The Bioactive Secondary Metabolites from *Talaromyces* species

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**Abstract** The focus of this review is placed on the chemical structures from the species of the genus *Talaromyces* reported with reference to their biological activities. 221 secondary metabolites, including 43 alkaloids and peptides, 88 esters, 31 polyketides, 19 quinones, 15 steroid and terpenoids, and 25 other structure type compounds, have been included, and 66 references are cited.

**Graphical Abstract**

**Keywords** *Talaromyces* · Secondary metabolites · Biological activities

1 Introduction

The name *Talaromyces* is derived from the Greek word for ‘basket’, which aptly describes the body in which ascii-pores are formed. In the past, species producing sexual stages with *Penicillium* anamorphs have been classified in *Eupenicillium* and *Talaromyces*. After July 2011, species formally classified in the *Penicillium* subgenus *Biverticillum* were classified in *Talaromyces*. The situation is complicated by the fact that many species now classified in *Talaromyces* will continue to be sought as *Penicillium* species in identifications [1]. So in this review, all of the
papers which reported the secondary metabolites from the species named Talaromyces were covered.

The genus Talaromyces (Trichocomaceae) is an important fungal genus because of its ubiquity which were isolated from soil, plants, sponges, and foods. Some of the species are heat resistant. Some of the species are famous because of their enzymes applicable in the synthesis of saccharides, preparation of chiral building blocks or biotransformations, and for its application in pest biocontrol. Many of its species are used in food and agricultural production. Interestingly, the T. pinophilus strain EMOO 13–3 is able to degrade agricultural waste [2]. However, although endemic in maize, T. fumiculosus also occurs in a wide range of other foods and sometimes causes spoilage [1]. Considering their importance, members of this genus have attracted the attention of chemists. Many studies have focused on the secondary metabolites.

2 The Secondary Metabolites

The secondary metabolites of Talaromyces mainly include alkaloids, peptides, lactones, polyketides, and miscellaneous structure type compounds. T. flavus, a microorganism remarkable for its secondary metabolites with unique biological activities, is the commonest species of the genus Talaromyces [3]. All of the natural products from the species of this genus are classified. The reported bioactivities are also represented below.

2.1 Alkaloids and Peptides

Alkaloid is a kind of important natural products. Many alkaloids have various kinds of biological activities, such as antibacterial, antifungal, cytotoxic, and nematicidal. The structures of alkaloids isolated from Talaromyces species are mainly nitrogen heterocyclic derivatives.

Two prenylated indole alkaloids, talathermophilins A and B (1 and 2), were isolated from a thermophilic fungus T. thermophilus strain YM1-3. And the ratio of 1 and 2 in the culture broths was unexpectedly rather constant (about 2:3), which even remained unchanged despite the addition of exogenous 1 or 2 suggesting that talathermophilins might be of special function for the thermophilic fungus. Those both compounds showed nematicidal toxicity (ca. 38 and 44 % inhibition, respectively) toward the worms of the free-living nematode Panagrellus redivivus at a concentration of 400 µg/mL for 72 h. The family of prenylated indole alkaloids is a well-known group of secondary metabolites mainly produced by Aspergillus and Penicillium sp. This is a first report about pyranoindol alkaloids from Talaromyces [4]. Other fourindole alkaloids with various levels of prenylation, talathermophilins C–E (3–5) and cyclo (glycyltryptophyl) (6), from the thermophilic fungus T. thermophilus strain YM3-4 which was collected in hot springs, were also elucidated by the same research group in 2011 [5]. Interestingly, authors found that only a very small group of amino acids (glycine, alanine, proline, and its derivatives) could be naturally chosen as a starting building block to form the 2,5-diketopiperazine with tryptophan [4, 5].

Seven known indole alkaloids (7–12) were obtained from the culture of the alga-endophytic fungus Talaromyces sp. cf-16. Bioassay results showed that 9 was more toxic to brine shrimp than the other compounds, and 8, 9, and 10 could inhibit Staphylococcus aureus [6].
Three known diketopiperazines, cyclo(L-proline-L-leucine) (13), cyclo(L-proline-L-phenylalanine) (14), and cyclo(L-tyrosine-L-phenylalanine) (15), were isolated from the methanolic extracts of the green Chinese onion-derived fungus *T. pinophilus* AF-02 [7].

An unprecedented class of PKS-NRPS hybrid metabolites possessing a 13-membered lactam-bearing macrolactone, thermolides A–F (16–21), were also obtained from *T. thermophilus* YM3-4. They showed that compounds 16 and 17 displayed potent inhibitory activity against three notorious nematodes with LC_{50} values of 0.5–1 μg/mL, as active as commercial avermectins. This is the first report on the discovery of hybrid macrolides from a fungus origin [8]. Afterwards, a combination of chemical screening, genome analyses, and genetic manipulation led to the identification of the thermolide biosynthetic genes from sister thermophilic fungi *T. thermophilus* and *Thermomyces lanuginosus* C5. And a novel macrolactone, thermolide G (22), was obtained from the cultural broth of *Thermomyces lanuginosus* C5. Their results revealed the first fungal hybrid iterative polyketide synthase–nonribosomal peptide synthetase (PKS–NRPS) genes involved in the biosynthesis of bacterial-like hybrid macrolactones instead of typical fungal tetramic acids-containing metabolites [9].
Four new tetramic acid derivatives, talaroconvolutins A–D (23–26), along with a known mitorubrin derivative, ZG-1494R (27), were isolated from the strain T. convolutes by the group of Shun-ichi Udagawa in 2000. The antifungal activity of the talaroconvolutins against the pathogenic fungi Aspergillus fumigatus, A. niger, Cryptococcus albicans, and C. neoformans, was determined. And the results showed that talaroconvolutins B (24) and C (25) and ZG-1494R (27) inhibited the growth of A. fumigatus, A. niger, and C. albicans [10].

