Comprehensive Analysis of *Penicillium Sclerotiorum*: Biology, Secondary Metabolites, and Bioactive Compound potential- review

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Abstract

The filamentous fungus *Penicillium sclerotiorum* is significant in the ecological and industrial domains due to its vast supply of secondary metabolites that have a diverse array of biological functions. We have gathered the metabolic potential and biological activities associated with *P. sclerotiorum* metabolites of various structures, based on extensive research of the latest literature. The review incorporated literature spanning from 2000 to 2023, drawing from reputable databases including Google Scholar, ScienceDirect, Scopus, PubMed, among others. Ranging from azaphilones, meroterpenoids, polyketides, and peptides group exhibits fascinating potential pharmacological activities such as antimicrobial, anti-inflammatory, and antitumor effects, holding promise in pharmaceutical and industrial sectors. Additionally, *P. sclerotiorum* showcases biotechnological potential through the production of enzymes like β-xylosidases, ß-D-Glucosidase and xylanases, pivotal in various industrial processes. This review underscores the need for further exploration into its genetic foundations and cultivation conditions to optimize the yield of valuable compounds and enzymes, highlighting the unexplored potential of *Penicillium sclerotiorum* in diverse applications across industries.

Keywords: *Penicillium sclerotiorum*, secondary metabolites; bioactive compounds, biological activity

1. Introduction:

One of the most prevalent and common groupings of fungus in nature is the genus *Penicillium.*[1] *The penicillium* species, a diverse group within the fungal kingdom, encompasses a multitude of organisms known for their profound impact on human life.[2] Some species are producers of the antibiotic penicillin, revolutionizing medicine and saving countless lives.[3] While these fungi contribute significantly to beneficial applications such as food fermentation and pharmaceuticals,[4] certain species exhibit pathogenicity, causing plant diseases with economic repercussions.[5] On the flip side, *Penicillium* strains also hold promise as biocontrol agents, showcasing antagonistic activities against various plant pathogens.[6] This dual nature underscores the complex ecological role of *Penicillium* species.[7] In this review, the focus on exploring one of *penicillum sp.,* such as *Penicillium sclerotiorum*, has gained significant attention due to its antagonistic mechanisms and potential agricultural applications.

P. sclerotiorum originally discovered in the air of java, Indonesia by van Beyma.[8] The species is named from its orange sclerotia, which are produced by some strains. It also features monoverticillate, vesiculate conidiophores and bright orange to red colony colors.[9] There is currently little research being done on the phylogeny of *Penicillium* section *Sclerotiora.*[10] Although they are separated from home dust, strains are regularly found in soil and occasionally in fabrics.[11] According to Houbraken & Samson, *Penicillium sclerotiorum* is now categorized under *Penicillium* subgenus *Aspergilloides*, section Sclerotiora.[12] This filamentous fungus has garnered significant attention due to its unique biological characteristics, its role as a pathogen in various contexts, and the exploration of bioactive compounds it produces.[13] As researchers investigate the sophisticated nature of its biological activities, a comprehensive understanding of *P. sclerotiorum* emerges, offering insights into its multifaceted nature and the broader implications it holds.[14]

The potential therapeutic applications of this fungus bioactive compound have collected significant attention, particularly in the realms of anti-inflammatory and antitumor activities.[15] The bioactive compounds produced by *P. sclerotiorum* exhibit promising properties that could be harnessed for combating inflammation and tumor progression.[16] Additionally, the exploration of the bioactive compounds produced by this fungus reveals a treasure trove of potential pharmaceutical and industrial applications, underscoring the importance of understanding its

biosynthetic capabilities.[17] Through this comprehensive exploration, we aspire to shed light on the multifaceted nature of *P. sclerotiorum*, illuminating its biological intricacies, secondary metabolites, and the transformative impact of its bioactive compounds.

