolites, which have proven to be a rich resource for exploring lead compounds with medicinal and/or agricultural importance. The genera *Aspergillus*, *Penicillium*, and *Talaromyces* are the most widely studied fungal groups, from which a plethora of bioactive metabolites have been characterized. However, relatively little attention has been paid to the genus *Paecilomyces*, which has been reported to possess great potential for its application as a biocontrol agent. Meanwhile, a wide structural array of metabolites with attractive bioactivities has been reported from this genus. This review attempts to provide a comprehensive overview of *Paecilomyces* species, with emphasis on the chemical diversity and relevant biological activities of these metabolic products. Herein, a total of 148 compounds and 80 references are cited in this review, which is expected to be beneficial for the development of medicines and agrochemicals in the near future.

## Introduction

The hyphomycete genus *Paecilomyces* was established by Bainier in 1907 [1]. It was characterized as being closely related to *Penicillium* species but differed in the absence of green colored colonies and the presence of verticillate conidiophores with short cylindrical phialides that taper into long distinct necks [2]. *Paecilomyces* species are common environmental molds, ubiquitous in soil and composts, and are often associated with the decay of food products. Although some species of *Paecilomyces* have been implicated as plant, animal (mainly insects), and human pathogens, *Paecilomyces* species have shown great application potential in industry, agriculture, and medicine. Moreover, several species of *Paecilomyces* have been regarded as important biocontrol agents, including *Paecilomyces carneus*, *Paecilomyces farinosus*, *Paecilomyces fumosoroseus*, and *Paecilomyces lilacinus*. These findings suggest that *Paecilomyces* species are a high-value microbial resource, not only for their potential use but also for their ability to produce various bioactive substances.

Filamentous fungi are distributed worldwide and play an important role in human history. The discovery of penicillin, the first broad-spectrum antibiotic agent, from the fungal genus *Penicillium* was a monument in medical research and has saved count-

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less lives. Subsequently, the study of fungi has become a hotspot, as fungi produce secondary metabolites with intriguing structures and potential pharmaceutical applications. The genera *Aspergillus, Penicillium*, and *Talaromyces* represent the most widely studied fungal groups, and a plethora of their bioactive metabolites have been characterized [3]. However, relatively little attention has been paid to the genus *Paecilomyces*.

Several interesting reviews related to various aspects of *Paecilomyces* species have been published. For example, Mioso et al. reviewed the chemical diversity of the secondary metabolites produced by the fungus *Paecilomyces variotii*, indicating that *P. variotii* and its active metabolites can provide leading compounds for new drug discoveries [4]. Zimmermann summarized the biology, ecology, and use of *Isaria farinosa* (formerly *Paecilomyces farinosus*) and *Isaria fumosorosea* (formerly *P. fumosoroseus*) as biocontrol agents against pest insects, plant pathogens, and nematodes in the laboratory and the field [5]. Only one review has specifically focused on the metabolites from *P. variotii* and their biological activities [4]. To the best of our knowledge, a comprehensive overview of *Paecilomyces* species, with an emphasis on the chemical diversity and relevant biological activities of these metabolic products, remains untouched. As part of our ongoing investigations of structurally diverse and biologically active secondary metabolites from *P. variotii* [6–10], we also performed a detailed and comprehensive literature survey on all *Paecilomyces* species. The literature search was performed using the combined key words *"Paecilomyces"* and "secondary metabolites" in the Web of Science Core Collection database, with a previously reported search method [11]. As a result, 80 references closely related to the scope of the review were selected. A total of 148 secondary metabolites isolated from *Paecilomyces* species were included. Their structures were classified within a biogenetic context as polyketides (macrolides, quinones, anthraquinones, and unsaturated lactones), terpenoids and steroids, peptides, including diketopiperazines, and alkaloids and other nitrogen-containing compounds. Herein, we describe the sources, chemical structures, and bioactivities of the reported compounds from *Paecilomyces* species with particular emphasis on their potential use as drug lead compounds.

## Taxonomy and Biocontrol Application of Paecilomyces Species

### Taxonomy

Taxonomically, the genus *Paecilomyces* belongs to the Ascomycota phylum, Eurotiales order, and its teleomorph is suggested to be within the genus *Byssochlamys*. According to the data from the Index Fungorum database (www.indexfungorum.org), 145 species of *Paecilomyces* have been reported worldwide. However, the taxonomic classification of this genus remains ill defined. The morphological descriptions of *Paecilomyces* as well as the delimitation of the genus and its relationship to other genera were published by Samson (1974) [12]. Samson defined the delimitation of the genus *Paecilomyces*, which was restricted to species with verticillate conidiophores of divergent whorls of branches and phialides [2, 12]. Accordingly, the species involved in *Paecilomyces* were divided into two sections. Section *Paecilomyces* often contains thermophilic species accompanied by *Talaromyces, Byssochlamys*, or *Thermoascus* in the ascigerous state, while section *Isarioidea* contains those mesophilic species without the ascigerous state, such as *Paecilomyces amoeneroseus, P. farinosus, P. fumosoroseus, Paecilomyces javanicus, P. lilacinus*, and *Paecilomyces tenuipes* [13]. However, the taxonomic classification of these fungi was mainly based on their morphological characteristics, which resulted in the construction of unreliable taxonomic systems [14]. Therefore, molecular phylogeny using various DNA markers was applied to unambiguously determine their phylogenetic relationships [2, 13–15].

After several years of research, phylogenetic analysis proved that the genus *Paecilomyces* is polyphyletic across two ascomycete orders, Eurotiales and Hypocreales [13–15]. Luangsa-ard et al. reported phylogenetic relationships of *Paecilomyces* sect. *Isarioidea* species using the $\beta$-tubulin gene and ITS rDNA and found that sect. *Paecilomyces* is polyphyletic within Hypocreales, while a group designated the *Isaria* clade was considered to be monophyletic [15]. These findings were also supported by a phylogenetic analysis of the ITS1–5.8S-ITS2 gene sequences [13]. Then, the generic name *Isaria* was designated and used for species previously assigned to *Paecilomyces* sect. *Isarioidea* [16, 17]. Further studies on the reclassification of the genus *Paecilomyces* led to the transfer of some species from *Paecilomyces* sect. *Isarioidea* into the genus *Isaria* [5]. Some species previously assigned to *Paecilomyces* sect. *Isarioidea*, such as *Isaria japonica, Isaria tenuipes, Paecilomyces cicadae, Isaria farinosus,* and *I. fumosoroseus*, are now assigned to the genus *Isaria*, within the order Hypocreales (Ascomycota) [5] (details are available in Supporting Information).

Herein, we do not obsess too much about the classification status of the genus *Paecilomyces*, although an in-depth review of the taxonomic revision of the genus *Paecilomyces* is urgently needed to clarify the phylogenetic relationships. It should be pointed out that, in this review, we focused only on the "true" *Paecilomyces* species that can be searched with the key word *"Paecilomyces"* in the Web of Science Core Collection database, ignoring their phylogenetic relationships and the species belonging to the genus *Isaria*.

## Biocontrol Application

*Paecilomyces* species possess great application potential in the industrial, agricultural, and pharmaceutical fields. For example, *Paecilomyces sinclairii* has been reported to possess the capability of producing high yields of natural-sourced red pigments, which have been widely used in the foodstuff, cosmetics, and pharmaceutical industries [18]. *P. variotii* exhibited excellent phenol degradation performance and can be applied in the treatment of industrial wastewater [19]. Meanwhile, *P. variotii* was used to convert toxic waste from castor beans into animal feed material and produce tannase and phytase, important enzymes used in agro-industry [20]. However, the most important and valuable applications are probably focused on biological control.

Many of the *Paecilomyces* species have proven to be highly promising biocontrol agents. *P. lilacinus* is one of the most widely studied biological control species for plant-parasitic nematodes,

such as root knot nematodes, cyst nematodes, and citrus nematodes, protecting the root systems of crops and thus increasing productivity [21]. Lara et al. demonstrated that the nematophagous fungus *P. lilacinus* reduced the root-knot nematode *Meloidogyne incognita* soil and root populations, parasitized the nematode eggs, and increased the tomato yield [22]. Kiewnick and Sikora also reported that the commercial *P. lilacinus* strain 251 provided significant control efficiency of *M. incognita* on tomatoes and suggested that the main activity occurred in soil; thus, a high concentration of conidia was critical for sufficient biocontrol [23]. Yang et al. described an antagonistic effect against oilseed rape rot *Sclerotinia sclerotiorum* in laboratory and field trials using a new transformant, pt361, derived from the wild strain *P. lilacinus*, indicating that the mutant pt361 of *P. lilacinus* was a novel and promising biocontrol agent for *S. sclerotiorum* in oilseed rape [24].

Apart from *P. lilacinus*, the saprophytic *P. fumosoroseus* is also well known and used as a whitefly biopesticide. Wraight et al. discovered that *P. fumosoroseus* can infect *Bemisia argentifolii* nymphs, which resulted in applications for the microbial control of nymphal whiteflies infesting cucurbit crops [25]. Further study revealed that *P. fumosoroseus* can produce highly abundant dipicolinic acid as the active molecular basis responsible for insecticidal activity [26]. Kavková and Čurn discovered that *P. fumosoroseus* significantly suppressed the development and spread of cucumber powdery mildew, suggesting *P. fumosoroseus* as a potential mycoparasite on *Sphaerotheca fuliginea* [27]. *P. fumosoroseus* also induced high mortality of *Spodoptera exigua*, indicating that this fungal strain possessed good potential to develop biopesticides to control beet armyworms [28].

Overall, *Paecilomyces* species exhibited outstanding performance in biological control and considerable potential applications to develop biopesticides. Thus, chemical investigations of these fungi are particularly needed to reveal their chemical basis.