A peptide analogue N-benzoylphenylalanyl-N-benzoylphenylalaninate (35) was isolated from the fungus T. thailandiasis, which was firstly found from a higher plant, Croton hieronymi [12]. Two new cyclic peptides, talaromins A and B (36 and 37) were yielded from the endophytic fungus T. wortmannii, isolated from Aloe vera by the group of Peter Proksch and Abdessamad Debbab. Both cyclopeptides contain ring systems comprised of six α-amino acid residues connected to β-amino acid. The absolute configurations of the α-amino acids were determined by Marfey’s method. Both compounds showed no activity when evaluated for their cytotoxicity against L5178Y mouse lymphoma cells and no antibacterial activity against a broad spectrum of bacterial strains up to a concentration of 64 µg/mL [13].

9-(3-L-alanylamino-3-carboxypropyl)adenine (NK374200, 38) with a peptidyl adenine nucleus was isolated from the culture broth of the fungus Talaromyces sp., which had been isolated from a soil sample. 38 was screened in various biological assay systems, and found to have anti-mosquito larval activity [14].

Four new drimane sesquiterpene lactones conjugated with N-acetyl-L-valine, minioluteumides A–D (28–31), and three known compounds, purpuride (32), berkedrimane B (33), and purpuride B (34), were isolated from the marine fungus, T. minioluteus (P. minioluteum) by the group of Prasat Kittakoop. The structure 28 was elucidated by single crystal X-ray analysis. 28, 31 and 33 showed cytotoxic activity against HepG2 with IC₅₀ ranges of 50.6–193.3 µM, but 28–34 did not shown any inhibit activity to caspase-3 [11].
Two quinazoline alkaloids, 2-[(S)-hydroxy(phenyl)methyl]-3-methylquinazolin-4(3H)-one (39) and 2-[(R)-hydroxy(phenyl)methyl]-3-methylquinazolin-4(3H)-one (40), and a pyridone derivative (41), were isolated and identified in a culture of the alga-endophytic fungus Talaromyces sp. cf-16 for the first time. Following chiral column chromatography, compounds 39 and 40 were identified as enantiomers by spectroscopic analyses and quantum chemical calculations [6].

(E)-3-(2,5-dioxo-3-(propan-2-ylidene)pyrrolidin-1-yl) acrylic acid (42) was isolated from the ethyl acetate extract of the culture broth of T. verruculosus, a rhizosphere fungus of Stellera chamaejasme L. In the antimicrobial activities, 42 gave slight active against the plant pathogenic fungi, Alternaria solani, Valsa mali, Curvularia lunata, and Botryosphaeria berengeriana, at 100 μg/mL and its MIC values against pathogenic bacteria, Staphylococcus aureus and Escherichia coli, were more than 100 μg/mL [15]. Emerin (43) was obtained from the extract of T. flavus IFM52668, and showed no activity against pathogenic filamentous fungi, Aspergillus fumigatus and A. niger, and pathogenic yeasts, Candida albicans and Cryptococcus neoformans, at 200 μg/disc [16].
2.2 Esters

The secondary metabolites of *Talaromyces* are mainly esters, including macrolides, linear polyesters, aromatic lactones, coumarins, phthalides, and five/six-membered saturated lactones.

Four novel 22-membered triene macrolides, wortmannilactones A–D (44–47), were obtained from the fungus *T. wortmannii* which isolated from a soil sample collected in China’s Yunnan province. 44–47 were screened for cytotoxic activity against a panel of human cancer cell lines (HCT-5, HCT-115, A549, MDA-MB-231, and K562). The IC$_{50}$ values range from 28.7 to 130.5 μM [17]. Vermiculine (48), a 16-membered macrolide dilactone antibiotic had been found in crystalline solid from *T. wortmannii*, isolated from a soil sample [18].

Seven 15G256 macrolide polyesters, 15G256 (49), 15G256β (50), 15G256α (51), talapolyester E (52), 15G256α-1 (53), talapolyester F (54), and 15G256α (55), were isolated from the wetland soil-derived fungus *T. flavus* BYD07-13 by Chinese researchers. Among these compounds, 50 and 55 exhibited significant activity against MCF-7 cell line with the IC$_{50}$ of 3.27 and 4.32 μM, respectively [19]. 51 [20, 21] and 53 [22] were also isolated from the soil-derived fungus *T. flavus* FKI-0076 by Japanese researchers. In the course of screening for synergist effects with clinic-used miconazole as well as antifungal agent, 51 was showed that can inhibit *Bacillus subtilis* (IC$_{50}$ 15 mg/L), *Staphylococcus aureus* (IC$_{50}$ 90 mg/L), *Micrococcus luteus* (IC$_{50}$ 100 mg/L), *Mucor racemosus* (IC$_{50}$ 40 mg/L) [20]. As proposed by Schlingmann, 15G256 polyesters are biosynthetically assembled by alternately linking 2,4-dihydroxy-6-(2-hydroxypropyl)benzoic acid and 3-hydroxybutyric acid moieties [23].
Four new linear polyesters, talapolyesters A–D (56–59), together with six known compounds (60–65), were isolated from the wetland soil-derived fungus T. flavus BYD07-13. Those compounds contained both 2,4-dihydroxy-6-(2-hydroxypropyl)benzoic acid or its derivatives and 3-hydroxybutyric acid or its derivatives. The cytotoxicity against five tumor cell lines of those compounds was examined, but all polyesters were inactive (IC$_{50}$ > 40 µM) as compared to cisplatin [19].
Three new oxaphenalenone dimers, bacillosporins A–C (66–68), were isolated from *T. bacillosporus* NHL 2660. 66 had the antibacterial activity against *Bacillus subtilis* and *Sarcina lutea* [24]. Other oligophenalenone dimers, bacillosporins D and E (69 and 70) and duclauxin (71), were isolated from the fungus *T. bacillisporus* from a soil sample. They were screened for in vitro cytotoxicity against three human tumor cell lines MCF-7, NCI-H-460 and SF-268, and 71 exhibited moderate inhibitory effects against all three cell lines but 70 showed little activity [25]. In 2015, two new oxaphenalenone dimers, talaromycesone A (72) and talaromycesone B (73), were isolated from the culture broth and mycelia of a marine fungus *Talaromyces* sp. strain LF458. 72 exhibited potent antibacterial activities with IC\(_{50}\) 3.70 \(\mu\)M against human pathogenic *Staphylococcus* strains, and 72 also displayed potent acetylcholinesterase inhibitory activities with IC\(_{50}\) 7.49 \(\mu\)M [26].