2. Morphological Characteristics of *Penicillium sclerotiorum*

Penicillium sclerotiorum, a filamentous fungus, holds a distinctive place in the taxonomy of the *Penicillium* genus.[18] Its unique characteristics, include monoverticillate, vesiculate conidiophores, vivid orange to red colony hues, and strains that produce recognizable orange sclerotia.[10] Initially classified in the subgenus *Aspergilloides*, section Sclerotiora, it has been identified in diverse regions, suggesting a cosmopolitan distribution, albeit infrequently reported.[9] Isolates commonly originate from soil, textiles, house dust, diseased grapefruit and stems, and also found as a potential endophyte of Coffea arabica berries. Recent classifications by Houbraken & Samson,[12] place *P. sclerotiorum* in *Penicillium* subgenus *Aspergilloides*, section Sclerotiora, revising the concept initially proposed by Pitt et al.[19]

The fungus under investigation was identified as a strain of *P. sclerotiorum* based on morphological characteristics observed during inoculation experiments.[10] The fungus exhibited radially sulcate or wrinkled mycelia, often with orange droplet exudation. Aerial mycelium displayed color variation, ranging from white or buff at the margin to saffron or deeper orange red near the inoculum, accompanied by scattered penicillin.[9] The morphological characteristics, including monoverticillate penicillate conidiophores and ellipsoidal conidia, aligned with the variation described for *P. sclerotiorum* van Beyma, although the mycelial extension values were lower than typically reported for the species.[20]

3. Secondary Metabolites from *Penicillium sclerotiorum*

The fungi known as *Penicillium spp*. are a large group of fungi that have over 1,300 metabolites, including azaphilones, cyclic peptides, steroids, alkaloids, terpenoids and polyketides. The majority of these metabolites have antibacterial, anti-insect, anti-viral, anti-tumor, or anti-cardiovascular disease properties.[21] The genus *Penicillium* is recognized for producing a wide variety of bioactive secondary metabolites, making it one of the varied groups of fungus originated from the sea.[22,23] Owing to the unique characteristics of the maritime environment, marine fungi's metabolites frequently exhibit innovative chemical structures and

powerful biological activities.[24] According to Blunt et al., marine fungus has the capacity to produce large quantities of highly bioactive secondary metabolites, which might provide valuable insights for the creation of novel pharmacological drugs.[25] *P. sclerotiorum*, one of the marine driving fungi, is capable of producing a wide variety of secondary metabolites, which greatly adds to its ecological and industrial significance.[26]