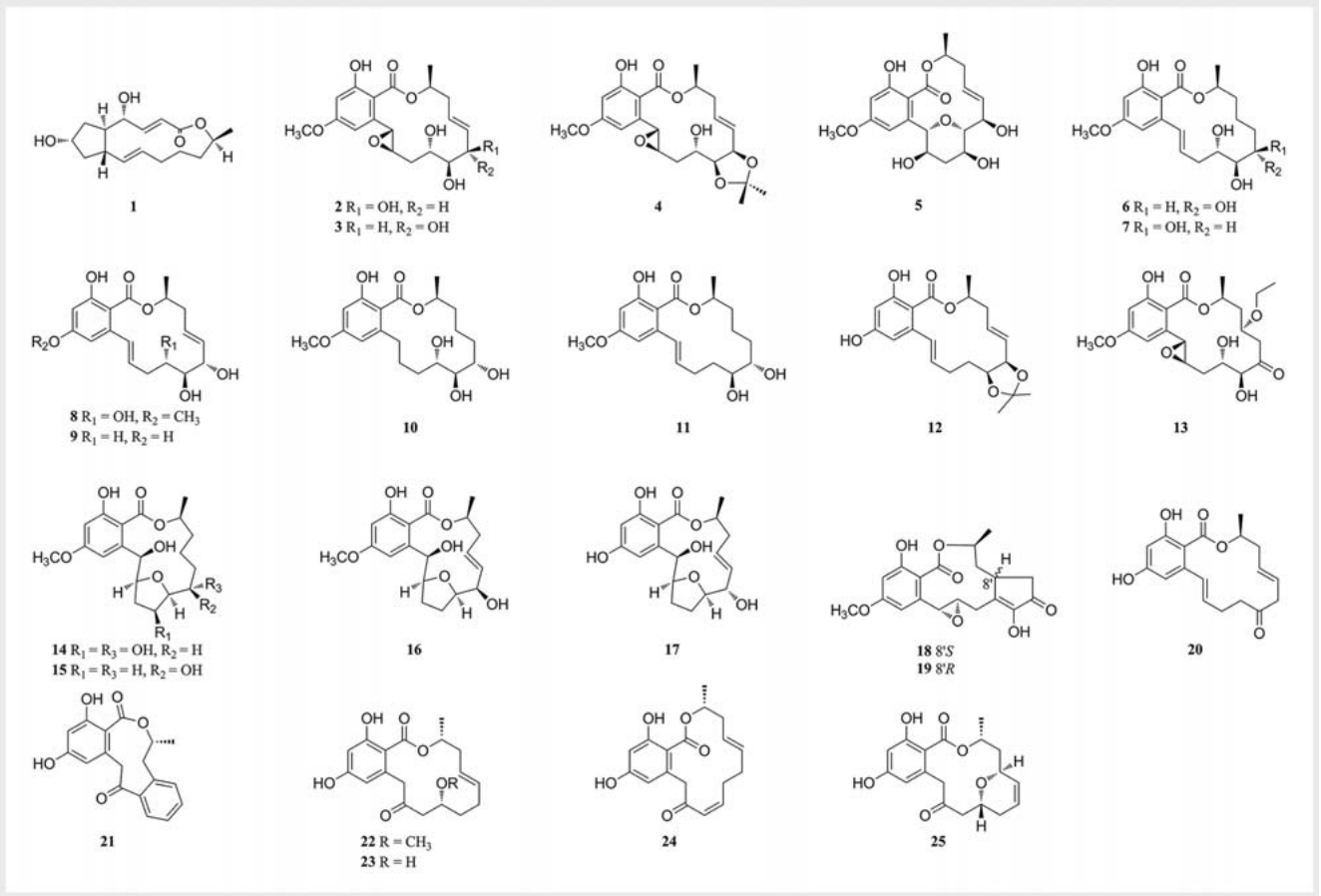
## Chemical Diversity of Secondary Metabolites

Filamentous fungi have been extensively studied in recent decades, and they have been shown to be an intriguing source of bioactive natural products. The fungal genomes encode a large number of enzymes, including nonribosomal peptide synthetases, polyketide synthases, and terpene synthases, that are responsible for synthesizing secondary metabolites. Consequently, fungi can produce an enormous array of structurally diverse metabolites with a wide range of biological properties, some of which are under consideration as lead compounds in the pharmaceutical and agrochemical arenas. To date, a wide structural array of metabolites with attractive bioactivities have been reported from *Paecilomyces* species. A total of 148 secondary metabolites isolated from this genus have been classified into four major categories: polyketides, terpenoids and steroids, peptides including diketopiperazines, and alkaloids and other nitrogen-containing compounds.

### Polyketides

Polyketides comprise a large family of structurally diverse molecules biosynthesized by polyketide synthases (PKSs). The main structural types reviewed in this section are macrolides and quinones. ▶ **Fig. 1** exhibits 25 macrolides characterized from *Paecilomyces* species, including 19 new compounds. Brefeldin A (**1**), also named decumbin, cyanein, ascotoxin, or synergisidin, is a 16-membered macrolide that has been previously isolated from a number of fungal genera: *Alternaria, Ascochyta, Cercospora, Curvularia, Penicillium*, and *Phyllosticta* [29]. Originally, brefeldin A was described as an antifungal, cytotoxic, and cancerostatic antibiotic. Wang et al. first reported the isolation of this cytotoxin from *Paecilomyces* sp. [30]. Four new *β*-resorcylic acid lactones (RALs), named paecilomycins A (**2**), B (**5**), E (**6**), and F (**7**), and four known congeners, aigilomycin B (**3**), zeaenol (**8**), aigialomycin D (**9**), and aigialospirol (**10**), were isolated from the mycelial solid culture of *Paecilomyces* sp. SC0924, which was obtained from a soil sample collected in the Dinghu Mountain Biosphere Reserve, Guangdong, China [31]. RALs are a group of fungal polyketide metabolites possessing a 14-membered lactone ring formed by a side chain with 11 carbons. Compound **4** was the artificial acetonide product of the treatment of **2** with 2,2-dimethoxypropane [31]. Afterwards, the research group obtained another 15 new RALs from the same fungal strain, including paecilomycins G–I (**11**–**13**) [32], paecilomycins J–M (**14**–**17**) [33], hypothemycin-type paecilomycins N–P (**18**–**20**), radicicol-type dechloropochonin I (**21**), monocillins VI (**22**) and VII (**23**), 4′-hydroxymonocillin IV (**24**), and 4′-methoxymonocillin IV (**25**) [34]. Among them, RALs showed structural diversity with epoxy, hydroxyl, carbonyl, and other oxygen-containing groups on the macrolide ring. For example, paecilomycins J–M (**14**–**17**) possessed an oxygen bridge between C-2′ and C-5′ to form a tetrahydrofuran ring [33], while paecilomycins N (**18**) and O (**19**) featured unprecedented 6/11/5 ring systems [34].

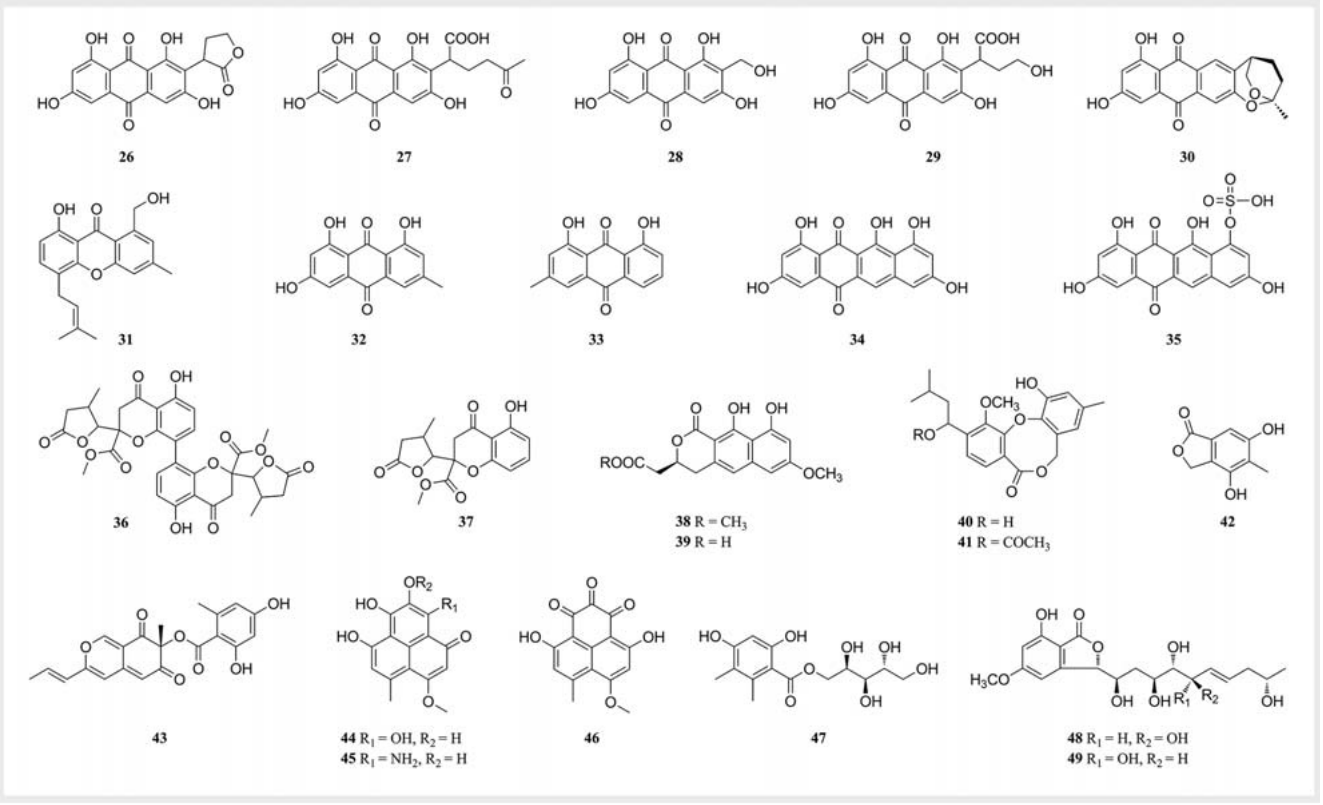
Five new anthraquinones, paeciloquinones A–E (**26**–**30**) (▶ **Fig. 2**), were characterized from the culture broth of the fungus *P. carneus* P-177, which was isolated from a soil sample [35]. Paeciloxanthone (**31**), a new xanthone, and two known compounds, emodin (**32**) and chrysophanol (**33**), were isolated from the extracts of *Paecilomyces* sp. Trees 1–7 from mangrove saprophytic bark [36]. Saintopin (**34**) was obtained from *Paecilomyces* sp. from soil collected at a vineyard in Yamanashi Prefecture, Japan, while UCE1022 (**35**) was isolated from *Paecilomyces* UOE1022 from soil collected in Koganei city, Tokyo [37, 38]. Chemical investigations of the endophytic fungus *Paecilomyces* sp. (trees 1–7) from mangrove bark led to the identification of a novel dimer chromone with a new carbon skeleton, paecilin A (**36**), and its monomer paecilin B (**37**) [39]. The fungus *P. variotii* Bainier, previously isolated from larvae of *Dendroctonus ponderosa* Hopk. (mountain pine beetle), was antagonistic to *Ophiostoma clavigerum*. The metabolites produced by *P. variotii* when grown in liquid culture have been studied, and two new 1*H*-naphtho [2,3-c]pyran-1-ones, semi-viriditoxin (**38**) and semi-viriditoxic acid (**39**), were discovered [40]. Cultivation of the marine-derived fungal strain *Paecilomyces* sp., an endophyte obtained from the saprophytic bark of a mangrove plant, afforded two new paeciloxocins, A (**40**) and B (**41**) [41]. Bioassay-guided isolation of advanced glycation end product (AGE) inhibitors from *Paecilomyces* sp. 3193B resulted in the identification of 4-*O*-demethylsilvaticol (**42**) and (−)-mitorubrin (**43**) [42]. By screening 50 strains of entomopathogenic fungi and rescreening 7 strains of *Paecilomyces gunnii*, a methanol extract of *P. gunnii* was found to possess



