Fungal Depsides Naturally Inspiring Molecules

Subjects: Allergy

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Depsides are a group of polyketides consisting of two or more ester-linked hydroxybenzoic acid moieties. They possess valuable bioactive properties, such as anticancer, antidiabetic, antibacterial, antiviral, anti-inflammatory, antifungal, antifouling, and antioxidant qualities, as well as various human enzyme-inhibitory activities.

fungi depsides biosynthesis spectral data biological activities

1. Introduction

Depsides are simple polyketides that are formed by the condensation of two or more hydroxybenzoic acid moieties via ester linkage; the COOH group of one molecule is esterified with a phenolic OH group of the second molecule. They could be β-orcinol (β-orsellinic acid) or orcinol (orsellinic acid) derivatives, relying on the existence of the C_3 methyl group on both rings (**Figure 1**). The ring with an ester-carbonyl is referred to as ring A and the other as ring B. Their major structural variations are the attached alkyl chains' length, the degree of chain oxidation, and the degree of methylation of OH and COOH groups [1]. The OH groups usually exist at the aromatic carbons, C-3′/C-4′/C-2 or C-4, and other oxygenated substituents are usually connected to the skeleton, such as carboxyl and methoxyl substituents [2].

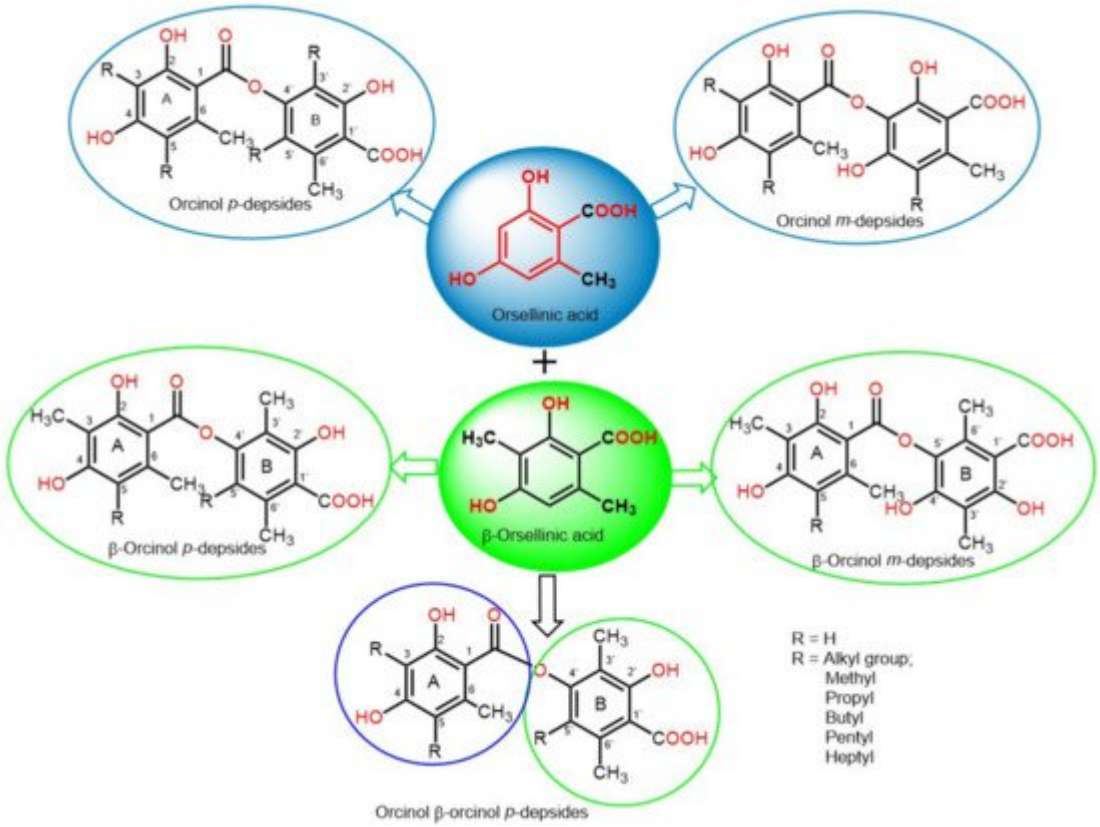

Figure 1. Basic structures of orcinol *para*depsides, orcinol *meta*depsides, β-orcinol *para*depsides, β-orcinol *meta*depsides, and mixed orcinol β-orcinol depsides.

Depsides are common lichen metabolites [3][4][5]. However, they have also been reported in some higher plants and fungi [2][6][7][8][9][10]. Contrary to the lichen depsides, fungal depsides are not widely distributed and are isolated only from a restricted number of fungi. It was reported that depsides possess remarkable bioactivities: anticancer, anti-diabetic, antibacterial, antiviral, anti-inflammatory, antifungal, antifouling, antioxidant, and various enzyme inhibitory activities.

2. Biosynthesis of Depsides

Depsides are acetyl-poly-malonyl-derived polyketides that are biosynthesized by polyketide synthase (PKS) [11][12][13][14][15][16][17]. PKS is composed of a minimal set of KS (ketosynthase), AT (acyltransferase), and ACP (acyl carrier protein) domains [13]. The non-reduced framework of the depside rings reveals that its corresponding PKS belongs to non-reducing PKSs (NR-PKSs). Depsides consist of two orsellinic acid molecules, connected by an ester linkage. Therefore, orsellinic acid can be considered the constructing unit of all depsides [11]. Biosynthetically, orsellinic acid is produced from a linear tetraketide chain. This chain is formed through an acetate-malonate pathway that is catalyzed by PKSs [12][13]. The tetraketide chain forming β-orsellinic acid (methyl-3-orsellinate) is produced by introducing a CH_3 group obtained from SAM (S-adenosylmethionine) by the methyltransferase (CMeT) domain of the corresponding PKS [14]. Then, the non-enzymatic 2,7-aldol condensation of these chains produces orsellinic and β-orsellinic acids. Furthermore, the molecular skeleton is probably designed by post-

biosynthetic tailoring enzymes, such as cyclases and hydrolases [1]. *p*-Depsides are produced by the condensation of either orsellinic acid and orcinol derivatives or by two methyl-3-orsellinate or orsellinate moieties, through the formation of an ester [18]. The consequent condensation of an additional unit produces a tri-depside, and two moieties yield a tetra-depside [15]. Moreover, depsides containing alkyl side-chains can be produced by the reduction of the terminal ketone groups, resulting in the required saturated alkyl moieties. *m*-Depsides are formed through the hydroxylation of the para-depside B-ring, subsequently followed by rearrangement [16] (**Figure 2**).

