Mycological Spectrum (e-ISSN:3107-6203)
https://mycologicalspectrum.org/
Published by Association of Fungal Biologists, India

Review Article

Fungi as a source of enzyme inhibitors: bioprospecting for new drugs

Sanjai Saxena[1,2]
[1]Department of Biotechnology, Thapar Institute of Engineering and Technology, Patiala, Punjab 147004.
[2]Founder, Agpharm Bioinnovations LLP, STEP- Thapar Institute of Engineering and Technology, Patiala, Punjab 147004

Corresponding Author: Sanjai Saxena**:** Emails: ssaxena@thapar.edu; sanjaibiotech@yahoo.com

Abstract

Fungi are prolific producers of structurally diverse secondary metabolites, many of which serve as potent enzyme inhibitors with therapeutic potential. Targeting important enzymes linked to cancer, diabetes, neurodegenerative, infectious, and metabolic diseases, this review examines fungal-derived enzyme inhibitors discovered between 2015 and 2025 based on research published in Google Scholar, ScienceDirect, Web of Knowledge, and Scopus. The study highlights fungal metabolites that inhibit proteasomes, tyrosine phosphatases (PTP1B), α-glucosidase, cholinesterase, BACE1, GSK-3, viral neuraminidase, histone acetyltransferases, and isocitrate dehydrogenases, among others. These bioactive compounds, sourced from fungi inhabiting diverse ecological niches—marine, endophytic, soil, and symbiotic—demonstrate unique chemotypes and novel mechanisms of enzyme inhibition. Their broad-spectrum activity and structural novelty present promising scaffolds for drug development. Fungi's amenability to fermentation, coupled with advances in genomics, synthetic biology, and computational tools, has enabled accelerated discovery and optimization of enzyme inhibitors. However, challenges such as suboptimal pharmacokinetics and potential toxicity necessitate rigorous *in silico* and experimental screening. The review underscores fungi as an underexploited reservoir for enzyme-targeted therapeutics and advocates continued bioprospecting and molecular characterization to unlock their full pharmaceutical potential. Integrating fungal chemical diversity with modern drug discovery platforms could significantly advance the development of next-generation therapeutics.

Keywords: Bioresource, drug discovery, enzyme kinetics, fungi, inhibitors, therapeutics.

Citation: Saxena S.(2026). Fungi as a source of enzyme inhibitors: bioprospecting for new drugs. *Mycological Spectrum 2(1),18-49.*

Received: 14 May 2025 | **Accepted**: 25 November 2025 | **Published**: 03 January 2026.

Handling Editor: Dr. S.K. Deshmukh | **Reviewers**: Prof. Abhijeet Kate and Prof. Nihar Ranjan.

1. Introduction

Today drug discovery and development process has become highly target specific based on the disease mechanisms to have efficacy of the therapeutic intervention being developed. As such the success rate of a molecule getting into therapeutic pipeline depends on the molecular recognition of the small molecule entity effectively binding to the target and providing the desired pharmacological activity with least side effects. Hence the drug discovery research groups define specific target molecules which are involved in disease mechanisms or pathologies and convert the best hit into a pharmacophore of choice which can pass through the clinical development process. Structure based drug discovery has taken a credence over the traditional phenotypic random screening since high risk and huge cost is involved in taking a molecule from bench to bedside (Batool et al., 2019).

The drug discovery research groups consider enzymes as the most desirable target for drug development (Kim, 2023). Enzyme inhibitors are molecules which render the enzyme inactive or abolish its activity. The relevance of enzyme inhibitors as drugs stems from the fact that they modulate a specific metabolic reaction which in turn affects the metabolic pathway, the dysregulation of which is responsible for a disease. The global market for enzyme inhibitors is valued ca. 26.97 billion USD in 2024 and is expected to reach USD 45.51 billion USD by 2032 growing at a Compounded Annual Growth Rate (CAGR) of 5.37% (Market Research Future, 2024).

Hence, emphasis is laid on the exploration of novel molecules which could be effectively optimized as an inhibitor for clinical use to alleviate chronic disorders ranging from cancer, diabetes, neurodegenerative disorders, infectious diseases, and are characterized by the overexpression or dysregulation of specific enzymes. Thus, enzyme inhibition represents a rational strategy for developing therapeutic interventions. Fungi have been widely recognized as the fountainheads of novel chemical entities which have been developed into therapeutic molecules like Penicillin's, Cephalosporins, Statins like Lovastatin, Mevalonic acid, immunomodulators like Cyclosporine, Mycophenolic acid, Mizoribine, and Fingolimod (Saxena et al., 2019; Prescott et al., 2023). Fungi have also been found to be sources of biomolecules that have proven efficacious in disaggregating misfolded proteins responsible for neurodegenerative diseases, such as Alzheimer's dementia and Parkinson's disease (Vats & Saxena, 2023) (Table 1).

Majority of the drugs developed have their targets around enzymes, hence it becomes imperative to explore novel scaffolds produced by fungi existing in diverse geographies like marine, antarctica to diverse interactions viz. plant- microbe, animal -microbe, insect- microbe for their enzyme inhibiting properties for potential development into a clinical candidate or therapeutic intervention. In this review we have presented enzyme inhibitors originating from diverse fungi in the last decade (2015-2025).

2. Inhibitors of Proteasome

The Ubiquitin-Proteasome System (UPS) is a fundamental process involved in the degradation of misfolded or aberrant proteins (Voges et al., 1999). The reaction cascade involves three enzymes: E1-ubiquitin-activating enzyme, E2-ubiquitin-conjugating enzyme, and E3-ubiquitin ligase. The proteasome degrades polyubiquitinated proteins, but prior to degradation, a deubiquitinating enzyme (DUB) removes ubiquitin from these proteins to recycle it (Glickman & Ciechanover, 2002). Thus, the UPS controls the quality of cellular proteins, and aberrations

in the UPS cause neurodegenerative disorders, cancers, inflammatory, and autoimmune disorders (Thompson, 2013; Huang & Dixit, 2016).

Previously several bioactive compounds have been reported to inhibit the proteasome (Tsukamato et al., 2014; El-Desoky et al., 2014), E1 (Yamanokuchi et al., 2012); E2 (Ushiyama et al., 2012); E3 (Nakamura et al., 2013) and DUB (Yamaguchi et al., 2013; Tanokashira et al., 2016). Using a cell-based reporter assay targeting UPS inhibitors, potent polyketides from a fungus *Remotididymella* sp. (18IF02908) were isolated and identified as Mellin A **(1)**, Mellin B **(2)** and Leptosphaerodione **(3)** and its acetone adduct **(4)**. All the compounds were found to be moderate inhibitors of UPS. High proteasome inhibitory activity was found in Leptosphaerodione **(3)**, and thus it holds a promise to be developed for treatment of cancer and other neurodegenerative and immunological disorders (Nishimura et al., 2022) (Fig.1).

3. Enzyme Inhibitors Targeting Diabetes

Type 2 Diabetes Mellitus (T2DM) is one of the most prominent metabolic disorders across the globe. There are several types of drugs and insulin for the management of T2DM, however there are some other enzyme-based targets which could be developed into clinical interventions.

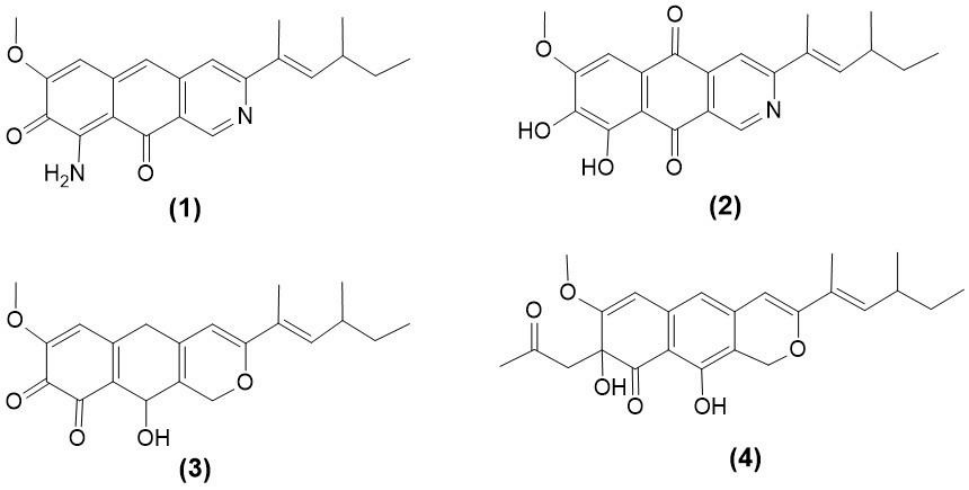

Figure 1. Proteasome inhibitors of fungal origin.

3.1. PTP1B Inhibitors

One of the promising and highly validated targets for T2DM is tyrosine-protein kinase non-receptor type 1, also known as protein-tyrosine phosphatase 1B (PTP1B), for insulin resistance and obesity (Elchebly et al., 1999; Klaman et al., 2000; Coombs, 2010). This enzyme plays a crucial role in control of the glucose and energy homeostasis. Several research groups are exploring PTP1B inhibitors.

Malbranchea albolutea produced alboluteins A-C **(5-7)** on solid rice-based medium which inhibited PTP1B with an IC_{50} ranging between 19-129 µM as compared to 29.8 µM of ursolic acid, which served as the positive control in the study. Kinetic analysis further revealed albolutein C (**7)** to be a non-competitive inhibitor (Diaz- Rojas et al., 2021). Aspergorakhin A **(8)** exhibited a selective PTP1B, SHP 1 (src homology region for 2 domain containing

phosphatase 1) and TCPTP (T-Cell protein tyrosine phosphatase, PTPN2) with IC_{50} values of 0.57, 1.19 and 22.97 μM respectively (Ji et al., 2021).

Two new compounds, which were 3,4,6-trisubstituted α-pyrone derivatives are Chrysopyrones A **(9)** and B **(10)** which were identified from the marine fungus, *Penicillium chrysogenum* SCSIO 07007, separated from deep sea hydrothermal vent environment in western Atlantic. Chrysopyrones A **(9)** and B **(10)** have been found to inhibit PTP1B with IC_{50} values of 40.33 μM and 64.06 μM respectively (Han et al., 2020). *Penicillium* sp. KFD28 isolated from a bivalve mollusk, *Meretrix lusoria* collected from Haikou Bay led to the isolation of four novel paxilline type indole terpenoids, penerpenes A-D **(11-14)**, known compounds paxilline **(15)** and emindole SB **(16)** from its fermentation broth. Penerpene A **(11)**, penerpene B **(12)** and emindole SB **(16)** exhibited a potent PTPIB and TCPTP inhibitory activity. The IC_{50} exhibited for PTP1B was 1.7μM, 2.4 μM and 0.7 μM for penerpene A **(11),** B **(12)** and emindole SB **(16)** respectively. Similarly, the IC_{50} for TCPTP inhibition was found to be 5.0 μM **(11)**, 4.5 μM **(12)** and 1.4 μM **(16)** (Kong et al., 2019). Asperitin B **(17)** isolated from *Aspergillus sydowii*, derived from a deep-sea sediment in Mediterranean region exhibited a robust PTP1B inhibitory activity with an IC_{50} of 2.05 μM outperforming suramin by sixfold (Weise et al., 2017). Fumosorinone **(18)**, a 2-pyridone alkaloid has been identified as a new PTP1B inhibitor from an entomogenous fungus *Isaria fumosorosea*. It is a non-competitive inhibitor of PTP1B with an IC_{50} of 14.04 μM which is complicated as a negative regulator for insulin receptor signalling and therefore serves as a potential target for T2DM (Liu et al., 2015). *Penicillium verruculosum* TPUB11, an Indonesian ascidian derived fungus produced Verruculides A **(19)** and B **(20)** along with three congeners Chordimanins A **(21)**, B **(22)** and H **(23)**. Verruculide A **(19)**, Chordrimanin A **(21)** and Chordrimanin H **(23)** inhibited PTP1B activity with IC_{50} value of 8.4, 8.5 and 14.9 μM respectively (Yamazaki et al., 2015) (Fig.2).

3.2. α- Glucosidase Inhibitors

Glycosidases catalyse the last stage of carbohydrate digestion by hydrolysing the glycosidic bonds of oligosaccharides. They are classified as α(alpha) or β(beta) as they are site specific at the anomeric carbon. Alpha glucosidase is present in the intestinal cells where it plays a crucial role in last stage of carbohydrate assimilation as alpha-glucose. In case the alpha-glucosidase is inhibited it will delay the glucose absorption and thus would regulate the post prandial hyperglycaemia (PPHG). Hence, Alpha glucosidase inhibitors (AGI's) are yet another validated and promising target for management of T2DM (Baron, 1998; Sheen et al., 2003, Chan et al., 2018). The post-prandial hyperglycaemia (PPHG) is attributed to alpha-glucosidase action and thus their inhibition serves as an important therapeutic intervention for treating diabetes related complications such as nephropathy, retinopathy, cardiovascular diseases etc. in patients with T2DM. Clinically approved carbohydrate mimetics or derivatives used which are used as AGIs are acarbose, miglitol and Voglibose. Though these control PPHG, they have multiple side effects ranging from abdominal discomfort, diarrhoea, flatulence etc., which limit their prolonged use (Hossain et al., 2020). Hence bioprospecting for new AGI's becomes important to explore molecules with their effects on their long-term prescription.

Biscogniauxia capnodes SWUF15-40 yielded 18 of compounds of which three new α-pyrones, biscogniapyrones A–C **(24–26)**, two new isocoumarins **(27 and 28)**, and thirteen known compounds. The IC_{50} of α-GI ranged between 41- 257 μM which was much lower as compared to acarbose with IC_{50} of 713 μM. Biscogniapyrone C **(26)** is the strongest inhibitor based on

in silico docking studies (Churat et al., 2025). 3-hydroxybenzoic acid **(29)** has also been identified as a potential AGI isolated from the endophytic fungus *Diaporthe* sp. isolated from the medicinal plant *Simarouba glauca* DC. It exhibited an IC_{50} of 165.4 µM (Mugaranja & Kulal, 2022). An endophytic *Fusarium incarnatum*, isolated from the medicinal plant, *Callicarpa kwangtungensis* Chun, afforded an anthraquinoid class of compound, (S)-1,3,6-trihydroxy-7-(1-hydroxyethyl) anthracene-9,10-dione **(30)** which exhibited a strong α-glucosidase inhibitory activity with an IC_{50} of 77.67 µM as compared to 711.8 µM of acarbose. Kinetically the compound was found to be an uncompetitive inhibitor (Fan et al., 2022).

Mangrove endophytic fungus, *Aspergillus* sp. 16-5c produced six new diketopiperazine alkaloids, Aspergiamides A-F **(31-36)** and other 10 known alkaloids. These were screened for α-glucosidase and PTP1B inhibitory enzyme activities. Aspergiamides A **(31)** and brevianamide K (**37)** exhibited significant AGI activity with IC_{50} values of 18.2 and 7.6 µM respectively while Aspergiamides C **(33)**, Brevianamide W **(38)**, N-prenyl-cyclo-L-tryphtophyl-L-proline **(39)**, Brevianamide M **(40)** exhibited moderate α-glucosidase inhibition with IC_{50} values ranging from 40.7 to 83.9 µM (Ye et al., 2021). Five compounds, (−)-cis-(3R*,4S*)-3,4,8-trihydroxy-6,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one **(41)**, 7-hydroxy-5-methoxy-2,3-dimethylchromone **(42)**; 2,3-dihydroxy-5-methoxy-2-methylchromen-4-one **(43)**; Helicascolides D **(44)**; Helicascolides A **(45)** were isolated from a mangrove derived fungus *Daldinia eschscholtzii* HJ004 isolated from the mangrove plant *Bruguiera sexangula* var. *rhynchopetala* collected in the South China Sea exhibited α-glucosidase inhibitory activity with IC_{50} values ranging from 15-21 µM. Compounds **(42)**, **(43)**, and **(45)** showed inhibitory activities against α-glucosidase with IC_{50} values of 13, 15, and 16 µM, respectively (Liao et al., 2019). Culture extract of *Zasmidium* sp. strain EM5-10 isolated from the mature leaves of *Laguncularia racemosa* was found to exhibit a good inhibition of α-glucosidase (91.3%). On fractionation of the extract, it yielded Tripalmitin **(46)** which exhibited an IC_{50} of 3.75 µM as compared to acarbose (Lopez et al., 2019*). Aspergillus candidus* isolated from the gorgonian coral *Anthogorgia ochracea*, provided two new flavones, Aspergivones A **(47)** and Aspergivones B **(48)**. Aspergivone B **(48)** exhibits a mild AGI activity with IC_{50} value of 680.99 µM (Ma et al., 2017).