There are many Secondary Metabolites that can be found and extracted from *Penicillium sclerotiorum*. Some of the methods are by using column chromatography such as Thin Layer Chromatography (TLC), High Performance Liquid Chromatography (HPLC), High-resolution electrospray ionization mass spectrometry (HRESIMS), Mass Spectroscopy (MS), Nuclear Magnetic Resonance (NMR), X-ray single-crystal diffraction and Ultraviolet Visible Spectroscopy (UV–vis).[30,31,29] In this review, total, **86** secondary metabolites were described to be biosynthesized by this *P. sclerotiorum* (Table 1), encompassing azaphilonidal derivatives, meroterpenoids, polyketides and peptides. Most of the metabolites that can be extracted and isolated from *P. sclerotiorum* azaphilones groups such Chlorogeumasnol **(1),**[38] *epi*-geumsanol D **(2),**[37] 8a-*epi*-eupenicilazaphilone C **(3),**[30] 8a-*epi*-hypocrellone A **(4),**[30] eupenicilazaphilone C **(5),**[30] 5-bromoisorotiorin **(6),**[30] 5-bromosclerotiorin **(7),**[30] 5-chloro-3-[(1E,3R,4R,5S)-3,4-dihydroxy-3,5-dimethyl-1-hepten-1-yl]-1,7,8,8a-tetrahydro-7,8-dihydroxy-7-methyl-(7R,8R,8aS)-6H-2-benzopyran-6-one **(8),**[27] 7-deacetylisochromophilone VI **(9),**[38] ((1*E*,3*E*)-3,5-dimethylhepta-1,3-dien-1-yl)-2,4-dihydroxy-3-methylbenzaldehyde **(10),**[30] Isochromophilone IV **(11),**[30] Isochromophilone H **(12),**[33] Isochromophilone J **(13),**[33] Ochlephilone **(14),**[33] Penazaphilones A- I **(15-23),**[31] Penazaphilone J-L **(24-26),**[31,32] Peniazaphilone A-E **(27-31),**[31,34] Penicilazaphilone B **(32),**[34] Penicilazaphilone C **(33),**[35] Penicilazaphilones D-E **(34-35),**[36] Penicilazaphilone F-G **(36-37),**[33] Penicilazaphilone I-N **(38-43),**[37] Penicilazaphilones H **(44),**[33] Penidioxolane C-D **(45-46),**[37] Sclerazaphilone A-I **(47-55),**[44] Sclerotioramine **(56),**[27] Sclerotiorin **(57),**[30] Sclerotiorin A-E **(58-62),**[29] Pencolide **(63).**[23] According to Jiang et al. meroterpenoids are a family of secondary metabolites that are frequently discovered in plants, marine creatures, and fungus.[42] They are most frequently linked to the *Aspergillus* and *Penicillium* species. These compounds, known for their diverse structures and significant pharmacological activities, are distributed widely among various organisms, including plants, animals, bacteria, and fungi.[43] Some meroterpenoid derivatives were identified from *P. sclerotiorum* such as Peniscmeroterpenoid A-N **(64-77).**[43,44] Various other derivatives, including polyketides, peptides,

147 and related compounds, have been identified such as Sclerketide A-D **(78-81),**[46] Penisclerotiorin
148 A **(82),**[41] Penidepsidone A **(83),**[41] Diaporthein C **(84),**[41] (2*S*,3*S*,5*S*)-2-allyl-3-hydroxy-5-(2-
149 hydroxypropan-2-yl)-2-methyltetrahydrofuran **(85),** and 2*S*,3*S*,5*S*)-2-(2-hydroxyethyl)-3-
150 hydroxy-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran **(86).**[28]

151 4. Pharmacological Properties of *P. sclerotiorum*

152 *Penicillium* species generate a wide range of secondary metabolites that hold significant
153 importance in food and industrial applications.[46] The recent discovery of *P. sclerotiorum*
154 capability to produce a diverse range of secondary metabolites further emphasizes its ecological
155 and industrial significance.[47] Azaphilone derivatives, a notable class of compounds synthesized
156 by this fungus, have exhibited a wide spectrum of biological activities, including antimicrobial,
157 antiviral, anti-inflammatory, antioxidant, cytotoxic, hypoglycemic, and nematocidal effects.[35,48]
158 Among these, sclerotiorin stands out for its recognized antioxidant properties, holding immense
159 promise for applications in pharmaceuticals and the food industry due to its potential health
160 benefits.[16] Further exploration into the environmental factors influencing the production of these
161 metabolites could pave the way for optimizing cultivation conditions. This optimization could
162 lead to enhanced yields of these valuable compounds, thereby facilitating their diverse
163 applications across various industrial sectors.

