Fruitful decade of fungal metabolites as anti-diabetic agents from 2010 to 2019: emphasis on \(\alpha\)-glucosidase inhibitors

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Abstract  In recent years the prevalence of diabetes has increased globally and by 2040 the number of diabetic people has been estimated to increase to 642 million. Various classes of drugs are available to treat Type II diabetes. However, these drugs are associated with certain side effects. \(\alpha\)-Glucosidase is an intriguing target enzyme to treat Type II diabetes, and \(\alpha\)-glucosidase inhibitors are considered as first-line drugs for Type II patients. Fungi, in general, produce natural products with some amazing chemical diversity and many fungal metabolites have illustrated a wide range of biological and pharmacological effects. In this review the focus is on describing the \(\alpha\)-glucosidase effects and their potential as anti-diabetic agents of various metabolites isolated from fungi.

Keywords  Fungi · Secondary metabolites · \(\alpha\)-Glucosidase · Anti-diabetic

Introduction

Diabetes mellitus (DM) is a metabolic disorder associated with insulin resistance and the inability of the pancreatic \(\beta\)-cells to produce insulin, which leads to hyperglycemia. Moreover, hyperglycemia is associated with polyuria, weight loss, ketoacidosis, polydipsia, and other life-threatening health conditions (Usman et al. 2019). AGIs are an intriguing class of pharmaceutical drugs most often considered as first-line antidiabetic drugs for Type II patients (Hossain and Pervin 2018; Usman et al. 2019). However, in
some studies, it has been reported that AGIs can be employed as second-line antidiabetic drugs if these inhibitors are used as combination therapy with metformin (Chan et al. 2018).

The α-glucosidase enzyme (EC 3.2.1.20) has been considered as an important therapeutic target to treat carbohydrate mediated illnesses. It is well known that the secretion of α-glucosidase occurs in the small intestine and this enzyme catalyzes the cleavage of disaccharides and oligosaccharides into monosaccharides in the final step of carbohydrate digestion. Moreover, the conversion of complex carbohydrates into monosaccharides enhances the glucose body level (Abbas et al. 2019). Numerous studies have demonstrated that α-glucosidase inhibitors slow down the absorption and digestion of carbohydrates and therefore reduce the postprandial blood glucose concentrations which thus require less demand for insulin. α-Glucosidase inhibitors are considered mild compared to other oral antihyperglycemic agents because of their confined operation in the intestine rather than regulating various complex biochemical operations within the body (Abbas et al. 2019).

Fungi are considered one of the richest sources of natural products among living organisms because fungi have a unique metabolic system and can synthesise various types of natural products with quite intriguing chemical diversity (Srivastava 2019). After the discovery of penicillin (penicillin F) in 1929 by Alexander Fleming, substantial research on fungi lead to the isolation of thousands of new fungal metabolites with a diverse range of biological and pharmacological effects (Srivastava 2019). Besides, penicillins (antibacterial), echinocandin B (antifungal), cyclosporin A (immunosuppressive, and lovastatin (cholesterol-lowering) are all fungal originated and marketed pharmaceutical drugs. Furthermore, these factors evidently illustrate the significance of fungal metabolites to be a sustainable resource for new pharmaceutical agents.

Currently, acarbose and miglitol are two commercially available drugs with activity described as α-glucosidase inhibitors (AGIs). These pharmaceutical drugs furthermore inhibit the absorption of carbohydrates from the gut and thus these anti-diabetic drugs are either administered alone or in combination with insulin (Bhatia et al. 2019; Hung et al. 2012). However, serious gastrointestinal damage and liver injuries have been associated with the use of these AGIs, and this has restricted their clinical usage (Yin et al. 2014; Kao et al. 2016; Usman et al. 2019). Therefore, there is a crucial need to discover and develop new and safer anti-diabetic drugs with low toxicity. Natural products for this purpose would be ideal if they could combat such diseases without creating other secondary health issues. Plant secondary metabolites have especially been widely studied for their potential anti-diabetic properties. It is thus conceivable that diverse compounds derived from fungal sources could be developed or transformed into new therapeutics against diabetes. This review article describes some small molecules isolated in the last decade (2010 to 2019) from various fungi and developed as inhibitors of α-glucosidase, and thus represent potential anti-diabetic drug leads.

Alkaloids

Alkaloids are nitrogen containing natural products and have been recognized substances in the treatment of human diseases for many years (Pervaiz et al. 2016; Rehman and Khan 2016). Literature indicated that a significant number of alkaloids from plant sources have been identified as α-glucosidase inhibitors (Yin et al. 2014). On the other hand, a number of alkaloids have been reported from various fungi possessing a diverse range of biological effects (Mahmood et al. 2010). Some alkaloids have also been reported from various fungi, which illustrated α-glucosidase inhibition. Valle et al. reported that benzomalvin A (1), quinolactacins A1 (2), A2 (3) in a mixture between B (4) and asperphenamate (5) (Fig. 1) were produced from the fungus Penicillium spathulatum (Valle et al. 2016).

Moreover, the crude extract of P. spathulatum displays α-glucosidase effects with IC_{50}: 56.5 μg/mL. Indeed, compounds 1 (IC_{50}: 383.2 μg/mL), the mixture of 2 and 3 (IC_{50}: 273.3 μg/mL), 4 (IC_{50}: 57.3 μg/mL), and 5 (IC_{50}: 8.3 μg/mL) display a reasonable degree of α-glucosidase inhibition (Table 1). With an in vivo oral sucrose tolerance evaluation; compound 1 was also tested in normal and hyperglycemic mice (p < 0.05). Further docking studies revealed a higher binding affinity of 1 to yeast and mammalian α-glucosidase and this activity has been reported as even higher than that of acarbose. The formalin assay studies substantiated antihyperalgesic activity.
(p < 0.05) of compound 1 in hyperglycemic mice (Valle et al. 2016). Benzomalvin A (1) was also previously reported from the fungus Penicillium sp (Sun et al. 1994), quinolactacins A1 (2), A2 (3) from the fungus Xylariaceae sp (Nong et al. 2014), and quinolactacin B (4) from the fungus Penicillium sp. (Takahashi et al. 2000; Kakinuma et al. 2000). On the other hand, asperphenamate (5) was reported as a fungal metabolite from Penicillium sp. (Frisvad et al. 2013; Arai et al. 2017) and the fungus Aspergillus versicolor (Hou et al. 2017) as well as a plant metabolite reported from Antidesma ghaesembilla (Schaefer et al. 2017) and Erythrina droogmansiana (Yaya et al. 2014).

Isoindolinone type alkaloids, viz., the sterenins A–C (6–8) (Ito-Kobayashi et al. 2008; Wang et al. 2014) and K–M (9–11) Wang et al. 2014) (Fig. 2) were reported from the fungus Stereum sp. and tested for their potential as α-glucosidase inhibitors. The chemical diversity generated among these alkaloids is mainly due to the different substituent groups on nitrogen (Wang et al. 2014). These compounds possess α-glucosidase effects with IC\(_{50}\) 3.31 to 36.6 μM (Table 1). Notably, alkaloid 8 illustrated potent inhibition with IC\(_{50}\) 3.31 μM. SAR studies demonstrated that the different substituents on nitrogen play a most important role and when there is no substituent (R = H) the activity was enhanced (alkaloid 8). On the other hand, various alkyl substituents attached to the nitrogen dramatically decreased activities (Wang et al. 2014). Penicidone C (12) was reported from Penicillium sp. (He et al. 2019; Ge et al. 2008) and demonstrated α-glucosidase inhibition with a low IC\(_{50}\) 51.9 μM (He et al. 2019).

**Azaphilones**

Most of the azaphilones have been reported from two fungi families viz., Xylariaceae and Trichocomaceae and most of these compounds were reported from the fungal genera viz., Chaetomium, Penicillium, Monascus and Talaromyces. The azaphilones illustrated interesting pharmacological effects viz., anti-fungal, antimicrobial, antioxidant, antiviral, anti-inflammatory, cytotoxic, and nematicidal activities (Osmanova et al. 2010; Gao et al. 2013). Talaraculones A (13) and B (14) (Fig. 3) were reported from the fungus Talaromyces aculeatus and compounds 13 and 14 illustrated α-glucosidase potential with IC\(_{50}\) 78.6 and 22.9 μM, respectively, which are lower than acarbose (IC\(_{50}\) 101.5 μM) (Ren et al. 2017). Chermesinone A (15), isolated from the fungus Penicillium chermesinum, illustrated α-glucosidase effects with IC\(_{50}\) 24.5 μM (Huang et al. 2011). In this regard, compound 15 was also reported from the
**Table 1** Fungal metabolites 1–39 as α-glucosidase inhibitors

| Compound | Source | α-Glucosidase activity | References |
|----------|--------|------------------------|------------|
| Benzomalvin A (1) | *Penicillium spathulatum* | IC₅₀: 383.2 μM | Valle et al. (2016) |
| Quinolactacins A1 (2), A2 (3); mixture | *Penicillium spathulatum* | IC₅₀: 273.3 μM | Valle et al. (2016) |
| Benzomalvin B (4) | *Penicillium spathulatum* | IC₅₀: 57.3 μM | Valle et al. (2016) |
| Asperphenamate (5) | *Penicillium spathulatum* | IC₅₀: 8.3 μM | Valle et al. (2016) |
| Sterenin A (6) | *Stereum hirsutum* | IC₅₀: 25.1 μM | Wang et al. (2014) |
| Sterenin B (7) | *Stereum hirsutum* | IC₅₀: 12.3 μM | Wang et al. (2014) |
| Sterenin C (8) | *Stereum hirsutum* | IC₅₀: 3.3 μM | Wang et al. (2014) |
| Sterenin K (9) | *Stereum hirsutum* | IC₅₀: 36.6 μM | Wang et al. (2014) |
| Sterenin L (10) | *Stereum hirsutum* | IC₅₀: 13.0 μM | Wang et al. (2014) |
| Sterenin M (11) | *Stereum hirsutum* | IC₅₀: 27.5 μM | Wang et al. (2014) |
| Penicidone (12) | *Penicillium sp.* | IC₅₀: 51.9 μM | He et al. (2019) |
| Talaraculone A (13) | *Talaromyces aculeatus* | IC₅₀: 78.6 μM | Ren et al. (2017) |
| Talaraculone B (14) | *Talaromyces aculeatus* | IC₅₀: 22.9 μM | Ren et al. (2017) |
| Chermesine A (15) | *Penicillium chermesinum* | IC₅₀: 24.5 μM | Huang et al. (2011) |
| Pinazaphilone A (16) | *Penicillium sp.* | IC₅₀: 81.7 μM | Liu et al. (2015) |
| Pinazaphilone B (17) | *Penicillium sp.* | IC₅₀: 28.0 μM | Liu et al. (2015) |
| Sch 1385568 (18) | *Penicillium sp.* | IC₅₀: 16.6 μM | Liu et al. (2015) |
| Sch 725680 (19) | *Penicillium sp.* | IC₅₀: 33.8 μM | He et al. (2019) |
| 6'-O-desmethylterphenyllin (20) | *Penicillium chermesinum* | IC₅₀: 2.5 μM | Huang et al. (2011) |
| 3-hydroxy-6'-O-desmethylterphenyllin (21) | *Penicillium chermesinum* | IC₅₀: 4.9 μM | Huang et al. (2011) |
| 3',3''-dihydroxy-6'-O-desmethylterphenyllin (22) | *Penicillium chermesinum* | IC₅₀: 0.9 μM | Huang et al. (2011) |
| Sarcoviolin β (23) | *Sarcodon leucopus* | IC₅₀: 0.58 μM | Ma et al. (2014) |
| Episarcoviolin β (24) | *Sarcodon leucopus* | IC₅₀: 1.07 μM | Ma et al. (2014) |
| 2',3',5',6'-Tetracetoxy-4,4'-dihydroxy-p-terphenyl (25) | *Sarcodon leucopus* | IC₅₀: 35 μM | Ma et al. (2014) |
| 2',3'-Diacetoxy-4,4',5',6'-tetrahydroxy-p-terphenyl (26) | *Sarcodon leucopus* | IC₅₀: 19 μM | Ma et al. (2014) |
| 2',3'-Diacetoxy-3,4',5',6'-pentahydroxy-p-terphenyl (27) | *Sarcodon leucopus* | IC₅₀: 3.3 μM | Ma et al. (2014) |
| Leucomeleone (28) | *Sarcodon leucopus* | IC₅₀: 3.5 μM | Ma et al. (2014) |
| Bl-V (29) | *Sarcodon leucopus* | IC₅₀: 6.2 μM | Ma et al. (2014) |
| Episarcodion α (30) | *Sarcodon leucopus* | IC₅₀: 3.6 μM | Ma et al. (2014) |
| Episarcodion (31) | *Sarcodon leucopus* | IC₅₀: 4.2 μM | Ma et al. (2014) |
| Sarcodon α (32) | *Sarcodon leucopus* | IC₅₀: 1.2 μM | Ma et al. (2014) |
| Concrescenin A (33) | *Hydnellum concrescens* | IC₅₀: 0.9 μM | Wang et al. (2014a) |
| Concrescenin B (34) | *Hydnellum concrescens* | IC₅₀: 3.1 μM | Wang et al. (2014a) |
| Thelephantin L (35) | *Hydnellum concrescens* | IC₅₀: 4.5 μM | Wang et al. (2014a) |
| Thelephantin I (36) | *Hydnellum concrescens* | IC₅₀: 18.7 μM | Wang et al. (2014a) |
| Thelephantin K (37) | *Hydnellum concrescens* | IC₅₀: 2.9 μM | Wang et al. (2014a) |
| Dihydrouran-tiacin dibenzoate (3) | *Hydnellum concrescens* | IC₅₀: 5.1 μM | Wang et al. (2014a) |
| Curtisian A (39) | *Hydnellum concrescens* | IC₅₀: 8.3 μM | Wang et al. (2014a) |
fungus Phomopsis sp. (Yang et al. 2015). Pinaza-
philones A (16: IC50: 81.7 μM) and B (17: IC50: 28.0 μM), and Sch 1385568 (18: IC50: 16.6 μM) were produced by the fungus Penicillium sp. and illustrated good to moderate α-glucosidase effects (Table 1) (Liu et al. 2015a). Sch 725680 (19) was reported from Penicillium sp. (He et al. 2019) and was shown to possess α-glucosidase effects with IC50: 33.8 μM.