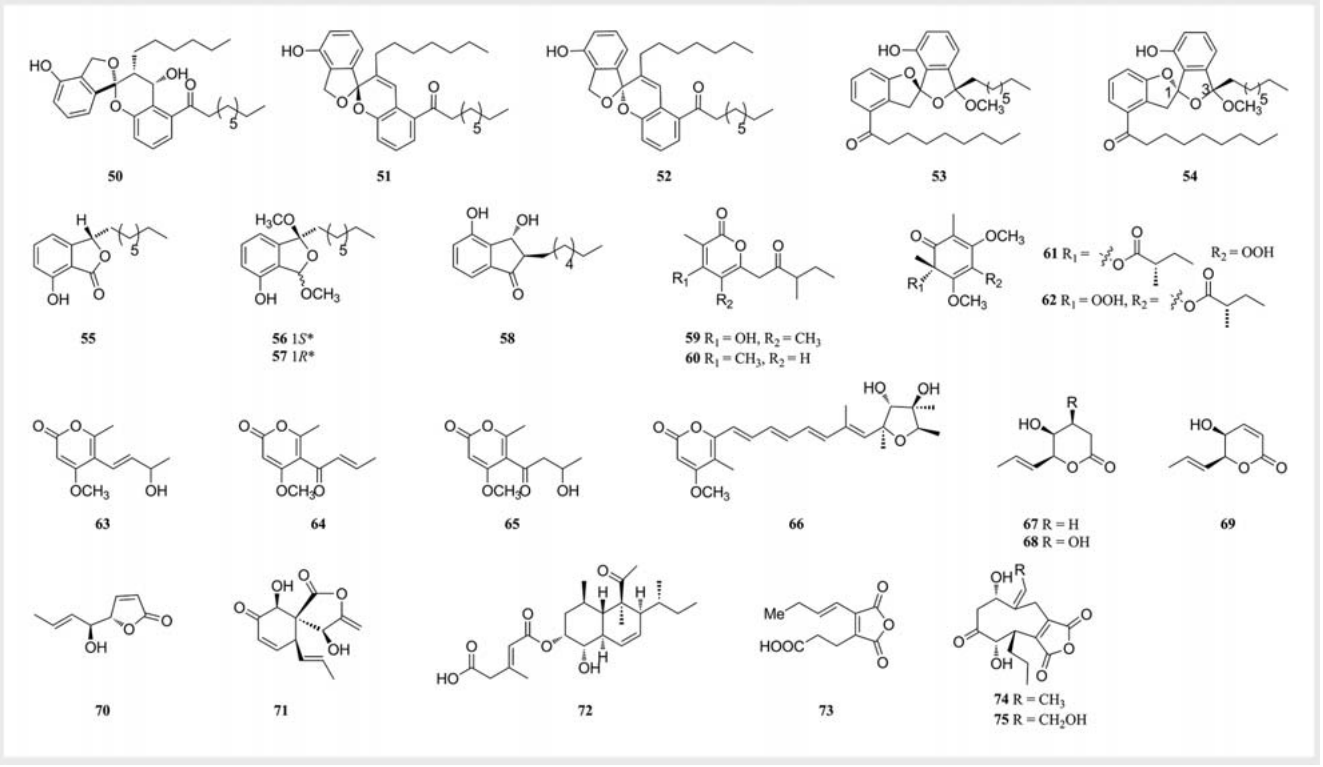

▶ **Fig. 1** Macrolides characterized from *Paecilomyces* species (**1**–**25**).

the strongest tyrosinase inhibitory activity. Chemical investigations of this strain resulted in the isolation of three new phenalenones, paecilomycones A–C (**44**–**46**) [43]. It should be pointed out that the structure of paecilomycone C (**45**) contains an $NH_2$ group. However, herein, we categorize it as a polyketide instead of a nitrogen-containing compound based on the biosynthetic origin of phenalenones. Paeciloside A (**47**), with a 5-methylorsellinic acid subunit and a pentite, was isolated from cultures of *Paecilomyces* sp. CAFT156, an endophytic fungus occurring in *Enantia chlorantha* Oliv (Annonaceae) leaves [44]. Apart from macrolides, the fungus *Paecilomyces* sp. SC0924 also yielded two new RAL derivatives, paecilomycins C (**48**) and D (**49**) [31]. Both compounds possess a dihydroisobenzofuranone ring and a polyhydroxylated linear $C_{10}$ side chain, which are unusual for RALs. Although **48** and **49** are RAL derivatives with similar biogenetic mechanisms, we distinguished them from the macrolide classification because the 14-membered macrolide ring is opened.

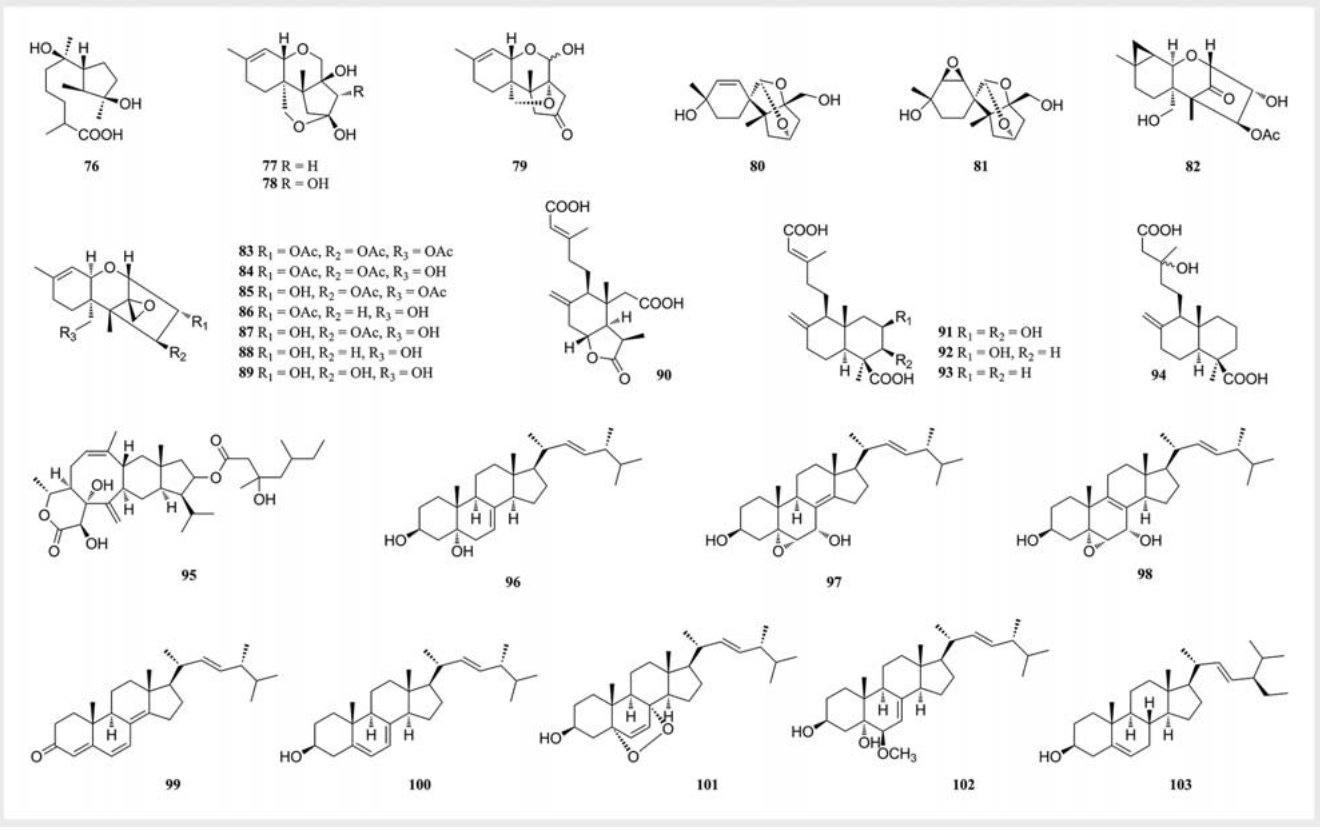
A spiroacetal compound named paecilospirone (**50**) (▶ **Fig. 3**) was isolated from the marine fungus *Paecilomyces* sp. collected at Yap Island [45]. Compound **50** was the first example of a unique skeletal structure, spiro[chroman-2,1′(3′*H*)-isobenzofuran], obtained from natural sources [45]. Then, four closely related dimeric octaketide spiroketals, paeciloketals (**51**–**54**), were isolated from the marine fungus *P. variotii* derived from the giant jellyfish *Nemopilema nomurai* [46]. Compounds **51** and **52** contain a benzannulated [5, 6]-spiroketal moiety, while compounds **53** and **54** possess a [5, 5]-spiroketal core skeleton. Four new polyketides, paecilocins A–D (**55**–**58**), were isolated from the same fungal strain, of which **55**–**57** contained a longer ($C_8$) alkyl chain [47]. Two new α-pyrones (**59** and **60**) and two new cyclohexenones (**61** and **62**) were isolated from the whole broth of the fungus *P. lilacinus*, a strain derived from a marine sponge *Petrosia* sp. [48]. Interestingly, cyclohexenones have been reported only from the genera *Phoma* and *Alternaria* belonging to the family Pleosporaceae (order Pleosporales). This study was the first to isolate these compounds (**61** and **62**) from the genus *Paecilomyces* belonging to the family Trichocomaceae (order Eurotiales). Thus, the isolation of the compounds reported herein from far distinct genera may be meaningful for the chemotaxonomic relationships among them [48]. The screening of antitrypanosomal agents from microbial metabolites led to the discovery of four α-pyrones (**63**–**66**) from *Paecilomyces* sp. FKI-3573 was collected from a soil sample, of which pyrenocine I (**63**) was isolated as a new compound [49]. Chemical investigation of the fungus *Paecilomyces cateniobliquus* YMF1.01799 led to the isolation and identification of four phomalactone-type metabolites (**67**–**70**), two of which were new compounds (**67** and **68**) [50]. The dicyclic spiro compound paecilospirone (**71**) was isolated as a new antibiotic from




▶ **Fig. 2** Polyketides characterized from *Paecilomyces* species (**26**–**49**).




▶ **Fig. 3** Polyketides characterized from *Paecilomyces* species (Continued) (**50**–**75**).




▶ **Fig. 4** Terpenoids and steroids characterized from *Paecilomyces* species (**76**–**103**).