Rubrofusarin (5,6-dihydroxy-8-methoxy-2-methyl-4H-naphtha [2,3-6] pyran-4-one) **(49)**, a natural pigment from *Aspergillus aculeatus* exhibited an inhibitory activity against mammalian α-glucosidase with an IC_{50} of 340.5 µM but did not exhibit any activity against *Saccharomyces cerevisiae* α-glucosidase (Dewi et al., 2016). Another endophytic fungus *Nectria* sp. HN001 which was isolated from the branch of mangrove plant, *Sonneratia ovata* was collected from South China sea. It yielded four new polyketides, nectriacids (A-C) **(50-52)**, 12-epicitreoisocoumarinol **(53)** and three known compounds viz. citreoisocoumarinol **(54)**, citreoisocoumarin **(55)** and macrocarpon C **(56)**. Nectriacids B **(51)** and C **(52)** exhibited potent AGI activity with IC_{50} values of 23.5 and 42.3 µM respectively compared to positive control acarbose, having IC_{50} of 815.3 µM (Cui et al., 2016).

Aspergillus versicolor identified as an endophyte in *Huperzia serrata* produced a potent AGI, 1,7-dihydroxy -8- (methoxy carbonyl) xanthone-3-carboxylic acid **(57)** which exhibited an IC_{50} of 0.24 µM as compared to 0.38 µM of acarbose (Ma et al., 2015). Similarly, Botryorhodine A **(58)**, Botryorhodine B **(59)**, Botryorhodine D **(60)**, Botryorhodine E **(61)**, Botryorhodine F **(62)**, Botryorhodine G **(63)** isolated from the endophytic fungus *Meyerozyma guilliermondii* HZ-Y2) residing in the mangrove plant *Kandelia obovate* were found to exhibit strong AGI activity with IC50 ranging between 2.1-13.3 µM. The strongest inhibition was exhibited by

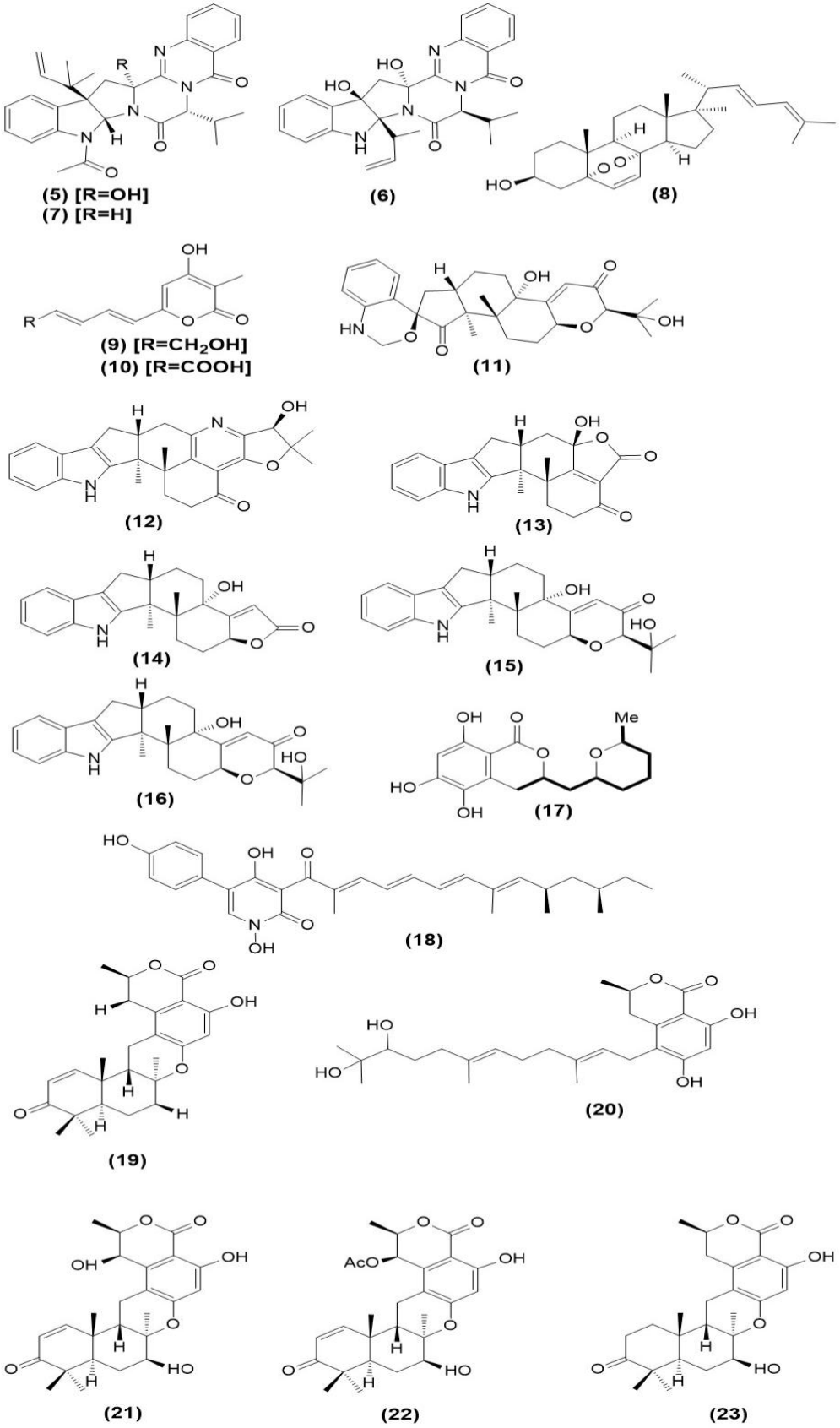

Figure 2. PTPIB inhibitors of fungal origin for the measurement of hyperglycemia.

with IC_{50} ranging between 2.1-13.3 µM. The strongest inhibition was exhibited by Botryorhodine D **(60)** with IC_{50} of 2.1 µM. Both Botryorhodine F **(62)** and Botryorhodine D **(60)** were non-competitive inhibitors of α-glucosidase (Chen et al., 2015).

Another strategy which was explored for screening AGIs was co-culturing. Co-culturing of mangrove endophytic fungus, *Trichoderma* sp. 307 with aquatic pathogenic bacterium *Acinetobacter johnsonii* B2 yielding new depsidone, Botryorhodine H1 **(64)** and three analogues, Botryorhodine C **(65)**, Botryorhodine D **(60)** and Botryorhodine G **(63)**. All the compounds exhibited potent AGI activity with IC_{50} values much lower than acarbose, viz. 8.1 µM for Botryorhodine H1 **(64)**, 10.3 µM for Botryorhodine D **(60)** and 54.1 µM for Botryorhodine G **(63)** (Zhang et al., 2017) (Fig.3).

4. Enzyme Inhibitors for Neurodegenerative Diseases Inhibitors

Alzheimer's and Parkinsons are the two-age related neurodegenerative disorders which generally are characterized by the degeneration of neurons leading to impairment in cognitive functions, motor functions and sensory perception. Current treatment approaches focus on alleviating the cognitive and motor symptoms of the patients using pharmacological interventions. However, there are number of side effects ranging from nausea, diarrhoea, loss of appetite, fatigue, headache to sleep disturbances caused by these agents on prolonged use. Hence the biggest challenge lies in balancing between the relieving symptoms and managing side effects of these medications. Thus, there is a continuous search for safer and more effective treatments.

Predominantly most treatment of Alzheimer's disease are based on the cholinergic hypothesis which is basically related to the deficiency of the neurotransmitter acetylcholine deficiency attributed to loss of cholinergic neurons largely due to the deposition of amyloid beta. It has been found that during the early onset of AD, ~80% of Acetylcholine is hydrolysed by Acetylcholinesterase while butyrylcholinesterase levels are increased which led to the formation of amyloid plaques. Hence inhibition of Acetylcholinesterase and Butyrlcholinesterase is considered as an effective intervention for the treatment of different stages of AD (Chen et al., 2022).

Neobrefeldin **(66)** was isolated from endophytic *Penicillium brefeldianum* F4a which exhibited a potent and selective acetylcholinesterase inhibitory activity with IC_{50} of 0.12 µM as compared to galantamine which has IC_{50} of 0.66 µM and used for the treatment of AD. Thus, neobrefeldin **(66)** appears to be a promising candidate for clinical development to treat early AD (Bai et al., 2024). Pinselin **(67)**, aloe-emodin **(68)** and citreoroseine **(69)** isolated from the sponge associated fungus *Penicillium* sp. SCS1041033 exhibited potent acetylcholinesterase inhibition with IC_{50} values of 152.86 µM, 157.3 µM and 152 µM respectively (Xu et al., 2023).

Colletotrichum lentis KU1 isolated from *Catharanthus roseus* produced two compounds, 9-Hexadecen-1-ol (70) and Erucamide (71) which exhibited acetylcholinesterase inhibition by 78.9 % and 86 % respectively at a concentration of 1 µM (Kallingal et al., 2022). An endophytic fungus *Aspergillus terreus* SGP-1 isolated from the roots of *Morus alba* L. produced Butryolactone VIII (72), Versilactone B (73), Butyrolactone I (74), Butryolactone VII (75), hydroxy-5-[[4-hydroxy-3-(3-methyl-2-buten-1-yl)phenylmethyl]-4-(4-hydroxyphenyl)-2-5H) -furanone (76) which exhibited butyrylcholinesterase inhibition competitively with IC50 in range of 18.4 - 45.8 µM (Cui et al., 2022).

