Genus *Thielavia*: phytochemicals, industrial importance and biological relevance

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ABSTRACT

*Thielavia* species (Chaetomiaceae) are a wealthy source of enzymes such as laccases, cutinases, glucuronoyl esterases, furu-loyl esterases, 1,4-β-endoglucanase and lytic polysaccharide monooxygenases that reported to have various biotechnological and industrial applications in dye decolorization, bio-refinery, biomass utilization, ester biosynthesis and biodegradation. Different metabolites have been reported from this genus as depsides, azaphilones, pyrazines, naphthodianthrones and anthraquinones derivatives. These metabolites have attracted research interest due to their fascinating structures and diverse bioactivities, including antimicrobial, cytotoxic, antioxidant, anti-diabetic, and superoxide anion generation, phospholipase, prostaglandins synthesis and proteasome inhibitory activities. Therefore, these compounds can be taken into account as candidates for the development of effective and novel pharmaceutical leads. The current review represents the relevant information for the *Thielavia* genus, in particular, its phytoconstituents and their pharmacological activities, as well as the biotechnological applications of *Thielavia* species published from 1981 till now. More than 40 metabolites are described and - 71 references are cited.

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Introduction

Fungi are a relatively understudied, biotechnologically, agricultural, and/or medically valuable groups of organisms (Ibrahim et al. 2015; Ibrahim, Mohamed et al. 2016; Ibrahim, Elkhayat et al. 2016; Khayat et al. 2019; Al-Rabia et al. 2020). They are widespread in nature and are essential for carbon cycling in nature when inhabit in the soil. It has been reported that only about 5% of ≈1.5 million different fungal species on earth have been characterized taxonomically (Brase et al. 2009). They have the potential to synthesize various bio-metabolites with uncommon structural features that may be utilized indirectly or directly as therapeutic agents against various diseases (Demain and Fang 2000; Calvo et al. 2002; Mohamed, Ibrahim, and Asfour 2020; Mohamed, Ibrahim, Alhakamy et al. 2020). Some fungal metabolites are also highly toxic mycotoxins (Ibrahim, Abdallah et al. 2018; Ibrahim, Mohamed, Al Haidari, Zayed et al. 2018, 2017). Genus *Thielavia* is belonging to the family Chaetomiaceae. It was established in 1876, by Zopf (Zopf 1876; Wang et al. 2019). According to MycoBank and Index Fungorum, the *Thielavia* genus includes 89 species that are commonly found in soil, including desert, grassland, or alkaline soils at pH up to 11 as well as seeds, animal’s dung, and decaying plant materials (Malloch and Cain 1973; Grum-Grzhimaylo et al. 2016). Some species can be endophytes, lichenicolous, coprophilous, and even marine-derived (Stchigel et al. 2002; Han et al. 2017; Wang et al. 2019). These species are characterized by dark-colored ascocarps, dark brown, smooth ascospores, and brown to hyaline vegetative mycelia (Malloch and Cain 1973). Some of its species are known to have biotechnological and industrial potentials (Mtibaà et al. 2018; Calderaro et al. 2020). As, they are a source of enzymes with industrial potential as laccases, cutinases, glucuronoyl esterases, feruloyl esterases, 1,4-β-endoglucanase, and lytic polysaccharide monooxygenases (LPMOs) (Yang et al. 2013; Gao et al. 2017; Mtibaà et al. 2018; Duan et al. 2019; Meng et al. 2019; Tang et al. 2019; Calderaro et al. 2020). *T. basicola* a species of this genus, is a phyto-pathogenic fungus that
attacks the roots of angiosperm plants (Alam et al. 2012). The phytochemical studies on *Thielavia* species revealed the existence of various classes of secondary metabolites such as depsides (e.g. thielocins and thielavins), azaphilones (spiro-, bis-spiro-, and nor-spiro-azaphilone), pyrazines, naphthodianthrones, and anthraquinones derivatives. Reviewing the available literature, no review concerning *Thielavia* species is available. In this review, we intend to provide a comprehensive insight into the reported metabolites from this genus and their pharmacological activities, as well as the biotechnological and industrial applications of *Thielavia* species. Also, it is aiming to provide knowledge to researchers for rapid identification of chemical constituents and pharmacological activities of *Thielavia* species.