Antibacterial binaphtho-\(\alpha\)-pyrones, talarodexines A and B (74 and 75) were isolated from a new heterothallic ascomycetous fungus, *T. dertii*, cultivated on rice. The antibacterial activities of the metabolites from *T. derxii* and their derivations against *Bacillus subtilis* indicated that only talarodexine, the mixture of 74 and 75, showed antibacterial activity, which was almost as strong as that of viriditoxin. And talarodexine had inhibitory activity toward 5-lipoxygenase, its IC\(_{50}\) value was determined as 3.8 \(\times\) 10\(^{-6}\) M [27].

Eight new dinapinones, AB1, AB2, AC1, AC2, AD1, AD2, AE1 and AE2 (76–83) were obtained from the culture broth of *T. pinophilus* FKI-3864. All these dinapinones possessed the same biaryl dihydronaphthopyranone skeleton consisting of a heterodimer with one monapinone A and one different monapinone. The effect of dinapinones was evaluated on the synthesis of [\(^{14}\)C] triacylglycerol (TG) and [\(^{14}\)C] cholesterol ester from [\(^{14}\)C] oleic acid in CHO-K1 cells and the results indicated that dinapinone (77) showed potent inhibition of TG synthesis in intact mammalian cells with an IC\(_{50}\) value of 1.17 \(\mu\)M, whereas the other dinapinones showed weak inhibition of TG synthesis [28].
Six diphenyl ether lactone derivatives (84, 85 and 86–88) and AS-186c (89) were isolated from amarine fungus *Talaromyces* sp. strain LF458. 89 exhibited potent antibacterial activities with IC50 1.34 μM against human pathogenic *Staphylococcus* strains, potent acetylcholinesterase inhibitory activities with IC50 2.60 μM, and phosphodiesterase PDE-4B2 inhibitory activities with IC50 2.63 μM [26]. Penicillide and dehydroisopenicillide (84 and 85) were isolated from *T. derxii* cultivated on rice [29]. Penicillide was also isolated from the methanolic extracts of the green Chinese onion-derived fungus *T. pinophilus* AF-02 [7].

A coumarin 90 was obtained from the organic extracts of the soil fungus *T. flavus* [30]. Two new coumarins, talacoumarins A (91) and B (92), were isolated from the ethyl acetate extract of the wetland soil-derived fungus *T. flavus* BYD07-13. They were evaluated for anti-Aβ42 aggregation, cytotoxic, and antimicrobial activities and the results showed that 91 and 92 had moderate anti-Aβ42 inhibitory aggregation activity, and this was the first report on the Aβ42 inhibitory aggregation activity of coumarins [31].
An O-methylated 3,4-dihydroisocoumarin \((93)\) was isolated from a previously undescribed fungus \(T. thailandiasis\) [12]. An isocoumarin derivate \((94)\) was isolated from the ethyl acetate extract of the culture broth of \(T. verruculosus\), a rhizosphere fungus of \(Stellera chamaejasme\) L. \(94\) exhibited the significant activities in vitro against \(Staphylococcus aureus\) and \(Escherichia coli\), with MIC values of 2.5 and 5.0 \(\mu g/mL\), respectively. And for the plant pathogenic fungi, \(94\) disclosed significant growth inhibitions of 92.6 ± 2.1, 97.3 ± 3.3, 87.2 ± 2.8 and 94.9 ± 1.9 % at 50 \(\mu g/mL\) against \(Alternaria solani\), \(Valsa mali\), \(Curvularia lunata\) and \(Botryosphaeria berengeriana\), respectively [15]. Two isocoumarin derivates \((95\) and \(96)\) were isolated from the organic extracts of the soil fungus \(T. flavus\) [30]. Sclerotinin A \((97)\) and alternariol \((98)\) were isolated from the methanolic extracts of the green Chinese onion-derived fungus \(T. pinophilus\) AF-02 [7].

Merodrimanes, thailandolides A \((99)\) and B \((100)\), a dimer linked through a tertiary oxygen to the dihydroisocoumarin, were isolated from a previously undescribed fungus \(T. thailandiasis\) [12]. A new meroterpenoid, chrodrimanin C \((101)\) together with chrodrimanins A and B \((102\) and \(103)\) from the strain YO-2 of \(Talaromyces\) sp. Chrodrimanin B exhibited insecticidal activity with an LD_{50} value of 10 \(\mu g/g\) of diet, while chrodrimanins A and C were inactive [32]. Four new meroterpenoids, named chrodrimanin D–G \((104–107)\), and a known compound chrodrimanin H \((108)\) were also isolated from the strain YO-2 of \(Talaromyces\) sp. Chrodrimanins D, E and F \((104–106)\) showed insecticidal activity against silkworms with respective LD_{50} values of 20, 10 and 50 \(\mu g/g\) of diet [33].
A phthalide derivative 109 and a spiro-phthalide derivative 110 were obtained from the organic extracts and from the water extracts of the soil fungus T. flavus [30, 34]. Another phthalide compound FKI-0076 B, vermistatin 111, was obtained from Talaromyces sp. during the screening programme for synergist of azoles antifungal antibiotics [20]. 111 was also isolated from the extract of T. flavus IFM52668 [16], and from the culture broth T. flavus FKI-0076 which isolated from a soil sample [21]. Other two analogues penisimplicissin (112) and hydroxydihydrovermistatin (113) were isolated from the fungus T. thailandi-asis [12].