**p-Terphenyls**

p-Terphenyls bearing a C-18 tricyclic or polycyclic aromatic core demonstrate a huge chemical diversity generated among these compounds by suitable changes in the middle aromatic ring or the linkages between the rings (Li et al. 2018). Over 230 p-terphenyl analogs have been reported as well as a number of isolated derivatives (Li et al. 2018). The majority of these compounds were reported from fungi (Li et al. 2018; Quang et al. 2003; Liu et al. 2004; Lee et al. 1996; Nagasawa et al. 2014). The three p-terphenyls 20–22 (Fig. 4) were isolated from the fungus Penicillium chermesinum and illustrated α-glucosidase effects with IC50 values of 2.5, 4.9, and 0.9 μM, respectively (Table 1). Notably, the activity of these compounds was higher than the reference genistein (IC50: 9.8 μM, Huang et al. 2011). Previously, compound 20 was reported from the fungus Penicillium raistrickii (Belofsky et al. 1998).

p-Terphenyls 23–32 were produced by the fungus Sarcodon leucopus and their structures were determined via extensive NMR techniques (Ma et al. 2014). All compounds displayed α-glucosidase effects with
IC$_{50}$ values ranging from 0.58 to 35.0 μM. Among these, sarcoviolin β (23) showed good and potent effects with an IC$_{50}$: 0.58 μM followed by an isomer of 24. Compounds 24 and 27–32 illustrated moderate inhibition with IC$_{50}$ values ranging from 1 to 10 μM (Table 1). On the other hand p-terphenyls 25 and 26 possess relatively weak effects with IC$_{50}$ values of 35.0 and 19.0 μM, respectively. An SAR analysis demonstrated that the configuration at N-1β and C-2β greatly effects the α-glucosidase activity. For instance, metabolites 23 and 32 having the cis N-1β and C-2β displayed better activity than metabolites 24 and 30 bearing a trans configuration (Ma et al. 2014).

p-Terphenyl analogs viz., concrescins A (33) and B (34), thelephants L (35), I (36), K (37), compound 38, and curtisian A (39) (Fig. 5) were reported from the fungus *Hydnellum concrescens* (Wang et al. 2014a). p-Terphenyl analogs 33–39 illustrated α-glucosidase effects with the IC$_{50}$ ranging from of 0.99 to 18.77 μM. Among the tested compounds, metabolite 33 (IC$_{50}$: 0.99 μM) possesses the strongest effects followed by metabolite 34 (IC$_{50}$: 3.11 μM) and 37 (IC$_{50}$: 2.98 μM) (Table 1). A preliminary SAR study demonstrated that the benzene core in the center of the p-terphenyl core enhances the α-glucosidase effects when compared to the benzoquinone ring as can be noticed by metabolites 33–35 and 37–39 displaying better activity than compound 36 (Wang et al. 2014a).

**Depsid**es

The fungus MEXU 27095 produces the tridepsides, thielavins A (40), J (41) and K (42) (Fig. 6). Moreover, the activities of thielavins A (40: IC$_{50}$: 23.8 μM; K$_i$: 27.8 μM), J (41: IC$_{50}$: 15.8 μM; K$_i$: 66.2 μM), and K (42: IC$_{50}$: 22.1 μM; K$_i$: 22.1 μM) illustrated good *Saccharomyces cerevisiae* α-glucosidase inhibition (Table 2). Notably, the activities of these compounds were higher than that of acarbose (IC$_{50}$: 545 μM). Metabolites 40–42 are reported as being non-competitive inhibitors with K$_i$ values ranging from 27.8 to 66.2 μM. Thielavin J (41: IC$_{50}$: 30.5 μM) also
inhibited the effects of *Bacillus stearothermophilus*-based α-glucosidase (Rivera-Chávez et al. 2013).

Sterenins E-J (43–48), MS-13 (49) and 50 were reported from *Stereum hirsutum* and these compounds were all shown to possess α-glucosidase effects with IC\textsubscript{50}: 3.06–72.50 μM (Table 2). Compounds 43–45 (IC\textsubscript{50}: 3.06 to 7.62 μM) illustrated higher activities than compounds 46–50 indicating that the ring B carbonyl moiety substitution can enhance the activity. Moreover, compound 43 has much stronger effects than metabolite 48 and this finding confirmed that the isoprenyl group significantly affects the inhibitory activity (Wang et al. 2014). Colletotric A (51: IC\textsubscript{50}: 36.2 μM), B (52: IC\textsubscript{50}: 35.8 μM), and C (53: IC\textsubscript{50}: 60.2 μM) were reported from the fungus *Phoma* sp. and showed α-glucosidase effects (Chen et al. 2019) (Table 2).

**Depsidones**

The depsidone talaromyone B (54) was reported from the fungus *Talaromyces stipitatus* (Cai et al. 2017) while purpactin A (55) was obtained from the fungi *T. stipitatus* (Cai et al. 2017) and *Penicillium* sp. (Tomoda et al. 1991; Nishida et al. 1991). In addition,
tenellic acid A (56) (Fig. 7) was isolated from the fungi *T. stipitatus* (Cai et al. 2017) and *Camposporium quercicola* (Wang et al. 2008) and its structure was established via NMR spectroscopic methods as well as employing the Mosher’s protocol. Compounds 54–56 illustrated moderate α-glucosidase activity (Table 2).
## Table 2 Fungal metabolites 40–73 as α-glucosidase inhibitors

| Compd.       | Source            | A-Glucosidase activity | References                  |
|--------------|-------------------|------------------------|-----------------------------|
| Thielavin A   | Fungus MEXU 27095 | IC₅₀: 23.8 μM; Kᵢ: 27.8 μM | Rivera-Chávez et al. (2013) |
| Thielavin J   | Fungus MEXU 27095 | IC₅₀: 15.8; Kᵢ: 66.2 μM  | Rivera-Chávez et al. (2013) |
| Thielavin K   | Fungi MEXU 27095  | IC₅₀: 22.1 μM; Kᵢ: 22.1 μM | Rivera-Chávez et al. (2013) |
| Sterenin E   | Stereum hirsutum  | IC₅₀: 7.6 μM            | Wang et al. (2014)          |
| Sterenin F   | Stereum hirsutum  | IC₅₀: 3.0 μM            | Wang et al. (2014)          |
| Sterenin G   | Stereum hirsutum  | IC₅₀: 6.0 μM            | Wang et al. (2014)          |
| Sterenin H   | Stereum hirsutum  | IC₅₀: 22.7 μM           | Wang et al. (2014)          |
| Sterenin I   | Stereum hirsutum  | IC₅₀: 72.5 μM           | Wang et al. (2014)          |
| Sterenin J   | Stereum hirsutum  | IC₅₀: 65.7 μM           | Wang et al. (2014)          |
| MS-13        | Stereum hirsutum  | IC₅₀: 23.8 μM           | Wang et al. (2014)          |
| 4-Hydroxy-3-methoxy-2-(3-methylbut-2-en-1-yl)phenyl 2,4-dihydroxy-6-methylbenzoate | Stereum hirsutum | IC₅₀: 14.7 μM            | Wang et al. (2014)          |
| Colletotric A| Phoma sp.         | IC₅₀: 36.2 μM           | Chen et al. (2019)          |
| Colletotric B| Phoma sp.         | IC₅₀: 35.8 μM           | Chen et al. (2019)          |
| Colletotric C| Phoma sp.         | IC₅₀: 60.2 μM           | Chen et al. (2019)          |
| Talaromyone B| Talaromyces stipitatus | IC₅₀: 48.4 μM   | Cai et al. (2017)          |
| Purpactin A  | Talaromyces stipitatus | IC₅₀: 80.9 μM   | Cai et al. (2017)          |
| Tenellic acid A| Talaromyces stipitatus | IC₅₀: 99.8 μM       | Cai et al. (2017)          |
| Botryorhodine E| Meyerozyma guilliermondii | IC₅₀: 15.4 μM  | Chen et al. (2015a)        |
| Botryorhodine F| Meyerozyma guilliermondii | IC₅₀: 9.8 μM    | Chen et al. (2015a)        |
| Botryorhodine G| Meyerozyma guilliermondii | IC₅₀: 12.4 μM   | Chen et al. (2015a)        |
| Botryorhodine A| Talaromyces stipitatus | IC₅₀: 54.1 μM      | Zhang et al. (2017)        |
| Botryorhodine B| Meyerozyma guilliermondii | IC₅₀: 13.3 μM  | Chen et al. (2015a)        |
| Botryorhodine D| Meyerozyma guilliermondii | IC₅₀: 11.7 μM    | Chen et al. (2015a)        |
| Botryorhodine H| Meyerozyma guilliermondii | IC₅₀: 2.1 μM     | Chen et al. (2015a)        |
| Botryorhodine C| Talaromyces stipitatus | IC₅₀: 10.3 μM      | Zhang et al. (2017)        |
| Compound 65  | Talaromyces anestolkiae | IC₅₀: 14.0 μM     | Chen et al. (2016)         |
| Compound 66  | Talaromyces anestolkiae | IC₅₀: 89.4 μM      | Chen et al. (2016)         |
| Compound 67  | Talaromyces anestolkiae | IC₅₀: 585.7 μM     | Chen et al. (2016)         |
| Compound 68  | Talaromyces anestolkiae | IC₅₀: 573.3 μM     | Chen et al. (2016)         |
with IC$_{50}$ values ranging from 48.4 to 99.8 µM (Cai et al. 2017).