**Materials and methods**

The literature review was performed through a computer search of data on ScienceDirect, Web of Knowledge, SCOPUS, Wiley Online Library, Taylor & Francis, PubMed, Springer, JACS and Google Scholar journal papers.

**Chemical constituents**

*Thielavia* species are a rich source of different classes of natural products with varying structural patterns. Several compounds have been identified from *Thielavia* species, including depsides (e.g. thielocins and thielavins), azaphilones (Spiro-, bis-Spiro- and nor-Spiro-azaphilone), pyrazines, naphthodianthrones and anthraquinones derivatives. The diversity in the isolated metabolites among species might be attributed to the different habitats from which the fungus isolated. It was reported that for the fungi to survive, they develop various strategies for communication and protection, one of them is the production of different types of secondary metabolites (Keller 2019). Herein, we have listed the chemical constituents that have been reported in the literature over the past decades from *Thielavia* species and provided their biological activities, structures, molecular weights, molecular formulae, name of the fungus from which they were isolated, and associated references (Figure 1–3 and Supplementary material Tables S1 and S2). Tables S1 and S2 (Supplementary material) and Figures 1–3 demonstrated that among the forty-four reported metabolites thirty-two are depside derivatives (thielavins and thielocins) which represent 72.7%. They are mainly reported from two species; *T. terricola* and *Thielavia* sp. UST030930-004. While, azaphilone, pyrazine, anthraquinone, isocoumarin and quinazoline derivatives represent 13.7, 4.5, 4.5, 2.3 and 2.3%, respectively. Accordingly, it could hypothesize that thielavins and thielocins might serve as chemotaxonomic characteristics of *Thielavia* genus. However, further studies to support this hypothesis should be carried out. Thielocins (1–13) and thielavins (26–44) are depside derivatives, which are a group of polyphenolic compounds composed of two or more 2,4-dihydroxybenzoic acid rings linked by ester bonds (Al Subeh et al. 2021; Nakashima et al. 2017; Matsutani et al. 1992; Kitahara et al. 1983). They are acetyl-polymalonyl-derived polyketides, each ring is synthesized by a polyketide synthase (Armaleo et al. 2011). These rings rely on the β-orsellinic acids structure. The ring having the esterified carbonyl is designated as A,
the other as B. They are classified into orcinol or β-orcinol series, depending on the existence of a methyl group on the C3 carbon of both rings (Ibrahim, Mohamed, Al Haidari, Zayed et al. 2018). They are commonly reported from lichens as well as from some fungi and higher plants (Ibrahim, Mohamed, Al Haidari, El-Kholy et al. 2018). On the other hand, thielavialides (18–23) belong to hydrogenated spiro-azaphilones which are known as fungal pigments and polyketides, featuring six-membered ring spiroketal system on the azaphilone skeleton (Chen et al. 2020; Wijeratne et al. 2014). They are majorly reported from fungi (Chen et al. 2020).

Biotechnological and industrial applications

Catalytic activity and structural stability at elevated temperatures are amongst the most appreciated properties of industrial enzymes. Various studies indicated that some Thielavia species secrete an array of biomass-degrading enzymes, which participate in the degradation of lignin and recalcitrant aromatic compounds, which cause serious environmental problems. Moreover, they are highly thermo-stable, efficient, and having great application potentials (Margaritis et al. 1986). Mtiba et al. 2020 reported that Thielavia sp HJ22 could be used as a potential tool of environmental bioremediation (Mtiba et al. 2020).

Dye decolorization

Fungal laccases are glycoproteins with tetrameric, dimeric, or monomeric structure having four redox-active copper atoms (Safary et al. 2016; Patel et al. 2018). Laccases have attracted great attention because of their huge applications in different industrial and biotechnological fields such as pulp bleaching, textile dye decolorization, environmental pollutants bioremediation and detoxification, and delignification or second-generation ethanol production (Wang et al. 2017; Patel et al. 2018). Mtiba et al.
(2018) purified and characterized an extracellular laccase from *Thielavia* sp. isolated from Tunisian arid soil. This enzyme displayed greater decolorization (90%) efficiency in Remazol Brilliant Blue R without redox mediator, which is a recalcitrant dye causing environmental problems (Mtibaà et al. 2018).