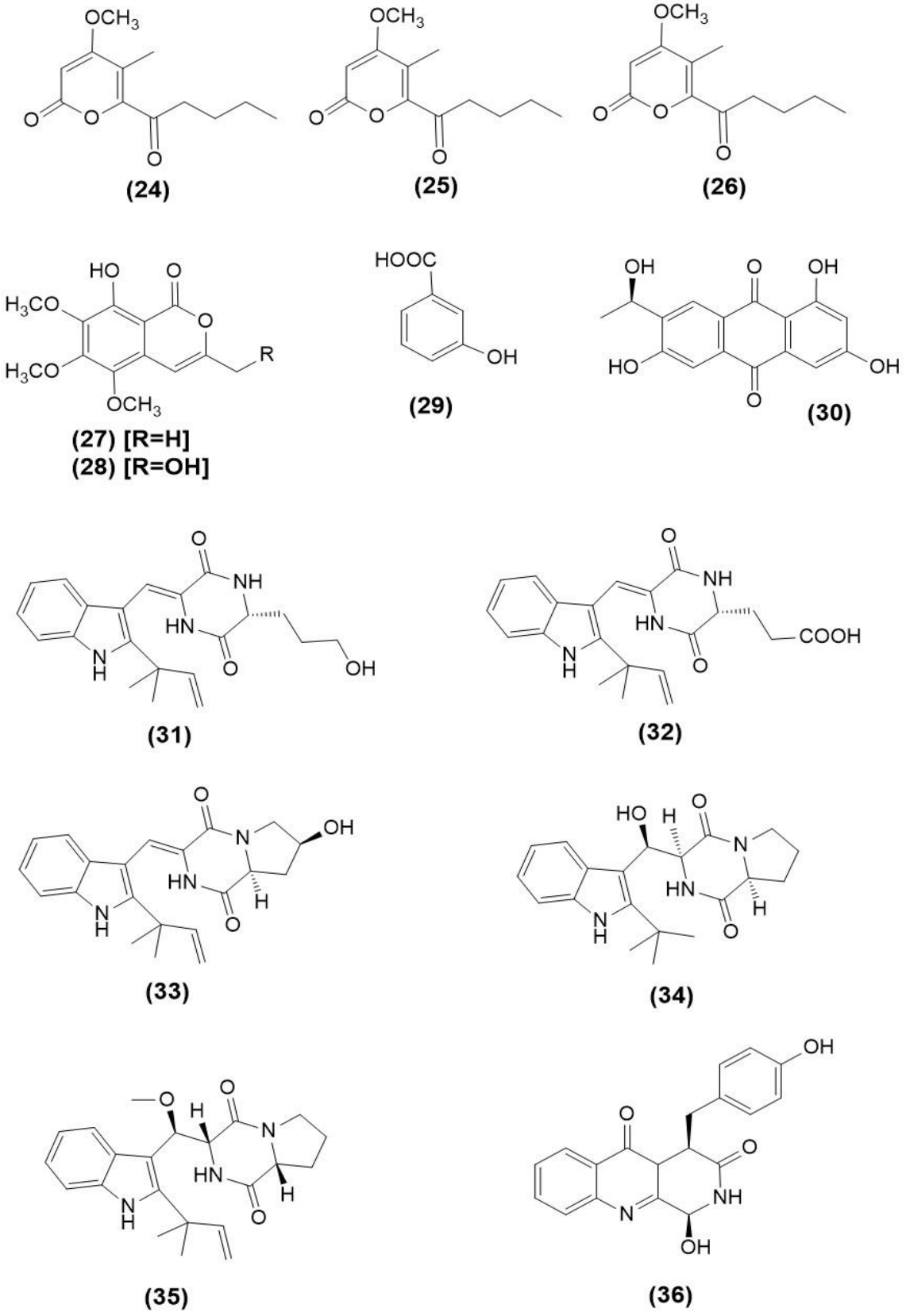

Figure 1. Alpha glucosidase inhibitors of fungal origin in management of PPHG

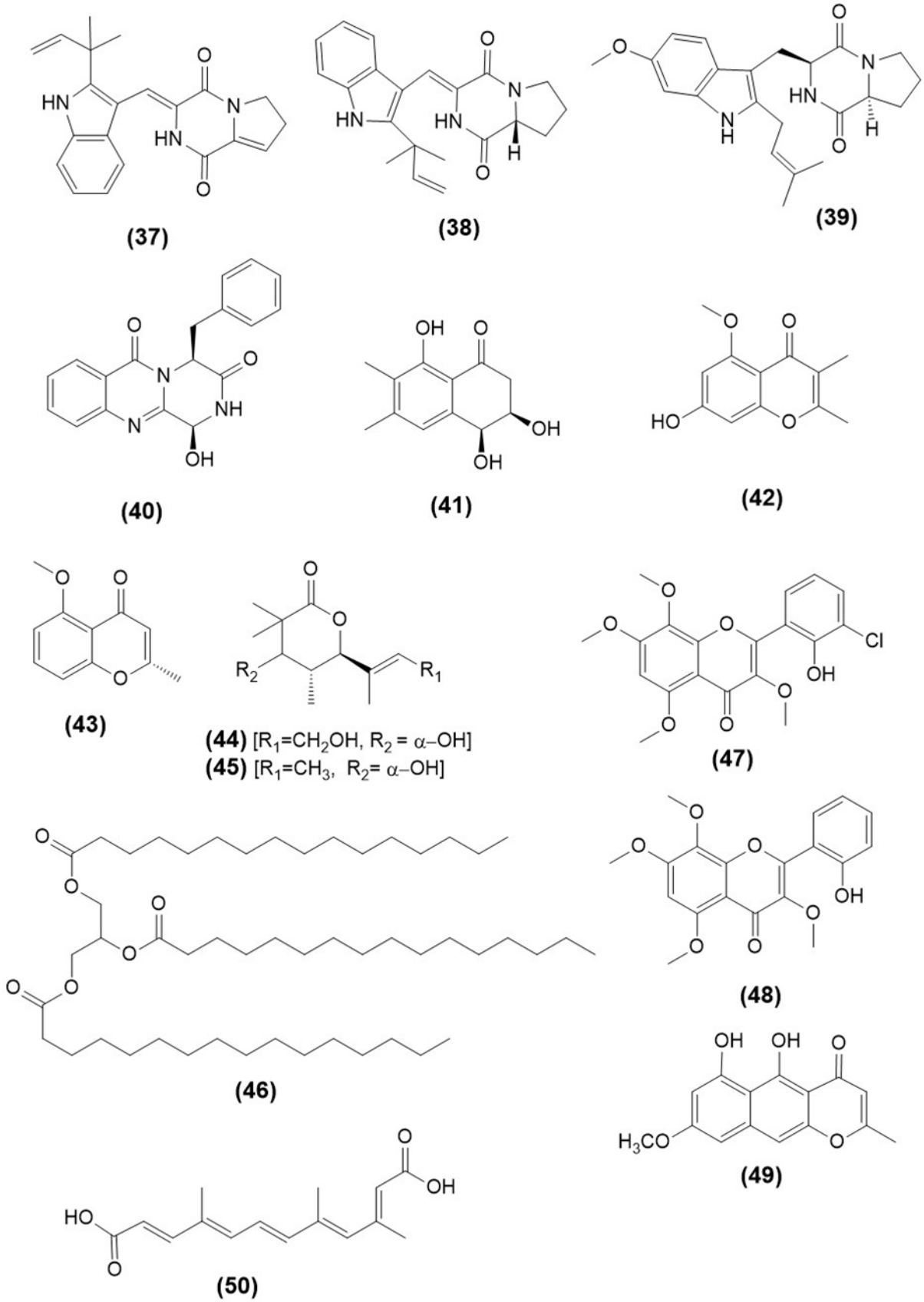

Figure 2. Alpha glucosidase inhibitors of fungal origin in management of PPHG (contd.)

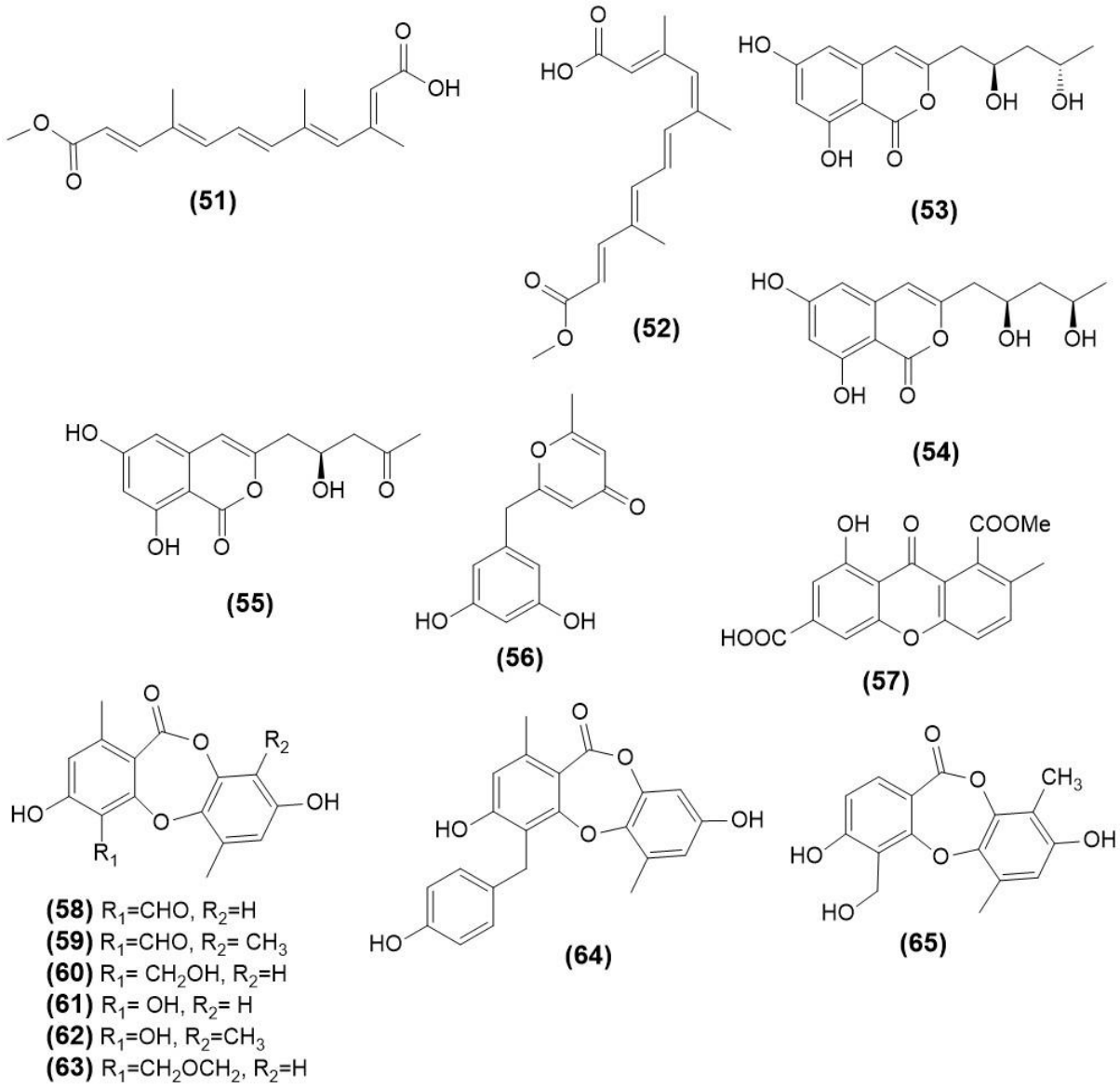

Figure 3. Alpha glucosidase inhibitors of fungal origin in management of PPHG (contd.)

5. Inhibitors of other Targeted Enzymes for Neurodegenerative Disease

Another interesting target for AD is BACE 1(β-site APP cleaving enzyme 1) which cleaves the amyloid precursor protein (APP) into a soluble β-APP fragment and a longer 99 amino acids peptide C99. Subsequently γ-secretase acts on C99 fragment generating Aβ peptides of different length (Koelsch, 2017). *Aspergillus terreus*, a soil fungus yielded Asperterpenes A **(77)**, B **(78)**, E **(79)**, F **(80)**, G **(81)** which exhibited BACE1 inhibiting properties. The IC_{50} of Asperterpene A **(77)** was 0.08 µM and it exhibited an activity like first orally bioavailable non-peptide BACE inhibitor LY2811376. The IC_{50} of other Asperterpenes viz. E **(79)**, F **(80)** and J **(82)** for BACE 1 inhibition were found to be 3.3, 5.9, 31.7 µM respectively (Qi et al., 2016). Endophytic isolate *Phomopsis* sp. TJ507A recovered from the medicinal plant, *Phyllanthus*

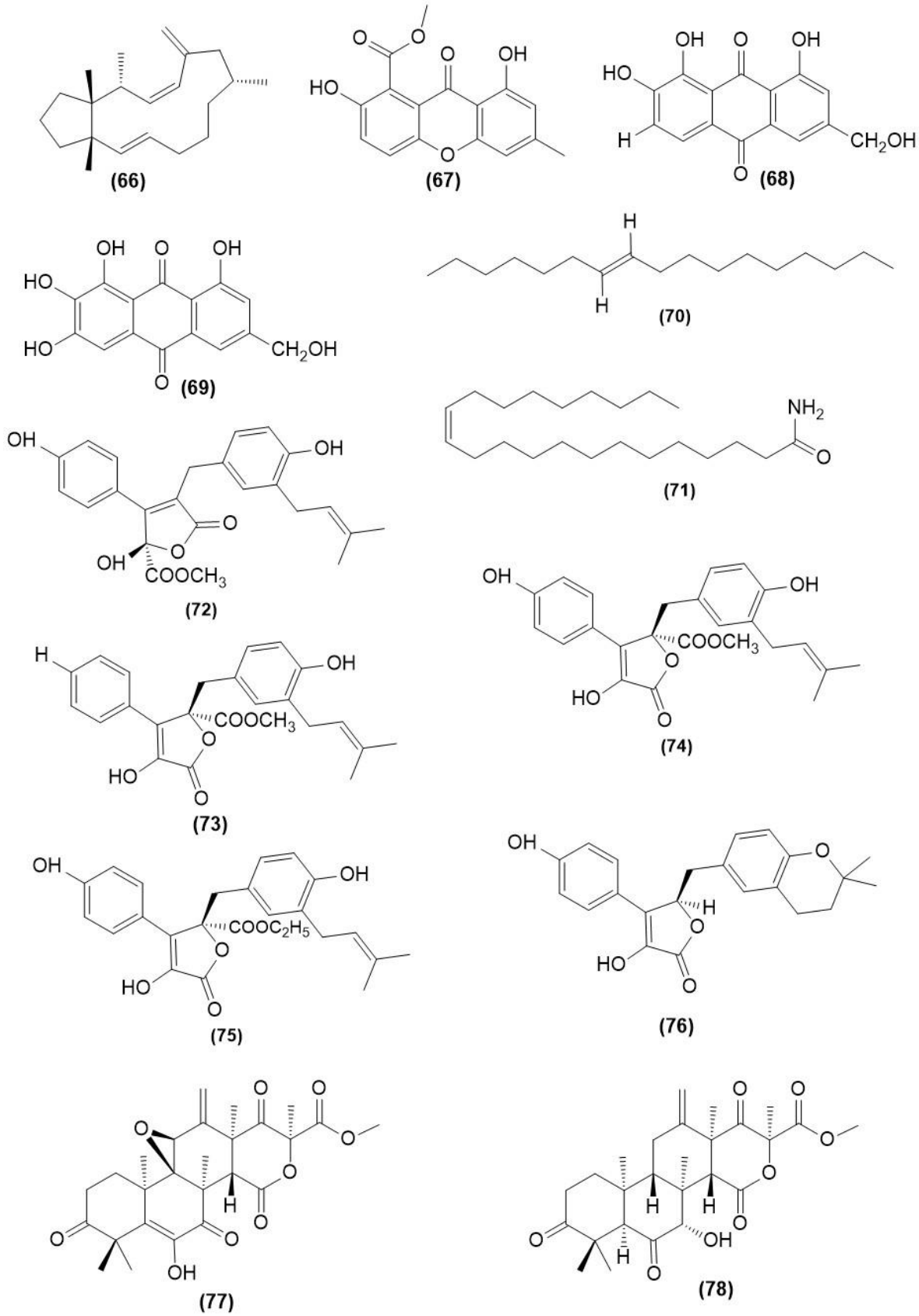

Figure 4. Fungal secondary metabolites exhibiting interference to enzymes involved in development of neurodegenerative disorders.

glaucus produced Phomophyllin B **(83)**, Phomophyllin C **(84)**, 2,3-phomophyllins D **(85)**, phomophyllins E **(86)**, phomophyllins F **(87)**, radulone B **(88)** and onitin **(89)** displayed BACE1 inhibitory activities ranging from 19.4 % to 43.8 % at the concentration of 40 μM (Xie et al., 2018). Glycogen synthase kinase-3 (GSK-3) enzyme also has a pivotal role in AD as it is involved in tau hyperphosphorylation, excessive Aβ formation and accumulation in the brain which results in the loss of memory. Wnt and insulin signalling a related to the increase in GSK-3 activity which probably leads to tau hyperphosphorylation and later formation of neurofibrillary tangles. It has already been reported that a deficit in brain insulin signaling results in and at times AD is regarded as Diabetes Type III. Hence GSK-3 enzyme is also an attractive target for AD (de la Monte et al., 2006; Hooper et al., 2008). Alternariol **(90)** and alternariol-9-methylether **(91)** were isolated from the fungus *Botryotinia fuckeliana* strain KF666 sourced from Wadden sea in Germany exhibited a GSK-3 inhibitory activity with an IC_{50} of 0.13 μM and 0.2 μM respectively. Pannorin **(92)** was isolated from *Aspergillus* species LF660 and exhibited an IC_{50} value of 0.35 μM for GSK-3 inhibition (Weise et al., 2016).

6. Enzyme Inhibitors as Antivirals

Antivirals comprise of drugs that combat the viral infections. Antiviral drugs are basically designed to target the virus itself or the host cell factors, which mediate the process of entry of the virus genetic information. Majority of the antivirals developed are around based on inhibiting the docking of the virus to the host cell, inhibiting entry of the virus into the host, uncoating inhibitors, variety of enzyme inhibitors ranging from protease, polymerase, reverse transcriptase, and integrase (Mahajan et al., 2021; Hangyu et al., 2024). Protease inhibitors play a critical role in viral replication. They selectively bind to viral proteases thereby blocking the proteolytic cleavage of the protein precursors that are necessary to produce infectious viral particles. The primary enzymatic target is 3-Chymotrypsin like protease and papain like protease which have been identified in coronaviruses as it is believed to be essential for viral replication. Several protease inhibitors have been identified for HIV-1 like Indinavir, Atazanavir, Ritonavir etc. which are in clinical use. RNA dependent RNA polymerase inhibitors favilavir and remdesivir have been effectively used to treat coronavirus infections, however, effective treatment to prevent SARS-COV-2 infections are still missing. ω-hydroxyemodin **(93)** and grieseoxanthone C **(94)** were identified as of the most potent inhibitors of Hepatitis C virus N53/4A protease isolated from *Fusarium equisetii*. The IC_{50} was 19.88 and 10.7 μM for grieseoxanthone C **(94)** and ω-hydroxyemodin **(93)** respectively (Hawas et al., 2016). The cap dependent endonuclease activity of the RNA polymerase of influenza virus produces capped fragments for priming viral mRNA synthesis, essential for the propagation of the virus. However, this enzyme is absent in any host cellular system, thus making it an attractive target for the anti-influenza drugs. Fermentation broth of *Penicillium* sp. f28743 yielded a compound, Flupyranochromene **(95)** which inhibited cap-dependent endonuclease. The IC_{50} of Flupyranochromene **(95)** was 0.8 μM (Yamasaki et al., 2019). Influenza A and B virus are responsible for serious and contagious respiratory infections which are markedly identified by cough, fever, sore throat, and general malaise which lasts for 1-2 weeks. Based on the replication cycle of the influenza virus, potential antiviral targets are identified of which Neuraminidase (NA) is the most important. NA is involved in several steps during the viral infection process such as, enhances the transport of virus through mucus, releasing the entrapped virus by removing the unwanted residues, helps in locating the hotspots on cell surface for endosomal uptake. Neuraminidase also helps in release of progeny virions from the cell surface and prevents their aggregation by removing sialic acid residues. Oseltamivir, Zanamivir and Laninamivir are natural product mimics being currently used as anti-influenza drugs (Eichberg et al., 2022). *Aspergillus austwickii* SCSIO 41227, a coral