Six further depsidones viz., botryorhodines E–G (57–59), botryorhodine A (60), B (61), D (62) were reported from the fungus *Meyerozyma guilliermondii* and all illustrated significant α-glucosidase potentials with IC$_{50}$: ranging from 2.1 to 15.4 µM (Table 2). Compound 62 was the most active with an IC$_{50}$ value of 2.1 µM followed by compounds 58, 61 and 59, which is significantly lower than that of acarbose (IC$_{50}$ = 553.7 µM). An SAR analysis suggests that the hydroxymethyl group at C-3 increases the α-glucosidase effects, whereas, the presence of a methyl group at C-3’ exerts no additional effect on the α-glucosidase inhibitory power of compounds 57–62 (Chen et al. 2015a).

**Table 2 continued**

| Compd. | Source | A-Glucosidase activity | References |
|--------|--------|------------------------|------------|
| S-(-)-5,6,8-trihydroxy-4-(1’-hydroxyethyl)isocoumarin (69) | *Talaromyces amestolkiae* | IC$_{50}$: 315.3 µM | Chen et al. (2016) |
| Sescandelin B (70) | *Talaromyces amestolkiae* | IC$_{50}$: 17.2 µM | Chen et al. (2016) |
| 6-Hydroxy-4-hydroxymethyl-8-methoxy-3-methyl-isocoumarin (71) | *Talaromyces amestolkiae* | IC$_{50}$: 302.6 µM | Chen et al. (2016) |
| 3,4-Dimethyl-6,8-dihydroxyisocoumarin (72) | *Talaromyces amestolkiae* | IC$_{50}$: 36.4 µM | Chen et al. (2016) |
| 28 sescandelin (73) | *Talaromyces amestolkiae* | IC$_{50}$: 417.8 µM | Chen et al. (2016) |

**Fig. 7** Structures of depsidones 54–62

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Another fungus *Trichoderma* sp. produces botryorhodines G (59) and H (63) (Fig. 8) and compound 59 posses moderate α-glucosidase effects with an IC₅₀: 54.1 μM. On the other hand, compound 63 illustrated potent α-glucosidase effects with IC₅₀: 8.1 μM and its activity was higher than the standard acarbose IC₅₀: 703.8 μM (Zhang et al. 2017). Moreover botryorhodines C (64) and D (62) possess significant α-glucosidase effects with IC₅₀: 11.2 and 10.3 μM (Zhang et al. 2017) respectively and these metabolites were reported from the fungi *Trichoderma* sp. (Zhang et al. 2017) and *Botryosphaeria rhodina* (Abdou et al. 2010). All these compounds illustrated α-glucosidase activity with IC₅₀ values ranging from 8.1 to 54.1 μM (Table 2). Compared to the reference drug acarbose (IC₅₀ = 703.8 μM), it can be concluded that compounds 62–64 are potent anti-diabetic depsidones. An SAR study showed that C-3 groups could affect α-glucosidase effects (compound 63 vs. 62 vs. 59) while on the other hand the C-3' methyl group exerts no effect on the activity (compound 64 vs. 62) (Zhang et al. 2017).

### Isocoumarins

Isocoumarins are a class of secondary metabolites bearing a lactone core and these compounds feature a wide range of chemical diversity with a most diverse range of biological effects. Notably, some isocoumarins have been entered into clinical trials for cancer and other diseases (Hampl et al. 2011; Yin et al. 2001; Salloum et al. 2000; Pochet et al. 2004). The fungus *Talaromyces amestolkiae* produced the library of isocoumarins (65–79) (Fig. 9) which were evaluated for their α-glucosidase inhibition. Isocoumarins 66, 70, 72 and 74 illustrated the most encouraging effects among all the tested compounds with IC₅₀ values ranging from 17.2 to 89.4 μM (Table 2). Furthermore metabolites 65, 75, 78 and 79 are interestingly, five-
fold more potent (IC\textsubscript{50} range: 140.8 to 193.1 \textmu M) than acarbose (IC\textsubscript{50}: 958.3 \textmu M) (Chen et al. 2016). Since metabolites 69, 71, 73, 76, and 77 illustrated moderate inhibition with IC\textsubscript{50} ranging from 266.3 to 431.4 \textmu M, respectively, it may be concluded that the 4-CH(OH)CH\textsubscript{3} moiety in metabolites 68, 69 and 73 decreases the activity level when compared with the activities with metabolites 70 and 71 bearing a 4-hydroxymethyl group. The compounds comprising an alkyl chain with the carbonyl group (as in compound 74) appear to possess higher activity in competition with compounds 75–79 which only have an hydroxyl moiety at the corresponding position (Chen et al. 2016).

The fungus Aspergillus sp. produces a range of furo[3,2-h]isocoumarin derivatives viz., asperisocoumarins A (80: IC\textsubscript{50}: 87.8 \textmu M), E (81: IC\textsubscript{50}: 52.3 \textmu M), and F (82: IC\textsubscript{50}: 95.6 \textmu M) and all displayed moderated \textalpha-glucosidase effects (Table 3) (Xiao et al. 2016). Furo[3,2-h]isocoumarins are uncommon and few members of this group have been reported in literature (Saeed 2016; Baba et al. 1991). Asperisocoumarin E (81) featured an isopentenyl group having two adjacent carboxyl moieties and asperisocoumarin F (82) represents an isocoumarin dimer via an ether linkage (Xiao et al. 2016). Furthermore, the same fungus Aspergillus sp. produced other isocoumarin analogues viz., asperisocoumarins C (83), E (84), F (85), G (86), I (87), J (89) (Fig. 10) along with compound 88 and their structures were all established via extensive NMR spectroscopic techniques. It was found that metabolites 83, 86, 87, and 89 illustrated significant \textalpha-glucosidase activities with IC\textsubscript{50} ranging from 38.1 to 78.1 \textmu M. Since metabolites 84 and 85 displayed only moderate inhibition (Table 3), it may be concluded that either an epoxide and/or an hydroxyl group at C-10/C-11 could enhance the \textalpha-glucosidase effects (Cai et al. 2018).

The isocoumarin 12-epicitreoisocoumarinol (90) is produced by the fungus Nectria sp., and illustrated \textalpha-glucosidase potential with IC\textsubscript{50}: 343.7 \textmu M (Cui et al. 2016). On the other hand citreoisocoumarinol (91) and citreoisocoumarin (92) (Fig. 11) were produced by the fungi Nectria sp. (Cui et al. 2016), Fusarium sp. (Ola et al. 2013) and Penicillium sp. (Lai et al. 1991) and display activity towards \textalpha-glucosidase with IC\textsubscript{50}: 392.5 and 538.7 \textmu M (Table 3) respectively (Cui et al. 2016). Notably, compounds 90–92 were more potent than acarbose (IC\textsubscript{50} = 815.3 \textmu M) (Cui et al. 2016). The fungus, Aspergillus sp. produced 6-O-demethylmonocerin (93: IC\textsubscript{50}: 0.027 mM), (+)-monocerin (94: IC\textsubscript{50}: 1.65 mM), fusarentin 6-methyl ether (95: IC\textsubscript{50}: 1.19 mM) and 6,7-O-dimethyl-4R-hydroxy-10-epifusarentin (96; IC\textsubscript{50}: 1.74 mM) and all were shown to possess \textalpha-glucosidase effects (Table 3). Among these metabolites, compound 93 displayed 35 times more potent inhibitory effects than acarbose (IC\textsubscript{50} = 0.95 mM) (Kong et al. 2015).

### \textbeta-Resorcylic acid derivatives

\textbeta-Resorcylic acid analogs have been reported from a number of natural sources and these compounds were reported to display a diverse range of biological activities viz., antimicrobial (Yang et al. 2006), antimalarial (Xu et al. 2010), cytotoxic (Buayairaksa et al. 2011) and kinases and ATPases inhibitions (Shen et al. 2015). In this regard, the fungus Lasiodiplodia sp. produced \textbeta-resorcylic acid analogs 97–99 (Fig. 12) and their structures were established by 1D, 2D NMR, and X-ray crystallography in addition to the Mosher protocol (Chen et al. 2015b). All the compounds were evaluated for their \textalpha-glucosidase effects and illustrated inhibition with IC\textsubscript{50} values ranging from 15.2 to 24.6 \textmu M (Table 3) and interestingly, their activities were better than the standard acarbose (IC\textsubscript{50} = 368 \textmu M) (Chen et al. 2015b). Moreover compound 100, which was reported from the fungus Lasiodiplodia sp. (Chen et al. 2015b) and the yeast Saccharomyces cerevisiae (Xu et al. 2014), proved to be a most potent \textalpha-glucosidase inhibitor with an IC\textsubscript{50}: 10.1 \textmu M (Chen et al. 2015b).

Compound 101, initially reported as a plant metabolite viz., from Euphorbia splendens (Lee et al. 1982) and later from the fungus Lasiodiplodia sp. (Chen et al. 2015b), illustrated \textalpha-glucosidase effects with IC\textsubscript{50}: 32.5 \textmu M (Chen et al. 2015b). Compound 102 was obtained from the fungus Lasiodiplodia sp. (Chen et al. 2015b; Aldridge et al. 1971), and compound 103 from the fungi Lasiodiplodia sp. (Chen et al. 2015b) as well as ZZF36 (Yang et al. 2006). Both compounds inhibited \textalpha-glucosidase activity with IC\textsubscript{50}: 13.6 and 35.9 \textmu M respectively (Chen et al. 2015b). SAR studies for compounds 97–103 demonstrated that the C-3 hydroxyl moiety in these compounds enhances the inhibitory effects (compound 99 vs. 100 and compound 101 vs. 102).
| Compd. | Source | A-Glucosidase activity | References |
|--------|--------|------------------------|------------|
| 21,22 aspergillmarin A (74) | *Talaromyces amestolkiae* | IC_{50}: 38.1 μM | Chen et al. (2016) |
| 24 aspergillmarin B (75) | *Talaromyces amestolkiae* | IC_{50}: 193.1 μM | Chen et al. (2016) |
| 24 penicimarin C (76) | *Talaromyces amestolkiae* | IC_{50}: 266.3 μM | Chen et al. (2016) |
| 26 and penicimarin B (77) | *Talaromyces amestolkiae* | IC_{50}: 431.4 μM | Chen et al. (2016) |
| Compound 78 | *Talaromyces amestolkiae* | IC_{50}: 162.5 μM | Chen et al. (2016) |
| Compound 79 | *Talaromyces amestolkiae* | IC_{50}: 142.1 μM | Chen et al. (2016) |
| Asperisocoumarin A (80) | *Aspergillus* sp. | IC_{50}: 87.8 μM | Xiao et al. (2016) |
| Asperisocoumarin E (81) | *Aspergillus* sp. | IC_{50}: 52.3 μM | Xiao et al. (2016) |
| Asperisocoumarin F (82) | *Aspergillus* sp. | IC_{50}: 95.6 μM | Xiao et al. (2016) |
| Asperisocoumarin C (83) | *Aspergillus* sp. | IC_{50}: 38.1 μM | Cai et al. (2018) |
| Asperisocoumarin E (84) | *Aspergillus* sp. | IC_{50}: 158.4 μM | Cai et al. (2018) |
| Asperisocoumarin F (85) | *Aspergillus* sp. | IC_{50}: 110.3 μM | Cai et al. (2018) |
| Asperisocoumarin G (86) | *Aspergillus* sp. | IC_{50}: 40.5 μM | Cai et al. (2018) |
| Asperisocoumarin I (87) | *Aspergillus* sp. | IC_{50}: 78.1 μM | Cai et al. (2018) |
| 3-[(R)-3,3-dichloro-2-hydroxypropyl]-8-hydroxy-6-methoxy-1H-isochromen-1-one (88) | *Aspergillus* sp. | IC_{50}: 102.4 μM | Cai et al. (2018) |
| Asperisocoumarin J (89) | *Aspergillus* sp. | IC_{50}: 45.1 μM | Cai et al. (2018) |
| 12-Epicitreoisocoumarinol (90) | *Nectria* sp. | IC_{50}: 343.7 μM | Cai et al. (2016) |
| Citreoisocoumarinol (91) | *Nectria* sp. | IC_{50}: 392.5 μM | Cai et al. (2016) |
| Citreoisocoumarin (92) | *Nectria* sp. | IC_{50}: 538.7 μM | Cui et al. (2016) |
| 6-O-demethylmonocerin (93) | *Aspergillus* sp. | IC_{50}: 0.027 mM | Kong et al. (2015) |
| (+)-monocerin (94) | *Aspergillus* sp. | IC_{50}: 1.65 mM | Kong et al. (2015) |
| fusarentin 6-methyl ether (95) | *Aspergillus* sp. | IC_{50}: 1.19 mM | Kong et al. (2015) |
| 6,7-O-dimethyl-4R-hydroxy-10-epifusarentin (96) | *Aspergillus* sp. | IC_{50}: 1.74 mM | Kong et al. (2015) |
| (R)-ethyl 3,5-dihydroxy-7-(8-hydroxyynonyl) benzoate (97) | *Lasiodiplodia* sp. | IC_{50}: 22.3 μM | Chen et al. (2015b) |
Furthermore, when comparing the activity of compound 97 and 102, it may be assumed that the aliphatic macrocyclic acid system is also necessary for the activity (Chen et al. 2015b). Another 12-membered ring system comprising a β-resorcylic acid analog, lasiodiplactone A (104), reported from the fungus Lasiodiplodia theobromae comprises an interesting and unique 12/6/6/5 tetracyclic system. Compound 104 inhibited α-glucosidase with an IC₅₀ of 36.7 µM which is better than the clinical acarbose (IC₅₀ = 367 µM) (Chen et al. 2017).