**Bio-refinery and biomass utilization**

Biomass saccharification into fermentable monomeric sugars by enzymatic hydrolysis is an important step in a bio-refinery. Improvement of the activity and stability of biomass-degrading enzymes facilitates biomass saccharification and makes bio-refinery a
commercially feasible process. LPMOs have the ability to boost the efficiency of cellulo-lytic enzymes in the saccharification of lingo-cellulosic biomass. LPMOs form today a crucial component in industrial enzyme preparations (Hu et al. 2015). *Taus*-LPMO9B is a novel fungal LPMO produced by the thermophilic fungus *T. australiensis*. *Taus*-LPMO9B was found to be stable at pH 4–6 and active on lingo-cellulosic feed-stocks, such as

Figure 3. Chemical structures of compounds 26–43.
acid pretreated corn stover, indicating its potential suitability for supplementing today’s commercial cellulase cocktails for biomass saccharification (Calderaro et al. 2020).

Glucuronoyl esterases play a unique role as accessory enzymes in lingo-cellulosic material biodegradation by the cleavage of the covalent ester linkage between lignin and 4-O-methyl-D-glucuronic acid (MeGlcA) in lignin-carbohydrate complexes (LCCs). TtGE1 and TtGE2 glucuronoyl esterases from T. terrestris, were expressed in P. pastoris. They substantially increased the release of monomeric sugars and glucuronic acid from corn bran into commercial xylanase. Therefore, these TtGEs could be used as promising accessory enzymes to improve the commercial enzymes’ hydrolysis efficiency in saccharification of lingo-cellulosic materials due to their thermo-philic characteristics (Tang et al. 2019).

Feruloyl esterases (FAEs) have great potential applications in the paper and breeding industry. Meng et al. (2019) identified a new thermo-stable type B feruloyl esterase (TtfaeB) from T. terrestris h408. It had a broad pH and temperature stability and could effectively release ferulic acid from agricultural by-products, thus it is a good candidate for bio-refinery and biomass utilization (Meng et al. 2019).

Decomposition of cellulose is very useful in various industrial applications such as food and feed manufacture, biofuel production, textile processing, and laundry (Kuhad et al. 2011). Endoglucanase is considered a key biocatalyst in cellulose decomposition, which catalyzes random hydrolysis of 1,4-β-glycosidic bonds cleaving cellulose main chain into smaller fragments (Gao et al. 2017). Gao et al. (2017) reported the identification and characterization of glycoside hydrolase family 45 1,4-β-endoglucanase (TtCel45A) from the thermophilic fungus T. terrestris. It exhibited high activity on amorphous cellulose, outstanding thermo-stability and had great potentials in commercial applications (Gao et al. 2017).

Ester biosynthesis and biodegradation

Cutinases can degrade cutin polymers and hydrolyze soluble esters, triglycerides, waxes, and various synthetic polyesters. Consequently, they are used to depose plastic waste and to hydrolyze butter to develop cheese flavors. It catalyzes trans-esterification and esterification reactions, making them useful in flavor esters synthesis and production of biodiesel (Chen et al. 2013; Yang et al. 2013). Yang et al. 2013 purified and biochemically characterized TtcutA, a low molecular mass cutinase from T. terrestris. It efficiently degraded various ester polymers, including polycaprolactone (PCL), cutin, poly(butylene succinate) (PBS) and polyethylene terephthalate (PET) (Yang et al. 2013). Moreover, the cutinase gene (TtCutopt) from T. terrestris was codon-optimized and expressed in Pichia pastoris. It displayed high yield, stability and esterification efficiency that make it an attractive candidate for ester biosynthesis and biodegradation (Duan et al. 2019).