164 4.1. Anti-inflammatory activity

165 Several compounds, including Azaphilones Peniazaphilone A **(27),**[34] Peniazaphilone C
166 **(29),**[31,34] Peniazaphilone D **(30),**[31,34] Penazaphilones L **(26),**[32] Penicilazaphilone N **(43),**[37]
167 Sclerketide A **(78),**[45] Sclerketide C **(80),**[45] Sclerketide D **(81),**[45] Penazaphilones A **(15),**[31]
168 Penazaphilones E **(19),**[31] Penazaphilone F **(20),**[31] Penazaphilone H **(22),**[31] peniscmeroterpenoids
169 A **(64)**, D **(67),**[43] penicilazaphilones F **(36)** and G **(37),**[33] Sclerazaphilone E **(68),** Sclerazaphilone
170 F **(69),** and Sclerazaphilone G **(53)** demonstrated varied but noteworthy anti-inflammatory
171 activities.[44] For instance, Peniazaphilone A **(27)**, **(29), (30),** and compound **(43)** exhibited
172 moderate activity by reducing nitric oxide (NO) release in LPS-induced RAW264.7 cells, with
173 IC_{50} values ranging from 4.71 to 42.23 μmol/L.[31,34,37] Penazaphilones L **(26)** significantly
174 reduced NO generation, COX-2, IL-6, IL-1β, and iNOS mRNA expression. They also inhibited
175 PI3K, PDK1, Akt, and GSK-3β phosphorylation, which stopped NF-κB translocation.[32]

Additionally, compounds Sclerketide A **(78),** Sclerketide C **(80),** and Sclerketide D **(81)** exhibited significant inhibition of NO production in the range of 2.5–18.0 μM, potentially downregulating iNOS and COX-2 expression at the mRNA level.[45] Penazaphilones A **(15), (19), (20)** and **(22)** demonstrated varying degrees of NO inhibition, while peniscmeroterpenoids A **(64)** and D **(67),** showed suppression of NO production and pro-inflammatory mediators.[31,43] Also, penicilazaphilones F **(36)** and G **(37)** demonstrated inhibitory effects on lipopolysaccharide-induced nitric oxide (NO) production in BV-2 cells, showing IC_{50} values of 31.7 and 34.5 μM, respectively.[33] Moreover, Sclerazaphilone E **(68), (69),** and **(53)** effectively inhibited NO production in LPS-induced RAW264.7 cells with IC_{50} values within the range of 6.30–9.45 μM, highlighting their potential as anti-inflammatory agents (Table 1).[44] Importantly, in this cellular context, these compounds demonstrated their promise as anti-inflammatory agents by displaying these actions without causing cytotoxicity.

4.2. Cytotoxic activity

The ability to destroy cancer cells, known as cytotoxic activity, plays a critical role in combating the growth of cancer.[61] Cancer can progress into malignancies and ultimately lead to death. Therefore, the discovery of a substance with cytotoxic properties is immensely significant in reducing the mortality and morbidity rates among cancer patients.[61] Some compounds were examined from *P. sclerotiorum* for their cytotoxic potential, including 8a-epi-hypocrellone A **(4),** 8a-epi-eupenicilazaphilone C **(3)**, eupenicilazaphilone C **(5)**, ((1E,3E)-3,5-dimethylhepta-1,3-dien-1-yl)-2,4-dihydroxy-3-methylbenzaldehyde **(10)**, and isochromophilone IV **(11).**[30] Among these, sclerotriorin **(57)** and 8a-epi-eupenicilazaphilone C respectively amplified and suppressed SMAD-mediated transcriptional activity induced by TGF-β.[30] Penicilazaphilones B **(32)** and C **(33)** displayed selective cytotoxicity against human gastric cancer cells and melanoma cells (B-16).[24,35] Additionally, penicilazaphilones F **(36)** and G **(37)** inhibited the lipopolysaccharide-induced production of nitric oxide in BV-2 cells.[33] Penidioxolane C **(45)** exhibited moderate inhibition in human myeloid leukemia, liver, stomach, non-small cell lung, and HeLa cervical cancer cells, suggesting some potential in curtailing their proliferation (Table 1).[37]