### Benzofurans

The fungus Eurotium rubrum SH-823, produced the benzofuran analogs eurothiocin A (105; IC₅₀ = 17.1 µM) and B (106; IC₅₀ = 42.6 µM) (Fig. 13), which inhibited the α-glucosidase activity as illustrated in Table 4. It is worth mentioning that both compounds exhibited considerably lower IC₅₀ values compared to the standard drug acarbose (IC₅₀ = 376.7 µM), which makes them interesting candidates for further studies (Liu et al. 2014a). In addition, epicoccolide B (107) was produce by the fungi Aspergillus flavipes (Wang et al. 2016) and Epicoccum sp. (Talontsi et al. 2013) and this compound inhibited α-glucosidase with an IC₅₀ of 33 µM (Wang et al. 2016).

### Table 3 continued

| Compd. | Source | A-Glucosidase activity | References |
|--------|--------|------------------------|------------|
| (R,E)-ethyl 2,4-dihydroxy-6-(8-hydroxynon-1-en-1-yl) benzoate (98) | Lasiodiplodia sp. | IC₅₀: 24.6 µM | Chen et al. (2015b) |
| 3-Methoxy-lasicicol (99) | Lasiodiplodia sp. | IC₅₀: 15.2 µM | Chen et al. (2015b) |
| Lasicicol (100) | Lasiodiplodia sp. | IC₅₀: 10.1 µM | Chen et al. (2015b) |
| Lasiodiplodin (101) | Lasiodiplodia sp. | IC₅₀: 32.5 µM | Chen et al. (2015b) |
| De-O-methyllasiodiplodin (102) | Lasiodiplodia sp. | IC₅₀: 13.6 µM | Chen et al. (2015b) |
| (E)-9-etheno-lasiodiplodin (103) | Lasiodiplodia sp. | IC₅₀: 35.9 µM | Chen et al. (2015b) |
| Lasiodiplactone A (104) | Lasiodiplodia theobromae | IC₅₀ = 367 µM | Chen et al. (2017) |
| Eurothiocin A (105) | Eurotium rubrum | IC₅₀ = 17.1 µM | Liu et al. (2014a) |
| Eurothiocin B (106) | Eurotium rubrum | IC₅₀ = 42.6 µM | Liu et al. (2014a) |
| Epicoccolide B (107) | Aspergillus flavipes | IC₅₀: 33 µM | Wang et al. (2016) |
| 6-Demethylpenisimplicissin (108) | Penicillium sp. | IC₅₀: 9.5 µM | Liu et al. (2014b) |
| 1′-Ephhydroxydihydrovermistatin (109) | Penicillium sp. | IC₅₀: 8.0 µM | Liu et al. (2014b) |
| Vermistatin (110) | Penicillium sp. | IC₅₀: 29.2 µM | Liu et al. (2014b) |
| Hydroxyvermistatin (111) | Penicillium sp. | IC₅₀: 20.3 µM | Liu et al. (2014b) |
| (+)-Geodin (112) | | IC₅₀ of 0.12 mM | Wang et al. (2018) |
In addition, kinetic studies demonstrated that benzofuran \(107\) acted as a noncompetitive inhibitor with \(K_i\) values of 2.5/7.2 \(\mu M\), and thus have been identified as displaying mixed behavior (Wang et al. 2016).

Benzofuran analogs, 6-demethylpenisimplicissin (108), 1''-epihydroxydihydrovermistatin (109), vermistatin (110) and hydroxyvermistatin (111) (Fig. 14) were obtained from \textit{Penicillium} sp. and tested for their anti-\(\alpha\)-glucosidase effects. The results revealed that metabolites 108 (IC\textsubscript{50}: 9.5 \(\mu M\)) and 109 (IC\textsubscript{50}: 8.0 \(\mu M\)) illustrated significant activity while the \(\alpha\)-
glucosidase inhibition capacity of compounds 110 (IC$_{50}$: 29.2 $\mu$M) and 111 (IC$_{50}$: 20.3 $\mu$M) (Table 4) were lower, but still higher that the reference resveratrol (IC$_{50}$ = 31.2 $\mu$M) (Liu et al. 2014b). (+)-Geodin (112), which is a biosynthetically a polyketide derived compound (Askenazi et al. 2003; Couch and Gaucher 2004; Sutherland, et al. 2001), was reported from the fungus *Penicillium chrysogenum* (Wang et al. 2018) along with the fungus *Aspergillus* sp. (Hargreaves et al. 2002), illustrated excellent $\alpha$-glucosidase effects with an IC$_{50}$ of 0.12 mM (Wang et al. 2018).

**Quinones and xanthones**

Emodin (113) is reported from various plant families (Izhaki 2002) as well as various fungal species viz *Penicillium* sp. (Shibata and Udagawa 1963; Natori et al. 1965; Ghosh et al. 1977), *Aspergillus* sp. Yamazaki et al. 1971; Wells et al. 1975; Anke et al. 1980; Wang et al. 2016), *Cladosporium fulvum* (Agosti et al. 1962), and *Penicilllospora clavariaeformis* (Shibata et al. 1957). Emodin (113) illustrated quite reasonable $\alpha$-glucosidase effects IC$_{50}$: 19 $\mu$M and kinetic studies demonstrated that compound 113 (Fig. 15) was a noncompetitive inhibitor with a $K_i$ value of 0.79 $\mu$M (Wang et al. 2016). On the other hand the fungus *Alternaria* sp. produced the tetracycloanthraquinone analogs, alterporriol S (114), alterporriol T (115) and anthraquinone 116 (Chen et al. 2014). Quinone 115 (IC$_{50}$: 7.2 $\mu$M) illustrated significant $\alpha$-glucosidase effects being higher than the positive control genistein (IC$_{50}$ = 13.6 $\mu$M). In this regard it is interesting to note that metabolites 114 (IC$_{50}$ = 72.0 $\mu$M) and 116 (IC$_{50}$ = 83.5 $\mu$M) displayed weaker activity (Table 4) (Chen et al. 2014).

The xanthone derivatives (+)- and (−)-ascomlactone A (117a and 117b) (Fig. 16) are produced by the fungus *Ascomycota* sp. and their structures were established based on spectroscopic methods. The activity studies revealed that as a racemic mixture, these metabolites inhibited the activity of $\alpha$-glucosidase with an IC$_{50}$ value of 36.1 $\mu$M. On the other hand, and interestingly, the pure enantiomer, (−)-ascomlactone A (117b) illustrated better inhibition with an IC$_{50}$ value of 27.9 $\mu$M, whereas, the enantiomer (+)-ascomlactone A (117a) demonstrated slightly weaker inhibition (IC$_{50}$ = 63.7 $\mu$M). When compared to the activity of acarbose (IC$_{50}$ = 477.0 $\mu$M), both pure enantiomers as well as the racemate is more potent (Liu et al. 2017). Chrysoxanthone (118) was obtained from the fungus *Penicillium chrysogenum* and illustrated $\alpha$-glucosidase effects with an IC$_{50}$ of 0.04 mM (Wang et al. 2018).
Tetralone and chromone derivatives

The fungus *Daldinia eschscholtzii* produced a small library of tetralones viz., daldiniones B–D (119–121) and tetralones 122–124 (Fig. 17) and their structures were established by NMR, GIAO based NMR and ECD spectroscopic methods. All these compounds illustrated α-glucosidase effects with IC50 values ranging from 21 to 155 μM (Table 5). Among these compounds, metabolite 124 was the most active (IC50: 21 μM) followed by compounds 121 (IC50: 35 μM) and 119 (IC50: 38 μM) (Liao et al. 2019). Moreover, *Daldinia eschscholtzii* also produced the chromone analogs, 125–128, which were also tested for their α-glucosidase effects. All these compounds inhibited α-glucosidase with IC50 ranging from 13 to 100 μM (Table 5). Notably, chromone analogs 125 (IC50: 13 μM) and 128 (IC50: 15 μM) proved to be the most active metabolites among the tested chromones (Liao et al. 2019).