Biological activities

Phospholipase inhibitory activities

Phospholipase A₂ (PLA₂) is a lipolytic enzyme that hydrolyzes specifically the sn-2 position of a glycerol-phospholipids to arachidonic acid and lysophospholipids, which
contribute to various inflammatory processes (Ong et al. 2015). The molecules that regulate the PLA2 activity would be implicated in the control of a wide range of pathological and physiological conditions such as asthma, inflammation, psoriasis, ischemia, rheumatoid arthritis, and pancreatitis (Folmer et al. 2010). Thielocin B3 (10) strongly inhibited human PLA2-II in a noncompetitive and reversible manner ($K_i$ 0.098 $\mu$M) with IC$_{50}$ 0.076 $\mu$M, however, it weakly inhibited human PLA2-I (IC$_{50}$ 18 $\mu$M). It also produced 100% quenching of the tryptophan fluorescence of Naja mocambique venom PLA2 at a thielocin B3/PLA2 molar ratio of 1.0. Interestingly, its inhibitory potential toward human PLA2-II and Naja mocambique PLA2 was markedly decreased by methylation of the two carboxyl groups. It was concluded that the two carboxyl groups did not participate in thielocin B3 binding to the enzyme, whereas they had a crucial role in the PLA2 inhibition. Furthermore, co-injection of 10 with carrageenan significantly lowered both PLA2 activity in the exudate and exudate volume in the rat carrageenan-induced pleurisy model. Thus, thielocin B3 had specific inhibitory activity towards human PLA2-II (Tanaka et al. 1994). Thielocin A1$\beta$ (2) isolated from T. terricola inhibited various PLA2$s$ in a dose-dependent manner. PLA2-II from rat was most sensitive to thielocin A1$\beta$ with IC$_{50}$ 0.0033 $\mu$M. Its PLA2-II inhibitory effect was independent of Ca$^{2+}$ and substrate concentration. In addition, its inhibition of rat PLA2-II was reversible and non-competitive ($K_i$ 0.0068 $\mu$M). Furthermore, it quenched the Naja naja venom PLA2 relative fluorescent intensity by 50% quench with a molar ratio of 2.2 of thielocin A1$\beta$/PLA2. Therefore, the inhibitory effect of thielocin A1$\beta$ was due to direct interaction with PLA2 (Yoshida et al. 1991; Tanaka et al. 1992). Thielocins A1$\alpha$ (1), A1$\beta$ (2), A2$\alpha$ (3), A2$\beta$ (4), A3 (7), B1 (8), B2 (9) and B3 (10) were isolated from T. terricola RF-143 by Yoshida et al. (1991) and Matsumoto et al. (1995) as a novel PLA2 inhibitors together with thielavins A-E (26–30) (Yoshida et al. 1991; Matsumoto et al. 1995). Thielocin A1$\beta$ possessed the most potent inhibitory potential with an IC$_{50}$ 0.0033 $\mu$M against rat PLA2-II followed by thielocins B1, B3, A1$\alpha$, A2$\beta$, A2$\alpha$ and B2 with IC$_{50}$s 0.0078, 0.012, 0.032, 0.038, 0.051 and 0.070 $\mu$M, respectively. However, 10 was the potent compound against PLA2-II (IC$_{50}$ 0.076 $\mu$M) followed by thielocins B1, A2$\beta$, A2$\alpha$, A1$\alpha$, B2 and B3 with IC$_{50}$ values of 0.17, 0.24, 0.31, 0.39, 2.7 and 6.12 $\mu$M, respectively (Matsumoto et al. 1995). Thielavin A-E (26–30) showed strong inhibitory activity against rat PLA2-II with IC$_{50}$ 43, 1.3, 0.45, 1.1 and 4.5 $\mu$M, respectively compared with manoalide (IC$_{50}$s 2.0 $\mu$M). On other hand, they showed significant potentials towards human PLA2-II with IC$_{50}$s 29, 2.4, 2.1, 6.2 and 9.3 $\mu$M, respectively in comparison to manoalide (IC$_{50}$ 1.5 $\mu$M) (Matsumoto et al. 1995). Moreover, 2 was found to prohibit the release of histamine from mast cells stimulated with secretory PLA2, therefore the effect of 2 against secretory PLA2 induced paw edema was assessed. Furthermore, 2 produced a dose-dependent inhibition of bee venom PLA2 (IC$_{50}$ 1.4 $\mu$M). Co-injection of thielocin A1$\beta$ (1 $\mu$g/paw) with bee venom PLA2 resulted in a 44.7% reduction of edema formation. This anti-edema action was not enhanced by cyproheptadine (antiserotonin/anti-histamine). These results suggested that thielocin A1$\beta$ had edema-reducing activity via inhibition of the PLA2 activity, which participates in mast cells histamine release (Tanaka et al. 1995). Murakami et al. (1992) stated that stimulated-degranulation in mouse and rat mast cells with various secretagogues was repressed by thielocin A1$\beta$, without influencing the synthesis of prostaglandin D2 (PGD$_2$) and
postulated that the release of secretory PLA2 from activated mast cells may have a remarkable role in the progression of the degranulation process. Thus, the inhibition of secretory PLA2 by 2 attenuated the inflammation severity via suppression of the degranulation process (Murakami et al. 1992, 1990).