4.3. Antimicrobial and Antiviral activity

Microorganisms, though unseen by the naked eye, play a significant role in causing various diseases.[63] Consequently, the search for antimicrobial agents becomes crucial in combating these

issues. Secondary metabolites identified from *P. sclerotiorum* extract that possess antimicrobial properties. Penicilazaphilone C **(33)** displayed potent antibacterial effects against *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*, surpassing the antibacterial activity of Penicilazaphilone B **(32).**[24] This compound emerged as a new azaphilonidal derivative, exhibiting strong antimicrobial properties along with selective cytotoxic effects.[24] Moreover, penicilazaphilones D (**34**) and E **(35)** exhibited notable effectiveness against HSV and EV71 viruses.[36] pencolide **(63)** Sclerotiorin **(57)** and isochromophilone VI **(11)** demonstrated potent antifouling activity against barnacle Balanus amphitrite larvae and pharmacological activity against six pathogenic bacteria, including *Bacillus subtilis*, *Bacillus cereus*, *Sarcina lutea*, *Micrococcus tetragenus*, and *Vibrio anguillarum;* and newly identified compound pencolide **(63)** showed antimicrobial activity against *Candida albicans, Streptomyces pyogenes, Staphylococcus aureus, Salmonella typhimurium and Escherichia coli.*[30,36] Other compounds like chlorogeumasnol **(1)**, peniazaphilone E **(31)**, and 7-deacetylisochromophilone VI **(9)** also exhibited antimicrobial activity as part of the diverse class of azaphilones.[31,38] These compounds, sourced from a fungus known for producing azaphilones, hold promise for various biological applications, including the food industry.[31,38] However, substances like 5-bromoisorotiorin **(77),** penicilazaphilones H **(44)**, and 5-bromosclerotiorin **(7)** showed limited antimicrobial activity against *Staphylococcus aureus* ATCC 25923 (Table 1).[30,33]

4.4. α-glycosidase inhibitory activity and phytotoxicity

Jing et al. identified two steroid compounds, (2S,3S,5S)-2-(2-hydroxyethyl)-3-hydroxy-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran **(85)** and (2S,3S,5S)-2-allyl-3-hydroxy-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran **(86),** isolated from *Penicillium sclerotiorum* HLL113.[28] These compounds, obtained from yellow oil, showed solubility in methanol and chloroform and demonstrated α-glucosidase inhibitory activity.[28]

Regarding phytotoxicity, compounds such as isochromophilone H **(12),**[33] sclerotiorins A **(58)** and B **(59),**[29] ochlephilone **(14),**[33] isochromophilone IV **(11)**[30] and isochromophilone J **(13)**[33] displayed effects on *Amaranthus retroflexus* L. Sclerotiorins A **(58)** and B **(59)** showed strong phytotoxicity against radicle and plumule formation, while ochlephilone **(14)** exhibited growth-inhibiting properties against velvet leaf.[33,29] Among these, sclerotiorin B and ochlephilone

demonstrated pronounced phytotoxicity towards the development of *A. retroflexus* L.'s plumule and radicle (Table 1).[33,29]

Penicillium sclerotiorum emerges as a significant source of compounds holding economic potential, particularly in the food industry.[38] Its diverse range of derived pigments not only offers natural alternatives to synthetic colorants but also presents versatile applications across various sectors, showcasing its potential as a valuable resource for sustainable and multifaceted solutions.[30]