Three new phthalide derivatives, talaromycolides A–C (114–116), and a known compound rubralide C (117), were isolated from the methanolic extracts of the green Chinese onion-derived fungus T. pinophilus AF-02. Talaromycolides A–C are rare phthalide derivatives with a novel linkage position between the phenyl and phthalide moieties, and exhibited significant antibacterial activity in response to some of the tested strains, Bacillus subtilis, B. megaterium, Escherichia coli, Clostridium perfringens, Micrococcus tetragenus, and no activity against the strain of MRSA (methicillin-resistant Staphylococcus aureus) [7].

A six-membered ring lactone (118) was isolated from the water extracts of the soil fungus T. flavus [34]. Two lactones (119 and 120) were isolated from an endophytic fungus, a close relative of Talaromyces sp., found in association with Cedrus deodara. They displayed a range of cytotoxicities against human cancer cell lines (HCT-116, A-549, HEP-1, THP-1, and PC-3), and induced apoptosis in HL-60 cells, as evidenced by fluorescence and scanning electron microscopy studies [35]. In the course of screening for apoptosis inducers in ras dependent Ba/F3-V12 cells, a new active compound, rasfonin (121) was isolated from the fermented mycelium of Talaromyces sp. 3656-A1. The cytotoxic activity indicated that rasfonin induced cell death in Ba/F3-V12 cells in an IL-3-free medium containing Dex (2 x 10^{-7}M) with an IC_{50} of 0.16 µg/mL and no cell death was observed in the presence of IL-3 at concentrations less than 1.25 µg/mL of rasfonin (IC_{50} 1.8 µg/mL) [36].

Wortmannilactones E–H (122–125), from the culture of the soil filamentous fungus T. wortmannii, showed inhibitory activities against cathepsin B with IC_{50} values of 4.3, 6.5, 13.0, and 6.0 µM, respectively [37]. In screening for NADH-fumarate reductase inhibitors led to the isolation of
a new ukulactone analog, ukulactone C (126), as a major polyene compound produced by *Talaromyces* sp. FKI-6713. Ukulactone C possessed a potent inhibitory activity (IC$_{50}$ 62 nM) against NADH-fumarate reductase of the roundworm *Ascaris suum* invivo [38].

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\begin{align*}
118 & \quad 119 & \quad 120 \\
121 & \quad 122 & \quad 123 \\
124 & \quad 125 & \quad 126
\end{align*}
\]

2.3 Polyketides

Polyketides, pyrones, xanthones, are both a major focus of many research efforts and a rich source of novel metabolites of *Talaromyces*. d-Glucono-1,4-lactone (127) was obtained from the organic extracts of the soil fungus *T. flavus* [30]. A new penicillic acid, coculnol (128) (five-membered ring lactone), was produced by a coculture of *Fusarium solani* FKI-6853 and *Talaromyces* sp. FKA-65. 128 showed an inhibitory effect (with IC$_{50}$ value of 283 µg/mL) against A/PR/8/34 (H1N1) with weak cytotoxicity against MDCK cells (IC$_{50}$ value of 781 µg/mL) [39]. Berkedienolactone (129) was isolated from the methanolic extracts of the green Chinese onion-derived fungus *T. pinophilus* AF-02 [7]. A new spiculisporic acid derivative, spiculisporic acid E (130), was isolated from the culture of the marine-sponge associated fungus *T. trachyspermus* (KUFA 0021) [40]. The ethoxylated of spiculisporic acid E (131) was isolated from the *T. panasenkoi* [41].

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\begin{align*}
127 & \quad 128 & \quad 129 \\
130 & \quad 131
\end{align*}
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Hydroxymethylmaltol (132) was isolated from the water extracts of the soil fungus *T. flavus* [34]. Funicone (133) and a new funicone derivative, 9,14-epoxy-11-deoxyfunicone (134), were isolated from the strain *T. flaus* IFM52668. As the results of the antifungal assay showed that 133 had the characteristic inhibition against a human pathogenic filamentous fungus, *A. fumigates* (11-mm inhibition zone at 100 µg/disc), whereas 134 showed the weak antifungal activity against *A. niger* (10-mm inhibition zone at 200 µg/disc) [16]. Deoxyfunicone (135) and actofunicone (136) were obtained from the culture broth *T. flavus* FKI-0076 which isolated from a soil sample. 135 and 136 showed no effect on the growth of *Candida albicans* up to 300 µM, and a slight inhibition (35%) was observed at that concentration for NG-012. But in the absence of the
funicones, the IC50 value of miconazole against *C. albicans* was calculated to be 19 μM, however, in combination with the funicones (50 μM), the IC50 values were decreased to 1.6–3.7 μM, demonstrating that they reinforced the inhibition *C. albicans* activity of miconazole [20, 21].

A benzopyrone derivative 137 was isolated from the organic extracts of the soil fungus *T. flavus* [30]. Benzopyrone derivatives 138 and 139 were isolated from a culture broth of a fungus, *Talaromyces* sp. 138 exhibited the weak anti-HBV activity with an IC50 value of 72.4 μM [42].

Moreover, in vitro cytotoxic activities indicated that 141 displayed very strong cytotoxicity against KB and KBv200 cell lines with IC50 values of 0.63 and 1.05 μg/mL, closed to those of the positive control (0.56 and 0.78 μg/mL). Whereas, the xanthone dimer 141 showed higher bioactivity than the xanthone monomer 140 [43].

A new isopentenylxanthone, talaroxanthone (142), was isolated from the culture broth and mycelia of a marine fungus *Talaromyces* sp. strain LF458. 142 displayed potent acetylcholinesterase inhibitory activities with IC50 1.61 μM. Interestingly, phosphodiesterase PDE-4B2 was inhibited by compounds 142 (IC50 7.25 μM) [26]. A new xanthone dimer talaroxanthone 143 was isolated from *Talaromyces* sp. which collected in the Amazonian rainforest from the medicinal plant *Duguetia stelechantha* [44].