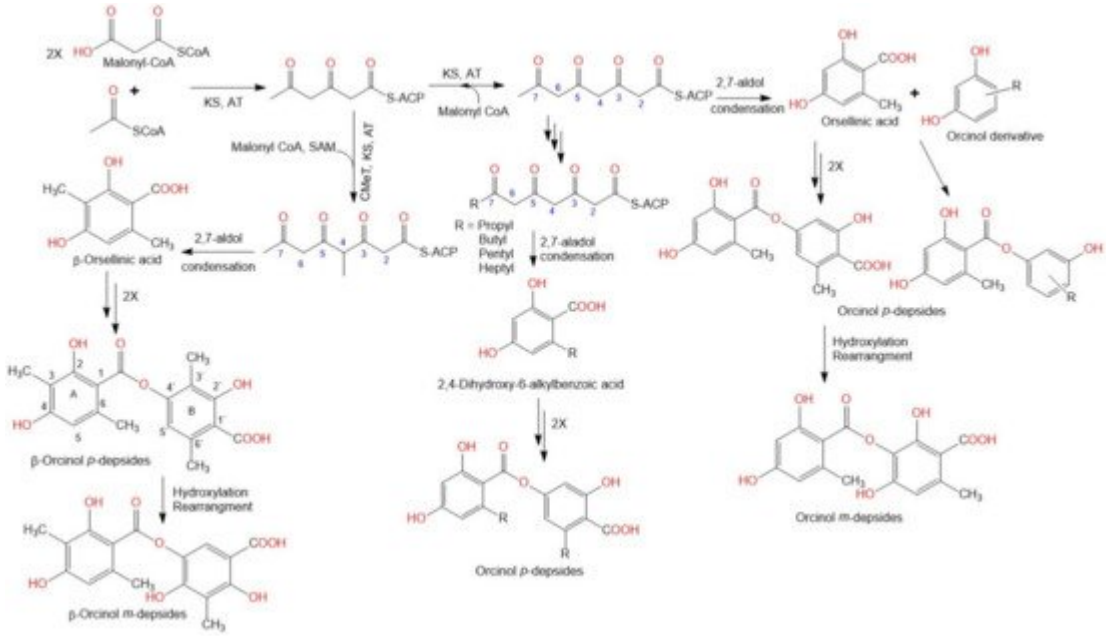

Figure 2. Biosynthesis of depsides [1][11][12][13][14][15][16].

3. Biological Activities

3.1. Antitumor Activity

Lünne et al. [19] evaluated the antitumor effect of lecanoric acid (**1**) and ethyl lecanorate (**2**) purified from *Claviceps purpurea* on HepG2 (human liver cancer cells) and CCF-STTG1 (human astrocytoma cells) using the CTC (5-cyano-2,3-bis(4-methylphenyl)-2H-tetrazolium chloride) assay. Both metabolites produced a dose-dependent antitumor effect on the tested cell lines. They reduced the CCF-STTG1 cell viability down to ~60%, at a concentration of 40 µM, and HepG2 cell viability by ~30% and 40%, respectively. Similar to HepG2 cells, **2** had the strongest antitumor effect on CCF cells (IC_{50} value of 54 µM) [19]. In the MTT ((3-(4,5-dimethylthiazol-2-yl))-2,5-diphenyl-2H-tetrazolium bromide) assay, aspergisides A (**3**), B (**4**), and C (**5**) showed weak antitumor activity, with IC_{50} values in the range of 45–114 µM toward Vero, MCF-7, and KB cell lines, compared with doxorubicin [20]. MS-3 (**22**) was inactive against Ehrlich ascites for leukemia and carcinoma in vivo; however, it was active toward Yoshida sarcoma cells (ID_{50} value of 85 µg/mL) in vitro. Its activity was suggested to be due to a glyoxalase inhibition, as it possessed a glyoxalase inhibitory effect with an ID_{50} value of 12 µg/mL in the spectrophotometric assay [21]. In addition, **23** possessed significant antitumor activity toward A549 and HepG2, with IC_{50} values of 13.14 and 49.02 µM, respectively, compared to cisplatin (IC_{50} 14.33 and 18.74, respectively) in the MTT assay [22].

Compounds **27**–**29** were assayed against NCI-H187, Vero, BC, and KB cells, employing an MTT assay. Compounds **27** and **28** exhibited a significant antitumor effect against BC, with IC_{50} values of 8.8 and 4.4 µM, respectively, compared to ellipticine (IC_{50} 0.49 µM), while they showed weak to moderate effectiveness toward other cell lines, with IC_{50} values ranging from 13.0 to 34.3 µM [23]. Arenicolins A (**30**) and B (**31**), two new depsides having C-glycosyl moiety and dual heptyl side-chains, were isolated from *Penicillium arenicola* and assessed for antitumor activity at a concentration of 30.0 µM toward IMR-32, HCT-116, and BT-474 cell lines using an ICC (immunocytochemistry) assay. Compound **30** reduced cell viability with IC_{50} values of 6.0, 7.3, and 9.7 µM, respectively, compared to 5-FU (5-fluorouracil, IC_{50} 6.5 µM for HCT-116 and 5.7 µM for IMR-32). However, **31** did not have a significant antitumor effect toward the tested cell lines at a concentration of > 30 µM [24].