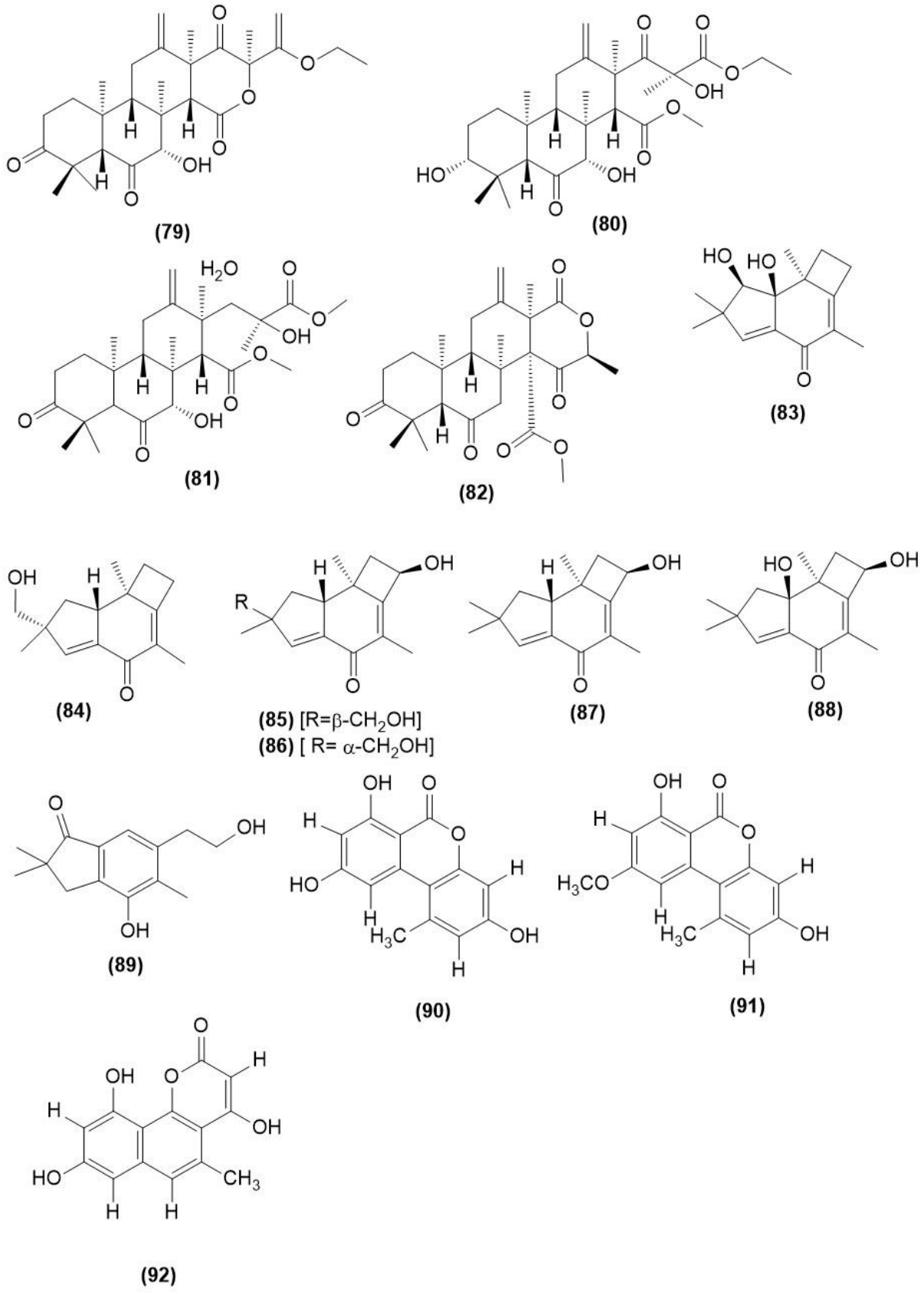

Figure 5. Antiviral potential of bioactive compounds produced by fungi.

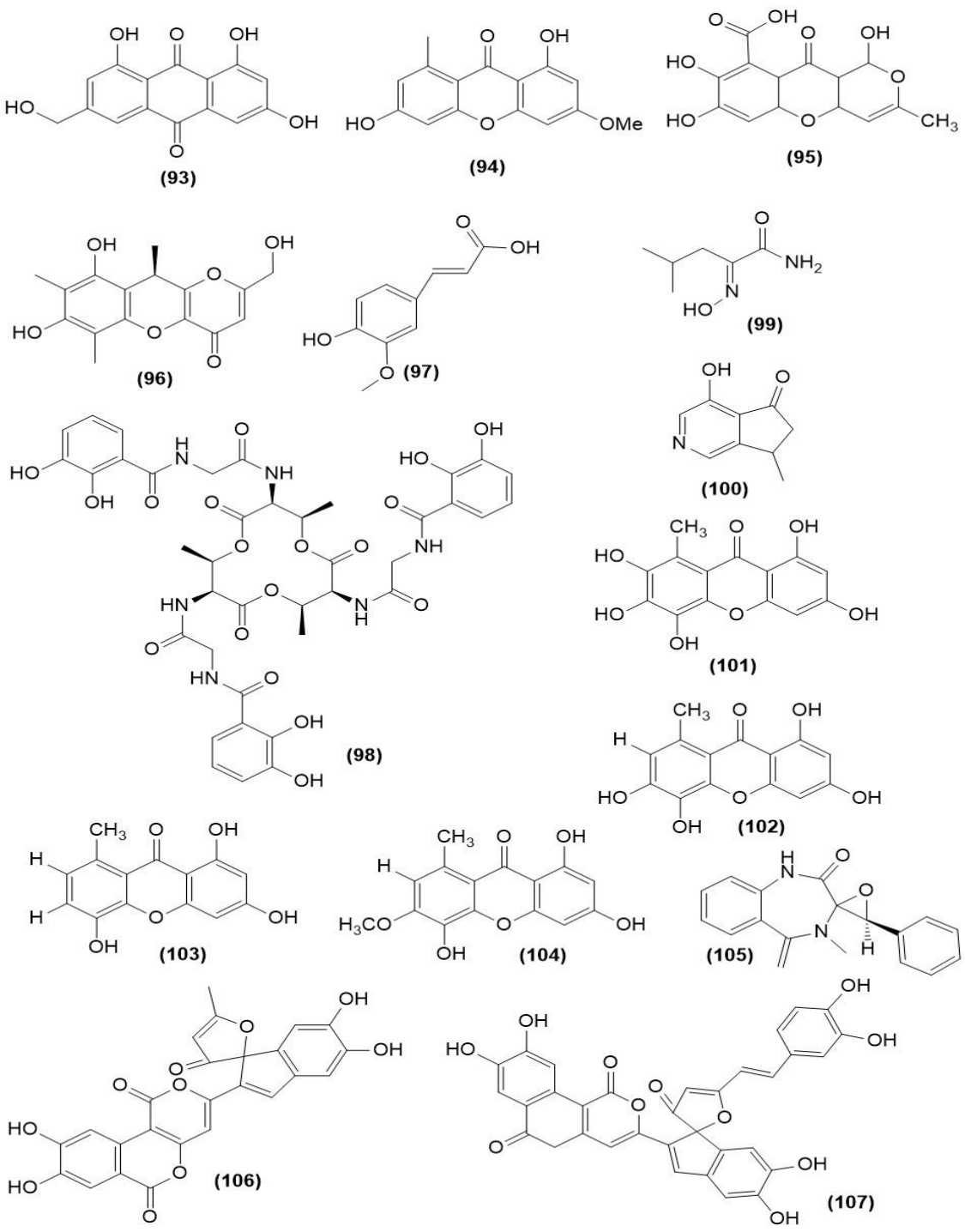

Figure 5. Antiviral potential of bioactive compounds produced by fungi (contd.)

derived fungus produced asperpentenones C **(96)** and trans-ferulic acid **(97)** which exhibited NA inhibitory effect with IC_{50} of 31.3 and 73.6 µM respectively (Chen et al., 2023).

Bacillibactin **(98)** isolated from marine derived fungus *Aspergillus sydowii* SCSIO 41041 isolated from *Creseis acicula* exhibited significant inhibitory against NA with IC_{50} of 24 µM which was nearly significant to positive drug Oseltamivir phosphate which exhibits an IC_{50} of

20 µM (Song et al., 2024). The mangrove soil-derived fungus *Arthrinium* sp. SCSIO 41305, produced a new alkaloid, (E)-2-(hydroxyimino)-4-methylpentanamide **(99)** and a new cyclopentano[b] pyridine, 4-hydroxy-7-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-5-one **(100)** apart from 10 known compounds. (E)-2-(hydroxyimino)-4-methylpentanamide **(99)** and bacillibactin **(98)** exhibited a potent NA inhibitory activity with an IC_{50} of 12.04, 1.92 µmol L^{-1} when compared to Oseltamivir exhibiting an IC_{50} of 20 µmol L−1. Anomalin B **(101)**, 1,3,5,6-tetrahydroxy-8-methyl-xanthone **(102)**, 1,3,6-trihydroxy-8-methyl xanthone **(103)** and Caloxanthone E **(104)** exhibited moderate NA inhibitory activity of 88.3 %, 91.5 %, 75.2 % and 75 % at 100 µg/ml respectively (Hu et al., 2023). *Penicillium polonicum* MCCC3A 00951, is a fungus derived from sediment of the mangrove forest in China. It produces Cyclopenin **(105)** which exhibit potent NA inhibition with IC_{50} of 5.02 µM (Liu et al., 2020). Fruiting bodies of *Phellinus igniarius* produced two phelligridins, E **(106)** and G **(107)**. The compound E **(106)** and G **(107)** exhibited an IC_{50} value of 6.7 µM for inhibition activity. Phellgridin E **(106)** exhibited H1N1and H5N1 neuraminidases inhibition activity with IC_{50} of 8.1 and 1.0 µM respectively while Phellgridin G **(107)** exhibited an IC_{50} value of 8.0 and 0.7 µM for H1N1 and H5N1 neuraminidase respectively (Kim et al., 2016).

7. Anticancer Potential of Enzyme Inhibitors

Cancer is defined as an uncontrolled growth proliferation of cells, which often takes over other cellular systems, thereby leading to death of the individual. Cancer is the second leading cause of death in the world. Cancer being a multifactorial disease can be controlled by modulating the signalling pathways of aberrant cells which are mediated via variety of biochemical pathways. Hence enzyme inhibitors play a crucial role in development of anti-cancer therapeutic interventions. Histone acetyltransferases (HAT) play a key role in normal and malignant haematopoiesis apart from regulating the normal blood cell development (Sun et al., 2013). Protein acetylation regulates the haematopoietic stem cells self-renewal, proliferation and differentiation into committed haematopoietic progenitors (Friedmann and Marmorstein, 2013). Chromosomal translocation involving HAT genes are commonly found in haematological malignancies. Cancer genome studies have identified HAT genes as a common target for mutations which result in haematological malignancies (Bruserud et al., 2006; Joosten et al., 2013). Recently, Anacardic acid derivatives (AAd's) have been isolated from a wild fungus, *Tyromyces fissilis* which have been previously reported as xanthine oxidase inhibitor. Nine AAds were screened for their acetyltransferase inhibitory activity. It is reported that two derivatives viz. AAd7 **(108)** and AAd11**(109)** inhibited the acetyltransferase activity of PCAF (P300/CBP-associated factor) at concentration of 50 and 100 µM respectively. The inhibition intensity was found to be similar to Anacardic acid **(110)** (Hatakeyama et al., 2024). Yet another target is Isocitrate dehydrogenase (IDH1) which are major subset of primary human brain cancers. A single reside mutation in IDH1 active site disables the enzyme's ability to convert isocitrate to α-ketoglutarate. Further this mutation causes IDH to carry out NADPH dependent reduction of α-ketoglutarate to R (-)-2-hydroxyglutarate (2HG). Excess of 2 HG leads to an elevated risk of malignant brain tumors in patients with inborn errors of 2HG metabolism (Dang et al., 2009). Coral derived fungus *Parengyodontium album* SCSIO 5X7W11 was isolated from *Arcoproa* sp. sample collected from South China sea produced two compounds Alternaphenol B2 **(111)** and Alternaphenol B **(112)** which selective inhibitory activity against IDH1 with IC_{50} of 41.9 and 27.7 µM respectively (Li et al., 2024). Cyclin dependent kinases (CDK) play an integral role in cell division and cell cycle apart from modulating transcription based on external and internal signals (Malumbres, 2014). An endophytic fungus, *Aspergillus* sp. TRL1 associated with the stems of *Tabebuia rosea*,

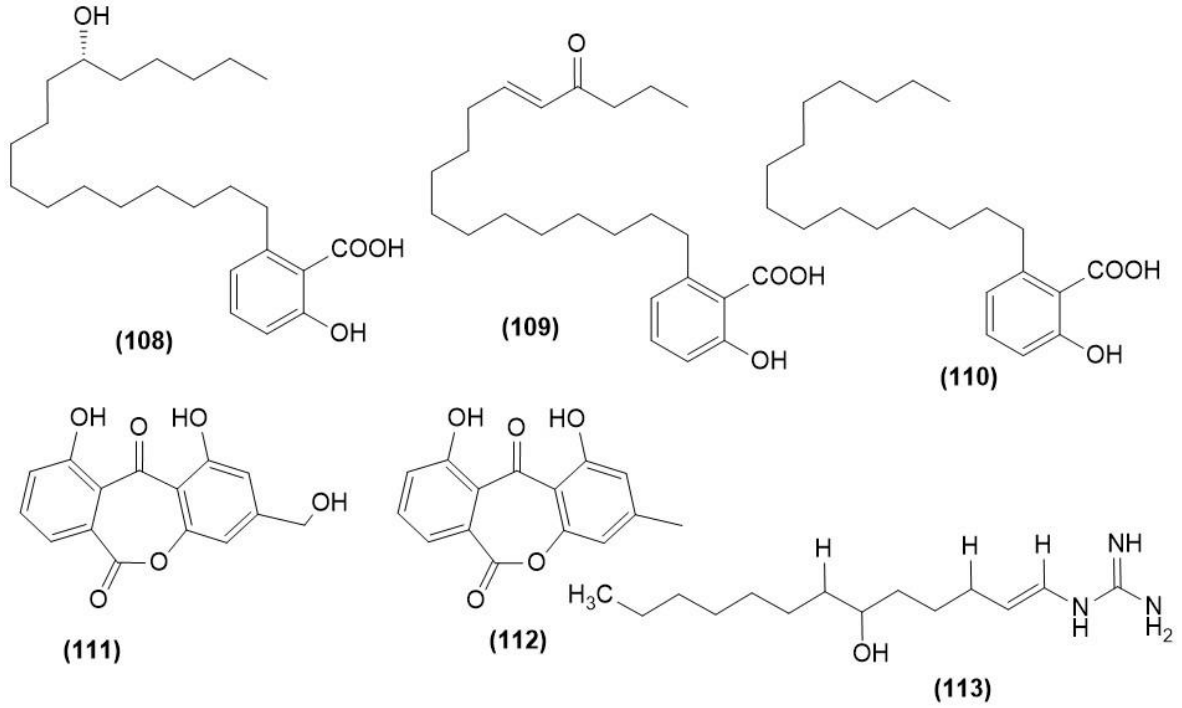

Figure 6. Fungal compounds as inhibitors in the mechanistic pathway of cancer.

produced Pulchranin A **(113)** for the first time, which not only exhibited cytotoxic activity but also potential inhibition of CDK. Pulchranin A **(113)** exhibited promising cytotoxic activity against MCF-7 (breast cancer), Hep-G2 (Liver) and HCT (Colorectal) cell lines with IC_{50} values of 243.9 µM, 308.7 µM, 351.13 µM respectively. It also inhibited cyclin dependent kinases, CDK1, CDK2 and CDK4 in MCF-7 cells with IC_{50} values of 37.9 µM, 60.2 µM and 10.42 µM respectively (Moussa et al., 2020).