Prostaglandins synthesis inhibitory activities

PGs are hormone-like chemical messengers that are involved in a wide range of biological processes such as regulation of the immune system, fever, and pain associated with hemostasis, inflammation, and blood pressure (Seo and Oh 2017). Thielavins A (26) and B (27) displayed significant anti-inflammatory activity with ID50 12 and 9 µM, respectively for the conversion of 14C-arachidonic acid into PGF$_2\alpha$ plus PGE$_2$ by microsomes of ram seminal vesicles (Kitahara et al. 1981). ID$_{50}$S of the conversion of arachidonic acid (AA) into PGH$_2$, PGH$_2$ into PGE$_2$ and thromboxane A$_2$ (TXA$_2$) synthetase are 10, 40, 150 µM for 26 in comparison to indomethacin (ID$_{50}$ 30 and 130 µM, for PGH$_2$ and PGE$_2$, respectively) and imidazole (ID$_{50}$ 200 µM for TXA$_2$ synthetase), meanwhile 27 had ID$_{50}$ 40, 9 and 350 µM, respectively. Therefore, 26 had a strong inhibitory effect on the conversion of AA into PGH$_2$. Whilst, 27 specifically inhibited the step involving the PGE$_2$ synthesis from PGH$_2$. Moreover, they inhibited TXA$_2$ synthesis in bovine platelet microsomes (ID$_{50}$ 150 and 350 µM, respectively) comparable to imidazole (200 µM, a specific TXA$_2$ synthetase inhibitor) (Kitahara et al. 1981). Both compounds (dose 50 mg/kg orally) showed no significant anti-inflammatory effects on carrageenan-induced edema in rats. However, 27 inhibited this edema system by 70% (dose 5 mg/kg, intravenous (IV)) while 26 (5 mg/kg) had no significant anti-inflammatory activity even on IV administration (Kitahara et al. 1981).

Superoxide anion generation inhibitory activities

Superoxide anion (SOA) is an oxygen-free radical that is released by neutrophils or macrophages, leading to harmful biological effects, such as lipid peroxidation and protein denaturation, that contribute to tissue damage production in ischemic or inflammatory processes (Hwang et al. 2006; Hayyan et al. 2016). Superoxide anion generation inhibitors (SOAIs) are effective in protecting against tissue damage in various cases of degenerative human diseases such as cancer and heart and cerebrovascular diseases. Nakano et al. (1991) assessed inhibitory capacities of OPC-15160 (14) and OPC-15161 (15) reported from T. minor on SOA generation by guinea pig peritoneal macrophages. The results declared that these compounds showed dose-dependent inhibitory potential. Interestingly, OPC-15161 (IC$_{50}$ 2.8 × 10$^{-5}$ M) was five times more active than OPC-15160 (IC$_{50}$ 1.4 × 10$^{-4}$ M) (Nakano et al. 1991).

Proteasome inhibitory activity

Proteasome is responsible for the degradation of damaged, misfolded, or unneeded cellular proteins, making it a crucial target for future therapeutic intervention in many diseases such as cystic fibrosis, neurodegenerative diseases, autoimmune diseases,
atherosclerosis, cancer, and diabetes (Thibaudeau and Smith 2019). Thielocin B1 (8) isolated from the fermentation broth of T. terricola RF-143 had potent proteasome assembling chaperone 3 homodimer (PAC3) (IC$_{50}$ 0.020 μM) inhibitory effect, whereas it did not inhibit PAC1/PAC2 heterodimer10 (IC$_{50}$ > 250 μM). It was considered as a superior proteasome inhibitor, which targeted the protein-protein interaction (PPI) interface. While, thielocins A1β (2) and B3 (10) did not prohibit the PAC3 homodimer even at higher concentrations (IC$_{50}$ > 250 μM) (Ohsawa et al. 2018). In-silico docking studies by Doi et al. (2014) in the binding mode of 8 to the PAC3 dimer interface revealed that it had five fully substituted aromatic rings which can be divided into the diaryl ether central core and two phenolic units on either flank (Doi et al. 2014).