3.2. Antimicrobial Activity

Phainuphong et al. purified three new depsides, aspergisides A–C (**3**–**5**) from *Aspergillus unguis*, and assessed their antimicrobial potential against MRSA (methicillin-resistant *S. aureus*), *S. aureus*, *C. albicans*, flucytosine-resistant *C. neoformans*, and *M. gypseum* [20]. Compound **3** had a weak antibacterial activity toward *S. aureus* and MRSA, with an MIC (minimal inhibitory concentrations) value of 8 µg/mL, while **4** and **5** were inactive, with MIC values of 32–200 µg/mL in the agar diffusion method [20]. *Setophoma* sp. associated with guava fruits produced compounds **6**–**8** and **66**–**69** [2]. They did not have growth inhibition activity toward *E. coli*. However, **66**–**69** demonstrated inhibition of *S. aureus* with MIC values of 100, 6.25, 50, and 25 µg/mL, respectively, in comparison to tetracycline (MIC 3.12 µg/mL) [2]. Compounds **6** and **7** were inactive. Moreover, all compounds did not exhibit quorum-sensing inhibitory activity. Studying the structural activity relationship revealed that the activity increased with the full methylation of the B-ring; however, the additional CH_3 group at ring A, especially at C-2, resulted in a decrease in activity [2]. The agonodepsides A (**12**) and B (**13**) were isolated from the filamentous fungus, F7524 [25]. In the fluorometric InhA assay, **12** inhibited *M. tuberculosis* InhA with an IC_{50} value of 75 µM, while **13** was inactive at 100 µM, compared with triclosan (IC_{50} 3.0 µM) [25].

3.3. Antifouling Activity

The anti-larval settlement activities of **15**, **48**, **56**, **58**, **59**, and **70**–**79** were assessed towards cyprid larvae of *B. amphitrite* [26]. Compounds **15**, **48**, **56**, **71**–**73**, and **76**–**78** deterred larval settlement, with EC_{50}s ranging from 2.95 to 69.19 µM in comparison to butenolide (EC_{50} 4.62 µM). At a concentration of 10 µM, **15, 71**–**73**, and **77** exhibited narcotic potential toward *B. amphitrite* cyprids. They caused the loss of the phototactic response of cyprids, in addition to decreasing the appendage activity and cyprids becoming completely immobilized. The recovery rates of cyprids treated with **15**, **71**–**73**, and **77** (concentration of 10 µM) revealed that larvae possessed the highest recovery rate after treatment with **71**, while no larvae recovered after treatment with **15** for 24 h. From all tested compounds, **71** had an excellent antifouling potential and cyprids treated with it had the highest recovery rate. Thus, **71**, **72**, and **77** were reversible inhibitors. Conversely, **58**–**59**, **74**, and **75** had no effect [26].

3.4. Anti-Diabetic Activity

Rivera-Chávez et al. reported that the tridepside, **59** (dose 3.1–31.6 mg/kg), reduced glucose blood levels after 30 min of oral administration of the sucrose load in mice (3.0 g/kg); however, only the highest dose (31.6 mg/kg) caused a marked reduction in blood glucose levels in NA-STZ (nicotinamide-streptozotocin) diabetic mice, indicating that **59** (doses of 3.1 and 10 mg/kg) reduced the blood glucose levels in both diabetic and normal mice [27].

3.5. D-Glucose-6-Phosphate Phosphohydrolase Inhibitory Activity

G6Pase (D-glucose-6-phosphate phosphohydrolase) is a hepatic metabolism-regulating enzyme, that catalyzes the last steps of glycogenolysis and gluconeogenesis pathways [28]. Its inhibition decreases the output of hepatic glucose from both pathways, leading to lowering the blood glucose levels in diabetes. The tetra-depside, **97** isolated from *Chloridium* sp. CL48903 prohibited G6Pase in rat liver microsomes (IC_{50} 1.6 µM) at a concentration of 133 µM, using a colorimetric assay and hepatocyte glucose output (81% inhibition), indicating the role of **97** as a G6Pase inhibitor [29].

3.6. α-Glucosidase Inhibitory (αGI) Activity

The α-glucosidase enzyme is an important therapeutic target for treating carbohydrate-mediated diseases. It catalyzes the breakdown of oligo- and disaccharides into monosaccharides in the final stage of carbohydrate digestion, leading to a rise in glucose levels [30][31][32][33]. Several studies revealed that α-glucosidase inhibitors (αGIs) slow down the digestion and absorption of carbohydrates, and thus reduce the postprandial blood glucose level [30][31][32][33]. The serious side effects of the current αGIs, such as liver injuries and gastrointestinal damage, have directed research efforts toward discovering and developing new and safer anti-diabetic agents.

3.7. Protein Tyrosine Phosphatase Inhibitory (PTP1BI) Activity

PTP1B (protein-tyrosine phosphatase 1B) is a negative regulator of the insulin signaling pathway. The inhibition of PTP1B activity has great promise for alleviating insulin and leptin resistance; hence, PTP-1BIs (PTP1B inhibitors) show potential for treating T2DM and other metabolic disorders [34].

Cosmospora sp. produced aquastatin A (**32**) (IC_{50} 0.19 µM) that showed modest but selective PTP1BI activity over other PTPs (protein tyrosine phosphatases) such as TCPTP (T-cell protein tyrosine phosphatase) (IC_{50} 0.51 µM), SHP-2 (IC_{50} > 44 µM), CD45 (IC_{50} > 44 µM), and LAR (IC_{50} > 44 µM), compared with ursolic acid (IC_{50} 2.5 µM). It was suggested that the 2,4-dihydroxy-6-pentadecylbenzoic acid moiety is critical for PTP1BI activity [35].

3.8. Diacylglycerol Acyltransferase Inhibitory (DGATI) Activity

Postprandial hypertriglyceridemia is considered the main risk factor for cardiovascular functions. Thus, triglyceride synthesis inhibition has remarkable therapeutic potential in metabolic disorder treatment. The enzymes known as diacylglycerol acyltransferases (DGATs) catalyze the final and only committed step in the biosynthesis of triglycerides [36]. Therefore, these enzymes could be a potential therapeutic target to combat cardio-metabolic

disorders [37][38][36]. Compound **9** also inhibited TG synthesis (IC_{50} 91 µM), as well as PC and PE syntheses, indicating that it had a non-specific DGATI effect [39]. The compounds **86** and **88**–**90** were purified from *Humicola* sp. by Tomoda et al. [40]. Compound **88** was the most potent DGATI, with an IC_{50} of 10.2 µM, followed by **86** (IC_{50} 17.5 µM), **89** (IC_{50} 19.2 µM), and **90** (IC_{50} 51.6 µM). They also inhibited the formation of triacylglycerol using Raji cells on the intact cell assay, with IC_{50} values ranging from 2.82 to 17.2 µM. At high concentrations, **86** moderately inhibited the formation of phosphatidylethanolamine (PE) and phosphatidylcholine (PC), whereas **89** possessed a weak effect, indicating that **89** specifically suppressed the formation of triacylglycerol (TG) [40].