### Table 4 Fungal metabolites 113–128 as α-glucosidase inhibitors

| Compd. | Source | A-Glucosidase activity (IC50 or K_i) | References |
|--------|--------|------------------------------------|------------|
| Emodin (113) | *Aspergillus flavipes* | IC50: 19 μM; K_i: 0.79 μM | Wang et al. (2016) |
| Alterporriol S (114) | *Alternaria* sp. | IC50 = 72.0 μM | Chen et al. (2014) |
| Alterporriol T (115) | *Alternaria* sp. | IC50: 7.2 μM | Chen et al. (2014) |
| Macrosporin (116) | *Alternaria* sp. | IC50 = 83.5 μM | Chen et al. (2014) |
| (+)-Ascomlactone A (117a) | *Ascomycota* sp. | IC50 = 63.7 μM | Liu et al. (2017) |
| (−)-Ascomlactone A (117b) | *Ascomycota* sp. | IC50 = 27.9 μM | Liu et al. (2017) |
| Chrysoxanthone (118) | *Penicillium chrysogenum* | IC50 = 0.04 mM | Wang et al. (2018) |
| Daldinione B (119) | *Daldinia eschscholtzii* | IC50 = 38 μM | Liao et al. (2019) |
| Daldinione C (120) | *Daldinia eschscholtzii* | IC50 = 155 μM | Liao et al. (2019) |
| Daldinione D (121) | *Daldinia eschscholtzii* | IC50 = 35 μM | Liao et al. (2019) |
| 4R-(O)-Methylsclerone (122) | *Daldinia eschscholtzii* | IC50 = 90 μM | Liao et al. (2019) |
| Isosclerone (123) | *Daldinia eschscholtzii* | IC50 = 70 μM | Liao et al. (2019) |
| (−)-cis-(3R*,4S*)-3,4,8-trihydroxy-6,7-dimethyl-3,4-dihyronaphthalen-1(2H)-one (124) | *Daldinia eschscholtzii* | IC50 = 21 μM | Liao et al. (2019) |
| 7-Hydroxy-5-methoxy-2,3-dimethylchromone (125) | *Daldinia eschscholtzii* | IC50 = 13 μM | Liao et al. (2019) |
| 5-Methoxy-2-propylchromone (126) | *Daldinia eschscholtzii* | IC50 = 84 μM | Liao et al. (2019) |
| 7-Ethyl-8-hydroxy-6-methoxy-2,3-dimethylchromone (127) | *Daldinia eschscholtzii* | IC50 = 100 μM | Liao et al. (2019) |
| 2,3-Dihydro-5-methoxy-2-methylchromen-4-one (128) | *Daldinia eschscholtzii* | IC50 = 15 μM | Liao et al. (2019) |
The fungus *Aspergillus terreus* produces (*±*)-asptteretals D (129) and E (130), flavipesolides B (131) and C (132), butyrolactones I (133) and II (134), butanolide 135 and aspermolide A (136) (Fig. 18). All these metabolites illustrated α-glucosidase inhibition with IC$_{50}$ values ranging from 7.6 to 85.1 μM (Table 5). Moreover, compound 132 proved to be the most potent since it displayed the lowest IC$_{50}$ value of 7.63 μM. Both enantiomerically pure isomers of compound 129 also exerted significant inhibition of the enzyme with IC$_{50}$ values of 8.65 μM ([(+)-129] and 9.98 μM ([−]-129] (Sun et al. 2018a). It has been reported that ([+]- and ([−]-129 are methanolysis artifacts of asptteretal E (Capon 2020; Sun et al. 2018b).

The fungus *A. terreus* furthermore produced (*±*)-asptteretones A-D (137a/b–140a/b) (Fig. 19), and
the racemate, asperteretone E (141) and all these metabolites demonstrated α-glucosidase inhibition with IC_{50} values ranging from 15.7 to 53.1 μM (Table 6). Butanolide 140a (IC_{50}: 15.7 μM) was the most active while 138a (IC_{50}: 17.3 μM), 138b (IC_{50}: 19.2 μM) and 140b (IC_{50}: 18.9 μM) also displayed comparable inhibitory potential. Although the other compounds showed moderate activity, their inhibition values were higher than the reference drug acarbose (IC_{50} = 154.7 μM) (Liu et al. 2018a). Notably, it was postulated that all enantiomers illustrated would most likely demonstrate similar α-glucosidase effects, suggesting that chirality may play a negligible role on their potential activities.
### Table 5  Fungal metabolites 129–152 as α-glucosidase inhibitors

| Compd. | Source | A-Glucosidase activity | References |
|--------|--------|------------------------|------------|
| (-)-Asperteretal D (129) | *Aspergillus terreus* | IC$_{50}$ = 9.9 µM | Sun et al. (2018a) |
| (+)-Asperteretal D (129) | *Aspergillus terreus* | IC$_{50}$ = 8.6 µM | Sun et al. (2018a) |
| Asperteretal E (130) | *Aspergillus terreus* | IC$_{50}$ = 13.3 µM | Sun et al. (2018a) |
| Flavipesolide B (131) | *Aspergillus terreus* | IC$_{50}$ = 10.3 µM | Sun et al. (2018a) |
| Flavipesolide C (132) | *Aspergillus terreus* | IC$_{50}$ = 7.63 µM | Sun et al. (2018a) |
| Butyrolactone I (133) | *Aspergillus terreus* | IC$_{50}$ = 14.1 µM | Sun et al. (2018a) |
| Butyrolactone II (134) | *Aspergillus terreus* | IC$_{50}$ = 85.3 µM | Sun et al. (2018a) |
| 5-[(3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-yl)-methyl]-3-hydroxy-4-(4-hydroxyphenyl)-2(5H)-furanone (135) | *Aspergillus terreus* | IC$_{50}$ = 11.6 µM | Sun et al. (2018a) |
| Aspernolide A (136) | *Aspergillus terreus* | IC$_{50}$ = 47.3 µM | Sun et al. (2018a) |
| (-)-Asperteretones A (137a) | *Aspergillus terreus* | IC$_{50}$ = 45.4 µM | Liu et al. (2018a) |
| (+)-Asperteretones A (137b) | *Aspergillus terreus* | IC$_{50}$ = 53.1 µM | Liu et al. (2018a) |
| (-)-Asperteretones B (138a) | *Aspergillus terreus* | IC$_{50}$ = 17.3 µM | Liu et al. (2018a) |
| (+)-Asperteretones B (138b) | *Aspergillus terreus* | IC$_{50}$ = 19.2 µM | Liu et al. (2018a) |
| (-)-Asperteretones C (139a) | *Aspergillus terreus* | IC$_{50}$ = 52.2 µM | Liu et al. (2018a) |
| (+)-Asperteretones C (139b) | *Aspergillus terreus* | IC$_{50}$ = 49.8 µM | Liu et al. (2018a) |
| (-)-Asperteretones C (140a) | *Aspergillus terreus* | IC$_{50}$ = 15.7 µM | Liu et al. (2018a) |
| (+)-Asperteretones C (140b) | *Aspergillus terreus* | IC$_{50}$ = 18.9 µM | Liu et al. (2018a) |
| Asperteretone E (141) | *Aspergillus terreus* | IC$_{50}$ = 48.9 µM | Liu et al. (2018a) |
| (R,E)-3-(2,2-Dimethylchroman-6-yl)-4-hydroxy-5-((2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-5-yl)methylene) furan-2(5H)-one (142) | *Aspergillus terreus* | IC$_{50}$ = 24.8 µM | Sun et al. (2018b) |
| Rubrolide S (143) | *Aspergillus terreus* | IC$_{50}$ = 1.2 µM; K$_i$: 1.42 µM | Sun et al. (2018b) |
| Avipesolide A (144); | *Aspergillus flavipes* | IC$_{50}$: 44 µM; K$_i$: 2.4 µM | Wang et al. (2016) |
| Avipesolide B (145); | *Aspergillus flavipes* | IC$_{50}$: 57 µM; K$_i$: 3.4 µM | Wang et al. (2016) |
| Avipesolide C (146); | *Aspergillus flavipes* | IC$_{50}$: 95 µM; K$_i$: 9.2 µM | Wang et al. (2016) |
| 5-[(3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-yl)methyl]-3-hydroxy-4-(4-hydroxyphenyl)-2(5H)furanone (147) | *Aspergillus flavipes* | IC$_{50}$: 34 µM; K$_i$: 0.43 µM | Wang et al. (2016) |
Further butenolides, compound 142 and rubrolide S (143) (Fig. 20) were obtained from the fungus A. terreus and demonstrated α-glucosidase effects with IC\textsubscript{50} values of 24.8 and 1.2 \textmu M, respectively. Additional enzyme kinetic studies were performed with compound 143, which revealed that it is an anticompetitive inhibitor with a \( K_i \) value of 1.42 \textmu M (Sun et al. 2018b). Another fungus varietal of Aspergillus sp., viz., Aspergillus flavipes produced antidiabetic avipesolides A–C (144–146) and butanolide 147 and these compounds inhibit α-glucosidase with IC\textsubscript{50} values ranging from 34 to 95 \textmu M (Table 6).

Appropriate enzyme kinetic studies have also been carried out which revealed that compound 147 (\( K_i \): 0.43 \textmu M) is a noncompetitive inhibitor while compounds 144–146 were demonstrated to be more competitive (\( K_i \): 2.5, 3.4, and 9.2 \textmu M respectively) (Wang et al. 2016).

Pulvinones have been reported from various fungi and illustrated interesting biological effects (Bernier et al. 2007; Xu et al. 2013). Pulvinones viz., pulvinone P (148: IC\textsubscript{50}: 0.079 mM) and Q (149: IC\textsubscript{50}: 0.022 mM) were reported from A. flavipes and illustrated significant α-glucosidase inhibition (Zhang et al. 2016a). Pulvinone P (148) and Q (149) were also obtained from the fungus A. terreus and demonstrated α-glucosidase effects with IC\textsubscript{50} values of 24.8 and 1.2 \textmu M, respectively. Additional enzyme kinetic studies were performed with compound 143, which revealed that it is an anticompetitive inhibitor with a \( K_i \) value of 1.42 \textmu M (Sun et al. 2018b). Another fungus varietal of Aspergillus sp., viz., Aspergillus flavipes produced antidiabetic avipesolides A–C (144–146) and butanolide 147 and these compounds inhibit α-glucosidase with IC\textsubscript{50} values ranging from 34 to 95 \textmu M (Table 6).
et al. 2016a). Methybutyrolactone III (150: IC₅₀ = 0.016 mM) and flavipesin B (151: IC₅₀ = 0.385 mM) (Fig. 21) were obtained from A. flavipes and all were shown to possess significant α-glucosidase inhibition (Table 6) when compared to the standard drug acarbose (IC₅₀ = 0.685 mM) (Zhang et al. 2016a). A butenolide analog, versicolactone G (152) was obtained from the fungus Aspergillus terreus and showed inhibitory potential towards α-glucosidase (IC₅₀ = 104.8 µM) and under the same conditions this compound was more potent than the standard acarbose (IC₅₀ = 154.7 µM) (Liu et al. 2018b).

Diphenyl ether and benzophenone derivatives

Neogedodin hydrate (153) (Zhang et al. 2016a; Jongrungrungruangchok et al. 2013) and methyl dichloroasterrate (154) (Liu et al. 2015b; Zhang et al. 2016a) were produced by various Aspergillus sp. and illustrated α-glucosidase effects with IC₅₀: 1.47 mM and 1.45 mM respectively (Zhang et al. 2016a). 2,4-Dichloroasterric acid (155) along with benzophenones 3-de-O-methylsulochrin (156) and compound 157 (Fig. 22) were also produced by Aspergillus sp. (Zhang et al. 2016a). All these compounds possess good α-glucosidase inhibition with IC₅₀ values.
Table 6 Fungal metabolites 153–189 as α-glucosidase inhibitors