**Antimicrobial activities**

Emodin (16) and hypericin (17) isolated from an endophytic fungus T. subthermophila associated with Hypericum perforatum possessed antimicrobial activity towards S. aureus ssp. aureus, K. pneumoniae ssp. ozaenae, P. aeruginosa, Salmonella enterica ssp. enterica, E. coli, Aspergillus niger and C. albicans comparable to authentic standards using the disk diffusion method (Kusari et al. 2008). Thielaviazoline (25) obtained from the marine-mudflat-derived fungus Thielavia sp. displayed antimicrobial potential towards multidrug-resistant and methicillin-resistant S. aureus (MRSA and MDRSA) with minimum inhibitory concentrations (MICs) 12.5 and 6.25 μg/mL, respectively using dilution method (Leutou et al. 2016). Thielavin B (27) inhibited the formation of peptido-glycan in an in vitro assay with IC$_{50}$ 5 μg/mL in E. faecalis A256 compared with a panel of antibiotics, suggesting that it could interfere with cell wall trans-glycosylation (Mani et al. 1998). Chen et al. (2010) investigated the antimicrobial activities of the endophytic fungal extract of T. californica associated with Dendrobium loddigesii Rolfe against S. aureus, B. subtilis, C. albicans, C. neoformans and A. fumigatus. It showed activity towards S. aureus and B. subtilis with inhibition zone diameters (IZDs) 13.3 and 16.3 mm, respectively (Chen et al. 2010).

**Cytotoxic activities**

Emodin (16) and hypericin (17) exhibited photodynamic cytotoxicity against the human acute monocytic leukemia cell line (THP-1) with 91.1 vs 1.0% and 92.7 vs 4.9% cell viability by ATPlite and resazurin assays, in dark and light, respectively (Kusari et al. 2008; 2009). OPC-15161 (15) inhibited the extracellular matrix production and proliferation of extracellular matrix-producing mesangial cells in the kidney in vivo. Compound 15 inhibited the cell number and uptake of [3H]thymidine in the HSCs. Moreover, it inhibited extracellular matrix production via suppressing the effect of transforming growth factorb1 (TGF-b1) on [3H]-hydroxyproline production. It also decreased intracellular Ca$^{2+}$ and D-myo-inositol 1,4,5-triphosphate (IP3) concentrations in the HSCs. Thus, 15 prevented liver fibrosis through inhibition of HSCs proliferation and hydroxyproline production in cultured rat HSCs (Sugawara et al. 1998). Togashi et al. (2001) reported that 27 isolated from T. terricola showed telomerase inhibitory
activity at 32 μM. Also, it inhibited the viral reverse transcriptase activity at the same concentration (Togashi et al. 2001).

**Antioxidant activities**

Thielaviazoline (25) showed potent radical-scavenging activity against DPPH with an IC₅₀ 11 μM, in comparison to L-ascorbic acid (IC₅₀ 20.0 μM) (Leutou et al. 2016).