3.9. Activity of 11β-Hydroxysteroid Dehydrogenase Inhibitory (11β-HSDI) Enzyme

High levels of glucocorticoid produce insulin resistance and glucose intolerance, leading to metabolic syndrome (MS) [41]. The enzyme 11β-HSD (11β-hydroxysteroid dehydrogenase) is accountable for the production of glucocorticoids in tissues, thus it plays a remarkable role in T2DM and MS. The 11β-HSD1 inhibitors (11β-HSD1Is) could be considered promising therapeutics in treating MS. Compounds **38**–**41** exhibited powerful and selective inhibitory activities against 11β-HSD1 in the HTRF immunoassay. They inhibited human 11β-HSD1 activity in a dose-dependent manner with IC_{50} values ranging from 240 to 6600 nM. Compounds **38** and **40** were the most active with IC_{50}s 240 and 230 nM, respectively, while they did not prohibit 11β-HSD2 (IC_{50} > 10,000 nM) [42].

3.10. Anti-Inflammatory Activities

Compound **23**, biosynthesized by *Stereum hirsutum*, exhibited noticeable NO inhibitory potential (IC_{50} 19.17 µM) in the LPS-induced macrophages, compared with hydrocortisone (IC_{50} 48.15 µM) [22]. Moreover, **48** (ID_{50} 12 µM) and **49** (ID_{50} 9 µM) possessed considerable anti-inflammatory potential for the conversion of ^{14}C-arachidonic acid into $PGF_2\alpha$ plus PGE_2 by the microsomes of ram seminal vesicles [43][44]. ID_{50}s of the conversion of arachidonic acid (AA) into PGH_2 (prostaglandin H_2), PGH_2 into (prostaglandin E_2), and thromboxane A_2 (TXA_2) synthetase are 10, 40, 150 µM, respectively, for **48** in comparison to indomethacin (ID_{50} 30 for PGH_2 and 130 µM for PGE_2) and imidazole (ID_{50} 200 µM for TXA_2 synthetase); meanwhile, **49** had ID_{50} values of 40, 9, and 350 µM, respectively. Compound **48** had a strong inhibitory effect on the conversion of AA into PGH_2, while **49** specifically inhibited the step involving PGE_2 synthesis from PGH_2. Moreover, they inhibited TXA_2 synthesis in bovine platelet microsomes (ID_{50} values of 150 and 350 µM, respectively), which was comparable to imidazole (200 µM) [43][44]. Both compounds (dose 50 mg/kg, orally) showed no significant anti-inflammatory effects on carrageenan-induced edema in rats. However, **49** caused a 70% inhibition of this edema system at an intravenous (IV) dose of 5 mg/kg, while **48** displayed no activity, even with IV administration [44].

3.11. Antimalarial Activity

Malaria is among many prevalent health concerns and is caused by the *Plasmodium* parasite in several of the world's tropical regions [45]. The emergence of malaria strains that are drug-resistant to the available therapeutics makes the discovery of new antimalarial agents a great scientific challenge [46][47].

The two new depside galactopyranosides, **28** and **29**, and their aglycone **27**, isolated from *Acremonium* sp., were tested against *Plasmodium falciparum* K1 using a microculture radioisotope technique. Only compound **27** was active towards *P. falciparum* K1, with an IC_{50} value of 9.9 µM compared with dihydroartemisinin (IC_{50} 0.0039 µM). However, **28** and **29** had weak effects (IC_{50} > 10 µM) [23].

3.12. Antioxidant Activity

The depsides, **23** and **24** showed weak radicals scavenging capacity with EC_{50} > 200 µM [22]. In the DPPH (2-diphenyl-1-picrylhydrazyl) assay, **11**, **45**, and **46** also had weak antioxidant activity, compared with ascorbic acid [48].

3.13. Ca^{2+}/CaM Dependent Phosphodiesterase Inhibitory (CaM-PDEI) Activity

Nakanishi et al. reported that **34** and **35**, purified from *Sporothrix* sp., inhibited heart and bovine brain PDEs (IC_{50} 4.3 and 1.8 µM and 5.9 and 15.0 µM, respectively) [49]. Moreover, they prohibited the CaM-dependent activities of CaM-PDEs but had a low effect against their CaM-independent effects, suggesting that these compounds interacted with CaM to inhibit Ca^{2+}/CaM-dependent enzymes. On the other hand, they had no inhibitory activities on protein kinase C [49]. Moreover, PS-990 (**47**), isolated from *Acremonium* sp., inhibited brain CaM-PDE with an IC_{50} value of 3 µg/mL and did not elevate the intracellular cyclic AMP level. It markedly induced the neurite extension of Neuro2A (mouse neuroblastoma) at concentrations ranging from 10 to 30 µg/mL, suggesting its neuritogenic effect. It inhibited both cell growth and thymidine incorporation into the cells at the same concentration range. Interestingly, **47** reversibly induced neurite formation, with cell growth arrest through a mechanism other than increasing the intracellular cyclic AMP concentration [50][51].

3.14. Antiviral Activity

HCMV (human cytomegalovirus) is the most familiar viral cause of congenital infections, which can lead to severe birth defects. Its current treatments include viral DNA polymerase inhibitors, which block the late stages of HCMV replication; however, they do not prohibit the viral induction of multiple cell activation events [52]. Thus, it may be beneficial to discover new treatments for HCMV infections.

Compounds **27**–**29** were assessed against HSV-1 (*Herpes simplex* virus type 1), using the SBR technique. Only **28** showed potent activity, with an IC_{50} value of 7.2 µM, compared with acyclovir (IC_{50} 10.2 µM), while **27** and **29** displayed weak activity, with IC_{50} values of > 1000 and > 50 µM, respectively [23]. *Cytonaema* sp. yielded novel *p*-tridepsides; **84** and **85** showed in vitro inhibitory activities to hCMV protease, with IC_{50} values of 43 and 11 µM, respectively, in the scintillation proximity assay 73].