Two xanthones, norlichexanthone (140) and secalonic acid A (141), were obtained from the extract of the mangrove endophytic fungus *Talaromyces* sp. ZH-154 which was isolated from the stem bark of *Kandelia candel* (L.) Druce, Rhizophoraceae. 141 exhibited high activities against six selected strains.
Two new polyketides, 7-epiausdiol (144) and 8-O-methylepiausdiol (145), were obtained from the extract of the mangrove endophytic fungus Talaromyces sp. ZH-154 which was isolated from the stem bark of Kandelia candel (L.) Druce, Rhizophoraceae. 144 showed significant inhibitory activity to Pseudomonas aeruginosa with a MIC value of 6.25 μg/mL [43]. Two new polyketides, TL-1 and -2 (luteusins A and B) (146 and 147) with monoamine oxidase (MAO) inhibitory effect were isolated from an ascomycete T. luctus [45]. Three new azaphilones, luteusins C, D, and E (148–150), together with 146 and 147, were isolated from an Ascomycete, T. luteus. As regards MAO-inhibitory activity, the IC50 values of 146 and 147 were 6.6 and 11 μM, respectively [46].

Kasanosins A (151) and B (152), novel azaphilones, were isolated from cultures of Talaromyces sp. derived from the seaweed. 151 and 152 selectively inhibited the activities of eukaryotic DNA polymerases β and λ (pols β and λ) in family X of pols, and 151 was a stronger inhibitor than 152, and the IC50 values of 151 on rat pol β and human polλ were 27.3 and 35.0 μM, respectively. And the results also suggested that 151 and 152 could identify the inhibition between pols β, λ, and terminal deoxynucleotidyl transferase (TdT) in family X [47]. Kasanosin C (153) and entonaemin A (154) were isolated from the solid fermentation of Talaromyces sp. T1BF derived from the old bast tissue of Taxus yunnanensis [48]. A known polyketide (155) was isolated from the strain T. wortmanii [49]. Deacetylisorwortmin (156) was isolated from the endophytic fungus T. wortmannii LGT-4 [50].
A new azaphilone derivative, monomethyl-(-)-mitorubrin (157), was isolated from the ascomata of *T. ardifaciens* derived from the paddy soil from Bhaktapur, Nepal [51]. Four new chlorinated azaphilones, helicusins A–D (158–161), were isolated from *T. helices*. 158–161 showed weak MAO-inhibitory effects [52]. Diaza-philonic acid (162) was obtained from *T. flavus* PF1195. 162 inhibited DNA amplification by polymerase chain reaction (PCR) with *Thermus thermophilus* DNA polymerase and the IC₅₀ value was 2.6 µg/mL. 162 dose-dependently inhibited the telomerase activity of MT1 (human leukemia) and almost completely inhibited the activity at 50 µM. But 162 showed no antimicrobial activity [53].
Three pigments, emodin (163), \( \omega \)-hydroxyemodin (164), and emodic acid (165), were obtained from the strain T. avellaneus [54]. Emodin, erythroglaucin (166), and catenarin (167), were isolated from the strain T. stipitatus [55]. A new atropisomer, biemodin (168), as well as five known metabolites (165 and 169–172), was isolated from the strain T. wortmannii, an endophyte of Aloe vera. 169 and 171 exhibited considerable antibiotic activity against Gram positive pathogenic bacteria with MIC values ranging between 4 and 16 \( \mu \)g/mL. 168 also showed strong activity against Gram positive bacteria, especially against MRSA, but was less active compared to compounds 169 and 171 [49]. Emodin (163) and skyrin (169) were also isolated from the extract of the mangrove endophytic fungus Talaromyces sp. ZH-154 derived from Kandelia candel (L.) Druce [43]. Skyrin (169) was also isolated from the strain T. wortmannii, an endophyte of Aloe vera [56].
Two bisdihydroanthracenone atropodiastereomeric pairs, homodimeric flavomannin A (173) and flavomannin B (174), two new unsymmetrical dimers 175 and 176, and two new mixed dihydroanthracenone/anthraquinone dimers 177 and 178, were isolated from *T. wortmannii*, an endophyte of *Aloe vera*. The compounds exhibited antibacterial activity, including (multi) drug-resistant clinical isolates and compounds 173–178 were predominantly active against *Staphylococci*, with MIC values from 4 to 8 μg/mL. Reporter gene analyses indicated induction of the SOS response for some of the derivatives, suggesting interference with DNA structure or metabolism. But the compounds showed no cytotoxic activity, encouraging their further evaluation as potential starting points for antibacterial drug development [56].
Two new tricyclic polyketides, vanitaracin A (179) and B (180), were isolated from a culture broth of a fungus, *Talaromyces* sp. 179 and 180 were evaluated for anti-HBV activity using HBV-susceptible HepG2-hNTCP-C4 cells and 179 exhibited the strong anti-HBV activity with an IC$_{50}$ value of 10.5 μM [42]. Stemphyperylenol (181) was isolated from the extract of the mangrove endophytic fungus *Talaromyces* sp. ZH-154, and showed inhibitory activity against *Sarcina ventriculi* with a MIC value of 3.12 μg/mL, lower than that of ampicillin (12.5 μg/mL) [43].

2.5 Steroids and Terpenoids

A steroid 182 was isolated from the genus of *Talaromyces* sp. T1BF for the first time which isolated from an endophyte from *Taxus yunnanensis* by chromatography techniques [57]. A new natural product 3-acetyl ergosterol 5,8-endoperoxide (183) was isolated from the culture of the marine-sponge associated fungus *T. trachyspermus* (KUFA 0021) [40]. Secovironolide (184) was purified from the culture broth of *T. wortmanni* and is the first example of a furanosteroid scaffold bearing a five-membered B ring.
Additional known viridian derivatives (185–188, 190) were isolated, including the new epoxide containing compound, epoxyvirone (189). Isolates were tested and showed only weak MAO inhibitory activity [50].