**Anti-diabetic activities**

Thielavin K (33) was evaluated for its anti-diabetic potential at a dose range from 3.1 to 31.6 mg/kg. At all tested doses, 33 decreased glucose blood levels 30 min after oral administration of the sucrose load (3.0 g/kg) in normal mice. In nicotinamide-streptozotocin (NA-STZ) diabetic mice only the highest dose (31.6 mg/kg) provoked a significant decrease in blood glucose levels. Its inhibition of postprandial peak was comparable to that of acarbose. Therefore, 33 at the doses of 3.1 and 10 mg/kg decreased blood glucose levels in normal and diabetic mice. The in vivo results suggested that 33 showed potential anti-diabetic action at different targets, namely inhibiting the α-glucosidases at the intestinal levels (Rivera-Chávez et al. 2013). Moreover, thielavins A (26), J (32) and K (33) inhibited Saccharomyces cerevisiae α-glucosidase (αGHY) with IC₅₀s 23.8, 15.8 and 22.1 μM, respectively in a concentration-dependent manner, which were higher than the inhibitory effect of acarbose (IC₅₀ 545 μM, positive control). They behaved as non-competitive inhibitors (ki 27.8, 66.2 and 55.4 μM, respectively and α values 1.0, 1.2 and 0.7, respectively) as acarbose (ki 156.1 μM) in the kinetic analysis. Also, 32 inhibited the activity of Bacillus stearothermophilus α-glucosidase (αGHBs, type IV α-glucosidase with maltase activity) with an IC₅₀ 30.5 μM, in comparison to acarbose (IC₅₀ 0.015 μM). In the kinetic analysis, 32 and acarbose behaved as non-competitive inhibitors towards αGHBs (kis 20.0 and 0.008 μM, respectively and α values 2.9 and 1.9 μM, respectively). The results indicated that these thielavins are better for sucrose-type α-glucosidases (Rivera-Chávez et al. 2013). This could be supported by Sakemi et al. (2002) study which reported that thielavins A, J and K isolated from Chaetomium carinthiacum possessed in-vitro glucose-6-phosphatase (G6Pase) inhibitory activity. Also, they inhibited glucose output from glucagon-stimulated hepatocytes (Sakemi et al. 2002). Moreover, a thielavin type, CJ-21,164, isolated from Chloridium sp. CL48903 fermentation, inhibited G6Pase in rat liver microsomes and glucose output from hepatocytes isolated from rat liver (Kim et al. 2002). Therefore, they could decrease the hepatic glucose output from glyconeogenesis and glycogenolysis, leading to lowering plasma glucose concentration in diabetes mellitus (Sakemi et al. 2002; Rivera-Chávez et al. 2013). It is noteworthy that a structure-activity relationship study revealed that the benzoic acid units and carboxylic acid functionality are essential for the G6Pase inhibitory activity (Sakemi et al. 2002).

**Antifouling activity**

The anti-larval settlement activities of thielavins A (26), H (31), J (32), K (33), W-Z (34–37) and Z₁–Z₇ (38–44) biosynthesized by Thielavia sp. UST030930-004 against
cyprid larvae of *B. Amphitrite* were assessed by Han et al. (2017). Compounds 34–36, 39–44, 26 and 31 deterred larval settlement with EC$_{50}$s ranging from 2.95 ± 0.59 to 69.19 ± 9.51 μM, respectively, in comparison to butenolide (EC$_{50}$ 4.62 μM). Moreover, 34–36, 40 and 44 (conc. 10 μM) possessed narcotic effects against cyprids of *B. amphitrite*. The active thielavins (conc. 10 μM) led to the loss of cyprids phototactic response as well as reducing appendage activity and becoming completely immobilized. The recovery rates of cyprids treated with 10 μM of 34–36, 40 and 44 demonstrated that larvae had the highest recovery rate from treatment with 34, while no larvae recovered from treatment with 44 for 24 h. Of all of the compounds, 34 had an excellent antifouling activity and cyprids treated with it showed the highest recovery rate. Thus, 34–35 and 40 were reversible inhibitors. On the other hand, thielavins 32–33 and 37–38 had no activity (Han et al. 2017).

**Conclusion**

Fungi are good sources for the discovery of new leads for drug development. *Thielavia* species are of biotechnological and industrial importance. Also, they are a wealthy pool of different classes of metabolites with varying structural patterns and pharmacological activities. Forty four metabolites have been separated and characterized in seven species of the genus *Thielavia* in the period 1981–2017. These compounds can be taken into account as favorable candidates for the evolution of effective and novel pharmaceutical leads. Among the reported metabolites from *Thielavia* species, the depside derivatives (thielavins and thielocins) are the main compounds. Accordingly, these metabolites might be considered and selected as potential chemical markers of this genus. However, further studies to support this hypothesis should be carried out. Several *Thielavia* species have not yet been deeply investigated and are awaiting that research groups spend some time to explore their chemical contents and bioactivities. Further, the role of the reported metabolites on the medical and agricultural applications of the *Thielavia* genus should be the focus of further research.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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