3.15. Human Leukocyte Elastase (HLE) Inhibitory Activity

HLE is one of the most destructive enzymes that can degrade tissue matrix proteins, such as collagen, elastin, fibronectin, proteoglycan, and laminin, by activating progelatinase, procollagenase, and prostromelysin [8]. It is

released from PMNLs (polymorphonuclear leukocytes) as a result of inflammatory mediators and stimuli. HLE is considered an important therapeutic target for treating many inflammation-linked disorders [53].

The depsides, **25** (IC_{50} 45.1 µM) and **26** (IC_{50} 92.6 µM), weakly inhibited HLE in the spectro-photometric immunoassay, while the tridepside, **83** (IC_{50} 1.8 µM), exhibited high HLE inhibitory activity compared to ulinastatin (IC_{50} 1.1 µg/mL), which was 25–50-fold greater than that of depsides [8].

3.16. Indoleamine 2,3-Dioxygenase Inhibitory (IDOI) Activity

IDO (indoleamine 2,3-dioxygenase) catalyzes the tryptophan catabolism initial step via the KP (kynurenine pathway) [54]. Dysregulation of the KP is accompanied by the IDO activity elevation and production of quinolinic acid (an excitotoxin), which has been engaged in the pathogenesis of neurodegenerative disorders, neuroinflammatory, HIV encephalitis, age-related cataract, and depression [54]. Therefore, IDO is a promising target of new therapeutics for treating neurological disorders and cancer, as well as other disorders characterized by a defect in tryptophan metabolism.

Compounds **49**, **54**, and **65** isolated from *Coniochaeta* sp., inhibited the activity of IDO with IC_{50} values of 21.2, 14.5, and, 26 µM, respectively in comparison to menadione (IC_{50} 3.7 µM) [54].

3.17. Adenosine Triphosphatase Inhibitory Activity

Na^+/K^+-ATPase (sodium/potassium adenosine triphosphatase) is an integral membrane protein that is accountable for maintaining Na^+ and K^+ gradients across the plasma membrane, an important process for mammalian cell survival. Currently, it is extensively studied as a potential target for cancer treatment, especially in glioblastoma and lung cancer [55]. The proton pump, H^+/K^+ ATPase, plays an important role in the stomach acidification process. Its inhibition in gastric parietal cells decreases gastric acid overproduction [56]. H^+/K^+ ATPase inhibitors can be utilized as a target for developing drugs against gastric acid production disturbances.

Aquastatin A (**32**) was biosynthesized by *Fusarium aquaeductuum*. It inhibited Na^+/K^+-ATPase (adenosine triphosphatase) (IC_{50} 7.1 µM) and H^+/K^+-ATPase (IC_{50} 6.2 µM) [57].

3.18. Proteasome Inhibitory Activity

Proteasome comprises one or two 19S RPs (regulatory particles) and 20S CPs (core particles). In humans, the 20S CP formation is assisted by proteasome-specific chaperones: PAC1–PAC4 and POMP (proteasome maturation protein) [58][59]. Proteasome accounts for misfolded, unneeded, or damaged cellular protein degradation. Therefore, it is a crucial target for the future treatment of various diseases, such as neurodegenerative and autoimmune diseases, cystic fibrosis, cancer, diabetes, and atherosclerosis [58]. The compound **105** (IC_{50} 0.020 µM) had a potent PAC3 (proteasome-assembling chaperone 3 homodimer) inhibitory effect, while **103** and **107** (IC_{50} > 250 µM) did not inhibit the PAC3 homodimer [59].

3.19. Phospholipase Inhibitory Activities

Phospholipase A2 (PLA2) catalyzes the hydrolysis of membrane phospholipids into arachidonic acid; therefore, its inhibitors have the potential for treating various inflammatory disorders [60]. Compound **107** showed a strong reversible and noncompetitive inhibition of human PLA_2-II (*Ki* value of 0.098 μM, IC_{50} value of 0.076 μM); however, it showed weak inhibition of human PLA_2-I (IC_{50} of 18 μM). Its inhibitory effect toward PLA_2-II human and PLA_2 *Naja mocambique* was noticeably reduced by methylation of the two COOH groups. Furthermore, **107**, upon co-injection with carrageenan, remarkably reduced PLA_2 activity and exudate volume in the carrageenan-induced pleurisy rat model [61].

4. Conclusions

Most of the reported depsides have been evaluated for their α-GI (α-glucosidase inhibitory), antimicrobial, antitumor, antifouling, PLA2 (phospholipase A2), and DGATI (diacylglycerol acyltransferase inhibitory) abilities (**Figure 3**). Thus, these studies revealed that fungal depsides are a rich source for the discovery of effective and novel pharmaceutical leads and should be further exploited.

They also demonstrate inhibitory activities against various enzymes that can be utilized as targets for the treatment of various diseases. These metabolites could have potential as lead compounds for treating metabolic syndrome, obesity, and diabetes via the inhibition of various enzymes, such as HSD, PTP1BI, α-GI, G6Pase, and DGAT. However, extensive explorations of their mechanism of action, as well as structure modification, chemical synthesis, and structure/activity relationship analysis are needed. Despite the extensive structural diversity of depsides, none of them has been approved by the FDA, and none of them has as yet progressed to clinical trials. Therefore, the impact of fungal depsides on human health concerns has to be considered in several ways.