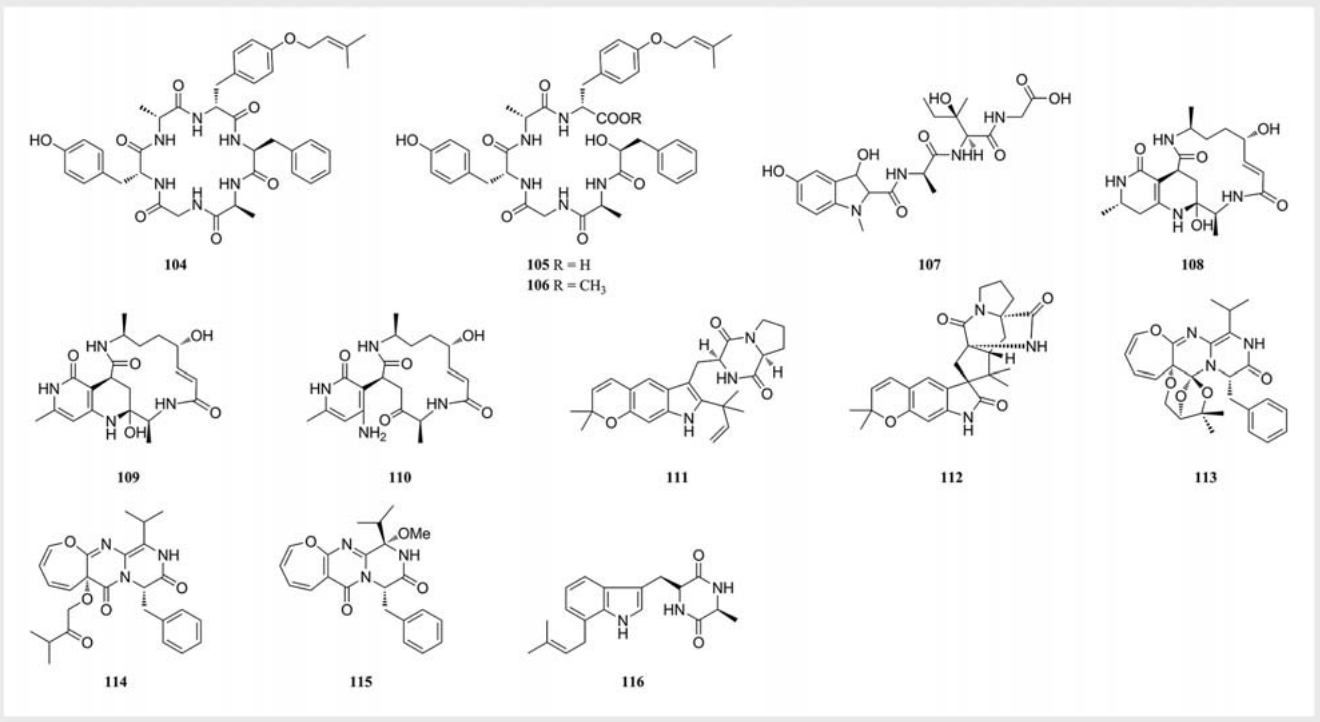
*Paecilomyces* sp. collected from a soil sample [51]. The saltwater culture of a *Paecilomyces* cf. *javanica* isolated from the marine sponge *Jaspis* cf. *Coriacea* yielded a new polyketide, deoxynortrichoharzin (**72**) [52]. A new tricarboxylic acid anhydride (**73**) was isolated in high yield from *P. variotii* Bain [53]. Shake flask cultures of *P. variotii* produced two phytotoxins, cornexistin (**74**) and 14-hydroxycornexistin (**75**) [54]. Compound **75** was a new member of the nonadride family with high herbicidal effects.

## Terpenoids and steroids

Catenioblin C (**76**) (▶ **Fig. 4**), a new sesquiterpenoid, was isolated from the fungus *P. cateniobliquus* YMF1.01799 [5]. *P. tenuipes*, also known as *I. japonica*, is a common entomopathogenic fungus used in folk medicine and health foods [55–57]. Cultivating the fruiting bodies of *P. tenuipes* resulted in the isolation of three new trichothecane-type sesquiterpenoids, paecilomycines A–C (**77**–**79**) [55], two novel spirocyclic spirotenuipesines A (**80**) and B (**81**) [56], as well as tenuipesine A (**82**), a novel trichothecane with an unprecedented carbon-migrated skeleton including a cyclopropane ring [57]. In addition, seven conventional trichothecenes (**83**–**89**) were also isolated [56]. These findings indicated that *P. tenuipes* was a rich source of novel trichothecanes. Two new diterpenoids, paecilomycines A (**90**) and B (**91**), including a novel skeleton with a five-membered lactone ring, together with three known labdane diterpenoids (**92**–**94**) were isolated from solid cultures of the insect pathogenic fungal strain *Paecilomyces* sp. ACCC 37762 [58]. The endophytic fungus *Paecilomyces formosus* LHL10 isolated from the roots of cucumber plants possesses significant inhibitory potential against urease and α-glucosidase [59]. Subsequent chromatographic separation led to the isolation of a sesterterpenoid (**95**). Metabolite **95** was shown to have an unusual tricarbocyclic sesterterpenoid δ-lactone skeleton [59]. Seven ergosterol derivatives (**96**–**102**) were isolated from silkworm larvae infected with *Paecilomyces* sp. J300 [60]. Stigmasterol (**103**), a phytosterol with a side chain containing ten carbon atoms attached at C-17 to the steroid skeleton, was isolated from marine sponge-derived fungal isolates of *Paecilomyces* sp. [61].

## Peptides including diketopiperazines

A new cyclohexadepsipeptide, paecilodepsipeptide A (**104**) (▶ **Fig. 5**), and its linear analogues paecilodepsipeptides B (**105**) and C (**106**) were isolated from the insect pathogenic fungus *Paecilomyces cinnamomeus* BCC 9616 [62]. Compound **104** possessed a unique structural feature with three D-amino acid residues, including an unusual *O*-prenyl-D-Tyr, whereas it contained only one L-Ala. Its linear analogues **105** and **106** are hydrolysis and methanolysis products, which are considered artifacts formed during separation processes [62]. A new indolinepeptide (**107**) was isolated from silkworm larvae infected with *Paecilomyces* sp. J300 [63]. Three new macrocyclic tetralactams, gunnilactams A–C (**108**–**110**), were characterized from the submerged fermentation broth of *P. gunnii*, an entomogenous fungus identified as the

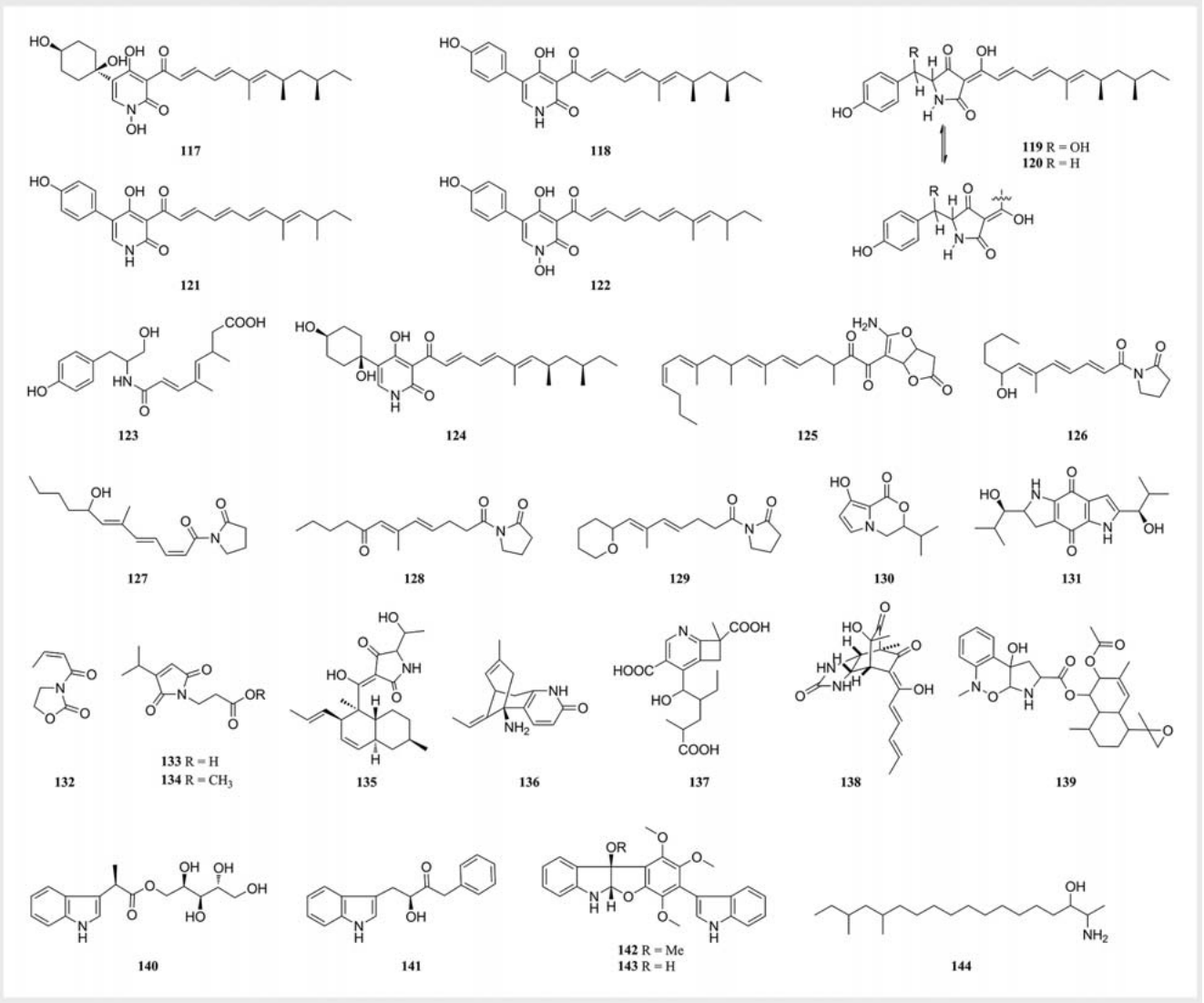



▶ **Fig. 5** Peptides including diketopiperazines characterized from *Paecilomyces* species (**104**–**116**).

anamorph of *Cordyceps gunnii* [64]. Compounds **108**–**110** were novel macrocyclic tetralactams with an unusual skeleton produced by an undescribed biosynthesis pathway [64]. Two new prenylated indole alkaloids (**111** and **112**) were identified from the marine-derived fungus *P. variotii* EN-291, which was isolated as an endophyte from *Grateloupia turuturu*, a marine red alga collected from the coast of Qingdao, China [7]. These alkaloids often contained a diketopiperazine or a bicyclo[2.2.2]diazaoctane ring biogenetically derived from tryptophan. Unlike other related compounds, compounds **111** and **112** were rare examples of possessing dimethyl-substituted pyran rings coupled with indole moieties at C-5 and C-6 [7]. From the same fungal strain *P. variotii* EN-291, three new oxepine-containing diketopiperazines (**113**–**115**) were also characterized [6, 9]. Varioxepine A (**113**) represented a novel 3*H*-oxepine-containing alkaloid characterized by a structurally unprecedented condensed 3,6,8-trioxabicyclo[3.2.1]octane motif [6]. The culture broth extract of the insect pathogen *P. cinnamomeus* BCC 9616 provided a known diketopiperazine, terezine D (**116**) [65].