8. Other Metabolic Diseases

There are other important enzymes across the human biochemistry, which can be attractive targets for a variety of diseases. 3-hydroxyl-3-methylglutamyl coenzyme A (HMG CoA) reductase is a crucial enzyme of lipid biosynthetic pathway. Lovastatin happened to be the first HMG CoA reductase inhibitor. Several semi-synthetic versions of lipid lowering drugs have been developed and are used in clinical settings. Collecapsins A **(114)** and B **(115)**, are two natural analogues of Lovastatin have been found to be produced by the endophytic fungus, *Colletotrichum capsici*. The IC_{50} values of Collecapsin A **(114)** and B **(115)** were found to be 8.72 µM and 15.28 µM respectively (Lu et al., 2025).

White-rot fungus *Irepex lacteus* has been found to produce three new pyridine derivatives Irpelactedines A-C **(116-118)** and a new furan derivative Irpelactedine D **(119)** and known compounds, Irpexidine A **(120)** and 5-carboxy-2-furanpropanoic acid **(121)**. Irpelactedine A **(116)** and Irpelactedine C **(118)** exhibited moderate inhibition of Angiotensin converting enzyme (ACE) which are regulators of hypertension with IC_{50} values of 161.5 µM and 389.12 µM respectively (Yu et al., 2025).

Adenosine deaminase (ADA) is a zinc containing enzyme which plays a critical role in purine catabolism. Biochemically it is responsible of adenosine and 2-deoxyadenosine into inosine and 2-deoxyinosine respectively thereby regulating the endogenous level of nucleotides. It also

plays an important role in differentiation and maturation of the lymphoid system cells as it is ubiquitously expressed and is found in serum as well as human tissues. Abnormal levels of ADA have been detected in AIDS (acquired immunodeficiency syndrome), anaemia, lymphomas and leukaemia. An endophytic *Aspergillus niger* QJ-4 isolated from *Gentialla macrophylla* afforded a compound, 3-(4-nitrophenyl-5-phenyl isoxazole) **(122)** which inhibited ADA by 94.7% uncompetitively (Zhang et al., 2018). Isocitrate lyase (ICL) is the key enzyme of glyoxylate cycle which is fundamentally shared between microorganisms, plants and certain invertebrates (Vanni et al., 1990). It plays a critical role in bacterial as well as fungal pathogenesis (Dunn et al., 2009). Upregulated expression of ICL has been reported in *Mycobacterium tuberculosis* while infecting macrophages (Munoz-Elias & McKinney, 2005), while a similar upregulated expression is observed in *Magnaporthe grisea* during rice blast disease (Wang et al., 2003). Isocitrate lyase (ICL) has been an attractive target for anti-fungal drug discovery since it is absent in mammalian cells. A marine fungus *Aspergillus quadrilineatus* strain FJJ093 led to an organic compound extract which exhibited inhibitory activity towards *Candida albicans* ICL. Bioassay guided isolation led to isolation of four epipolythiodioxopiperazine alkaloids, namely secoemestrin C **(123)**, dethiosecoemestrin **(124)**, emestrin **(125)** and emestrin B **(126)**. Secoemestrin C **(123)** was found to be a potent inhibitor of ICL with IC_{50} of 4.77 ± 0.08 μM and holds promise for the development of anti-candidal drugs (Hwang et al., 2021).

Another enzyme, Sterol-O-acetyltransferase (SOAT) is an endoplasmic reticulum enzyme/ protein which plays a prominent role in cholesterol regulation, is a prominent target for the development of anti-atherosclerotic agents (Guan et al.,2020). Further molecular studies have revealed that SOAT has two isomers, SOAT1 and SOAT2. SOAT1 is a ubiquitously expressed in all the tissues and cells while SOAT2 is predominantly expressed in hepatocytes and intestines (Andersen et al., 1998). Inhibitors of SOAT1 and SOAT2 have been evaluated using cell-based assays primarily utilizing CHO cells as well as *in vitro* enzymatic assays. A marine derived fungus, *Aspergillus ungui* NKM-007 collected from Suruga Bay in Japan produced a new depsidone, 7-chlorofolipstatin (**127**) which exhibited an IC_{50} of 3.2 μM and 4.5 μM for SOAT 1 and SOAT2 respectively in cell-based assays while in enzymatic assay the IC_{50} was 6.5 μM for SOAT1 and 19 μM for SOAT2 thus exhibiting moderate inhibitory activity (Uchida et al., 2016). A soil isolate of *Aspergillus nidulans* BF-0142 was found to produce Helvamide as a mixture of rotamers 1 **(128)** and 2 **(129)** along with a new furanone metabolite, designated as Helvafuranone **(130)**. Helvamide inhibited cholesterol ester synthesis in SOAT1-CHO and SOAT2-CHO cells with IC_{50} of 22 μM and 6.7 μM respectively. Helvamide did not affect the phospholipid biosynthesis and it was not cytotoxic to the CHO cells at a dose of 44 μM (Fukuda et al., 2019). Trypsin is a protein digesting enzyme that is essential for growth and regeneration of bone, muscle, cartilage, skin and blood (Baird, 2013). Trypsin inhibitors have different roles in treating diseases such as inflammation, Alzheimer's disease, pancreatitis, and cancer prognosis (de Lima et al., 2019). Endophytic *Nigrospora sphaerica* AVA-1 residing in *Dendrophthae falcata* was found to produce a trypsin inhibitor (TI), which was identified as Quercetin **(131)** (Kallingal et al., 2021).

9. Biosynthetic Gene Clusters (BGCs) & Inhibitors

Biosynthetic Gene Clusters (BGCs) are contiguous sets of genes which encode for enzymes, transporters, regulatory proteins which are required for the synthesis of secondary metabolites (Toppo et al., 2023). Pivotal enzymes encoded by BGCs comprise of polyketide synthases (PKS). Non- ribosomal peptide synthetases (NRPSs), hybrid PKS-NRPSs, terpene synthases and an array of tailoring enzymes. BGCs are highly variable in different fungal taxa, of which

endophytes exhibit unique clusters, generally not found in other fungi probably attributed to the mutualistic evolution. Identification of silent BGCs and their activation is one of the recent strategies for identification of novel SMs as inhibitors. The activation of genes/ gene clusters can be achieved at genome, proteome, transcriptome or metabolome levels (Scherlech & Hertweek, 2021).

Genome mining of *Helotiales* sp. BL73 isolated from the medicinal plant *Bergenia pacumbis* exhibited 77 SM biosynthetic gene clusters which could be associated with previously reported bioactive molecules or new ones. Four codons terpene synthase genes were optimized from BL73 genome and expressed together with farnesyl-, geranyl-, and geranylgeranyl-pyrophosphate synthases, in *Streptomyces* spp. Recombinant strains produced linalool and its oxidized forms apart from terpenoids typically associated with the plant. This study indicated that this *Helotiales* isolate exhibits huge potential to produce diverse secondary metabolites belonging to polyketides, NRPs, terpenoids, and ribosomally synthesized and post-translationally modified peptides (RiPPs). Further the establishment of link between the meroterpenoids and xanthones produced by this isolate and their putative biosynthetic genes provides a platform to investigate their respective biosynthetic pathways (Oberhofer et al, 2022).

Another endophytic fungus, *Calcarisporium arbuscula* produced a compound, a tetramic acid, named as MCA17-1 **(132)** was produced by aurovertin null production mutant by activation of a silent gene *mca17 b*y overexpression of a pathway specific zinc-finger transcriptional regulator. The biosynthesis of MCA17-1 was proposed to be from the core PKS-NRPS hybrid enzyme. MCA 17-1 suppressed the LX-2 activation when challenged by TGF-β (transforming growth factor-β) and had stronger bioactivity than the positive control obeticholic acid (OCA) against liver fibrosis (Cheng et al.,2021).

Genome mining tools FunBGCeX was used to screen approximately 2500 fungal genomes. This led to identification of a BGC designated as the pts cluster, which encodes an acetolactate synthase (ALS) homologue. ALS catalyses the first step of branched chain amino acid (Valine, Leucine and Isoleucine) synthesis in plants and microorganisms. Characterization of pts cluster led to the discovery of a compound pterrespiramide A **(133)** which contains of spirotetramate and decalin moieties. It exhibits antifungal and herbicidal activities. (Chan et al., 2025). Discovery of pterrespiramide A **(133)** demonstrates the potential of resistance gene-guided genome mining to uncover previously undescribed bioactive natural products.

Thus, biosynthetic clusters represent nature's richest source of bioactive molecules, with inhibitors derived from BGC products constituting a substantial portion of clinically used drugs.

10. Discussion & Conclusion

Fungal secondary metabolites are an unlimited pool of rich and chemically diverse inhibitors with broad therapeutic relevance. Presumably roughly half of the known bioactive microbial metabolites ~15600 compounds are of fungal origin (Conrado et al., 2022). In summary, findings from 2015- 2025 highlight the potential of fungi as underexplored pools of inhibitors of all major druggable enzymes such as protease, kinases, glucosidases, cholinesterase, polymerases and many more as newer targets of different diseases are being explored with applications spanning cancer, diabetes, neurodegeneration, viral infections, and metabolic disorders. These unexplored pools of fungal compounds can be from extremophilic

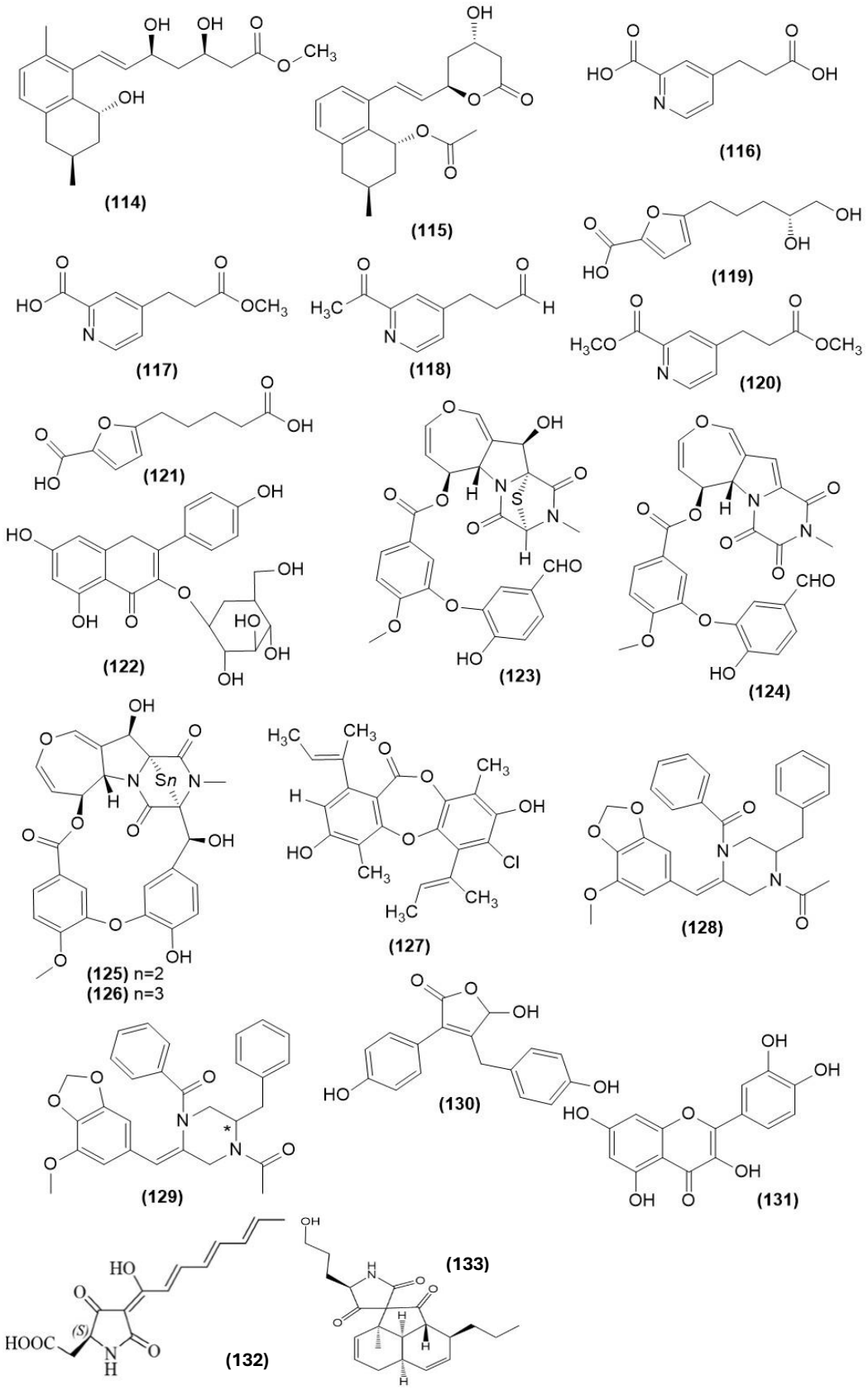

Figure 7. Enzyme inhibitors produced by fungi with enzymes or reactions responsible for different metabolic diseases.

Table 1. Summary of some promising key inhibitors isolated from fungi.

S No.	Inhibitor (Figure No.)	Organisms name	Target Site	IC_{50} (μM)	Inhibition Type*	Reference
1	Albolutein C **(7)**	*Malbranchea albolutea*	protein- tyrosinase phosphate 1B (PTP1B)	129.5	N-C	Diaz_Rojas et al., (2021)
2	Aspergorakhin A **(8)**	*Aspergillus gorakhpurensis*	PTPB1; SHP 1; TCPTP (T-cell protein tyrosine phosphate)	0.57; 1.19; 22.97	C	Jia et al., (2021)
3	Asperitin B **(17)**	*Aspergillus sydowii*	PTP1B	2.05	C	Weise et al., (2017)
4	Aspergiamides A **(31)**	*Aspergillus sp. 16-5c*	α-glucosidase	18.2	C	Ye et al., (2021)
5	Asperterpenes A **(77)**	*Aspergillus terreus*	BACE 1	0.08	NS	Qi et al., (2016)
6	Asperterpenes E **(79)**	*Aspergillus terreus*	BACE 1	3.3	NS	Qi et al., (2016)
7	Asperterpenes F **(80)**	*Aspergillus terreus*	BACE 1	5.9	NS	Qi et al., (2016)
8	Asperterpenes J **(82)**	*Aspergillus terreus*	BACE 1	31.7	NS	Qi et al., (2016)
9	Alternariol **(90)**	*Botryotinia fuckeliana* strain KF666	Glycogen synthase kinase-3 (GSK-3)	0.13	NS	Weise et al., (2016)
10	Alternariol monomethyl ether **(91)**	*Botryotinia fuckeliana* strain KF666	GSK-3	0.2	NS	Weise et al., (2016)
11	Asperpentenones C **(96)**	*Aspergillus austwickii* SCSIO 41227	Neuraminidase	31.3	C	Chen et al., (2023)
12	Alternaphenol B2**(111)**	*Parengyodontium album* SCSIO 5X7W11	Isocitrate dehydrogenase (IDH1)	41.9	N-C	Li et al., (2024)
13	Alternaphenol B **(112)**	*Parengyodontium album* SCSIO 5X7W11	IDH1	27.7	N-C	Li et al., (2024)
14	Biscogniapyrone C **(26)**	*Biscogniauxia capnodes* SWUF15	α -glucosidase	58	N-C	Churat et al., (2025)
15	Brevianamide K **(37)**	*Aspergillus sp.* 16-5c	α -glucosidase	7.6	C	Ye et al., (2021)
16	Botryorhodine D **(60)**	*Meyerozyma guilliermondii*	α -glucosidase	2.1	C	Chen et al., (2015)
17	Botryorhodine F **(62)**	*Meyerozyma guilliermondii*	α -glucosidase	9.8	C	Chen et al., (2015)
18	Botryorhodine G **(63)**	*Meyerozyma guilliermondii*	α -glucosidase	12.4	C	Chen et al., (2015)
19	Botryorhodine H1 **(64)**	*Trichoderma sp.* 307	α -glucosidase	8.1	C/M	Zhang et al., (2017)
20	Butyrolactone I **(74)**	*Aspergillus terreus* SGP-1	Butyrylcholinesterase	35.5	C	Cui et al., (2022)
21	Butryolactone VII **(75)**	*Aspergillus terreus* SGP-1	Butyrylcholinesterase	18.4	C	Cui et al., (2022)
22	Bacillibactin **(98)**	*Aspergillus sydowii* SCSIO 41041	Neuraminidase	24	NS	Song et al., (2024)