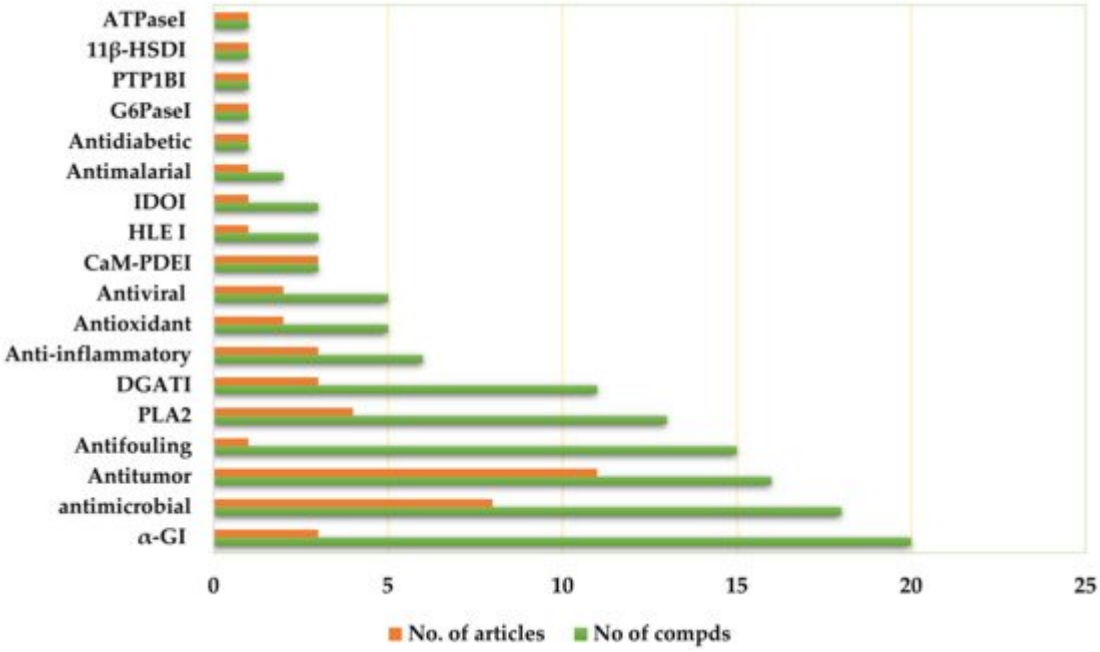

Figure 3. Biological activities of isolated depsides and the number of articles.

References

1. Stocker-Wörgötter, E. Metabolic diversity of lichen-forming ascomycetous fungi: Culturing, polyketide and shikimate metabolite production, and PKS genes. Nat. Prod. Rep. 2008, 25, 188–200.
2. De Medeiros, L.S.; Abreu, L.M.; Nielsen, A.; Ingmer, H.; Larsen, T.O.; Nielsen, K.F.; Rodrigues-Filho, E. Dereplication-guided isolation of depsides thielavins S-T and lecanorins D-F from the endophytic fungus Setophoma sp. Phytochemistry 2015, 111, 154–162.
3. Shukla, V.; Joshi, G.P.; Rawat, M.S.M. Lichens as a potential natural source of bioactive compounds: A review. Phytochem. Rev. 2010, 9, 303–314.
4. Dembitsky, V.M.; Tolstikov, G.A. Halogenated phenol compounds in lichens and fungi. Chem. Sustain. Dev. 2003, 11, 557–565.
5. Seshadri, T.R. A Theory of Biogenesis of Lichen Depsides and Depsidones. Indian Acadademy Sci. 1944, 20, 1–14.
6. Jin, Q.; Hu, X.; Deng, Y.; Hou, J.; Lei, M.; Ji, H.; Zhou, J.; Qu, H.; Wu, W.; Guo, D. Four New Depsides isolated from Salvia miltiorrhiza and their significant nerve-protective activities. Molecules 2018, 23, 3274.
7. Li, Q.; Zhang, X.; Cao, J.; Guo, Z.; Lou, Y.; Ding, M.; Zhao, Y. Depside derivatives with anti-hepatic fibrosis and anti-diabetic activities from Impatiens balsamina L. flowers. Fitoterapia 2015, 105, 234–239.
8. Zheng, Z.; Zhang, S.; Lu, X.; Ma, Y.; Fan, Y.; Shi, Y.; Dong, A.; Duan, B. Trivaric acid, a potent depside human leukocyte elastase inhibitor. Biol. Pharm. Bull. 2012, 35, 2247–2251.
9. Umezawa, H.; Shibamoto, N.; Naganawa, H.; Ayukawa, S.; Matsuzaki, M.; Takeuchi, T.; Kono, K.; Sakamoto, T. Isolation of lecanoric acid, an inhibitor of histidine decarboxylase from a fungus. J. Antibiot. 1974, 27, 587–596.
10. Yamamoto, Y.; Nishimura, K.; Kiriyama, N. Transformation of asterriquinone diacetate to asterriquinone monoalkyl ether via its monoacetal. Chem. Pharm. Bull. 1976, 24, 1853–1859.
11. Legaz, M.E.; de Armas, R.; Vicente, C. Bioproduction of Depsidones for Pharmaceutical Purposes; IntechOpen: Rijeka, Croatia, 2011; Volume 19, pp. 487–508.
12. Muggia, L.; Grube, M. Type III polyketide synthases in lichen mycobionts. Fungal Biol. 2010, 114, 379–385.