| Compd.                                                                 | Source                  | α-Glucosidase activity | References            |
|------------------------------------------------------------------------|-------------------------|------------------------|-----------------------|
| Neogeodin hydrate (153),                                               | *Aspergillus flavipes*  | IC_{50}: 1.47 mM       | Zhang et al. (2016a)  |
|                                                                        |                         |                        |                       |
| Methyl dichloroasterrate (154),                                        | *Aspergillus flavipes*  | IC_{50}: 1.45 mM       | Zhang et al. (2016a)  |
|                                                                        |                         | IC_{50}: 90 µM; K_{i}: | Wang et al. (2016)    |
|                                                                        |                         | 2.8 µM                 |                       |
| 2,4-Dichloroasterric acid (155)                                        | *Aspergillus flavipes*  | IC_{50}: 0.091 mM      |                       |
| 3-de-O-methylsulochrin (156)                                           | *Aspergillus flavipes*  | IC_{50}: 0.19 mM       |                       |
| 2-(3,5-Dichloro-2,6-dihydroxy-4-methylbenzoyl)-5-hydroxy-3-methoxybenzoic acid (157) | *Aspergillus flavipes*  | IC_{50}: 0.042 mM      |                       |
| Monomethylsulochrin (158)                                              | *Aspergillus flavipes*  | IC_{50}: 9.9 µM        |                       |
| Chrysines B (159)                                                     | *Penicillium chrysogenum* | IC_{50}: 0.35 mM     | Wang et al. (2018)    |
| Chrysines C (160)                                                     | *Penicillium chrysogenum* | IC_{50}: 0.20 mM     | Wang et al. (2018)    |
| Methyl-3′-methoxy-3,5-dichloroasterric acid (161)                      | *Penicillium chrysogenum* | IC_{50}: 0.15 mM     | Wang et al. (2018)    |
| Methyl chloroasterrate (162)                                           | *Penicillium chrysogenum* | IC_{50}: 0.14 mM     | Wang et al. (2018)    |
| Mono-chlorosulochrin (163)                                             | *Penicillium chrysogenum* | IC_{50}: 0.14 mM     | Wang et al. (2018)    |
| Compound 164                                                          | *Aspergillus flavus*    | IC_{50}: 165.2 µM      | Wu et al. (2018)      |
| Compound 165                                                          | *Aspergillus flavus*    | IC_{50}: 129.9 µM      | Wu et al. (2018)      |
| Peniciaculin A (166)                                                  | *Aspergillus flavus*    | IC_{50}: 1.5 µM        | Wu et al. (2018)      |
| Expansol D (167)                                                      | *Aspergillus flavus*    | IC_{50}: 2.3 µM        | Wu et al. (2018)      |
| Dichloroorcinol (168)                                                 | *Penicillium chrysogenum* | IC_{50}: 0.16 mM     | Wang et al. (2018)    |
| Daldinione E (169)                                                    | *Daldinia eschscholtzii* | IC_{50}: 54 µM        | Liao et al. (2019)    |
| Bacillisorpin A (170)                                                 | *Penicillium aculeatum* | IC_{50}: 95.8 µM      | Huang et al. (2017)   |
| Bacillisorpin B (171)                                                 | *Penicillium aculeatum* | IC_{50}: 33.5 µM      | Huang et al. (2017)   |
| 6′-Methyl-[1,1’-biphenyl]-3,3′,4′,5-tetraol (172)                     | *Penicillium sp.*       | IC_{50}: 2.2 µM        | Liu et al. (2015)     |
| (±)-Penifupyrone (173)                                                | *Penicillium sp.*       | IC_{50} = 14.4 µM      | Liu et al. (2015)     |
| Flaviphenalenone B (174)                                              | *Aspergillus flavipes*  | IC_{50}: 94.9 µM       | Zhang et al. (2016b)  |
ranging from 0.042 to 1.47 mM (Table 6). Among these tested metabolites, compounds 157 (IC$_{50}$: 0.042 mM) was the most active followed by 155 (IC$_{50}$: 0.091 mM) and their effects were higher than acarbose (IC$_{50}$: 0.685 mM) (Zhang et al. 2016a). In another investigation of the fungus A. flavipes, compounds 153 and 154 along with monomethylosoic acid (158) were also isolated (Wang et al. 2016). Compounds 153 (IC$_{50}$: 55 μM) and 154 (IC$_{50}$: 90 μM) along with monomethylosoic acid (158; IC$_{50}$: 9.9 μM) inhibited α-glucosidase while a corresponding kinetic study revealed that compound 154 is a noncompetitive inhibitor with $K_i$: 2.8 μM (Wang et al. 2016).

The fungus Penicillium chrysogenum produced diphen ethers, chrysines B (159), C (160), compound 161, and methyl chloroasterrate (162), together with benzophenone, mono-chlorosulochrin (163) (Fig. 23). The group demonstrated that all these compounds illustrated α-glucosidase effects with IC$_{50}$ ranging from 0.15 mM to 0.35 mM (Table 6). Most of the compounds were more potent than the standard acarbose with an IC$_{50}$ of 0.28 mM (Wang et al. 2018). The fungus Aspergillus flavus produced compounds 164–167 whose structures were established via spectroscopic techniques. Compounds 166 and 167 exhibited significant inhibition potential with IC$_{50}$ values of 1.5, and 2.3 μM, respectively. Furthermore,

### Table 6 continued

| Compd. | Source | α-Glucosidase activity | References |
|--------|--------|------------------------|------------|
| Flaviphenalenone C (175) | Aspergillus flavipes | IC$_{50}$: 78.9 μM | Zhang et al. (2016b) |
| Cryptosporioptide (176) | Cryptosporiopsis sp. | IC$_{50}$: 50.5 μM | Tousif et al. (2014) |
| Cryptosporioptide A (177) | Cryptosporiopsis sp. | IC$_{50}$: 44.9 μM | Tousif et al. (2014) |
| Cryptosporioptide B (178) | Cryptosporiopsis sp. | IC$_{50}$: 41.2 μM | Tousif et al. (2014) |
| Compound 179 | Aspergillus flavus | IC$_{50}$: 4.5 μM | Wu et al. (2018) |
| Compound 180 | Aspergillus flavus | IC$_{50}$: 3.1 μM | Wu et al. (2018) |
| Aeclodepsipeptide A (181) | Paecilomyces formosus | IC$_{50}$: 74.2 μg/mL | Bilal et al. (2018) |
| YW3548 (182) | Paecilomyces formosus | IC$_{50}$: 61.8 μg/mL | Bilal et al. (2018) |
| Nectriacid A (183) | Nectria sp. | IC$_{50}$ = 121.8 μM | Cui et al. (2016) |
| Nectriacid B (184) | Nectria sp. | IC$_{50}$ = 23.5 μM | Cui et al. (2016) |
| Nectriacid C (185) | Nectria sp. | IC$_{50}$ = 42.3 μM | Cui et al. (2016) |
| Helicascolide A (186) | Daldinia eschscholtzii | IC$_{50}$: 16 μM), | Liao et al. (2019) |
| Helicascolide B (187) | Daldinia eschscholtzii | IC$_{50}$: 31 μM | Liao et al. (2019) |
| Helicascolide D (188) | Daldinia eschscholtzii | IC$_{50}$: 20 μM | Liao et al. (2019) |
| Helicascolide E (189) | Daldinia eschscholtzii | IC$_{50}$: 240 μM | Liao et al. (2019) |
metabolites 164 and 165 were only moderately active with IC\textsubscript{50} values of 165 and 129 \mu M, respectively. However, their effects were higher than acarbose which had an IC\textsubscript{50}: 840.2 \mu M (Wu et al. 2018).

**Miscellaneous**

The fungus *Penicillium chrysogenum* produces dichloroorcinol (168) (Fig. 24) which demonstrated good \(\alpha\)-glucosidase effects with an IC\textsubscript{50}: 0.16 mM (Wang et al. 2018). Daldinione E (169: IC\textsubscript{50}: 54 \mu M) was obtained from the fungus *Daldinia eschscholtzii* and illustrated \(\alpha\)-glucosidase effects (Liao et al. 2019). In another investigation, bacillisporin A (170: IC\textsubscript{50}: 95.8 \mu M) and bacillisporin B (171: IC\textsubscript{50}: 33.5 \mu M) were isolated from the fungus *Penicillium aculeatum* and both substances inhibited \(\alpha\)-glucosidase activity (Huang et al. 2017; Lin et al. 2008). The fungus *Penicillium* sp. produced compound 172 (IC\textsubscript{50}: 2.2 \mu M) and (±)-penifupyrone (173: IC\textsubscript{50} = 14.4 \mu M) and both compounds inhibited \(\alpha\)-glucosidase (Liu et al. 2015a). Flaviphenalenones B (174: IC\textsubscript{50}: 94.9 \mu M) and C (175: IC\textsubscript{50}: 78.9 \mu M) were isolated from the fungus *Aspergillus flavipes* and illustrated anti-\(\alpha\)-glucosidase effects (Table 6). Moreover, these compounds demonstrated a greater potency than that of the acarbose (IC\textsubscript{50}: 685 \mu M) but were less effective than quercetin (IC\textsubscript{50}: 14.5 \mu M) (Zhang et al. 2016b).

Cryptosporioptide (176: IC\textsubscript{50}: 50.5 \mu M) along with cryptosporioptide A (177: IC\textsubscript{50}: 44.9 \mu M) and B (178: IC\textsubscript{50}: 41.2.5 \mu M) (Fig. 25) were obtained from the fungus *Cryptosporiopsis* sp. and all three compounds inhibited \(\alpha\)-glucosidase with comparable activity to the standard acarbose with an IC\textsubscript{50} value of 38.2 \mu M (Tousif et al. 2014). The fungus *Aspergillus flavus* furthermore produced compounds 179 and 180 which exhibited significant potential with IC\textsubscript{50} values of 4.5 and 3.1 \mu M, respectively. Interestingly the effects of...
these compounds were higher than the reference compound acarbose IC$_{50}$: 840.2 µM) (Wu et al. 2018). Aecilodepsipeptide A (181: IC$_{50}$: 74.2 µg/mL) and YW3548 (182: IC$_{50}$: 61.8 µg/mL) were obtained from the fungus Paecilomyces formosus and illustrated good anti-α-glucosidase effects (Bilal et al. 2018). The polyketides, nectriacids A-C (183–185) were isolated from the fungus Nectria sp. In this regard polyketides 184 (IC$_{50}$ = 23.5 µM) and 185 (IC$_{50}$ = 42.3 µM) illustrated rather good α-glucosidase
effects which were higher than acarbose ($IC_{50} = 815.3 \mu M$). On the other hand nectriacid A (183) also possessed good $\alpha$-glucosidase effects with $IC_{50} = 121.8 \mu M$ (Cui et al. 2016).

Helicascolides A (186: $IC_{50}: 16 \mu M$), B (187: $IC_{50}: 31 \mu M$), D (188: $IC_{50}: 20 \mu M$), and E (189: $IC_{50}: 240 \mu M$) (Fig. 26) are all produced by the fungus *Daldinia eschscholtzii* and these isolated compounds illustrated excellent $\alpha$-glucosidase effects (Table 7). Compound 186 was the most potent followed by compound 188 while metabolite 189 was the least active. The activity difference between compounds 188 and 189 indicated that it was indeed the acetyl group at C-8 that was responsible for the reduced activity (Liao et al. 2019). Polyketides viz., aspergones A (190), B (191), E (192), J (193), K (194), N-Q
(195–198) were isolated from the fungus Aspergillus sp. and all these compounds inhibited α-glucosidase with IC$_{50}$ values ranging from 1.30 to 2.37 mM (Table 7). Moreover all the compounds were less effective than acarbose (IC$_{50}$: 0.95 mM) (Kong et al. 2015). The fungus Penicillium expansum produced expansolides C (199) and D (200). An epimeric mixture of compounds 199 and 200 (2:1) potentially inhibited α-glucosidase (IC$_{50}$ = 0.50 mM) and thus was more potent than acarbose (IC$_{50}$ = 1.90 mM) (Ying et al. 2017).

The fungus Ganoderma lucidum produces nortriterpenoids, (201), D (202), E (203) (Fig. 27). Metabolite 202 exerted potent α-glucosidase effects among these compounds, with an IC$_{50}$ value of 41.7 μM, followed by metabolites 201 (IC$_{50}$ = 81.8 μM) and 203 (IC$_{50}$ = 91.3 μM). All these compounds were more potent than acarbose (IC$_{50}$: 669.7 μM) (Zhao et al. 2015). A pair of enantiomers: (+)-1-hydroxyboivinianic acid (204a), (−)-1-hydroxyboivinianic acid (204b) along with 7-deoxy-7,14-didehydroxydonol (205) were separated from the fungus Aspergillus versicolor and evaluated for their α-glucosidase inhibition. Metabolite 205 (IC$_{50}$: 7.5 μM) was the most potent inhibitor when compared with the activity of acarbose (IC$_{50}$ = 350 μM). On the other hand compounds (−)-204 (IC$_{50}$: 120.3 μM) and (−)-204 (IC$_{50}$: 113.3 μM) are reported as moderate inhibitors (Cui et al. 2018).