23	Chordimanin A **(21)**	*Penicillium verruculosum* TPUB11	PTP1B	8.5	C	Yamazaki et al., (2016)
24	Chordimanin H **(23)**	*Penicillium verruculosum* TPUB11	PTP1B	14.9	N-C	Yamazaki et al., (2017)
25	Cyclopenin **(105)**	*Penicillium polonicum* MCCC3A 00951	Neuraminidase	5.02	NS	Liu et al., (2020)
26	Collecapsins A **(114)**	*Colletotrichum capsici*	HMG CoA reductase	8.72	C	Lu et al., (2025)
27	Collecapsins B **(115)**	*Colletotrichum capsici*	HMG CoA reductase	15.28	C	Lu et al., (2025)
28	Chlorofolipstatin **(127)**	*Aspergillus ungui* NKM-007	Sterol-O-acetyltransferase (SOAT) 1	3.2	C	Uchida et al., (2016)
			SOAT 2	4.5	C	
29	Emindole SB **(16)**	*Penicillium species* KFD28	PTP1B; TCPTP	0.7; 1.4	N-C	Kong et al., (2019)
30	(E)-2-(hydroxyimino)-4-methylpentanamide **(99)**	*Arthrinium sp.* SCSIO 41305	Neuraminidase	12.04	C	Song et al., (2024)
31	Fumosorinone **(18)**	*Isaria fumosorosea*	PTP1B	14.04	N-C	Liu et al., (2015)
32	Flupyranochromene **(95)**	*Penicillium* sp. f28743	Influenza virus RNA polymerase	0.8	NS	Yamasaki et al., (2019)
33	Grieseoxanthone C **(94)**	*Fusarium equisetii*	Hepatitis C virus N53/4A protease	19.88	C	Hawas et al., (2016)
34	Helicascolides A **(45)**	*Daldinia eschscholtzii* HJ004	α -glucosidase	16	M	Liao et al., (2021)
35	Helvamide **(128/129)**	*Aspergillus nidulans* BF-0142	SOAT1-CHO	22	C	Fukuda et al., (2019)
			SOAT2-CHO	6.7	C	
36	Hydroxy-5-[[4-hydroxy-3-(3-methyl-2-buten-1-yl) phenylmethyl]-4-(4-hydroxyphenyl) -2-(5H)-furanone **(76)**	*Aspergillus terreus* SGP-1	Butyrylcholines-terase	45.1	N-C/M	Cui et al., (2022)
37	Leptosphaeridone **(3)**	*Remotididymella sp.*	Proteasome		C	Nishimura et al., (2022)
38	Nectriacids B **(51)**	*Nectria sp.*HN001	α -glucosidase	23.5	NS	Cui et al., (2016)
39	Nectriacids C **(52)**	*Nectria sp.*HN001	α -glucosidase	42.3	C	Cui et al., (2016)
40	Neobrefeldin **(66)**	*Penicillium brefeldianum F4a*	Acetylcholinesterase	0.12	M	Bai et al., (2024)
41	Penerpene A **(11)**	*Penicillium species* KFD28	PTP1B; TCPTP	1.7; 5.0	C	Kong et al., (2019)

42	Penerpene B **(12)**	*Penicillium species* KFD28	PTP1B; TCPTP	2.4; 4.5	C	Kong et al., (2019)
43	Pannorin **(92)**	*Aspergillus sp. LF660*	GSK-3	0.35	C	Weise et al., (2016)
44	Phellgridin E **(106)**	*Phellinus igniarius*	H3N2 neuraminidase	6.7	C	Kim et al., (2016)
45	Phellgridin G **(107)**	*Phellinus igniarius*	H3N2 neuraminidase	6.7	C	Kim et al., (2016)
46	Pulchranin A **(113)**	*Aspergillus sp. TRL1*	Cyclic dependent kinases (CDK) CDK1	37.9	C	Moussa et al., (2020)
			CDK4	60.2	C	
			CDK7	10.42	C	
47	Pterrespiramide A **(133)**	*Fungal Biosynthesis Gene Cluster pts*	Acetolactate synthase	1.5	NS	Chen et al., (2025)
48	Secoemestrin C **(123)**	*Aspergillus quadrilineatus strain FJJ093*	*C. albicans* Isocitrate lyase (ICL)	4.77	U-C	Hwang et al., (2021)
49	Trans-ferulic acid **(97)**	*Aspergillus austwickii* SCSIO 41228	Neuraminidase	73.6	C	Chen et al., (2023)
50	Tripalmitin **(46)**	*Zasmidium sp. strain* EM5-10	α -glucosidase	3.75	M	Lopez et al., (2019)
51	Verruculides A **(19)**	*Penicillium verruculosum* TPUB11	PTP1B	8.4	C	Yamazaki et al., (2015)
52	Versilactone B **(73)**	*Aspergillus terreus* SGP-1	butyrylcholinesterase	44.3	NS	Cui et al., (2022)
53	ω-hydroxyemodin **(93)**	*Fusarium equisetii*	Hepatitis C virus N53/4A protease	10.7	C	Hawas et al., (2016)
54	1,7-dihydroxy -8-(methoxy carbonyl) xanthone-3-carboxylic acid **(57)**	*Aspergillus versicolor*	α -glucosidase	0.24	N-C	Ma et al., (2015)
55	(s)-1,3,6,-trihydroxy-7-(-1-hydroxyethyl) anthracene-9,10-dione **(30)**	*Fusarium incarnatum*	α -glucosidase	77.67	U-C	Fan et al., (2022)
56	2,3-dihydroxy-5-methoxy-2-methyl chromen-4-one **(43)**	*Daldinia eschscholtzii HJ004*	α -glucosidase	15	NS	Liao et al., (2020)
57	3-hydroxybenzoic acid **(29)**	*Diaporthe species*	α -glucosidase	165.4	C	Mugaranja & Kulal, (2022)
58	7-hydroxy-5-methoxy-2,3-dimethyl chromone **(42)**	*Daldinia eschscholtzii HJ004*	α -glucosidase	13	C/M	Liao et al., (2019)

** Abbreviations used: N-C: Non-competitive; C- competitive; NS: Not specified; C/M: competitive or mixed; N-C/M: Non-competitive or mixed; U-C: Uncompetitive*

environments such as marine fungi or high altitude. Such a diverse "arsenal" of fungal molecules reinforces the potential of fungi in enzyme-targeted drug discovery.

The chemical scaffolds produced by fungi bear unprecedented ring systems, stereochemistry or hybrid biosynthetic origin which is beyond the imagination of a synthetic chemist as they are absent or rare in synthetic libraries. Deep-sea and plant-associated fungi are especially abled in producing these structures, implying that nature is the ultimate chemist. These novel chemical architectures offer fresh starting points for inhibitor design. Moreover, fungi occupy diverse ecosystems (marine, terrestrial, endophytes, extremophiles), expanding the chemical space. This ecological breadth means fungal libraries contain halogenated, polycyclic, and otherwise rare chemotypes that often evade synthetic bias (Takahasi et al., 2021). Many fungal inhibitors act via mechanisms (e.g. covalent binding, chelation) that are difficult to rationally design, providing innovative modes of action. The best part of fungal metabolites is that they are often produced by fermentation process as fungi are amenable to large-scale culture and the production cost is much lower as compared to total synthesis. Moreover, many classical fungi-derived inhibitors are off-patent thereby opening avenues for reformulation or analogs development with fewer intellectual property hurdles. Taken together, these advantages make fungi attractive for lead generation and downstream development. Despite these strengths, many fungal secondary metabolites, exhibit suboptimal pharmacokinetics, high molecular weight, poor solubility or membrane permeability can limit oral bioavailability. This makes imperative use of *in silico* ADMET screening of these natural products produced by fungi. Those which qualify tend to progress to the development pipeline.

Fungal toxins (mycotoxins as well as phytotoxins) illustrate a fine line between poison and drug; some enzyme inhibitors may have off-target effects or toxicity. There are a variety of approaches by which the toxicity can be reduced one of them being QSAR (Quantitative structure activity relationship). Some classical examples wherein poisons/ toxin have been converted into drugs comprise of Cyclosporin A, Fingolimod, Enniatins, Plinabulin and Irofulven. Cyclosporin A was isolated from *Tolypocladium inflatum*, act as an immunosuppressant by inhibition of calcineurin pathway to block the T-cell activation and is therefore clinically used as organ transplantation drug (Survase et al., 2011). Fingolimod is yet another fungal toxin derived medicine, based on myriocin from *Isaria sinclarii*. It is used for treating multiple sclerosis by modulating immune response. Fingolimod (FTY720) works by binding and modulating the sphingosine-1-phosphate (S1P) receptor, which traps lymphocytes in lymph nodes and prevents them from migrating to the central nervous system (Chiba, 2020). Fusafungine, is a mixture of enniatins produced by different species of *Fusarium* which is used as a topical treatment of upper respiratory tract infections by oral/nasal inhalations (Sy-Cordero et al., 2012).

Plinabulin, is a derivative of phenylahistin isolated from a marine fungus, *Aspergillus* species (Nicholson et al., 2006). Another anti-cancer drug Irofulven is a semi-synthetic derivative of Illudin S (MGI 114, NSC 683863), a natural toxin found in *Omphalotus illudens,* Jack O'Lantern mushroom (Kelner et al., 2006). It is also imperative to understand the mechanistic process of inhibition of fungal secondary metabolites which have been identified in phenotypic screening or enzyme screening. Enzyme kinetics, crystallographic studies and proteomics can provide an insight to these for developing superior versions of the pharmacophore with more drug likeliness. Hence medicinal chemistry plays a critical role to define the mechanism of action, optimization and rationale of therapeutic use.

Thus, one can clearly emphasize that fungi remain an underutilized treasure trove for enzyme targeted drug discovery having been known for their structurally diverse metabolites with broad bioactivity of which some are already into clinical use. The present review has highlighted the fungal inhibitors already approved as well as many promising leads. The breadth of fungal chemo-diversity is reflected in the numerous biosynthetic gene clusters uncovered by genomics and indicates that we have only scratched the surface of their potential. Heterologous expression of fungal gene clusters (synthetic biology) has further propelled in identifying dozens of new metabolites by exploiting genomic sequencing, bioinformatic mining for cryptic biosynthetic gene clusters encoding for novel enzyme inhibitors. Alongside computational drug design and high-throughput screening, these tools create a pipeline to move fungal inhibitors from petri dish to clinic. In sum, the unique chemical diversity of fungi, when harnessed with genomics, metabolomics and synthetic biology, offers a powerful strategy to discover enzyme inhibitors for future therapeutics. By continuing to explore and engineer fungal biosynthetic potential, we may uncover the next generation of drugs to address diseases beyond the reach of current treatments.

References

Anderson, R. A., Joyce, C., Davis, M., Reagan, J. W., Clark, M., Shelness, G. S., & Rudel, L. L. (1998). Identification of a form of Acyl-CoA: Cholesterol acyltransferase specific to liver and intestine in nonhuman primates. *Journal of Biological Chemistry, 273*(41), 26747–26754. https://doi.org/10.1074/jbc.273.41.26747

Bai, Y., Ma, X., Ren, D., Yu, G., Hu, J., Hua, H., & Pan, H. (2024). Peniapyrones A–I, Cytotoxic Tricyclic-Fused α-Pyrone Derivatives from an Endophytic *Penicillium brefeldianum F4a*. *Journal of Natural Products, 87*(6), 1643–1651. https://doi.org/10.1021/acs.jnatprod.4c00383

Baron A. D. (1998). Postprandial hyperglycemia and alpha-glucosidase inhibitors. *Diabetes research and clinical practice*, *40 Suppl*, S51–S55. https://doi.org/10.1016/s0168-8227(98)00043-6

Batool, M., Ahmad, B., & Choi, S. (2019). A Structure-Based drug discovery paradigm. *International Journal of Molecular Sciences, 20*(11), 2783. https://doi.org/10.3390/ijms20112783

Bruserud, Ø., Stapnes, C., Tronstad, K. J., Ryningen, A., Anensen, N., & Gjertsen, B. T. (2006). Protein lysine acetylation in normal and leukaemic haematopoiesis: HDACs as possible therapeutic targets in adult AML. *Expert Opinion on Therapeutic Targets, 10*(1), 51–68. https://doi.org/10.1517/14728222.10.1.51

Chan, C. W., Yu, C. L., Lin, J. C., Hsieh, Y. C., Lin, C. C., Hung, C. Y., Li, C. H., Liao, Y. C., Lo, C. P., Huang, J. L., Lin, C. H., & Wu, T. J. (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. *Cardiovascular Diabetology, 17(*1), 20. https://doi.org/10.1186/s12933-018-0663-6

Chan, T. K., Wei, X., Ma, L., Wang, H., Liao, P., & Matsuda, Y. (2025). Resistance Gene-Guided Discovery of a Fungal Spirotetramate as an Acetolactate Synthase Inhibitor. *Journal of the American Chemical Society, 147*(45), 42100–42109. https://doi.org/10.1021/ jacs.5c16272

Chen, S., Liu, Z., Liu, Y., Lu, Y., He, L., She, Z. (2015). New depsidones and isoindolinones from the mangrove endophytic fungus *Meyerozyma guilliermondii* (HZ-Y2) isolated from the South China Sea. *Beilstein J. Org. Chem.*, *11*, 1187-1193. https://doi.org/10.3762/bjoc.11.133

Chen, Y., He, Y., Pang, X., Zhou, X., Liu, Y., & Yang, B. (2023). Secondary Metabolites from the Coral-Derived Fungus *Aspergillus austwickii* SCSIO41227 with Pancreatic Lipase and Neuraminidase Inhibitory Activities. *Marine Drugs, 21*(11), 567. https://doi.org/10.3390/md21110567

Chen, Z., Huang, J., Yang, S., & Hong, F. (2022). Role of cholinergic signaling in Alzheimer's disease. *Molecules, 27*(6), 1816. https://doi.org/10.3390/molecules27061816

Chiba, K. (2020). Discovery of fingolimod based on the chemical modification of a natural product from the fungus, *Isaria sinclairii*. *The Journal of Antibiotics, 73*(10), 666–678. https://doi.org/10.1038/s41429-020-0351-0

Churat, A., Katrun, P., Laohpongspaisan, C., Mongkolthanaruk, W., Champasri, C., Moontragoon, P., Suwannasai, N., Sangvichien, E., Poonsukkho, P., & McCloskey, S. (2025). Potential α-glucosidase inhibitors from cultures of *Biscogniauxia capnodes* SWUF15-40 fungus. *Journal of Natural Medicines, 79*(3), 488–498. https://doi.org/10.1007/s11418-025-01876-9

Cheng, J., Wang, H., Yu, J., Sun, C., Cao, F., Jiang, X., Chen, X., Zhao, Q., Gan, L., Xie, R., Wang, S., Li, J., Zang, Y., & Mao, X. (2021). Discovery of a Potential Liver Fibrosis Inhibitor from a Mushroom Endophytic Fungus by Genome Mining of a Silent Biosynthetic Gene Cluster. *Journal of Agricultural and Food Chemistry, 69*(38), 11303–11310. https://doi.org/10.1021/acs.jafc.1c03639