A new nardosinane-type sesquiterpene, talaflavuterpenoid A (191), was isolated from the wetland soil-derived fungus T. flavus BYD07-13. 191 was tested for the cytotoxic activity against five human tumor cell lines and the antimicrobial activity, however, 191 showed no cytotoxic (IC_{50} > 40 \mu M) and antimicrobial activities (MIC > 1.0 mg/mL) [58]. Four new norsesquiterpene peroxydes, named talaperoxides A–D (192–195), as well as a known analogue, steperoxide B (196), had been isolated from a mangrove endophytic fungus, T. flavus. Cytotoxic activities of 192–196 were evaluated in vitro against human cancer cell lines MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3. 193 and 195 showed activity against the five human cancer cell lines with IC_{50} values between 0.70 and 2.78 \mu g/mL [59].

2.6 Others

(−)-Epoformin (197) and (1S*,3R*,5R*)-3-methyl-2-oxabicyclo[3.3.1]nonan-7-one (198) were isolated from an endophytic fungus Talaromyces sp., found in association with Cedrus deodara. The sulforhodamine B cytotoxicity assay indicated that 197 was found to be the most active followed by compound 198 [35]. Four new spiroketal-talaromycins (199–202) had been isolated from the strain T. stipitatus [60]. A new metabolite, trachyspic acid (203) that inhibited heparanase, was isolated from the culture broth of T. trachyspermus SANK 12191. Its structure was determined from NMR spectral analyses and chemical reactions as a tricarboxylic acid derivative containing a spiroketal. The IC_{50} value of trachyspic acid against heparanase was 36 \mu M [61].
A novel benzene derivative (204) was isolated from a culture broth of a fungus, *Talaromyces* sp., and it was evaluated for anti-HBV activity using HBV-susceptible HepG2-hNTCP-C4 cells, but 204 exhibited the weak anti-HBV activity [42]. 5-Hydroxymethylfurfural (205) and two benzene derivatives 206 and 207 were isolated from the organic extracts of the soil fungus *T. flavus* [30]. 207 was also evaluated for its ability to inhibit HIV-1 integrase in coupled and strand-transfer assays and the data indicated that 207 with IC_{50} values of 19 \mu M in the coupled assay and 25 \mu M in the strand-transfer assay [62]. Two benzene derivatives 208 and 209 from the genus of *Talaromyces* sp. T1BF which isolated from an endophyte from *Taxus yunnanensis* by chromatography techniques [57].

Three diphenyl ether derivatives including two new natural products, tenelates A (210) and B (211), together with the known compound, tenellic acid C (212), were isolated from the mangrove endophytic fungus *Talaromyces* sp. (SBE-14), from the South China Sea [63]. Three new derivatives of *p*-hydroxybenzoic acid (213–215) had been isolated from the culture filtrate of *T. derxii* [64].

A new long-chain dicarboxylic acid, 2-hydroxyradiclonic acid (216), and four known compounds, benzoic acid (217), (Z)-3-phenyl propenal (218), 2-formyl-3,5-dihydroxy-4-methylbenzoic acid (219), and radiclonic acid (220), were isolated from the methanolic extracts of the green Chinese onion-derived fungus *T. pinophilus* AF-02. 216 showed significant antibacterial activities against *E. coli* [7].
A new antibiotic, fosfonochlorin (221), was found in the culture filtrate of four strains of fungi freshly isolated from soil samples including T. flavus. The biological activity indicated that it was active against Proteus mirabilis and P. vulgaris and weakly active against Salmonella enteritidis, Klebsiella pneumoniae and Providencia rettgeri, and its synergistic effect with glucose-6-phosphate was observed on Staphylococcus aureus and Escherichia coli [65].

A new antifungal antibiotic, named talaron, had been isolated from the culture of T. vermiculatus (M-3224). Talaron is water-soluble acidic polysaccharide containing nitrogen and phosphorus, and its molecular weight was estimated to be 7000–8000. Talaron had strong fungicidal activity against filamentous dermatophytes and exhibited inhibitory activity against the spore germination of Trichophyto asteroides and showed cytotoxic effect at 1 mcg/mL on HeLa cells, and at 0.2 mcg/mL on mouse embryo fibroblast cells, but no antibacterial activity [66].

3 Conclusions

The Talaromyces genus includes many species with a variety of uses, some of which are important in the food products and agriculture. Since, several anthraquinone metabolites from T. avellaneus were isolated in 1965 [54], lots of secondary metabolites described in this report were obtained from this genus fungi which from a soil sample, from the plant, or from a marine sponge. The 221 compounds, including 43 alkaloids and peptides, 88 esters, 31 polyketides, 19 quinones, 15 steroid and terpenoids, and 25 other structure compounds, described in this review were isolated from 28 species, which 19 species have been determined and 9 species were not given the specific names (Table 1). The secondary metabolite studies were mainly performed on the commonest species of the genus, T. flavus [3]. The stereochemistry of many compounds was determined via circular dichroism spectrum [7], Mosher’s analysis method [8], Marley’s method [13], a single-crystal X-ray diffraction experiment using Cu Kα radiation [59], or quantum chemical calculation [6]. Those fungi were cultivated with varying media: potato dextrose, barley grains [10], rice [25], WSP30 [26], ISP2 broth [44], or other modified medium.