243 **Table 1: Compounds isolated from *P. sclerotiorum*.**

Chemical attribute	Compound Name	Molecular Formula	Bioactivity	Reference
Azaphilones	Chlorogeumasnol **(1)**	$C_{23}H_{27}ClO_7$	Economic interests in the food industry and antimicrobial activity	Hebra et al. [38]
	epi-geumsanol D **(2)**	$C_{21}H_{30}O_7$		Zeng et al. [37]
	8a-*epi*-eupenicilazaphilone C **(3)**	$C_{21}H_{29}ClO_7$	Alternative sources of natural pigments.	Wang et at.[30]
	8a-*epi*-hypocrellone A **(4)**	$C_{21}H_{29}ClO_7$	Inhibited the TNF-α-induced NFκB phosphorylation	Wang et at.[30]
	eupenicilazaphilone C **(5)**	$C_{21}H_{29}ClO_7$	Cytotoxic, anti-inflammatory, Bioactivity and anti-fibrosis activities	Wang et at.[30]
	5-bromoisorotiorin **(6)**	$C_{23}H_{23}BrO_5$	Antibacterial activities against *Staphylococcus aureus* ATCC 25923	Wang et at.[30]
	5-bromosclerotiorin **(7)**	$C_{21}H_{24}BrO_5$	Antibacterial activities against Staphylococcus aureus ATCC 25923	Wang et at.[30]
	5-chloro-3-[(1E,3R,4R,5S)-3,4-dihydroxy-3,5-dimethyl-1-hepten-1-yl]-1,7,8,8a-tetrahydro-7,8-dihydroxy-7-methyl- (7R,8R,8aS)-6H-2-benzopyran-6-one **(8)**	$C_{18}H_{25}ClO_5$		Wu et al.[27]
	7-deacetylisochromophilone VI **(9)**	$C_{21}H_{26}NClO_4$	Antimicrobial biological activity and economic interests in the food industry	Hebra et al.[38]
	((1*E*,3*E*)-3,5-dimethylhepta-1,3-dien-1-yl)-2,4-dihydroxy-3-methylbenzaldehyde **(10)**	$C_{21}H_{27}ClO_5$	Cytotoxic, anti-inflammatory, Bioactivity and anti-fibrosis activities	Wang et at.[30]
	Isochromophilone IV **(11)**	$C_{21}H_{27}ClO_5$	Bacteriostatic activity against all Gram-positive and Gram-negative bacteria and Antitumor activity by inhibiting the interaction of Grb2-Shc	Wang et at.[30]
	Isochromophilone H **(12)**	$C_{25}H_{31}ClO_6$		Wang et al.[33]
	Isochromophilone J **(13)**	$C_{19}H_{25}ClO_4$	Strong phytotoxicity against the development of plumule and radicle.	Wang et al.[33]
	Ochlephilone **(14)**	$C_{23}H_{26}O_5$	Strong phytotoxicity against the development of plumule	Wang et al.[33]

		and radicle.	
Penazaphilones A **(15)**	$C_{27}H_{35}NClO_6$	LPS-stimulated RAW 264.7: inhibition of NO generation and anti-inflammatory action	Tang et al.[31]
Penazaphilones B **(16)**	$C_{28}H_{37}NClO_6$		Tang et al.[31]
Penazaphilones C **(17)**	$C_{23}H_{29}NClO_6$		Tang et al.[31]
Penazaphilones D **(18)**	$C_{25}H_{32}N_2ClO_5$		Tang et al.[31]
Penazaphilones E **(19)**	$C_{21}H_{25}NClO_4$	LPS-stimulated RAW 264.7: inhibition of NO generation and anti-inflammatory action	Tang et al.[31]
Penazaphilone F **(20)**	$C_{26}H_{33}NClO_6$	LPS-stimulated RAW 264.7: inhibition of NO generation and anti-inflammatory action	Tang et al.[31]
Penazaphilone G **(21)**	$C_{46}H_{55}N_2Cl_2O_8$		Tang et al.[31]
Penazaphilone H **(22)**	$C_{23}H_{29}NClO_5$	LPS-stimulated RAW 264.7: inhibition of NO generation and anti-inflammatory action	Tang et al.[31]
Penazaphilone I **(23)**	$C_{25}H_{30}NClO_6$	LPS-stimulated RAW 264.7: inhibition of NO generation and anti-inflammatory action	Tang et al.[31]
Penazaphilone J **(24)**	$C_{26}H_{36}NPClO_{10}$		Zhang et al.[32] Tang et al.[31]
Penazaphilone K **(25)**	$C_{27}H_{36}N_2ClO_6$		Zhang et al.[32]
Penazaphilone L **(26)**	$C_{26}H_{34}N_2ClO_6$	Efficacy against inflammation without overt cytotoxicity	Zhang et al.[32]
Peniazaphilone A **(27)**	$C_{19}H_{21}NO_3$	Strong and a significant reduction in NO generation in RAW 264.7 cells	Yang et al.[34] Tang et al.[31]
Peniazaphilone B **(28)**	$C_{23}H_{23}BrO_5$	Moderate inhibition of LPS-induced NO release from RAW264.7 without obvious cytotoxicity	Yang et al.[34] Tang et al.[31]
Peniazaphilone C **(29)**	$C_{23}H_{29}NClO_6$	Moderate inhibition of LPS-induced NO release from RAW264.7 without obvious cytotoxicity	Tang et al.[31]
Peniazaphilone D **(30)**	$C_{20}H_{26}O_5$	Moderate inhibition of LPS-induced NO release from RAW264.7 without obvious cytotoxicity	Yang et al.[34] Tang et al.[31]
Peniazaphilone E **(31)**	$C_{23}H_{32}O_6$	Biological action of antimicrobial agents and financial incentives in the food industry	Hebra et al. [38] Tang et al.[31]
Penicilazaphilone B **(32)**	$C_{19}H_{28}O_6$	Week antibacterial activity	Zhou et al.[24]