13. Schümann, J.; Hertweck, C. Advances in cloning, functional analysis and heterologous expression of fungal polyketide synthase genes. J. Biotechnol. 2006, 124, 690–703.
14. Rawlings, B. Biosynthesis of polyketides (other than Actinomycete Macrolides). Nat. Prod. Rep. 1999, 16, 425–484.
15. Elix, J.A. Biochemistry and secondary metabolites. In Lichen Biology; Cambridge University Press: Cambridge, UK, 1996; pp. 154–180.
16. Elix, J.A.; Gaul, K.L. The interconversion of the lichen depsides para- and meta-scrobiculin, and the biosynthetic implications. Aust. J. Chem. 1986, 39, 613–624.
17. Nagai, H.; Kim, Y.H. Cancer prevention from the perspective of global cancer burden patterns. J. Thorac. Dis. 2017, 9, 448–451.
18. Ibrahim, S.R.M.; Mohamed, G.A.; Al Haidari, R.A.; El-Kholy, A.A.; Zayed, M.F.; Khayat, M.T. Biologically active fungal depsidones: Chemistry, biosynthesis, structural characterization, and bioactivities. Fitoterapia 2018, 129, 317–365.
19. Lünne, F.; Niehaus, E.M.; Lipinski, S.; Kunigkeit, J.; Kalinina, S.A.; Humpf, H.U. Identification of the polyketide synthase PKS7 responsible for the production of lecanoric acid and ethyl lecanorate in Claviceps purpurea. Fungal Genet. Biol. 2020, 145, 103481.
20. Phainuphong, P.; Rukachaisirikul, V.; Phongpaichit, S.; Sakayaroj, J.; Kanjanasirirat, P.; Borwornpinyo, S.; Akrimajirachoote, N.; Yimnual, C.; Muanprasat, C. Depsides and depsidones from the soil-derived fungus Aspergillus unguis PSU-RSPG204. Tetrahedron 2018, 74, 5691–5699.
21. Kurasawa, S.; Takeuchi, T.; Umezawa, H. Studies on glyoxalase inhibitor: Isolation of a new active agent, MS-3, from a mushroom. Agric. Biol. Chem. 1975, 39, 2003–2008.
22. Ma, K.; Bao, L.; Han, J.; Jin, T.; Yang, X.; Zhao, F.; Li, S.; Song, F.; Liu, M.; Liu, H. New benzoate derivatives and hirsutane type sesquiterpenoids with antimicrobial activity and cytotoxicity from the solid-state fermented rice by the medicinal mushroom Stereum hirsutum. Food Chem. 2014, 143, 239–245.
23. Bunyapaiboonsri, T.; Yoiprommarat, S.; Khonsanit, A.; Komwijit, S. Phenolic glycosides from the filamentous fungus Acremonium sp. BCC 14080. J. Nat. Prod. 2008, 71, 891–894.
24. Perlatti, B.; Lan, N.; Earp, C.E.; AghaAmiri, S.; Vargas, S.H.; Azhdarinia, A.; Bills, G.F.; Gloer, J.B. Arenicolins: C-glycosylated depsides from Penicillium arenicola. J. Nat. Prod. 2020, 83, 668–674.
25. Cao, S.; Lee, A.S.; Huang, Y.; Flotow, H.; Ng, S.; Butler, M.S.; Buss, A.D. Agonodepsides a and B: Two new depsides from a filamentous fungus F7524. J. Nat. Prod. 2002, 65, 1037–1038.
26. Han, Z.; Li, Y.X.; Liu, L.L.; Lu, L.; Guo, X.R.; Zhang, X.X.; Zhang, X.Y.; Qi, S.H.; Xu, Y.; Qian, P.Y. Thielavins W-Z_7, New Antifouling Thielavins from the Marine-Derived Fungus Thielavia sp.

UST030930-004. Mar. Drugs 2017, 15, 128.

27. Rivera-Chávez, J.; González-Andrade, M.; González, M.; Glenn, A.E.; Mata, R. Thielavins A, J and K: α-Glucosidase inhibitors from MEXU 27095, an endophytic fungus from Hintonia latiflora. Phytochemistry 2013, 94, 198–205.
28. Van Schaftingen, E.; Gerin, I. The glucose-6-phosphatase system. Biochem. J. 2002, 362, 513–532.
29. Kim, Y.J.; Nishida, H.; Pang, C.H.; Saito, T.; Sakemi, S.; Tonai-Kachi, H.; Yoshikawa, N.; Vanvolkenburg, M.A.; Parker, J.C.; Kojima, Y. CJ-21,164, a new D-glucose-6-phosphate phosphohydrolase inhibitor produced by a fungus Chloridium sp. J. Antibiot. 2002, 55, 121–127.
30. Ibrahim, S.R.M.; Mohamed, G.A.; Zayed, M.F.; Ross, S.A. 8-Hydroxyirilone 5-methyl ether and 8-hydroxyirilone, new antioxidant and α-amylase inhibitors isoflavonoids from Iris germanica rhizomes. Bioorg. Chem. 2017, 70, 192–198.
31. Ibrahim, S.R.M.; Mohamed, G.A.; Khayat, M.T.; Ahmed, S.; Abo-Haded, H.; Alshali, K.Z. Mangostanaxanthone VIIII, a new xanthone from Garcinia mangostana pericarps, α-amylase inhibitory activity, and molecular docking studies. Rev. Bras. Farmacogn. 2019, 29, 206–212.
32. Ibrahim, S.R.M.; Mohamed, G.A.; Khayat, M.T.; Ahmed, S.; Abo-Haded, H. Garcixanthone D, a new xanthone, and other xanthone derivatives from Garcinia mangostana Pericarps: Their α-amylase inhibitory potential and molecular docking studies. Starch-Stärke 2019, 71, 1800354.
33. Ibrahim, S.R.M.; Mohamed, G.A.; Khayat, M.T.; Ahmed, S.; Abo-Haded, H. α-Amylase inhibitors xanthones from Garcinia mangostana pericarps and its possible use for the treatment of diabetes with their molecular docking studies. J. Food Biochem. 2019, 43, e12844.
34. Kennedy, B.P. Role of protein tyrosine phosphatase-1B in diabetes and obesity. Biomed. Pharmacother. 1999, 53, 466–470.
35. Seo, C.; Sohn, J.H.; Oh, H.; Kim, B.Y.; Ahn, J.S. Isolation of the protein tyrosine phosphatase 1B inhibitory metabolite from the marine-derived fungus Cosmospora sp. SF-5060. Bioorg. Med. Chem. Lett. 2009, 19, 6095–6097.
36. King, A.J.; Judd, A.S.; Souers, A.J. Inhibitors of diacylglycerol acyltransferase: A review of 2008 patents. Expert Opin. Ther. Pat. 2010, 20, 19–29.
37. Inokoshi, J.; Takagi, Y.; Uchida, R.; Masuma, R.; Omura, S.; Tomoda, H. Production of a new type of amidepsine with a sugar moiety by static fermentation of Humicola sp. FO-2942. J. Antibiot. 2010, 63, 9–16.
38. Inokoshi, J.; Kawamoto, K.; Takagi, Y.; Matsuhama, M.; Omura, S.; Tomoda, H. Expression of two human acyl-CoA:diacylglycerol acyltransferase isozymes in yeast and selectivity of microbial inhibitors toward the isozymes. J. Antibiot. 2009, 62, 51–54.