The fungus Setosphaeria rostrata produced thiodiketopiperazine, exserohilone (206) (Fig. 28) and possess α-glucosidase activity with an IC$_{50}$ value of 82 μg/mL (Centko et al. 2017). Moreover, asperpanoid A (207) was obtained from Aspergillus sp. and
possesses α-glucosidase activity with IC_{50}: 12.4 μM (Cai et al. 2019). The fungus Zasmidium sp. produced tripalmitin (208: IC_{50}: 3.75 μM) which illustrated potent α-glucosidase activity (Lopéz et al. 2019). Metabolites dothiorelone K (209: IC_{50}: 22 μg/mL), L (210: IC_{50}: 77.9 μg/mL), and I (211: IC_{50}: 5.4 μg/mL) were reported from the fungus Dothiorella sp. and illustrated α-glucosidase effects (Zheng et al. 2019).

**Conclusion**

Fungi are known as prolific producers of diverse secondary metabolites. Fungal metabolites range from simple small molecules to more complex systems viz., proteins and polypeptides with a wide range of biological activities. Since the scourge of diabetes has increased worldwide, it is estimated that by 2040, the number of diabetic people will increase to 642 million around the globe. There is thus a critical need to find new antidiabetic drugs with less side effects. In spite of the fact that drug treatment for diabetes has improved over the last decade, drug resistance too has become an important issue in diabetic drug discovery and consequently new and improved strategies will have to be sought. One such strategy would be to either inhibit or decrease the manufacture of glucose in the small intestine. α-Glucosidase inhibitors can reduce the digestion of carbohydrates and thus could be considered as one of the most effective strategies to reduce post-prandial hyperglycemia. α-Glucosidase inhibitors are thus an important group of therapeutic agents to treat diabetes which currently comprises of three drugs viz., acarbose, miglitol, and voglibose (Derosa and Maffioli 2012). Numerous studies have been conducted to analyze the clinical efficacy and safety of acarbose, miglitol, and voglibose α-glucosidase with respect to glycemic control, atherosclerosis, and inflammation. It has been reported that these three α-glucosidase inhibitors are considered to be safe and effective both in monotherapy as well as in combination with additional anti-diabetic drugs (Dash et al. 2018; Derosa and Maffioli 2012).

In this context, the last decade has been noted to be a most fruitful period in isolating low molecular weight antidiabetic compounds from fungi. During this decade (2010 to 2019), more than 200 natural products have been isolated from various fungal sources and screened for their α-glucosidase inhibitory activity. Among the alkaloids, compound 8 exhibited an IC_{50} value of 3.3 μM, which showed that the pyrrolidine-2-one system coupled with a phenolic function are important functional groups for the development of antidiabetic drugs. Moreover, among...
**Table 7** Fungal metabolites 190–211 as α-glucosidase inhibitors

| Compd. | Source | IC₅₀ | References |
|--------|--------|------|------------|
| Aspergone A (190) | Aspergillus sp. | 2.36 mM | Kong et al. (2015) |
| Aspergone B (191) | Aspergillus sp. | 1.65 mM | Kong et al. (2015) |
| Aspergone E (192) | Aspergillus sp. | 1.30 mM | Kong et al. (2015) |
| Aspergone J (193) | Aspergillus sp. | 2.37 mM | Kong et al. (2015) |
| Aspergone K (194) | Aspergillus sp. | 2.70 mM | Kong et al. (2015) |
| Aspergone N (195) | Aspergillus sp. | 1.36 mM | Kong et al. (2015) |
| Aspergone O (196) | Aspergillus sp. | 1.54 mM | Kong et al. (2015) |
| Aspergone P (197) | Aspergillus sp. | 2.21 mM | Kong et al. (2015) |
| Expansolide C (199) | Penicillium expansum | 0.50 mM | Ying et al. (2017) |
| Expansolide D (200) | Penicillium expansum | | Ying et al. (2017) |
| Ganoderlactone B (201) | Ganoderma lucidum | 81.8 μM | Zhao et al. (2015) |
| Ganoderlactone D (202) | Ganoderma lucidum | 41.7 μM | Zhao et al. (2015) |
| Ganoderlactone E (203) | Ganoderma lucidum | 91.3 μM | Zhao et al. (2015) |
| (+)-1-Hydroxyboivinianic acid (204a) | Aspergillus versicolor | 120.3 μM | Cui et al. (2018) |
| (−)-1-Hydroxyboivinianic acid (204b) | Aspergillus versicolor | 113.3 μM | Cui et al. (2018) |
| 7-Deoxy-7,14-didehydrosydonol (205) | Aspergillus versicolor | 7.5 μM | Cui et al. (2018) |
| Exserohilone (206) | Setosphaeria rostrata | 82 μg/mL | Centko et al. (2017) |
| Asperpanoid A (207) | Aspergillus sp. | 12.4 μM | Cai et al. (2019) |
| Tripalmitin (208) | Zasmidium sp. | 3.75 μM | Lopeñ et al. (2019) |
| Dothiorelone K (209) | Dothiorella sp. | 22 μg/mL | Zheng et al. (2019) |
| Dothiorelone L (210) | Dothiorella sp. | 77.9 μg/mL | Zheng et al. (2019) |
| Dothiorelone I (211) | Dothiorella sp. | 5.4 μg/mL | Zheng et al. (2019) |

**Fig. 27** Structures of butanolides 201–205
p-terphenyls as α-glucosidase inhibitors, sarcoviolin β (23, IC50 = 0.58 μM), 3,3′-dihydroxy-6′-O-desmethylterphenyllin (22, IC50 = 0.9 μM) and concrecsein A (33, IC50: 0.9 μM) were found to be the most potent α-glucosidase inhibitors. Depsides 43–45 showed α-glucosidase inhibiton with IC50: 3–7.6 μM, and thus offer their strong candidature to be studied further for development as antidiabetic drugs. Among the depsidones, botryorhodine D (62, IC50 = 2.1 μM) has been identified as a potential α-glucosidase inhibitor. Since two more depsides (63 and 64) also showed significant inhibition, this fact revealed that the dioxygenase system is important and is also supported by other functional groups attached at C-3 to improve the α-glucosidase activity. A reasonable number (25) of isocoumarins have been identifed from various fungi as α-glucosidase inhibitors. Notably compound 93 (IC50: 0.027 mM) was found to be 35 fold more potent than the standard drug acarbose which indicated that a substituted tetrahydrofuran system might be playing a key role in the inhibitory activity. Among the benzo-furans, 6-demethylpenisimplicissin (108, IC50: 9.5 μM) and 1′′-epihydroxydihydrovermistatin (109, IC50: 8.0 μM) have also shown their potential as antidiabetic drug candidates. However, among the few quinone examples, only compound 115 (IC50: 7.2 μM) exerted potential inhibition of α-glucosidase being higher than the positive control genistein (IC50 = 13.6 μM), whereas, chromosome analogs 125 (IC50: 13 μM) and 128 (IC50: 15 μM) proved to be the most active metabolites. Butanolide polyketides are another major class identified as antidiabetic fungal metabolites. A total of 29 compounds forming this group were isolated from various fungi during the last decade and almost all showed remarkable α-glucosidase inhibitory activity. Rubrolide S (143, IC50: 1.2 μM) with a Ki value of 1.42 μM has been identified as the most potent inhibitor. Further studies on this compound may lead to the development of a new and novel antidiabetic agent. Among the diphenyl ether derivatives, peniciaculin A (166, IC50: 1.5 μM) and expansol D (167, IC50: 2.3 μM) showed their potential as future drug candidates to treat diabetes mellitus. Other than these metabolites, 6′-Methyl-[1,1′-biphenyl]-3,3′,4′,5-tetraol (172, IC50: 2.2 μM), meroterpenoids 179 (IC50: 4.5 μM) and 180 (IC50: 3.1 μM), sesquiterpenoid; 7-deoxy-7,14-didehydroso-ydonol (205, IC50: 7.5 μM), tripalmitin (208, IC50: 3.75 μM) and dothiorelone I (211, IC50: 5.4 μg/mL) are also considered as powerful candidates as α-glucosidase inhibitors. The above information clearly demonstrates that fungi are one of the most vital sources of novel substances with diverse structural features, which can be further explored as new and novel antidiabetic agents.

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References

Abbas G, Ahmed Al-Harrasic A, Hussain H et al (2019) The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2). Bioorg Chem 86:305–315

Abdou R, Scherlach K, Dahse HM et al (2010) Botryorhodines. Biochemistry 71:110–116

Agosti G, Birkinshaw JH, Chaplen P (1962) Studies in the biochemistry of micro-organisms. 112. Anthraquinone pigments of strains of Cladosporium fulvum Cooke. Biochem J 85:528–530

Aldridge DC, Galt S, Turner WB (1971) Metabolites of Lasiodiplodia theobromae. J Chem Soc 113:1623–1627

Anke H, Kolthoum I, Laatsch H (1980) Metabolic products of microorganisms. 192. Anthraquinonone derivatives, 14-deacetoxy-1-deoxypebrolide and 7'-hydroxyasperphenamate isolated from Penicillium sp. IFM6525. Heterocycles 94(2):326–333

Askenazi M, Driggers EM, Holtzman DA et al (2003) Integrating transcriptional and metabolite profiles to direct the engineering of lovastatin-producing fungal strains. Nat Biotechnol 21:150–156

Baba K, Xiao YQ, Taniguchi M et al (1991) Isocoumarins from Penicillium sp. ZJ-68. Mar Drugs 17:46–80

Bilal S, Ali L, Khan AL et al (2018) Endophytic fungus Paecilomyces formosus HXW3548 and cyclic peptide that inhibit urease and α-glucosidase and α-amylase inhibiting thiodiketopiperazines from the endophytic fungus Setosphaeria rostrata isolated from the medicinal plant Costus speciosus in Sri Lanka. Phytochem Lett 22:76–80

Cai R, Jiang H, Zang Z et al (2019) New Benzofuranonoids and Phenylpropanoids from the Mangrove Endophytic Fungus, Aspergillus sp. ZJ-68. Mar Drugs 17:478

Capon RJ (2020) Extracting value: mechanistic insights into the formation of natural product artifacts—case studies in marine natural products. Nat Prod Rep 37:55–79

Centko RM, Ratnaweera PB, Tysoe C et al (2017) Alpha-glucosidase and alpha-amylase inhibiting thiodiketopiperazines from the endophytic fungus Setosphaeria rostrata isolated from the medicinal plant Costus speciosus in Sri Lanka. Phytochem Lett 22:76–80

Chan CW, Yu CL, Lin JC et al (2018) Glitazones and alpha-glucosidase inhibitors as the second-line oral anti-diabetic agents added to metformin reduce cardiovascular risk in Type 2 diabetes patients: a nationwide cohort observational study. Cardiovasc Diabetol 17(1):20

Chen B, Shen Q, Zhu X et al (2014) The anthraquinone derivatives from the fungus Alternaria sp. XZSBG-1 from the saline lake in Bange, Tibet. China. Molecules 19:16529–16542

Chen S, Liu Z, Liu Y et al (2015a) New depsidones and isoidinolones from the mangrove endophytic fungus Meyerozyma guilliermondii (HZ-Y2) isolated from the South China Sea. Biostat J 11:1187–1193

Chen S, Liu Z, Li H et al (2015b) β-Resorcylic acid derivatives with α-glucosidase inhibitory activity from Lasiodiplodia sp. ZJ-HQ 1, an endophytic fungus in the medicinal plant Acanthus Illicifolius. Phytochem Lett 13:141–146