In the early years of secondary metabolite of those genus species research was less emphasis on biological testing, but increasingly there has been a focus on the biological properties of these compounds. Inhibitory activity to tumour cells [17], bacteria [7], fungi [10], HBV [42], nematode [8], HIV-1-integrase [62], caspase-3 [11], mosquito larval [14], 5-lipoxygenase [27], and other activities were performed. Some of the isolated compounds have been used as pigments. Studies on total synthesis and biotransformation of some of those compounds have been described. Structure–activity relationships have also been undertaken. Recently,
there has been great interest in the study of biosynthesis genes based on secondary metabolites from the genus. However, systematic secondary metabolites–biosynthesis genes relationship might give insight into the molecular level, seem to be absent. This might be a promising direction in which work in the field of the secondary constituents from this genus fungi may proceed.

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Compliance with ethical standards  The authors declare no conflict of interest.

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Table 1  The source of Talaromyces species

| Species          | Source                                      | References |
|------------------|---------------------------------------------|------------|
| *Talaromyces* sp.| A soil sample                               | [6], [36], [20], [22], [42], [33] |
|                  | Marine sponge *Axinella verrucosa*          | [14], [32], [38], [39] |
|                  | Plants                                      |            |
|                  | *Cedrus deodara*                            | [35]       |
|                  | *Duquetia stelechantha*                     | [44]       |
|                  | *Kandelia candel*                           | [43], [63] |
|                  | *Taxus yunnanensis*                         | [48], [57] |
|                  | Sand                                        | [42]       |
|                  | Seaweed                                     | [47]       |
| *T. ardifaciens* | Paddy soil                                  | [51]       |
| *T. avellaneus*  | A Soil sample                               | [54]       |
| *T. bacillosporus* | A soil sample                            | [24]       |
| *T. convolutes*  | A soil sample                               | [10]       |
| *T. deroxii*     | A soil sample                               | [27], [29], [64] |
| *T. flavus*      | A soil sample                               | [53], [62], [16] |
|                  | Wetland soil                                | [21], [30], [34], [65] |
|                  | Leaves, *Sonneratia apetala*                | [59]       |
| *T. helices*     |                                            |            |
| *T. luteus*      |                                            |            |
| *T. minioluteus* | A marine sponge                             | [11]       |
| *T. panasenki*   | A soil sample                               | [41]       |
| *T. pinophilus*  | A soil sample                               | [28]       |
|                  | Green Chinese onion                         | [7]        |
| *T. stipitatus*  |                                            |            |
| *T. tardifaciens*| Paddy soil                                  | [51]       |
| *T. thailandiasis* | A soil sample                          | [12]       |
| *T. thermophilus*| Hot springs                                 | [4], [5], [8], [9] |
| *T. trachyspermus* | Marine sponge  *Clathria reianwardii*      | [40]       |
|                  | A soil sample                               | [61]       |
| *T. verruculatus*|                                            |            |
| *T. verruculosus*| Rhizosphere soil of *Stellera chamaejasme*  | [15]       |
| *T. wortmannii*  | A soil sample                               | [17], [18], [37] |
|                  | Plants, *Aloe vera*                         | [13], [49], [56] |
|                  | Plants, *Tripterygium wilfordii*            | [50]       |