## Alkaloids and other nitrogen-containing compounds

A new pyridone alkaloid, militarinone A (**117**) (▶ **Fig. 6**), was identified by neuritogenic activity-guided fractionation from the mycelia of the entomogenous fungus *Paecilomyces militaris* RCEF 0095 [66]. Compound **117** featured an unprecedented side chain and a *cis*-(1,4-dihydroxycylohexyl) moiety formed by the condensation of phenylalanine and polyketide precursors. Subsequently, a new pyridone alkaloid, militarinone D (**118**), and two novel 3-acyl tetramic acids, militarinones B (**119**) and C (**120**), were obtained from this insect pathogenic fungus [67]. Compounds **119** and **120**, having a pyrrolidin-2,4-dione ring and a conjugated side chain, were among the polyenoyltetramic acids occurring as red or yellow pigments in *Penicillium* and *Streptomyces* strains [67]. Interestingly, in solution, 3-acylated tetramic acids can form rapidly interchanging internal tautomers, and their NMR data may appear as distinct sets of signals. The NMR spectra of compounds **119** and **120** were also indicative of two *exo*- and *endo*-forms of tautomers [67]. To search for more structurally related compounds, other entomogenous fungal strains, *P. farinosus* RCEF 0101 and *P. farinosus* RCEF 0097, were chosen. Further chromatographic separation of the fungus RCEF 0101 afforded three additional pyridone alkaloids, farinosones A–C (**121**–**123**) [68]. Farinosones A (**121**) and B (**122**) were closely related to militarinones, while farinosone C (**123**) was derived from the initial condensation step in the proposed biosynthetic pathway [68]. Chemical investigations of the fungus RCEF 0097 led to the isolation of a new pyridone alkaloid, (+)-*N*-deoxymilitarinone A (**124**), with a cyclohexyl moiety [68]. The marine fungus *Paecilomyces* sp. derived from the marine sponge was cultivated to produce a new nitrogen-containing compound, **125** [61]. Variotin (**126**) and three novel compounds, formosusins A–C (**127**–**129**), were isolated from cultures of the fungus *P. formosus* [69]. A large-scale culture of the marine mudflat-derived fungus *P. formosus* yielded a new pyrrolooxazine, formoxazine (**130**), a previously reported dipyrroloquinone derivative (**131**), and a 2-oxazolidinone analogue (**132**) [70]. Two maleimide-bearing compounds, including the new farinomalein (**133**), were identified from the fungus *P. farinosus* HF599 [70]. A new tetramic acid derivative, paecilosetin (**135**), was characterized from the fungus *P. farinosus* isolated from infected insect larvae [71]. Huperzine A (**136**), a naturally occurring alkaloid in the




▶ **Fig. 6** Alkaloids and other nitrogen-containing compounds characterized from *Paecilomyces* species (**117**–**144**).

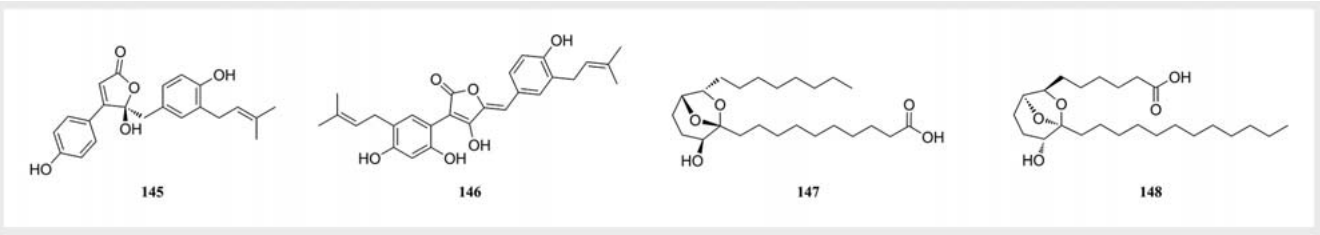
plant family Huperziaceae, was produced by *Paecilomyces tenuis* YS-13, an endophytic fungus isolated from *Huperzia serrata* [72]. A new pyridine (**137**) was isolated from the nematicidal active fungal strain of *Paecilomyces* sp. YMF1.01761 [73]. A ureido Diels-Alder adduct of sorbicillinol **138** was isolated from an intertidal marine *Paecilomyces marquandii* strain [74]. A novel nematicidal antibiotic, paeciloxazine (**139**), with a pyrrolobenzoxazine skeleton, was characterized from the culture broth of the fungus *Paecilomyces* sp. BAUA3058 strain [75]. An indole alkaloid acremoauxin A (**140**) was isolated from cultures of *Paecilomyces* sp. CAFT156, an endophytic fungus residing in *E. chlorantha* Oliv (Annonaceae) leaves [44]. Kurasoin B (**141**) was obtained from the cultured broth of *Paecilomyces* sp. FO-3684 [76]. Two cyclized bisindolyl benzenoid derivatives (**142**–**143**), including the new varioloid A (**142**), were isolated from the marine alga-derived endophytic fungus *P. variotii* EN-291 [10]. Finally, the amino alcohol compound paecilaminol (**144**) was isolated from the cultured broth of the fungus *Paecilomyces* sp. FKI-0550 [77].

### Shikimate-derived metabolites and lipids

Bioassay-guided fractionation of the marine-derived endophytic fungus *P. variotii* EN-291 resulted in the isolation of two new butenolides, butyrolactone IX (**145**) and aspulvinone O (**146**) [7] (▶ **Fig. 7**). Finally, two new bicyclic fatty acids with a 6,8-dioxabicyclo[3.2.1]octane core skeleton, paecilonic acids A and B (**147** and **148**), were characterized from the marine fungus *P. variotii* derived from jellyfish [78].

## Biological Activities of Secondary Metabolites

The producing strain, environment source, and biological activities of compounds 1–148 have been detailed in ▶ **Table 1**. Anticancer, antimicrobial, and insecticidal activities were the three main indexes used to assess the pharmacological activity of these natural compounds. In this section, the detailed descriptions of compounds with potent biological activities are provided below.



▶ **Fig. 7** Shikimate-derived metabolites and lipids characterized from *Paecilomyces* species (**145**–**148**).

## Anticancer activity

Brefeldin A (**1**) was found to show potent cytotoxicity against HL-60, KB, HeLa, MCF-7, and Spc-A-1 cell lines with $IC_{50}$ values ranging from 1 to 10 ng/mL, which were close to or higher than those of Taxol. Therefore, brefeldin A is regarded as a very promising lead compound in cancer therapy [30]. The isolated new RALs were evaluated for their cytotoxicity against A549, HeLa, and MCF-7 tumor cells. In general, RALs with no bridging within the macrocycle, such as **20, 22**, and **23**, exhibited promising cytotoxicity ($IC_{50}$ < 10 µM) against at least one of the three tested cell lines, while the RALs featuring bridged macrolactones, such as **14**–**17** with a tetrahydrofuran ring, **18** and **19** with the 6/11/5, and **21** with the 6/10/6 ring system, were almost inactive. Paeciloxanthone (**31**) was tested for cytotoxicity against HepG2 cell lines and showed significant activity with an $IC_{50}$ value of 1.08 µg/mL [36]. Saintopin (**34**) and UCE1022 (**35**) showed cytotoxic activity against a human tumor cell line, HeLa S3, with $IC_{50}$ values of 1.0 and 6.1 µM, respectively [37, 38]. Paeciloxocin A (**40**) exhibited strong cytotoxicity against HepG2 cells with an $IC_{50}$ value of 1 µg/mL [41]. Two α-pyrones, pyrenocines A (**64**) and B (**65**), showed potent cytotoxic activity against a human embryonic lung fibroblast cell line, MRC-5, with $IC_{50}$ values of 0.38 and 0.98 µg/mL, respectively [49]. Acetoxyscirpenediol (**87**) possessed potent cytotoxic activities against the human gastric tumor cell line (SNU-1), human hepatoma cell line (SNU-354), human colorectal tumor cell line (SNU-C4), and murine sarcoma-180 with $IC_{50}$s of 1.2, 4.0, 2.2, and 1.9 µM, respectively [79]. The cytotoxic effect of **87** was approximately 4.0–6.6 times stronger than that of cisplatin, which is currently used clinically for cancer patients [79]. The ergosterol derivatives (**98**–**102**) showed nonspecific moderate cytotoxicity against five human tumor cell lines [60]. The cyclic depsipeptide paecilodepsipeptide A (**104**) showed promising cytotoxicity toward two cancer cell lines, KB ($IC_{50}$ of 5.9 µM) and BC ($IC_{50}$ of 6.6 µM); however, its linear analogues **105** and **106** were inactive, indicating that the cyclic depsipeptide structure is necessary for its biological activities [62]. The macrocyclic tetralactam gunnilactam A (**108**) displayed selective inhibitory activity against C42B cells with an $IC_{50}$ value of 5.4 µM [64]. Prenylated indole alkaloids **111** and **112** showed weak cytotoxic activity against NCI-H460 (human large cell lung carcinoma cell line) with $IC_{50}$ values of 69.3 and 55.9 µM, respectively [8]. Paecilosetin (**135**) exhibited moderate activity against the murine leukemic P388 cell line with an $IC_{50}$ value of 3.2 µg/mL [71]. Two cyclized bisindolyl benzenoid derivatives (**142** and **143**) exhibited cytotoxicity against A549, HCT116, and HepG2 cell lines with $IC_{50}$ values ranging from 2.6 to 8.2 µg/mL [10].