Combs, A. P. (2009). Recent advances in the discovery of competitive protein tyrosine phosphatase 1B inhibitors for the treatment of diabetes, obesity, and cancer. *Journal of Medicinal Chemistry, 53*(6), 2333–2344. https://doi.org/10.1021/jm901090b

Conrado, R., Gomes, T. C., Roque, G. S. C., & De Souza, A. O. (2022). Overview of Bioactive Fungal Secondary Metabolites: Cytotoxic and Antimicrobial Compounds. *Antibiotics* (Basel, Switzerland), *11*(11), 1604. https://doi.org/10.3390/antibiotics 11111604

Cui, H., Liu, Y., Nie, Y., Liu, Z., Chen, S., Zhang, Z., Lu, Y., He, L., Huang, X., & She, Z. (2016). Polyketides from the mangrove-derived endophytic fungus *Nectria* sp. HN001 and their α-Glucosidase inhibitory activity. *Marine Drugs, 14*(5), 86. https://doi.org/10.3390/md14050086

Cui, X., Deng, S., Li, G., Zhang, Y., Wang, L., Wu, C., & Deng, Y. (2022). Butenolide derivatives from *Aspergillus terreus* selectively inhibit butyrylcholinesterase. *Frontiers in Chemistry, 10,* 1063284. https://doi.org/10.3389/fchem.2022.1063284

Dang, L., White, D. W., Gross, S., Bennett, B. D., Bittinger, M. A., Driggers, E. M., Fantin, V. R., Jang, H. G., Jin, S., Keenan, M. C., Marks, K. M., Prins, R. M., Ward, P. S., Yen, K. E., Liau, L. M., Rabinowitz, J. D., Cantley, L. C., Thompson, C. B., Heiden, M. G. V., & Su, S. M. (2009). Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature, 462*(7274), 739–744. https://doi.org/10.1038/nature08617

De La Monte, S. M., Tong, M., Lester-Coll, N., Plater, M., Jr, & Wands, J. R. (2006). Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: Relevance to Alzheimer's disease. *Journal of Alzheimer S Disease, 10(*1), 89–109. https://doi.org/10.3233/jad-2006-10113

De Lima, V.C.O., Piuvezam, G., Maciel, B. L. L., & De Araújo Morais, A. H. (2019). Trypsin inhibitors: promising candidate satietogenic proteins as complementary treatment for obesity and metabolic disorders? *Journal of Enzyme Inhibition and Medicinal Chemistry 34(*1), 405–419. https://doi.org/10.1080/14756366.2018.1542387

Dewi, R. T., Suparman, A., Mulyani, H., Darmawan, A., & Lotulung, P. D. N. (2025). Identification of a New Compound as α-Glucosidase Inhibitor from *Aspergillus aculeatus*. *Annales Bogorienses 20(*1), 19–24. https://ejournal.brin.go.id/annales/article/view/7692

Díaz-Rojas, M., Raja, H., González-Andrade, M., Rivera-Chávez, J., Rangel-Grimaldo, M., Rivero-Cruz, I., & Mata, R. (2021). Protein tyrosine phosphatase 1B inhibitors from the fungus *Malbranchea albolutea*. *Phytochemistry*, *184*, 112664. https://doi.org/ 10.1016/j.phytochem.2021.112664

Dunn, M. F., Ramírez-Trujillo, J. A., & Hernández-Lucas, I. (2009). Major roles of isocitrate lyase and malate synthase in bacterial and fungal pathogenesis. *Microbiology, 155*(10), 3166–3175. https://doi.org/10.1099/mic.0.030858-0

Eichberg, J., Maiworm, E., Oberpaul, M., Czudai-Matwich, V., Lüddecke, T., Vilcinskas, A., & Hardes, K. (2022). Antiviral Potential of Natural Resources against Influenza Virus Infections. *Viruses 14*(11), 2452. https://doi.org/10.3390/v14112452

Elchebly, M., Payette, P., Michaliszyn, E., Cromlish, W., Collins, S., Loy, A. L., Normandin, D., Cheng, A., Himms-Hagen, J., Chan, C., Ramachandran, C., Gresser, M. J., Tremblay, M. L., & Kennedy, B. P. (1999). Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine Phosphatase-1B gene. *Science 283(*5407), 1544–1548. https://doi.org/10.1126/science.283.5407.1544

El-Desoky, A. H., Kato, H., Eguchi, K., Kawabata, T., Fujiwara, Y., Losung, F., Mangindaan, R. E. P., De Voogd, N. J., Takeya, M., Yokosawa, H., & Tsukamoto, S. (2014). Acantholactam and Pre-neo-kauluamine, Manzamine-Related Alkaloids from the Indonesian Marine Sponge *Acanthostrongylophora ingens*. *Journal of Natural Products 77*(6), 1536–1540. https://doi.org/10.1021/np500290a

Fan, J., Lv, C., Li, Z., Guo, M., Yin, Y., Wang, H., Wang, W., & Sun, S. (2022). α-Glucosidase inhibitory effect of an anthraquinonoid produced by *Fusarium incarnatum* GDZZ-G2. *Journal of Basic Microbiology, 62*(11), 1360–1370. https://doi.org/10.1002/jobm.202200166

Friedmann, D. R., & Marmorstein, R. (2013). Structure and mechanism of non-histone protein acetyltransferase enzymes. *FEBS Journal, 280*(22), 5570–5581. https://doi.org/ 10.1111/febs.12373

Fukuda, T., Furukawa, T., Kobayashi, K., Nagai, K., Uchida, R., & Tomoda, H. (2018). Helvamide, a new inhibitor of sterol O-acyltransferase produced by the fungus *Aspergillus nidul*ans BF-0142. *The Journal of Antibiotics, 72*(1), 8–14. https://doi.org/10.1038/s41429-018-0101-8

Glickman, M. H., & Ciechanover, A. (2002). The Ubiquitin-Proteasome proteolytic Pathway: Destruction for the sake of construction. *Physiological Reviews, 82*(2), 373–428. https://doi.org/10.1152/physrev.00027.2001

Guan, C., Niu, Y., Chen, S., Kang, Y., Wu, J., Nishi, K., Chang, C. C. Y., Chang, T., Luo, T., & Chen, L. (2020). Structural insights into the inhibition mechanism of human sterol O-acyltransferase 1 by a competitive inhibitor. *Nature Communications, 11*(1), 2478. https://doi.org/10.1038/s41467-020-16288-4

Han, W., Cai, J., Zhong, W., Xu, G., Wang, F., Tian, X., Zhou, X., Liu, Q., Liu, Y., & Wang, J. (2020). Protein tyrosine phosphatase 1B (PTP1B) inhibitors from the deep-sea fungus *Penicillium chrysogenum* SCSIO 07007. *Bioorganic Chemistry, 96*, 103646. https://doi.org/10.1016/j.bioorg.2020.103646

Hangyu, W., Panpan, L., Jie, S., Hongyan, W., Linmiao, W., Kangning, H., Yichen, S., Shuai, W., & Cheng, W. (2024b). Advancements in Antiviral Drug Development: Comprehensive Insights into Design Strategies and Mechanisms Targeting Key Viral Proteins. *Journal of Microbiology and Biotechnology, 34*(7), 1376–1384. https://doi.org/10.4014/jmb.2403.03008

Hatakeyama, D., Tanii, H., Nishikawa, E., Takahira, M., Honjo, T., Ebisuda, N., Abe, N., Shinohara, Y., Mitomo, S., Tsutsui, A., Fujita, T., & Kuzuhara, T. (2024). Anacardic

Acid Derivatives Isolated from Fungal Species *Tyromyces fis*silis as New Histone Acetyltransferase Inhibitors. *Biological and Pharmaceutical Bulletin, 47*(12), 2076–2082. https://doi.org/10.1248/bpb.b24-00112

Hawas, U., Al-Farawati, R., El-Kassem, L. A., & Turki, A. (2016). Different culture metabolites of the red sea fungus *Fusarium equiseti* optimize the inhibition of hepatitis C virus NS3/4A Protease (HCV PR). *Marine Drugs, 14*(10), 190. https://doi.org/10.3390/md14100190

Hooper, C., Killick, R., & Lovestone, S. (2007). The GSK3 hypothesis of Alzheimer's disease. *Journal of Neurochemistry, 104*(6), 1433–1439. https://doi.org/10.1111/j.1471-4159.2007.05194.x

Hossain, U., Das, A. K., Ghosh, S., & Sil, P. C. (2020). An overview on the role of bioactive α-glucosidase inhibitors in ameliorating diabetic complications. *Food and Chemical Toxicology, 145,* 111738. https://doi.org/10.1016/j.fct.2020.111738

Hu, Y., Zhao, K., Zhu, J., Qi, X., Chen, W., Song, Y., Pang, X., Liu, Y., & Wang, J. (2023). New Neuraminidase Inhibitory Alkaloids from the Mangrove Soil-Derived Fungus Arthrinium sp. SCSIO 41305. *Journal of Ocean University of China, 22*(5), 1446–1451. https://doi.org/10.1007/s11802-023-5439-2

Huang, X., & Dixit, V. M. (2016). Drugging the undruggables: exploring the ubiquitin system for drug development. *Cell Research, 26*(4), 484–498. https://doi.org/10.1038/cr.2016.31

Hughes, P. J., Cretton-Scott, E., Teague, A., & Wensel, T. M. (2011). Protease inhibitors for patients with HIV-1 infection: a comparative overview. *Pharmacy & Therapeutics, 36*(6), 332–345.

Hwang, J., Chung, B., Kwon, O., Park, S.C., Cho, E., Oh, D., Shin, J., & Oh, K. (2021). Inhibitory effects of epipolythiodioxopiperazine fungal metabolites on isocitrate lyase in the glyoxylate cycle of *Candida albicans*. *Marine Drugs, 19(*6), 295. https://doi.org/10.3390/md19060295

Ji, Y., Zhou, Q., Liu, G., Zhu, T., Wang, Y., Fu, Y., Li, Y., Li, R., Zhang, X., Dong, M., Sauriol, F., Gu, Y., Shi, Q., Lu, X., & Ni, Z. (2021). New protein tyrosine phosphatase inhibitors from fungus *Aspergillus gorakhpurensis* F07ZB1707. *RSC Advances, 11*(17), 10144–10153. https://doi.org/10.1039/d1ra00788b

Joosten, M., Seitz, V., Zimmermann, K., Sommerfeld, A., Berg, E., Lenze, D., Leser, U., Stein, H., & Hummel, M. (2012). Histone acetylation and DNA demethylation of T cells result in an anaplastic large cell lymphoma-like phenotype. *Haematologica, 98*(2), 247–254. https://doi.org/10.3324/haematol.2011.054619

Kallingal, A., Ayyolath, A., Kundil, V. T., Suresh, A. M., Joseph, T. M., Haponiuk, J., Thomas, S., & Augustine, A. (2022). Divulging the anti-acetylcholinesterase activity of *Colletotrichum lentis* strain KU1 extract as sustainable AChE active site inhibitors. *Archives of Microbiology, 204*(12), 713. https://doi.org/10.1007/s00203-022-03288-9

Kallingal, A., Kundil, V. T., Ayyolath, A., Joseph, T. M., Mahapatra, D. K., Haponiuk, J. T., & Variyar, E. J. (2021). Identification of sustainable trypsin active-site inhibitors from *Nigrospora sphaerica* strain AVA-1. *Journal of Basic Microbiology, 61*(8), 709–720. https://doi.org/10.1002/jobm.202100221

Kim, J., Kim, D., Hwang, B. S., Woo, E., Lee, Y., Jeong, K., Lee, I., & Yun, B. (2016). Neuraminidase inhibitors from the fruiting body of *Phellinus igniarius*. *Microbiology, 44*(2), 117–120. https://doi.org/10.5941/myco.2016.44.2.117

Kim, S. (2023). Enzymes as targets for drug development II. *International Journal of Molecular Sciences, 24*(4), 3258. https://doi.org/10.3390/ijms24043258

Klaman, L. D., Boss, O., Peroni, O. D., Kim, J. K., Martino, J. L., Zabolotny, J. M., Moghal, N., Lubkin, M., Kim, Y., Sharpe, A. H., Stricker-Krongrad, A., Shulman, G. I., Neel, B. G., & Kahn, B. B. (2000). Increased energy expenditure, decreased adiposity, and Tissue-Specific insulin sensitivity in Protein-Tyrosine phosphatase 1B-Deficient mice. *Molecular and Cellular Biology, 20*(15), 5479–5489. https://doi.org/10.1128/mcb.20.15.5479-5489.2000

Kelner, M.J., McMorris, T.C., Staake, M.D., Kashinatham, A., Shah, A., Kiorpes, A.L., Webber, J.G., Van Laar, E.S., Waters. S.J. (2006). MGI 4184: A novel acylfulvene with differential pharmacokinetic profile and marked activity *in vitro* and *in vivo*. *Cancer Research, 66*(8), 1334. https://aacrjournals.org/cancerres/article/66/8_Supplement/1334/532188/MGI-4184-A-novel-acylfulvene-with-differential

Koelsch, G. (2017). BACE1 function and inhibition: Implications of intervention in the amyloid pathway of Alzheimer's disease pathology. *Molecules, 22*(10), 1723. https://doi.org/10.3390/molecules22101723

Kong, F., Fan, P., Zhou, L., Ma, Q., Xie, Q., Zheng, H., Zheng, Z., Zhang, R., Yuan, J., Dai, H., Luo, D., & Zhao, Y. (2019). Penerpenes A–D, Four Indole Terpenoids with Potent Protein Tyrosine Phosphatase Inhibitory Activity from the Marine-Derived Fungus *Penicillium* sp. KFD28. *Organic Letters,* 21(12), 4864–4867. https://doi.org/10.1021/acs.orglett.9b01751

Li, X., Shen, W., Li, G., Song, Y., Lu, X., Wong, N. K., & Yan, Y. (2023). Alternaphenol B2, a new IDH1 inhibitor from the coral-derived fungus *Parengyodontium album* SCSIO SX7W11. *Natural Product Research, 38*(22), 3917–3923. https://doi.org/10.1080/14786419.2023.2269462

Liao, H., Shao, T., Mei, R., Huang, G., Zhou, X., Zheng, C., & Wang, C. (2019). Bioactive secondary metabolites from the culture of the mangrove-derived fungus *Daldinia eschscholtzii* HJ004. *Marine Drugs,* 17(12), 710. https://doi.org/10.3390/md17120710

Liu, L., Zhang, J., Chen, C., Teng, J., Wang, C., & Luo, D. (2015). Structure and biosynthesis of fumosorinone, a new protein tyrosine phosphatase 1B inhibitor firstly isolated from the entomogenous fungus *Isaria fumosorosea*. *Fungal Genetics and Biology, 81,* 191–200. https://doi.org/10.1016/j.fgb.2015.03.009

Liu, S. Z., He, F. M., Bin, Y. L., Li, C. F., Xie, B. Y., Tang, X. X., & Qiu, Y. K. (2021). Bioactive compounds derived from the marine-derived fungus MCCC3A00951 and their influenza neuraminidase inhibition activity *in vitro* and *in silico*. *Natural Product Research, 35*(24), 5621–5628. https://doi.org/10.1080/14786419.2020.1817015

Lopéz, D., Cherigo, L., Mejia, L. C., Loza-Mejía, M. A., & Martínez-Luis, S. (2019). α-Glucosidase inhibitors from a mangrove associated fungus, *Zasmidium* sp. strain EM5-10. *BMC Chemistry, 13*(1), 22. https://doi.org/10.1186/s13065-019-0540-8

Lu, Y., Xu, Q., Pang, L., Liu, Y., Li, L., Yan, J., Zhang, Y., & Huang, Z. (2023). HMG-CoA reductase inhibitor from the endophytic fungus *Colletotrichum capsici*. *Natural Product Research, 39*(4), 749–757. https://doi.org/10.1080/14786419.2023.2289085