39. Tomoda, H.; Yamaguchi, Y.; Tabata, N.; Kobayashi, T.; Masuma, R.; Tanaka, H.; Omura, S. Amidepsine E, an inhibitor of diacylglycerol acyltransferase produced by Humicola sp. FO-5969. J. Antibiot. 1996, 49, 929–931.
40. Tomoda, H.; Ito, M.; Tabata, N.; Masuma, R.; Yamaguchi, Y.; Omura, S. Amidepsines, inhibitors of diacylglycerol acyltransferase produced by Humicola sp. FO-2942. I. Production, isolation and biological properties. J. Antibiot. 1995, 48, 937–941.
41. Ferris, H.A.; Kahn, C.R. New mechanisms of glucocorticoid-induced insulin resistance: Make no bones about it. J. Clin. Invest. 2012, 122, 3854–3857.
42. Ito-Kobayashi, M.; Aoyagi, A.; Tanaka, I.; Muramatsu, Y.; Umetani, M.; Takatsu, T. Sterenin A, B, C and D, novel 11beta-hydroxysteroid dehydrogenase type 1 inhibitors from Stereum sp. SANK 21205. J. Antibiot. 2008, 61, 128–135.
43. Matsumoto, K.; Tanaka, K.; Matsutani, S.; Sakazaki, R.; Hinoo, H.; Uotani, N.; Tanimoto, T.; Kawamura, Y.; Nakamoto, S.; Yoshida, T. Isolation and biological activity of thielocins: Novel phospholipase A2 inhibitors produced by Thielavia terricola RF-143. J. Antibiot. 1995, 48, 106–112.
44. Kitahara, N.; Haruyama, H.; Hata, T.; Takahashi, S. The structures of thielavins A., B and C. Prostaglandin synthetase inhibitors from fungi. J. Antibiot. 1983, 36, 599–600.
45. Nieves, K.; Prudhomme, J.; Le Roch, K.G.; Franzblau, S.G.; Rodríguez, A.D. Natural product-based synthesis of novel anti-infective isothiocyanate- and isoselenocyanate-functionalized amphilectane diterpenes. Bioorg. Med. Chem. Lett. 2016, 26, 854–857.
46. Ibrahim, S.R.M.; Mohamed, G.A.; Al Haidari, R.A.; El-Kholy, A.A.; Zayed, M.F. Potential anti-malarial agents from endophytic fungi: A review. Mini. Rev. Med. Chem. 2018, 18, 1110–1132.
47. Martínez-Luis, S.; Pérez-Vásquez, A.; Mata, R. Natural products with calmodulin inhibitor properties. Phytochemistry 2007, 68, 1882–1903.
48. Chen, Y.; Yang, W.; Zou, G.; Chen, S.; Pang, J.; She, Z. Bioactive polyketides from the mangrove endophytic fungi Phoma sp. SYSU-SK-7. Fitoterapia 2019, 139, 104369.
49. Nakanishi, S.; Ando, K.; Kawamoto, I.; Kase, H. KS-501 and KS-502, new inhibitors of Ca2+ and calmodulin-dependent cyclic-nucleotide phosphodiesterase from Sporothrix sp. J. Antibiot. 1989, 42, 1049–1055.
50. Toki, S.; Ando, K.; Yoshida, M.; Matsuda, Y. PS-990, a novel neuritogenic compound from Acremonium sp. J. Antibiot. 1994, 47, 1175–1181.
51. Evers, D.L.; Chao, C.F.; Wang, X.; Zhang, Z.; Huong, S.M.; Huang, E.S. Human cytomegalovirus-inhibitory flavonoids: Studies on antiviral activity and mechanism of action. Antiviral Res. 2005, 68, 124–134.

52. Guo, B.; Dai, J.R.; Ng, S.; Huang, Y.; Leong, C.; Ong, W.; Carté, B.K. Cytonic acids A and B: Novel tridepside inhibitors of hCMV protease from the endophytic fungus Cytonaema species. J. Nat. Prod. 2000, 63, 602–604.
53. Jang, J.P.; Jang, J.H.; Oh, M.; Son, S.; Kim, S.M.; Kim, H.M.; Shin, K.S.; Oh, H.; Soung, N.K.; Hong, Y.S. Inhibition of indoleamine 2,3-dioxygenase by thielavin derivatives from a soil fungus, Coniochaeta sp. 10F058. J. Antibiot. 2014, 67, 331–333.
54. Bejček, J.; Spiwok, V.; Kmoníčková, E.; Rimpelová, S. Na+/K+-ATPase Revisited: On Its Mechanism of Action, Role in Cancer, and Activity Modulation. Molecules 2021, 26, 1905.
55. Tjandrawinata, R.R.; Nailufar, F.; Arifin, P.F. Hydrogen potassium adenosine triphosphatase activity inhibition and downregulation of its expression by bioactive fraction DLBS2411 from Cinnamomum burmannii in gastric parietal cells. Int. J. Gen. Med. 2013, 6, 807–815.
56. Hamano, K.; Kinoshita-Okami, M.; Minagawa, K.; Haruyama, H.; Kinoshita, T.; Hosoya, T.; Furuya, K.; Kinoshita, K.; Tabata, K.; Hemmi, A. Aquastatin A, an inhibitor of mammalian adenosine triphosphatases from Fusarium aquaeductuum. Taxonomy, fermentation, isolation, structure determination and biological properties. J. Antibiot. 1993, 46, 1648–1657.
57. Wang, H.; Yang, Q.; Dou, Q.P.; Yang, H. Discovery of natural proteasome inhibitors as novel anticancer therapeutics: Current status and perspectives. Curr. Protein Pept. Sci. 2018, 19, 358–367.
58. Ohsawa, K.; Yoshida, M.; Izumikawa, M.; Takagi, M.; Shin-Ya, K.; Goshima, N.; Hirokawa, T.; Natsume, T.; Doi, T. Synthesis and biological evaluation of thielocin B1 analogues as protein-protein interaction inhibitors of PAC3 homodimer. Bioorg. Med. Chem. 2018, 26, 6023–6034.
59. Folmer, F.; Jaspars, M.; Schumacher, M.; Dicato, M.; Diederich, M. Marine natural products targeting phospholipases A2. Biochem. Pharmacol. 2010, 80, 1793–1800.
60. Tanaka, K.; Matsutani, S.; Kanda, A.; Kato, T.; Yoshida, T. Thielocin B3, a novel antiinflammatory human group II phospholipase A2 specific inhibitor from ascomycetes. J. Antibiot. 1994, 47, 631–638.
61. Tanaka, K.; Matsutani, S.; Matsumoto, K.; Yoshida, T. A novel type of phospholipase A2 inhibitor, thielocin A1 beta, and mechanism of action. J. Antibiot. 1992, 45, 1071–1078.