## Antimicrobial activity

Of the RALs, paecilomycins G–I (**11**–**13**) and paecilomycin M (**17**) showed weak antifungal activity against the phytopathogenic fungus *Peronophythora litchii*, while compounds **22**–**24** exhibited moderate activity against *P. litchii* with $IC_{50}$ values of 9.2, 41.0, and 19.3 µM, respectively [32, 33]. Paeciloxocin A (**40**) inhibited the growth of *Curvularia lunata* (Walker) Boedijn and *Candida albicans* ATCC 10231 with inhibition zones of 12 and 10 mm, respectively [41]. The dimeric octaketide spiroketal **51** showed modest antibacterial activity against the marine pathogen *Vibrio ichthyoenteri* [46]. Paecilocins B (**56**) and C (**57**) showed moderate antibacterial activity against *Staphylococcus aureus* SG 511 and methicillin-resistant *S. aureus* 3089 (MRSA) with MIC values ranging from 5 to 40 µg/mL [47]. Paecilospirone (**71**) showed antimicrobial activity against *Bacillus subtilis* with an MIC value of 5 µg/mL at 25 °C, but at 37 °C, **71** did not show any effect due to rapid destruction [51]. The new oxepine-containing diketopiperazines **113**–**115** exhibited potent antifungal activity against the plant-pathogenic fungus *Fusarium graminearum* with MIC values ranging from 4 to 8 µg/mL [6, 9]. Compound **125** moderately inhibited MRSA with an inhibition zone of 8 mm [61]. Compound **130** displayed antibacterial activity against MRSA and multidrug-resistant *S. aureus* (MDRSA) with MICs of 6.25 µg/mL [70]. Farinomalein (**133**) significantly inhibited the plant pathogen *Phytophthora sojae* with an MIC value of 5 µg/disk, whereas the MIC of the antifungal agent amphotericin B was 10 µg/disk [80]. Paecilosetin (**135**) caused considerable growth inhibition of *Bacillus subtilis* and the pathogenic fungi *Cladosporium resinae* and *Trichophyton mentagrophytes* [71].

## Insecticidal activity

Compounds **2**–**10** were evaluated for their antiplasmodial activity against the chloroquine-susceptible line *Plasmodium falciparum* 3D7 and the chloroquine-resistant line Dd2. The new compound paecilomycin E (**6**) exhibited potent activity against 3D7 with an $IC_{50}$ value of 20.0 nM, which was comparable to the positive controls artemisinin and chloroquine, while other compounds showed only moderate activity [31]. However, in the assay against the line Dd2, only compounds **3, 6, 7**, and **9** exhibited moderate activity with $IC_{50}$ values ranging from 1.7 to 10.5 µM [31]. These findings implied RALs as models for the discovery of new antimalarial molecules. The new α-pyrone pyrenocine I (**63**) showed

▶ **Table 1** The producing strain, environment source, and biological activities of **1–148**.

| NO. | Producing strain | Environment source | Biological activities | Reference |
|---|---|---|---|---|
| 1 | *Paecilomyces* sp. | Isolated as an endophyte from traditional Chinese medical plants *Taxus mairei* and *Torreya grandis*. | Potent cytotoxicity against HL-60, KB, Hela, MCF-7, and Spc-A-1 cell lines. | [30] |
| 2–10 | *Paecilomyces* sp. SC0924 | Isolated from a soil sample collected in the Dinghu Mountain Biosphere Reserve, Guangdong, China. | Potent antiplasmodial activity against *Plasmodium falciparum* lines. | [31] |
| 11–13 | *Paecilomyces* sp. SC0924 | Isolated from a soil sample collected in the Dinghu Mountain Biosphere Reserve, Guangdong, China. | Weak or no antifungal activity against *Peronophythora litchi*. | [32] |
| 14–17 | *Paecilomyces* sp. SC0924 | Isolated from a soil sample collected in the Dinghu Mountain Biosphere Reserve, Guangdong, China. | Weak antifungal activity against *Peronophythora litchii*. | [33] |
| 18–25 | *Paecilomyces* sp. SC0924 | Isolated from a soil sample collected in the Dinghu Mountain Biosphere Reserve, Guangdong, China. | Either cytotoxic against MCF-7, A549, and HeLa cells or antifungal activity against *Peronophythora litchi*. | [34] |
| 26–30 | *P. carneus* P-177 | Isolated from a soil sample collected in a jungle region of Bolivia. | Potent inhibitory activity against protein tyrosine kinase in the micromolar range. | [35] |
| 31–33 | *Paecilomyces* sp. | Isolated from an estuarine mangrove from the Taiwan Strait. | Cytotoxicity against HepG2; acetylcholinesterase inhibitory and antimicrobial activities. | [36] |
| 34 | *Paecilomyces* sp. | Isolated from soil collected at a vineyard in Yamanashi Prefecture, Japan. | Topoisomerase II-dependent DNA cleavage activity, weak antimicrobial activity against gram-positive bacteria, and potent cytotoxic activity against HeLa S3. | [38] |
| 35 | *Paecilomyces* UOE1022 (FERM BP-4066). | Isolated from soil collected in Koganei city, Tokyo, Japan. | Topoisomerase I mediated DNA cleavage activity and cytotoxic activity against HeLa S3. | [37] |
| 36, 37 | *Paecilomyces* sp. | Isolated as an endophyte from mangrove bark from Xiamen. | No obvious cytotoxic activity. | [39] |
| 38, 39 | *P. variotii* | Isolated from an egg gallery of mountain pine beetle in lodgepole pine at Invermere, British Columbia. | Weak antibacterial activity. | [40] |
| 40, 41 | *Paecilomyces* sp. | Isolated from the saprophytic bark of mangrove from the Taiwan Strait. | Significant cytotoxicity against HepG2 and antimicrobial activity. | [41] |
| 42, 43 | *Paecilomyces* sp. 3193B | Source not given. | Moderate to potent inhibitory activity against AGE formation. | [42] |
| 44–46 | *P. gunnii* | Source not given. | Strong tyrosinase inhibitory activity. | [43] |
| 47, 140 | *Paecilomyces* sp. CAFT156 | Isolated as an endophyte from leaves of *Enantia chlorantha* Oliv. | Weak antibacterial activity and moderate cytotoxicity towards brine shrimp larvae (*Artemia salina*). | [44] |
| 48–49 | *Paecilomyces* sp. SC0924 | Isolated from a soil sample collected in the Dinghu Mountain Biosphere Reserve, Guangdong, China. | No obvious bioactivity. | [31] |
| 50 | *Paecilomyces* sp. | Isolated from the coral reef at Yap Island, Federated States of Micronesia. | No obvious bioactivity. | [45] |
| 51–54 | *P. variotii* J08NF-1 | Isolated from the jellyfish *Nemopilema nomurai* collected off the southern coast of Korea. | Modest antibacterial activity against the marine pathogen *Vibrio ichthyoenteri*. | [46] |
| 55–58 | *P. variotii* | Isolated from the jellyfish *Nemopilema nomurai* collected off the southern coast of Korea. | Moderate antibacterial activity against methicillin-resistant *Staphylococcus aureus*. | [47] |
| 59–62 | *P. lilacinus* (J04J-1) F-9 | Isolated from a marine sponge *Petrosia* sp. collected from Jeju Island, South Korea. | No obvious cytotoxicity. | [48] |
| 63–66 | *Paecilomyces* sp. FKI-3573 | Isolated from a soil sample collected in Hilo, HI, USA. | Potent antitrypanosomal activity against *Trypanosoma brucei brucei* and cytotoxic activity. | [49] |
| 67–70, 76 | *P. cateniobliquus* YMF1.01799 | Source not given. | Significant inhibitory effect on the growth of cotton bollworm *Helicoverpa armigera*. | [50] |

*continued*

▶ **Table 1** *Continued*

| NO. | Producing strain | Environment source | Biological activities | Reference |
|---|---|---|---|---|
| **71** | *Paecilomyces* sp. | Isolated from a soil sample collected in Takatsuki City. | Antimicrobial activity against *Bacillus subtilis*. | [51] |
| **72** | *Paecilomyces* cf. *javanica* | Isolated from the marine sponge *Jaspis* cf. *Coriacea* | No obvious cytotoxicity. | [52] |
| **73** | *P. variotii* Bain | Source not given. | No biological activity tested. | [53] |
| **74, 75** | *P. variotii* Bainier SANK 21086 | Source not given. | High herbicidal activity against broadleaf weeds and selectivity to corn. | [54] |
| **77–79** | *P. tenuipes* | Source not given. | Potent neurotrophic factor biosynthesis activity in glial cells. | [55] |
| **80, 81, 83–89** | *P. tenuipes* | Source not given. | Potent neurotrophic factor biosynthesis activity in glial cells. | [56] |
| **82** | *P. tenuipes* | Source not given. | No biological activity tested. | [57] |
| **90–94** | *Paecilomyces* sp. ACCC 37762 | Isolated from an unidentified Lepidopteran collected in Hebei Province, China. | No biological activity tested. | [58] |
| **95** | *P. formosus* LHL10 | Isolated from the root of a cucumber plant. | Remarkable enzymes inhibitory activity against $\alpha$-glucosidase and urease. | [59] |
| **96–102** | *Paecilomyces* sp. J300 | Source not given. | Moderate cytotoxicity against five tumor cells. | [60] |
| **103, 125** | *Paecilomyces* sp. | Isolated from the marine sponge collected along Tinggi Island, Malaysia. | Moderate antimicrobial activity against MRSA. | [61] |
| **104–106** | *P. cinnamomeus* BCC 9616 | Isolated from a Homoptera scale insect collected in Thailand. | Antimalarial activity against the malarial parasite *Plasmodium falciparum* K1 and cytotoxicity toward two cancer cell lines. | [62] |
| **107** | *Paecilomyces* sp. J300 | Source not given. | No biological activity tested. | [63] |
| **108–110** | *P. gunnii* | Source not given. | Selective cytotoxic activity against human prostate cancer C42B cells. | [64] |
| **111, 112** | *P. variotii* EN-291 | Isolated from a marine red alga *Grateloupia turuturu* collected from the coast of Qingdao, China. | Weak cytotoxic activity against NCI-H460. | [7] |
| **113** | *P. variotii* EN-291 | Isolated from a marine red alga *Grateloupia turuturu*. | Potent antifungal activity against plant pathogenic fungus *Fusarium graminearum*. | [6] |
| **114, 115** | *P. variotii* EN-291 | Isolated from a marine red alga *Grateloupia turuturu*. | Potent antifungal activity against *Fusarium graminearum*. | [9] |
| **116** | *P. cinnamomeus* BCC 9616 | Isolated from a Homoptera scale insect collected in Thailand. | No biological activity tested. | [65] |
| **117** | *P. militaris* RCEF 0095 | Isolated from a Lepidopteran pupa collected in Anhui province, China. | Pronounced neurotrophic effect in PC-12 cells. | [66] |
| **118–120** | *P. militaris* RCEF 0095 | Isolated from a Lepidopteran pupa collected in Anhui province, China. | Weak neuritogenic activity in PC-12 cells. | [67] |
| **121–123** | *P. farinosus* RCEF 0101 | Isolated from an unidentified Lepidopteran collected in Anhui Province, China. | Considerable neuritogenic activity in PC-12 cells. | [68] |
| **124** | *P. farinosus* RCEF 0097 | Isolated from a Lepidopteran species collected in Yunnan Province, China. | Induced neurite sprouting in PC-12 cells when tested at 33 and 100 µM concentrations. | [80] |
| **126–129** | *P. formosus* | Isolated from the seaside in Japan. | Inhibited the activity of mammalian DNA polymerase $\beta$. | [69] |
| **130–132** | *P. formosus* | Isolated from the marine mudflat collected at Suncheon Bay, Korea. | Antibacterial activity against MRSA and MDRSA, and potent radical-scavenging activity against DPPH. | [70] |
| **133, 134** | *P. farinosus* HF599 | Isolated from a Lepidopteran larval cadaver collected on Mt. Tsukuba, Ibaraki, Japan. | Potent antifungal activity against the plant pathogenic *Phytophthora sojae*. | [70] |
| **135** | *P. farinosus* | Isolated from an infected insect larva from leaf litter collected from a suburban garden in New Zealand. | Moderate to weak cytotoxic activity against the P388 cell line and antimicrobial activity. | [71] |