Chen S, Liu Y, Liu Z et al (2016) Isocoumarins and benzofurans from the mangrove endophytic fungus Talaromyces amestolkiae possess α-glucosidase inhibitory and antibacterial activities. RSC Adv 6:26412–26420

Chen S, Liu Z, Liu H et al (2017) Lasiodiplactone A, a novel lactone from the mangrove endophytic fungus Lasiodiplodia theobromae ZJ-HQ1. Org Biomol Chem 15:6338–6341

Chen Y, Yang W, Zou G et al (2019) Bioactive polyketides from the mangrove endophytic fungi Phoma sp. SYSU-SK-7. Fitoterapia 139:104369

Couch RD, Gaucher GM (2004) Rational elimination of Aspergillus terreus sulochrin production. J Biotechnol 108:171–178

Cui H, Liu Y, Nie Y et al (2016) Polyketides from the mangrove endophytic fungus Nectria amestolkiae ZJ-HQ1. Org Biomol Chem 15:15954–15960

Dash RP, Babu RJ, Srinivas NR (2018) Reappraisal and perspectives of clinical drug–drug interaction potential of α-glucosidase inhibitors such as acarbose, voglibose and miglitol in the treatment of type 2 diabetes mellitus. Xenobiotica 48:89–108

Derosa G, Maffioli P (2012) α-Glucosidase inhibitors and their use in clinical practice. Arch Med Sci 8:899–906

Dresvad JC, Houbraken J, Popma S et al (2013) Two new Penicillium species, Penicillium buchwaldii and Penicillium spathulatum, producing the anticancer compound asperphenamate Quick View Other Sources FEMS. Microbiol Lett 339(2):77–92
Gao JM, Yang SX, Qin JC (2013) Azaphilones: chemistry and biology. Chem Rev 113:4755–4811

Ge HM, Shen Y, Zhu CH et al (2008) Penicidones A–C, three cytotoxic alkaloidal metabolites of an endophytic Penicillium sp. Phytochemistry 69(2):571–576

Ghosh AC, Mannade A, Demain AL (1977) Toxins from Penicillium islandicum Sopp. In: Rodricks JV, Hesseltine CW, Mehlman MA (eds) Mycotoxins in human and animal health. Pathotox, Chicago, pp 625–638

Hampel V, Wetzel I, Bracher F et al (2011) New substituted isocoumarins and dihydroisocoumarins and their cytotoxic activities. Sci Pharm 79:21–30

Hargreaves J, Park J, Ghisalberti E et al (2002) New chlorinated diphenyl ethers from an Aspergillus sp. Phytochemistry 69(2):571–576

Hou XM, Zhang YH, Hai Y et al (2017) Aspersymmetide A, a new centrosymmetric cyclohexapeptide from the marine-derived fungus Aspergillus versicolor. Mar Drugs 15(11):3631–3638

Huang H, Feng X, Xiao Z et al (2011) Azaphilones and p-terphenyls from the mangrove endophytic fungus Penicillium chermesinum (ZH4-E2) isolated from the South China Sea. J Nat Prod 74:997–1002

Huang H, Liu T, Wu X et al (2017) A new antibacterial chromone derivative from mangrove-derived fungus Penicillium aculeatum (No. 9 EB). Nat Prod Res 31(22):2593–2598

Hung HY, Qian K, Morris-Natschke SL et al (2012) Recent discovery of plant-derived anti-diabetic natural products. Nat Prod Rep 29:580–606

Izhaki I (2002) Emodin—a secondary metabolite with multiple ecological functions in higher plants. New Phytol 155:205–217

Jongrungruangchok S, Aree T, Sureram S et al (2013) Crystal structure of 2-(2-carboxy-4-hydroxy-6-methoxyphenyl)-3,5-dichloro-6-hydroxy-4-methylbenzoic Acid 1-methyl ester. Chin J Struct Chem 32:1742

Kakunuma N, Iwai H, Takahashi S et al (2000) Quinolactacins A, B and C: novel quinolone compounds from Penicillium sp. EPF-6. I. Taxonomy, production, isolation and biological properties. J Antibiot 53(11):1247–1251

Kao CC, Wu PC, Wu CH et al (2016) Risk of liver injury after α-glucosidase inhibitor therapy in advanced chronic kidney disease patients. Sci Rep 6:18996

Kobayashi MI, Aoyagi A, Tanaka I et al (2008) Sterenin A, B, C and D, novel 11b-hydroxysteroid dehydrogenase type 1 inhibitors from Stereum sp SANK 21205. J Antibiot 61(3):128–135

Kong F, Zhao C, Hao J et al (2015) New α-glucosidase inhibitors from a marine sponge-derived fungus, Aspergillus sp. OUCMDZ-1583. RSC Adv 5:68852–68863

Lai S, Shizuri Y, Yamamura S et al (1991) Three new phenolic metabolites from Penicillium species. Heterocycles 32:297–305

Lee KH, Hayaws N, Okanos M et al (1982) Lasiodiplodin, a potent antileukemic macrolide from Euphorbia splendens. Phytochemistry 21:1119–1121

Lee IK, Yun BS, Cho SM et al (1996) Betulinans A and B, two benzoquinone compounds from Leucites betulina. J Nat Prod 59:1090–1092

Li W, Li XB, Lou HX (2018) Structural and biological diversity of natural p-terphenyls. J Asian Nat Prod Res 20:1–13

Liao HX, Zheng CJ, Huang GL et al (2019) Bioactive polyketide derivatives from the mangrove-derived fungus Daldinia escholtzii HJ004. J Nat Prod 82:2211–2219

Lin Z, Zhu T, Fang Y et al (2008) Polyketides from Penicillium sp. JP-1, an endophytic fungus associated with the mangrove plant Aegiceras corniculatum. Phytochemistry 69:1273–1278

Liu JK, Hu L, Dong ZJ et al (2004) DPPH radical scavenging activity of ten natural p-terphenyl derivatives obtained from three edible mushrooms indigenous to China. Chem Biodivers 1:601–605

Liu Y, Yang Q, Xia G et al (2015a) Polyketides with α-glucosidase inhibitory activity from a mangrove endophytic fungus, Penicillium sp. HN29-3B1. J Nat Prod 78:1816–1822

Liu Z, Xia G, Chen S et al (2014a) Eurothiocin A and B, sulfur-containing benzofurans from a soft coral-derived fungus Eurotium rubrum SH-823. Mar Drugs 12:3669–3680

Liu Y, Xia G, Li H et al (2014b) Vermistatin derivatives with α-glucosidase inhibitory activity from the mangrove endophytic fungus Penicillium sp. HN29-3B1. Planta Med 80:912–917

Liu DS, Yan L, Ma LY et al (2015b) Diphenyl derivatives from coastal saline soil fungus Aspergillus izukae. Arch Pharmacol Res 38:1038–1043

Liu Z, Chen S, Qiu P et al (2017) (+)- and (−)-Ascomlactone A: a pair of novel dimeric polyketides from a mangrove endophytic fungus Ascomycota sp. SK2YWS-L.Org. Biol Mol Chem 15:10276–10280

Liu M, Qi C, Sun W et al (2018a) α-Glucosidase inhibitors from the coral-associated fungus Aspergillus terreus. Front Chem 6:422

Liu M, Sun W, Wang J et al (2018b) Bioactive secondary metabolites from the marine-associated fungus Aspergillus terreus. Bioorg Chem 80:525–530

Lopéz D, Cherigo L, Mejia LC et al (2019) α-Glucosidase inhibitors from a mangrove associated fungus, Zasmidium sp. strain EM5-10. BMC Chem 13:22

Ma K, Han J, Bao L et al (2014) Two sarcoviolins with antioxidantive and α-glucosidase inhibitory activity from the edible mushroom sarcodon leucopus collected in Tibet. J Nat Prod 77:942–947

Mahmood ZA, Ahmed SW, Azhar I et al (2010) Bioactive alkaloids produced by fungi. 1. Updates on alkaloids from the species of the genera Boletus, Fusarium and psilocybe. Pak J Pharm Sci 23(3):349–357

Nagasawa I, Kaneko A, Suzuki T et al (2014) Potential anti-angiogenesis effects of p-terphenyl compounds from Polyozellus multiplex. J Nat Prod 77:963–968
Xiao Z, Chen S, Cai R et al (2016) New furoisocoumarins and isocoumarins from the mangrove endophytic fungus *Aspergillus* sp. 085242. Beilstein J Org Chem 12:2077–2085

Xu L, He Z, Xue J et al (2010) β-Resorcylic acid lactones from a Paecilomyces fungus. J Nat Prod 73:885–889

Xu HW, Xu C, Fan Z et al (2013) A facile synthesis, antibacterial activity of pulvinone and its derivatives. Bioorg Med Chem Lett 23:737–739

Xu Y, Zhou T, Patricia EA et al (2014) Insights into the biosynthesis of 12-membered resorcylic acid lactones from heterologous production in Saccharomyces cerevisiae. Chem Biol 9:1119–1127

Yamazaki M, Maebayashi Y, Miyaki K (1971) The isolation of secalonic acid A from *Aspergillus ochraceus* cultured on rice. Chem Pharm Bull 19:199–201

Yang R, Li C, Lin Y et al (2006) Lactones from a brown alga endophytic fungus (No. ZZF36) from the South China Sea and their antimicrobial activities. Bioorg Med Chem Lett 16:4205–4208

Yang ZJ, Yin Y, Ge M (2015) A novel chromene with anti-tumor activities from fungus Phomopsis sp. Zhongguo Zhongyao Zazhi 40(4):667–671

Yaya AJG, Feumba RD, Emmanuel T et al (2014) Antioxidant activity of compounds isolated from the root woods of *Erythrina droogmansiana*. Int J Pharm Sci Drug Res 6(2):160–163

Yin L, Ohno T, Weichselbaum R et al (2001) The novel isocoumarin 2-(8-hydroxy-6-methoxy-1-oxo-1H-2-benzopyran-3-yl) propionic acid (NM-3) induces lethality of human carcinoma cells by generation of reactive oxygen species. Mol Cancer Ther 1:43–48

Yin Z, Zhang W, Feng F et al (2014) α-Glucosidase inhibitors isolated from medicinal plants. Food Sci Hum Wellness 3:136–174

Ying YM, Fang CA, Yao FQ et al (2017) Bergamotane sesquiterpenes with alpha-glucosidase inhibitory activity from the plant pathogenic fungus *Penicillium expansum*. Chem Biodiv 14:e160018

Zhang LH, Feng BM, Zhao YQ et al (2016a) Polyketide butenolide, diphenyl ether, and benzophenone derivatives from the fungus *Aspergillus flavipes* PJJ03-11. Bioorg Med Chem Lett 26:346–350

Zhang LH, Feng BM, Sun Y et al (2016b) Flaviphenalenes A–C, three new phenalenone derivatives from the fungus *Aspergillus flavipes* PJJ03-11. Tetrahedron Lett 57:645–649

Zhang L, Niaz SI, Wang Z et al (2017) α-Glucosidase inhibitory and cytotoxic botryorhodines from mangrove endophytic fungus *Trichoderma* sp. 307. Nat Prod Res 32:2887–2892

Zhao XR, Huo XK, Dong PP et al (2015) Inhibitory effects of highly oxygenated lanostane derivatives from the fungus *Ganoderma lucidum* on P-glycoprotein and α-glucosidase. J Nat Prod 78:1868–1876

Zheng CJ, Huang GL, Liao HX et al (2019) Bioactive cytosporone derivatives isolated from the mangrove-derived fungus *Dothiorella* sp. ML002. Bioorg Chem 85:382–385

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