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References

1. J. Pitt, in *Penicillium and Talaromyces: Introduction, Penicillium*, Encyclopedia of Food Microbiology (2nd edn) (2014), pp. 6–13
2. N.E.A. El-Naggar, S.A. Haroun, E.A. Oweis, A.A. Sherief, Prep. Biochem. Biotechnol. 45(7), 712–729 (2015)
3. B. Proksa, Chem. Pap. 64(6), 696–714 (2010)
4. Y.S. Chu, X.M. Niu, Y.L. Wang, J.P. Guo, W.Z. Pan, X.W. Huang, K.Q. Zhang, Org. Lett. 12(19), 4336–4339 (2010)
5. J.P. Guo, J.L. Tan, Y.L. Wang, H.Y. Wu, C.P. Zhang, X.M. Niu, W.Z. Pan, X.W. Huang, K.Q. Zhang, J. Nat. Prod. 74(10), 2278–2281 (2011)
6. H.B. Yang, F. Li, N.Y. Ji, Chin. J. Oceanol. Limnol. (2015). doi:10.1007/s00343-015-4316-2
7. M.M. Zhai, H.T. Niu, J. Li, H. Xiao, Y.P. Shi, D.L. Di, P. Crews, Q.X. Wu, J. Agric. Food Chem. 63(43), 9558–9564 (2015)
8. J.P. Guo, C.Y. Zhu, C.P. Zhang, Y.S. Chu, Y.L. Wang, J.X. Zhang, D.K. Wu, K.Q. Zhang, X.M. Niu, J. Am. Chem. Soc. 134(50), 20306–20309 (2012)
9. X.M. Niu, L. Chen, Q. Yue, B.L. Wang, J.X. Zhang, C.Y. Zhu, K.Q. Zhang, G.F. Bills, Z.Q. An, Org. Lett. 16(14), 3744–3747 (2014)
10. S. Suzuki, T. Hosoe, K. Nozawa, K.I. Kawai, T. Yaguchi, S.I. Udagawa, J. Nat. Prod. 63(6), 768–772 (2000)
11. S. Ngokpol, W. Suwakulsiri, S. Sureram, K. Lirdprapamongkol, T. Dethoup, L. Manoch, A. Kijjoa, M. Pinto, L. Gales, A.M. Silva, A. Kijjoa, Nat. Prod. 70(7), 1200–1202 (2007)
12. R. Bara, A.H. Aly, V. Wray, W.H. Lin, P. Proksch, A. Debbab, Tetrahedron Lett. 54(13), 1686–1689 (2013)
13. T. Morino, M. Nishimoto, A. Masuda, T. Fujita, T. Ishikiori, S. Hoshiko, J. Antibiot. 58, 159–160 (1995)
14. T. Morino, M. Nishimoto, A. Masuda, T. Fujita, T. Ishikiori, S. Hoshiko, J. Antibiot. 53(8), 848–850 (2000)
15. Y.S. Dong, J. Lin, X.H. Lu, Z.H. Zheng, X. Ren, H. Zhang, J.G. He, J.S. Yang, Helv. Chim. Acta 92(3), 567–574 (2009)
16. S. Kaifuuchi, M. Morii, K. Nonaka, R. Masuma, S. Omura, K. Shiomi, J. Gen. Appl. Microbiol. 61(2), 57–62 (2015)
17. K. Nonaka, T. Chiba, T. Suiga, Y. Asami, M. Iwatsuki, R. Masuma, S. Omura, K. Shiomi, J. Antibiot. 68(8), 530–532 (2015)
18. D. Kumla, T. Dethoup, S. Butchon, N. Singburgaudion, A.M.S. Silva, A. Kijjoa, Nat. Prod. Comm. 9(8), 1147–1150 (2014)
19. H. Fujimoto, J. Yisai, Y. Morie, M. Yamazaki, Mycotoxins 27, 15–19 (1988)
20. H. Matsunaga, S. Kamitsuki, M. Kaneko, Y. Yamaguchi, T. Takeuchi, K. Wataishi, F. Sugawara, Bioorg. Med. Chem. Lett. 25(19), 4325–4328 (2015)
21. F. Liu, X.L. Cai, H. Yang, X.Z. Guo, J. Yuan, M.F. Li, Z.G. She, Y.C. Lin, Plant Med. 76(2), 185–189 (2010)
22. H.H.F. Koolen, L.S. Menezes, M.P. Souza, F.M.A. Silva, F.G.O. Almeida, A.Q.L. de Souza, A. Barison, F.H. da Silva, D.E. Evangelista, A.D.L. de Souza, J. Braz. Chem. Soc. 24(5), 880–883 (2013)
23. H. Fujimoto, T. Matsudo, A. Yamaguchi, M. Yamazaki, Heterocycles 30(1), 607–616 (1990)
24. E. Yoshida, H. Fujimoto, M. Yamazaki, Chem. Pharm. Bull. 44(2), 284–287 (1996)
25. T. Kimura, M. Nishida, K. Kuramochi, F. Sugawara, H. Yoshida, Y. Mizushima, Bioorg. Med. Chem. 16(8), 4594–4599 (2008)
26. L.Q. Li, Y.G. Yang, Y. Zeng, C. Zou, P.J. Zhao, Molecules 15(6), 3993–3997 (2010)
27. R. Bara, A.H. Aly, A. Pretsch, V. Wray, B.G. Wang, P. Proksch, A. Debbab, J. Antibiot. 66(8), 491–493 (2013)
28. H.E. Ding, Z.D. Yang, H. Yao, Molecules 19(48), 6754–6757 (2012)
29. K. Nozawa, R. Saito, S.I. Udagawa, S. Nakajima, K.I. Kawai, Phytochemistry 39(3), 719–721 (1995)
30. E. Yoshida, H. Fujimoto, M. Baba, M. Yamazaki, Chem. Pharm. Bull. 43(8), 1307–1310 (1995)
31. T. Tabata, S. Ikegami, T. Yaguchi, T. Sasaki, S. Hoshiko, S. Sakuma, K. Shin-Ya, H. Seto, J. Antibiot. 52(4), 412–414 (1999)
32. S. Natori, F. Sato, S.I. Udagawa, Chem. Pharm. Bull. 13(3), 385–386 (1965)
33. G.W. van Eijik, Experientia 29(5), 522–523 (1973)
34. R. Bara, I. Zerfass, A.H. Aly, H. Goldbach-Geche, V. Raghavan, P. Sass, A. Mändi, V. Wray, P.L. Polavarapu, A. Pretsch, W.H.
Lin, T., Kurtán, A., Debbab, H., Brötz-Oesterhelt, P., Proksch, J., Med. Chem. 56(8), 3257–3272 (2013)

57. L.Q. Li, Y.G. Yang, Y. Zeng, C. Zou, P.J. Zhao, Guangxi Zhiwu 31(5), 699–701 (2011)

58. J.W. He, H.X. Liang, H. Gao, R.Q. Kuang, G.D. Chen, D. Hu, C.X. Wang, X.Z. Liu, Y. Li, X.S. Yao, J. Asian Nat. Prod. Res. 16(10), 1029–1034 (2014)

59. H.X. Li, H.B. Huang, C.L. Shao, H.R. Huang, J.Y. Jiang, X. Zhu, Y.Y. Liu, L. Liu, Y.J. Lu, M.F. Li, Y.C. Lin, Z.G. She, J. Nat. Prod. 74(5), 1230–1235 (2011)

60. N.J. Phillips, R.J. Cole, D.G. Lynn, Tetrahedron Lett. 28(15), 1619–1622 (1987)

61. H. Shiozawa, M. Takahashi, T. Takatsu, T. Kinoshita, K. Tanzawa, T. Hosoya, K. Furuya, S. Takahashi, J. Antibiot. 48(5), 357–362 (1995)

62. S.B. Singh, H. Jayasuriya, R. Dewey, J.D. Polishook, A.W. Dombrowski, D.L. Zink, Z.Q. Guan, J. Collado, G. Platas, F. Pelaez, P.J. Felock, D.J. Hazuda, J. Ind. Microbiol. Biotechnol. 30(12), 721–731 (2003)

63. F. Liu, Q. Li, H. Yang, X.L. Cai, X.K. Xia, S.P. Chen, M.F. Li, Z.G. She, Y.C. Lin, Magn. Reson. Chem. 47(5), 453–455 (2009)

64. K. Nozawa, M. Takada, S.I. Udagawa, S. Nakajima, K.I. Kawai, Phytochemistry 28(2), 655–656 (1989)

65. M. Takeuchi, M. Nakajima, T. Ogita, M. Inukai, K. Kodama, K. Furuya, H. Nagaki, T. Haneishi, J. Antibiot. 42(2), 198–205 (1989)

66. K. Mizuno, A. Yagi, M. Takada, K. Matsuura, K. Yamaguchi, K. Asano, J. Antibiot. 27(7), 560–563 (1974)