*continued*

▶ **Table 1** *Continued*

| NO. | Producing strain | Environment source | Biological activities | Reference |
|---|---|---|---|---|
| **136** | *P. tenuis* YS-13 | Isolated as an endophyte from *Huperzia serrata*. | No biological activity tested. | [72] |
| **137** | *Paecilomyces* sp. YMF1.01761 | Isolated from soil in Yunnan Province, China. | Nematicidal activity against *Bursaphelenchus xylophilus* and *Meloidogyne arenaria*. | [73] |
| **138** | *P. marquandii* BAFC 486 | Isolated from an intertidal marine sediment sample. | No biological activity tested. | [74] |
| **139** | *Paecilomyces* sp. BAUA3058 | Isolated from a soil sample collected in Ibaraki Prefecture, Japan. | Moderate nematicidal and insecticidal activity against *Plutella xylostella*. | [75] |
| **141** | *Paecilomyces* sp. FO-36841 | Isolated from a soil sample collected in Kurashiki City, Japan. | Moderate activity in inhibiting protein farnesyltransferase. | [76] |
| **142, 143** | *P. variotii* EN-291 | Isolated from *Grateloupia turuturu*, a marine red alga collected from the coast of Qingdao, China. | Cytotoxicity against A549, HCT116, and HepG2 cell lines. | [10] |
| **144** | *Paecilomyces* sp. FKI-0550 | Isolated from a soil sample collected on Miyakojima Island, Okinawa Prefecture, Japan. | Inhibitory activity against NADH-fumarate reductase. | [77] |
| **145, 146** | *P. variotii* EN-291 | Isolated from *Grateloupia turuturu*, a marine red alga collected from the coast of Qingdao, China. | Potent DPPH radical scavenging activity. | [7] |
| **147, 148** | *P. variotii* | Isolated from the inner tissues of the jellyfish *Nemopilema nomurai*. | No biological activity tested. | [78] |

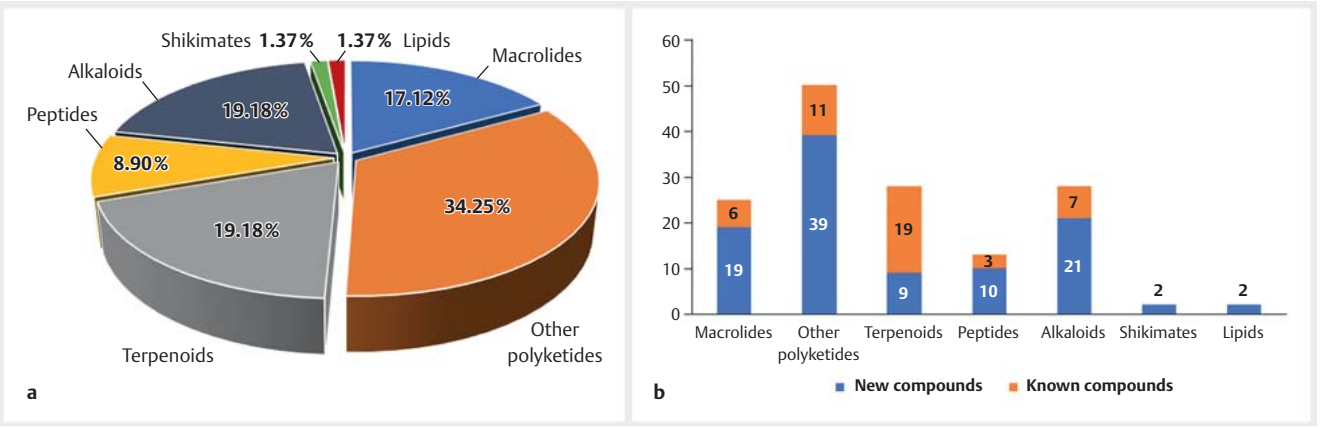
a similar antitrypanosomal activity against *Trypanosoma brucei* ($IC_{50}$ of 1.8 µg/mL) compared to the commonly used drug suramin, while pyrenocine A (**64**) showed the most potent activity with an $IC_{50}$ value of 0.12 µg/mL [49]. The polyketide-derived compound **69** showed a significant inhibitory effect on the overall growth of the cotton bollworm *Helicoverpa armigera*, while surprisingly, the terpenoid-derived metabolite **76** significantly promoted the growth of the larvae, revealing that *P. cateniobliquus* could produce diverse metabolites to regulate the growth of the insect [50]. The cyclic depsipeptide paecilodepsipeptide A (**104**) exhibited activity against the malarial parasite *P. falciparum* K1 with an $IC_{50}$ value of 4.9 µM [62]. The new pyridine **137** displayed nematicidal activity against *Bursaphelenchus xylophilus, Meloidogyne arenaria*, and *Panagrellus redivivus* with $LD_{50}$ values of 167.7, 47.1, and 50.86 mg/L, respectively [73]. Pyrolobenzoxazine **139** showed moderate nematicidal activity against *Rhabditis pseudoelongata* and insecticidal activity against *Culex pipiens pallens* [75].

## Enzyme inhibitory activity

The novel anthraquinones (**26–30**) significantly inhibited the epidermal growth factor receptor protein tyrosine kinase (PTK) in the micromolar range. Two metabolites, **26** and **28**, were proven to be potent and selective inhibitors of v-abl PTK with an $IC_{50}$ value of 0.4 µM [35]. The new xanthone paeciloxanthone (**31**) displayed acetylcholinesterase inhibition activity *in vitro* with an $IC_{50}$ value of 2.25 µg/mL [36]. Saintopin (**34**) possessed topoisomerase II-dependent DNA cleavage activity, while UCE1022 (**35**) selectively inhibited the breakage-rejoining reaction of topoisomerase I by stabilizing a cleavable complex [37, 38]. The three new phenalenones paecilomycones A–C (**44–46**) exhibited strong tyrosinase inhibitory activity with $IC_{50}$s of 0.11, 0.17, and 0.14 mM, respectively, which were equal to or higher than those of the positive controls kojic acid (0.10 mM) and arbutin (0.20 mM) [43]. The enzyme inhibition bioassay indicated that sesterterpenoid **95** exhibited remarkable inhibition against α-glucosidase and urease with $IC_{50}$ values of 61.80 and 74.25 µg/g, respectively [59]. Formosusins B (**127**), a new *cis*-olefin analog of compound **126**, selectively inhibited the activity of mammalian DNA polymerase *β in vitro*, with an $IC_{50}$ of 35.6 µM, while other compounds were inactive [69]. Kurasoin B (**141**) moderately inhibited protein farnesyltransferase in a dose-dependent manner [76]. The amino alcohol **144** exhibited an $IC_{50}$ value of 5.1 µM against *Ascaris suum* NADH-fumarate reductase [77].

## Neuritogenic activity

Paecilomycin A (**77**) showed potent activity in neurotrophic factor biosynthesis in glial cells, which was 1000 times higher than that of scabronine G [55]. Trichothecanes **80** and **81** were also active in neurotrophic factor biosynthesis [56]. The isolation of trichothecane-type sesquiterpenoids indicated that these compounds probably had potential as lead compounds for neurodegenerative diseases such as Alzheimer's disease [55, 56]. The new pyridone alkaloid **117** was evaluated for its potential to stimulate neuronal differentiation of PC-12 cells and found to induce a pronounced neurotrophic effect [66]. However, in contrast to **117**, structurally related compounds **118–120** showed only negligible neurotrophic activity in PC-12 cells [67]. Compounds **121** and **123** also induced neurite outgrowth in the PC-12 cell line at a concentration of 50 µM, while compound **122** was inactive [68]. Compound **124** induced neurite sprouting in PC-12 cells when tested at concentrations of 33 and 100 µM. The neurotrophic effect of **124** is thus weaker than that of militarinone A (**117**) [81].




▶ **Fig. 8** **a** Percentage of distribution of compounds from *Paecilomyces* species based on their putative biogenetic origin. **b** New compounds produced by *Paecilomyces* species.

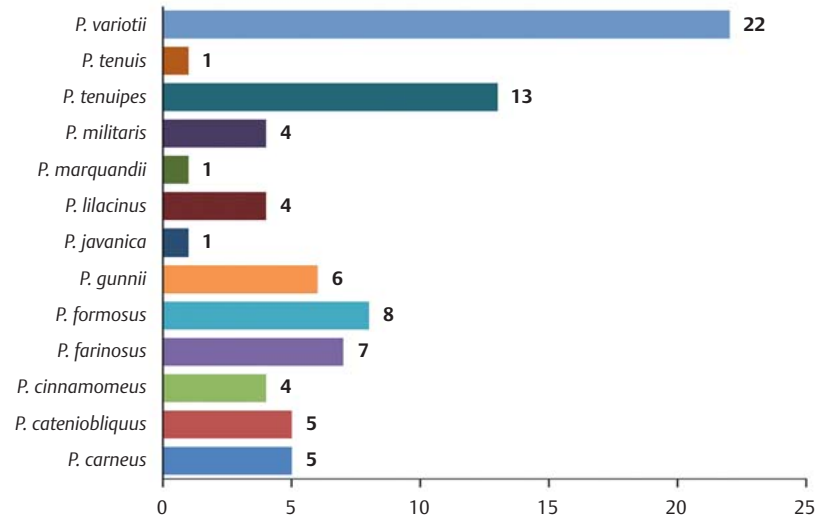
### Other bioactivities

4-*O*-Demethylsilvaticol (**42**) and (−)-mitorubrin (**43**), isolated as Maillard reaction inhibitors, showed potent inhibitory activity against cross-linked protein formation and AGE formation [42]. Both compounds possessed a 1,3-dihydroxybenzene moiety that might contribute to trapping methylglyoxal in the formation of AGEs. Paeciloside A (**47**) displayed moderate cytotoxicity toward brine shrimp larvae (*Artemia salina*) with a mortality rate of 31% at a concentration of 10 µg/mL [44]. 14-Hydroxycornexistin (**75**) possessed high herbicidal activity against weeds and low phytotoxicity to corn, suggesting that other nonadrides may be of interest for evaluation as potential herbicides [54]. Compounds **130** and **132** displayed potent radical scavenging activity against DPPH with $IC_{50}$ values of 0.1 and 10 µM, respectively, which were 200 times higher than that of the positive control ascorbic acid ($IC_{50}$ of 20 µM) [70]. Butenolide **146** displayed potent DPPH radical scavenging activity with an $IC_{50}$ value of 11.6 µM, which was stronger than that of the positive control BHT (butylated hydroxytoluene) (with an $IC_{50}$ of 117.7 µM) [7].