Ma, J., Zhang, X., Wang, Y., Zheng, J., Wang, C., & Shao, C. (2016). Aspergivones A and B, two new flavones isolated from a gorgonian-derived *Aspergillus candidus* fungus. *Natural Product Research, 31*(1), 32–36. https://doi.org/10.1080/14786419.2016.1207073

Ma, T., Shan, W., Ying, Y., Ma, L., Liu, W., & Zhan, Z. (2015). Xanthones with α-Glucosidase inhibitory activities from *Aspergillus versicolor*, a fungal endophyte of *Huperzia serrata*. *Helvetica Chimica Acta,* 98(1), 148–152. https://doi.org/10. 1002/hlca.201400165

Mahajan, S., Choudhary, S., Kumar, P., & Tomar, S. (2021). Antiviral strategies targeting host factors and mechanisms obliging +ssRNA viral pathogens. *Bioorganic & Medicinal Chemistry, 46,* 116356. https://doi.org/10.1016/j.bmc.2021.116356

Malumbres, M. (2014). Cyclin-dependent kinases. *Genome Biology*, *15*(6), 122. https:// doi.org/ 10.1186/gb4184

Market Research Future (2024). Enzyme inhibitors market research, ID: MRFR/HC/25475-HCR | 128 Pages | Author: Rahul Gotadk, Source: https://www.marketresearchfuture.com/ reports/ enzyme-inhibitors-market-27145

Moussa, A. Y., Mostafa, N. M., & Singab, A. N. B. (2019). Pulchranin A: First report of isolation from an endophytic fungus and its inhibitory activity on cyclin dependent kinases. *Natural Product Research, 34*(19), 2715–2722. https://doi.org/10.1080/14786419.2019.1585846

Mugaranja, K. P., & Kulal, A. (2022). Inhibition of alpha-glucosidase enzyme and antioxidant activity of the metabolites purified from an endophytic fungus of *Simarouba glauca* DC. *South African Journal of Botany, 149*, 134–144. https://doi.org/10.1016/j.sajb.2022.05.045

Muñoz-Elías, E. J., & McKinney, J. D. (2005). *Mycobacterium tuberculosis* isocitrate lyases 1 and 2 are jointly required for in vivo growth and virulence. *Nature Medicine, 11*(6), 638–644. https://doi.org/10.1038/nm1252

Nakamura, Y., Kato, H., Nishikawa, T., Iwasaki, N., Suwa, Y., Rotinsulu, H., Losung, F., Maarisit, W., Mangindaan, R. E. P., Morioka, H., Yokosawa, H., & Tsukamoto, S. (2012). Siladenoserinols A–L: New Sulfonated Serinol Derivatives from a Tunicate as Inhibitors of p53–Hdm2 Interaction. *Organic Letters, 15*(2), 322–325. https://doi.org/10.1021/ol3032363

Nicholson, B., Lloyd, G. K., Miller, B. R., Palladino, M. A., Kiso, Y., Hayashi, Y., & Neuteboom, S. T. (2005). NPI-2358 is a tubulin-depolymerizing agent: *in-vitro* evidence for activity as a tumor vascular-disrupting agent. *Anti-Cancer Drugs, 17*(1), 25–31. https://doi.org/10.1097/01.cad.0000182745.01612.8a

Nishimura, S., Hitora, Y., Kawahara, T., Tanabe, M., Ogata, E., Kato, H., Srikoon, P., Watanabe, T., & Tsukamoto, S. (2022). Cell-based screening of extracts of natural sources to search for inhibitors of the ubiquitin-proteasome system and identification of proteasome inhibitors from the fungus *Remotididymella* sp. *Bioorganic & Medicinal Chemistry Letters, 59*, 128566. https://doi.org/10.1016/j.bmcl.2022.128566

Oberhofer, M., Malfent, F., Zehl, M., Urban, E., Wackerlig, J., Reznicek, G., Vignolle, G. A., Rückert, C., Busche, T., Wibberg, D., & Zotchev, S. B. (2022). Biosynthetic potential of the endophytic fungus *Helotiales* sp. BL73 Revealed via compound identification and genome mining. *Applied and Environmental Microbiology, 88*(6), e0251021. https://doi.org/10.1128/aem.02510-21

Prescott, T. A. K., Hill, R., Mas-Claret, E., Gaya, E., & Burns, E. (2023). Fungal drug discovery for Chronic disease: History, new discoveries and new approaches. *Biomolecules, 13*(6), 986. https://doi.org/10.3390/biom13060986

Qi, C., Bao, J., Wang, J., Zhu, H., Xue, Y., Wang, X., Li, H., Sun, W., Gao, W., Lai, Y., Chen, J., & Zhang, Y. (2016). Asperterpenes A and B, two unprecedented meroterpenoids from *Aspergillus terreus* with BACE1 inhibitory activities. *Chemical Science, 7*(10), 6563–6572. https://doi.org/10.1039/c6sc02464e

Saxena, S., Chhibber, M., & Singh, I. P. (2018). Fungal bioactive compounds in pharmaceutical research and development. *Current Bioactive Compounds, 15*(2), 211–231. https://doi.org/10.2174/1573407214666180622104720

Scheen A. J. (2003). Is there a role for alpha-glucosidase inhibitors in the prevention of type 2 diabetes mellitus? *Drugs 63*(10), 933–951. https://doi.org/10.2165/00003495-200363100-00002

Scherlach, K., & Hertweck, C. (2021). Mining and unearthing hidden biosynthetic potential. *Nature Communications, 12*(1), 3864. https://doi.org/10.1038/s41467-021-24133-5

Song, Y., Liu, Q., Pang, X., Chen, Z., Huang, H., Wang, J., & Liu, Y. (2023). Bisabolane-type sesquiterpenoids and bacillibactin from the marine-derived fungus *Aspergillus sydowii SCSIO* 41041 and their enzyme inhibiting activity. *Natural Product Research, 38*(22), 4055–4058. https://doi.org/10.1080/14786419.2023.2269470

Sun, X., Man, N., Tan, Y., Nimer, S.D., & Wang, L. (2015). The role of histone acetyltransferases in normal and malignant hematopoiesis. *Frontiers in Oncology, 5*, 108. https://doi.org/10.3389/fonc.2015.00108

Survase, S. A., Kagliwal, L. D., Annapure, U. S., & Singhal, R. S. (2011). Cyclosporin A — A review on fermentative production, downstream processing, and pharmacological applications. *Biotechnology Advances, 29*(4), 418–435. https://doi.org/10.1016/j.biotechadv.2011.03.004

Sy-Cordero, A. A., Pearce, C. J., & Oberlies, N. H. (2012). Revisiting the enniatins: a review of their isolation, biosynthesis, structure determination and biological activities. *The Journal of Antibiotics, 65*(11), 541–549. https://doi.org/10.1038/ja.2012.71

Takahashi, J. A., Barbosa, B. V. R., Lima, M. T. N. S., Cardoso, P. G., Contigli, C., & Pimenta, L. P. S. (2021). Antiviral fungal metabolites and some insights into their contribution to the current COVID-19 pandemic. *Bioorganic & Medicinal Chemistry, 46,* 116366. https://doi.org/10.1016/j.bmc.2021.116366

Tanokashira, N., Kukita, S., Kato, H., Nehira, T., Angkouw, E. D., Mangindaan, R. E., De Voogd, N. J., & Tsukamoto, S. (2016c). Petroquinones: trimeric and dimeric xestoquinone derivatives isolated from the marine sponge *Petrosia alfiani*. *Tetrahedron, 72*(35), 5530–5540. https://doi.org/10.1016/j.tet.2016.07.045

Thompson J.L. (2013). Carfilzomib: a second-generation proteasome inhibitor for the treatment of relapsed and refractory multiple myeloma. *The Annals of Pharmacotherapy, 47*(1), 56–62. https://doi.org/10.1345/aph.1R561

Tsukamoto, S., Yamakuma, M., Kato, H., Matsuo, K., El-Desoky, A. H., Kawabata, T., Losung, F., Mangindaan, R. E. P., De Voogd, N. J., & Yokosawa, H. (2014). 1-Hydroxyethylhalenaquinone: A New Proteasome Inhibitor from the Marine Sponge *Xestospongia* sp. *Heterocycles* 89(11), 2605. https://doi.org/10.3987/com-14-13087

Uchida, R., Nakajyo, K., Kobayashi, K., Ohshiro, T., Terahara, T., Imada, C., & Tomoda, H. (2016). 7-Chlorofolipastatin, an inhibitor of sterol O-acyltransferase, produced by marine-derived *Aspergillus ungui* NKH-007. *The Journal of Antibiotics, 69*(8), 647–651. https://doi.org/10.1038/ja.2016.27

Ushiyama, S., Umaoka, H., Kato, H., Suwa, Y., Morioka, H., Rotinsulu, H., Losung, F., Mangindaan, R. E. P., De Voogd, N. J., Yokosawa, H., & Tsukamoto, S. (2012). Manadosterols A and B, Sulfonated Sterol Dimers Inhibiting the Ubc13–Uev1A Interaction, Isolated from the Marine Sponge *Lissodendryx fibrosa*. *Journal of Natural Products, 75*(8), 1495–1499. https://doi.org/10.1021/np300352u

Vanni, P., Giachetti, E., Pinzauti, G., & McFadden, B. A. (1990). Comparative structure, function and regulation of isocitrate lyase, an important assimilatory enzyme. *Comparative Biochemistry and Physiology Part B Comparative Biochemistry, 95*(3), 431–458. https://doi.org/10.1016/0305-0491(90)90002-b

Vats, S., & Saxena, S. (2023). Endophytic *Fusarium* species, a unique bioresource for disaggregator of misfolded alpha-synuclein. *Archives of Microbiology, 205*(6). https://doi. org/10.1007/s00203-023-03575-z

Voges, D., Zwickl, P., & Baumeister, W. (1999). The 26S proteasome: a molecular machine designed for controlled proteolysis. *Annual Review of Biochemistry, 68*(1), 1015–1068. https://doi.org/10.1146/annurev.biochem.68.1.1015

Wang, Z., Thornton, C. R., Kershaw, M. J., Debao, L., & Talbot, N. J. (2003). The glyoxylate cycle is required for temporal regulation of virulence by the plant pathogenic fungus *Magnaporthe grisea*. *Molecular Microbiology, 47*(6), 1601–1612. https://doi.org/10.1046/j.1365-2958.2003.03412.x

Wiese, J., Aldemir, H., Schmaljohann, R., Gulder, T. a. M., & Imhoff, J. F. (2017). Asperentin B, a new inhibitor of the protein tyrosine phosphatase 1B. *Marine Drugs, 15*(6), 191. https://doi.org/10.3390/md15060191

Wiese, J., Imhoff, J., Gulder, T., Labes, A., & Schmaljohann, R. (2016). Marine fungi as producers of benzocoumarins, a new class of inhibitors of Glycogen-Synthase-Kinase 3B. *Marine Drugs*, *14*(11), 200. https://doi.org/10.3390/md14110200

Xie, S., Wu, Y., Qiao, Y., Guo, Y., Wang, J., Hu, Z., Zhang, Q., Li, X., Huang, J., Zhou, Q., Luo, Z., Liu, J., Zhu, H., Xue, Y., & Zhang, Y. (2018). Protoilludane, Illudalane, and Botryane Sesquiterpenoids from the endophytic fungus *Phomopsis* sp. TJ507A. *Journal of Natural Products, 81*(6), 1311–1320. https://doi.org/10.1021/acs.jnatprod.7b00889

Xu, F., Chen, W., Ye, Y., Qi, X., Zhao, K., Long, J., Pang, X., Liu, Y., & Wang, J. (2022). A new quinolone and acetylcholinesterase inhibitors from a sponge-associated fungus *Penicillium* SCSIO 41033. *Natural Product Research, 37*(17), 2871–2877. https://doi.org/ 10.1080/14786419.2022.2139694

Yamaguchi, M., Miyazaki, M., Kodrasov, M. P., Rotinsulu, H., Losung, F., Mangindaan, R. E., De Voogd, N. J., Yokosawa, H., Nicholson, B., & Tsukamoto, S. (2013). Spongiacidin C, a pyrrole alkaloid from the marine sponge *Stylissa massa*, functions as a USP7 inhibitor. *Bioorganic & Medicinal Chemistry Letters, 23*(13), 3884–3886. https://doi.org/10.1016/j.bmcl.2013.04.066

Yamanokuchi, R., Imada, K., Miyazaki, M., Kato, H., Watanabe, T., Fujimuro, M., Saeki, Y., Yoshinaga, S., Terasawa, H., Iwasaki, N., Rotinsulu, H., Losung, F., Mangindaan, R. E., Namikoshi, M., De Voogd, N. J., Yokosawa, H., & Tsukamoto, S. (2012). Hyrtioreticulins A–E, indole alkaloids inhibiting the ubiquitin-activating enzyme, from the marine sponge *Hyrtios reticulatus*. *Bioorganic & Medicinal Chemistry, 20*(14), 4437–4442. https://doi.org/10.1016/j.bmc.2012.05.044

Yamasaki, M., Igarashi, M., Sawa, R., Nosaka, C., Umekita, M., Hatano, M., Kimura, T., Iijima, K., Takizawa, N., Kato, T., Mizumoto, K., & Nomoto, A. (2019). Flupyranochromene, a novel inhibitor of influenza virus cap-dependent endonuclease, from *Penicillium* sp. f28743. *The Journal of Antibiotics, 72*(3), 125–133. https://doi.org/10. 1038/s41429-018-0134-z

Yamazaki, H., Nakayama, W., Takahashi, O., Kirikoshi, R., Izumikawa, Y., Iwasaki, K., Toraiwa, K., Ukai, K., Rotinsulu, H., Wewengkang, D. S., Sumilat, D. A., Mangindaan, R. E., & Namikoshi, M. (2015). Verruculides A and B, two new protein tyrosine phosphatase 1B inhibitors from an Indonesian ascidian-derived *Penicillium verruculosum*. *Bioorganic & Medicinal Chemistry Letters, 25*(16), 3087–3090. https://doi.org/10.1016/j.bmcl. 2015.06.026

Ye, G., Huang, C., Li, J., Chen, T., Tang, J., Liu, W., & Long, Y. (2021). Isolation, structural characterization and antidiabetic activity of new diketopiperazine alkaloids from

mangrove endophytic fungus *Aspergillus* sp. 16-5c. *Marine Drugs, 19*(7), 402. https://doi.org/10.3390/md19070402

Yu, G., Shang, Z., Li, W., Peng, J., Mo, X., Yang, S., & Tan, L. (2025). Pyridine derivatives and furan derivatives identified from the medicinal Mushroom *Irpex lacteus* SY1002. *Chemistry & Biodiversity, 22*(6), e202403124. https://doi.org/10.1002/ cbdv.202403124

Zephyr, J., Yilmaz, N. K., & Schiffer, C. A. (2021). Viral proteases: structure, mechanism and inhibition. *Enzymes,* 50, 301–333. https://doi.org/10.1016/bs.enz.2021.09.004

Zhang, L., Niaz, S. I., Khan, D., Wang, Z., Zhu, Y., Zhou, H., Lin, Y., Li, J., & Liu, L. (2017). Induction of diverse bioactive secondary metabolites from the mangrove endophytic fungus *Trichoderma* sp. (Strain 307) by co-cultivation with *Acinetobacter johnsonii* (Strain B2). *Marine Drugs, 15*(2), 35. https://doi.org/10.3390/md15020035

Zhang, X., Liu, J., Tang, P., Liu, Z., Guo, G., Sun, Q., & Yin, J. (2017). Identification of a new uncompetitive inhibitor of adenosine deaminase from endophyte *Aspergillus niger* sp. *Current Microbiology, 75*(5), 565–573. https://doi.org/10.1007/s00284-017-1418-4