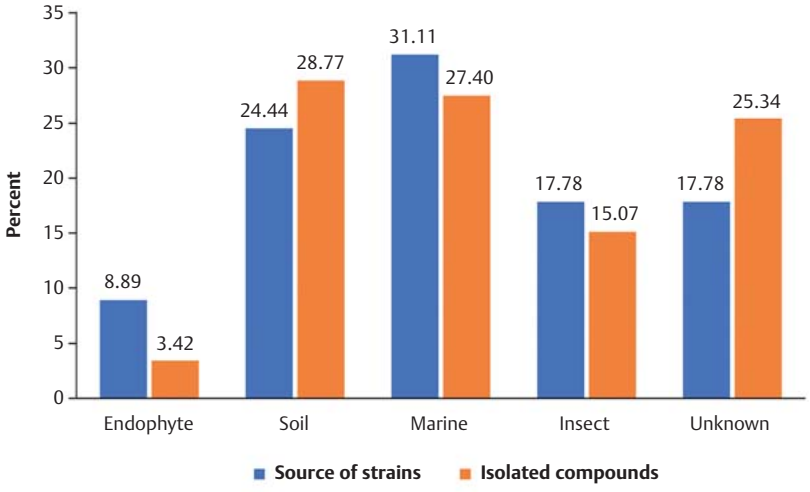
## Conclusions and Future Perspectives

Species from the *Paecilomyces* genus are capable of producing a variety of secondary metabolites with diverse chemical classes and biological activities. They have emerged as a treasure house for finding novel pharmaceutical and/or agrochemical lead compounds. ▶ **Fig. 8** summarizes the structural/biogenetic types of the 148 chemical structures isolated from *Paecilomyces* species. Based on their putative biogenetic origin, these metabolites were classified into polyketides (including macrolides) (**1**–**25** for macrolides and **26**–**75** for other polyketides), terpenoids and steroids (**76**–**103**), peptides including diketopiperazines (**104**–**116**), alkaloids and other nitrogen-containing compounds (**117**–**144**), and shikimate-derived metabolites and lipids (**145**–**148**). It should be pointed out that in most cases, the classification of a certain metabolite depends only on structural considerations just represents the individual judgment of the authors. The structural classification of secondary metabolites according to biogenetic categories is to some degree arbitrary, since a number of compounds derive from mixed biogenesis, such as PKS-NRPS (PKS: polyketide synthases; NRPS: nonribosomal peptide synthetases) hybrids and miscellaneous nitrogenated derivatives. For example, paecilomycone C (**45**) contains an $NH_2$ group in its structure and hence can be considered a nitrogen-containing compound. Herein, however, we categorize it as a polyketide based on the biosynthetic origin of phenalenones. As evident from ▶ **Fig. 8**, among the 148 metabolites observed, approximately 51% were polyketide derived. We specifically list macrolides as an individual group, since this kind of compound constitutes 17.1% of the metabolites reported, nearly as many as terpenoids and alkaloids. Moreover, among the 25 macrolides reported, 19 compounds were described as new macrolides (▶ **Fig. 8b**). Taking other polyketides into account, the number of new compounds is up to 58. These findings indicate that *Paecilomyces* species are promising producing strains of novel polyketides.

As mentioned above, the taxonomic classification of *Paecilomyces* species was ill-defined due to their similar morphological characteristics and insufficient molecular identification. To the best of our knowledge, a total of 45 fungal strains have been reported as producing the described secondary metabolites. However, most of them were unable to be adequately identified. Only 13 strains, including *P. carneus*, *P. cateniobliquus*, *P. cinnamomeus*, *P. farinosus*, *P. formosus*, *P. gunnii*, *P. javanica*, *P. lilacinus*, *P. marquandii*, *P. militaris*, *P. tenuipes*, *P. tenuis*, and *P. variotii*, had absolutely determined phylogenetic positions (▶ **Fig. 9**). Among them, *P. variotii* was the most prolific in producing strains, with 22 metabolites identified from this species. The fungus *P. variotii* is well known for its metabolic potential to produce abundant bioactive secondary metabolites. Our chemical studies of *P. variotii* EN-291, an endophytic fungus isolated from the red alga *G. turuturu*, led to the identification of three new oxepine-containing alkaloids (**113**–**115**) with antimicrobial activity [6, 9], two new butenolide derivatives (**145** and **146**) with DPPH radical scavenging activity [7], two new prenylated indole alkaloids (**111** and **112**) with cytotoxic activity [8], and a new cyclized bisindolyl benzenoid derivative (**142**) with cytotoxic activity [10]. Following *P. variotii*, *P. tenuipes* was also a very promising source of producing strains, with 13 novel trichothecane-type sesquiterpenoids characterized [55–57]. The unidenti-



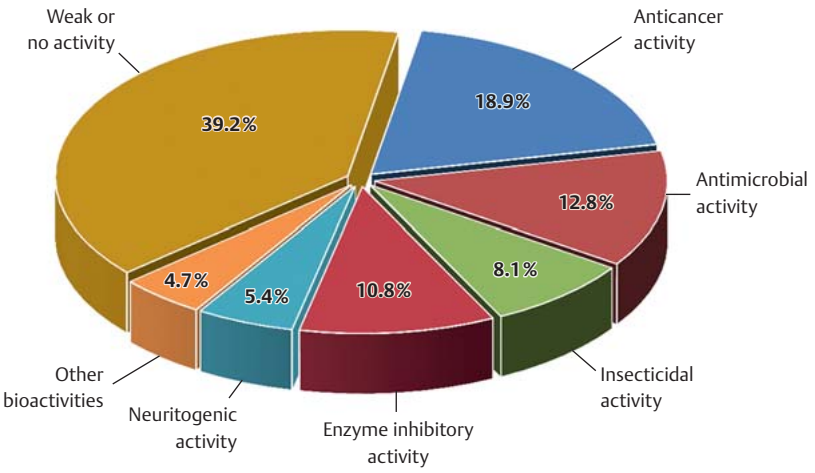

▶ **Fig. 9** Compounds characterized from different producing strains.




▶ **Fig. 10** Percentage of distribution of producing strains and isolated compounds from different sources.

fied strains not only confounded the phylogenetic positions within this species but also hampered the use of diagnostic chemical markers to distinguish them from a chemotaxonomy point of view.

*Paecilomyces* species are widely distributed and commonly occur in air, compost, and various foodstuffs. The distribution of these fungal communities reported for chemical research is shown in ▶ **Fig. 10**. It can be estimated that 31% of these producing strains were isolated from marine environments, with approximately 27% of the compounds characterized. Producing strains can be isolated from a vast range of marine habitats, such as nonliving marine sediments and mudflats, marine invertebrates (including sponges, corals, and jellyfish), and marine plants (algae and mangroves). The fungal strains isolated from a marine environment were usually cultured in natural or artificial seawater with a certain salinity (ranging from 50 to 100%), while those from a terrestrial environment were cultured in distilled water. It is believed that the different cultural manner may affect the richness of the secondary metabolites. In a hyperhaline environment, the fungal strains may produce more structurally diverse metabolites to induce resistance to high salt stress. Soil is also an important source of these fungal strains. As summarized in ▶ **Fig. 10**, nearly 24% of the 45 producing strains and 28% of the reported compounds come from soil. Other strains are also isolated as endophytes from medicinal plants or isolated from insects. Although a small sample cannot yield statistically significant conclusions, it appears that the marine environment and soil are better sources of these strains than others. Therefore, further studies should be




▶ **Fig. 11** Bioactivity categories of the reported metabolites.

particularly focused on the marine environment and soil as potential sources to search for more producing strains.

These secondary metabolites not only possess intriguing structures but also exhibit a variety of biological activities, including anticancer, antimicrobial, insecticidal, enzyme inhibitory, and neuritogenic activities (▶ **Fig. 11**). Among the 148 metabolites presented in this review, an extraordinarily high proportion (60.8%) of the isolated metabolites showed moderate to potent activities. Most importantly, some of the compounds showed potent (or significant) activities compared to those of the positive controls (usually commercial medicines), which indicates that they could be used as potential alternatives to traditional drugs. These include the anticancer lead compound acetoxyscirpenediol (**87**), the antimicrobial farinomalein (**133**), the antiplasmodial paecilomycin E (**6**), and the tyrosinase inhibitors paecilomycones A–C (**44**–**46**). Acetoxyscirpenediol (**87**) showed potent cytotoxicities against SNU-1, SNU-354, SNU-C4, and murine sarcoma-180 with $IC_{50}$ values of 1.2, 4.0, 2.2, and 1.9 µM, respectively [79]. The cytotoxic effect of **87** was 4.0–6.6 times stronger than that of cisplatin, a strong and widely used chemotherapy drug for cancer patients [79]. Farinomalein (**133**) showed potent antifungal effects on the plant pathogen *P. sojae* with an MIC value of 5 µg/disk, whereas the MIC of the antifungal agent amphotericin B was 10 µg/disk [80]. Paecilomycin E (**6**) exhibited potent antiplasmodial activity against *P. falciparum* 3D7 with an $IC_{50}$ value of 20.0 nM, which was equal to that of the positive controls artemisinin and chloroquine [31]. Paecilomycones A–C (**44**–**46**) exhibited strong tyrosinase inhibitory activity with $IC_{50}$ values of 0.11, 0.17, and 0.14 mM, respectively, which were equal to or higher than those of the positive controls kojic acid (0.10 mM) and arbutin (0.20 mM) [43]. Paecilomycin A (**77**) showed potent activity in neurotrophic factor biosynthesis, 1000 times higher than that of scabronine G [55]. These remarkable activities make many of these compounds suitable candidates for new drug discovery and may lead to future synthesis studies.

Overall, *Paecilomyces* species possess great potential for their applications as biocontrol agents. This species is considered to be a rich and innovative source for exploring lead compounds with medicinal and/or agricultural importance. Chemical studies of these fungal strains have led to the characterization of 148 bioactive metabolites. Among them, some compounds showed potent activities that are expected to be beneficial for the development of new medicines and agrochemicals in the near future.

## Supporting information

Phylogenetic analyses of *Paecilomyces* species using ITS rDNA and *β*-tubulin genes are available as Supporting Information.

## Contributors' Statement

Drafting the manuscript: X. Q. Li, K. Xu; design of the review: P. Zhang, X. M. Liu; critical revision of the manuscript: P. Zhang, K. Xu.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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