Penic ilazaphilone C **(33)**	$C_{22}H_{29}ClO_6$	Cytotoxic and antibacterial effects	Wang et al.[35]
Penicilazaphilones D **(34)**	$C_{14}H_{16}ClO_5$		Wang, et al.[36]
Penicilazaphilone E **(35)**	$C_{22}H_{30}O_6$		Wang, et al.[36]
Penicilazaphilone F **(36)**	$C_{22}H_{32}O_7$	Inhibited the lipopolysaccharide-induced production of nitric oxide (NO) in BV-2 cells	Wang et al.[33]
Penicilazaphilone G **(37)**	$C_{22}H_{32}O_7$	Inhibited the lipopolysaccharide-induced production of nitric oxide (NO) in BV-2 cells	Wang et al.[33]
Penicilazaphilone I **(38)**	$C_{22}H_{32}O_7$	Week anti-inflammatory properties	Zeng et al.[37]
Penicilazaphilone J **(39)**	$C_{44}H_{64}O_{14}$	Week anti-inflammatory properties	Zeng et al.[37]
Penicilazaphilone K **(40)**	$C_{14}H_{17}O_5$	Week anti-inflammatory properties	Zeng et al.[37]
Penicilazaphilone L **(41)**	$C_{16}H_{19}O_6$	Week anti-inflammatory properties	Zeng et al.[37]
Penicilazaphilone M **(42)**	$C_{16}H_{20}O_6$	Week anti-inflammatory properties	Zeng et al.[37]
Penicilazaphilone N **(43)**	$C_{18}H_{16}O_6$	Moderate anti-inflammatory activity, inhibition of nitric oxide production	Zeng et al.[37]
Penicilazaphilones H **(44)**	$C_{19}H_{25}ClO_5$	Antibacterial activities against *Staphylococcus aureus* ATCC 25923	Wang et al.[33]
Penidioxolane C **(45)**	$C_{26}H_{38}O_7$	Moderate inhibition against human lung cancer cells, human gastric cancer, human liver cancer, and human hela cervical cancer	Zeng et al.[37]
Penidioxolane D **(46)**	$C_{26}H_{39}O_7$	Week anti-inflammatory properties	Zeng et al.[37]
Sclerazaphilone A **(47)**	$C_{22}H_{28}NO_6$		Jiang et al.[44]
Sclerazaphilone B **(48)**	$C_{23}H_{30}NO_6$		Jiang et al.[44]
Sclerazaphilone C **(49)**	$C_{20}H_{26}NO_5$		Jiang et al.[44]
Sclerazaphilone D **(50)**	$C_{21}H_{28}NO_5$		Jiang et al.[44]
Sclerazaphilone E **(51)**	$C_{28}H_{37}NClO_6$	Inhibitory effects on the nitric oxide (NO)	Jiang et al.[44]
Sclerazaphilone F **(52)**	$C_{27}H_{35}NClO_6$	Inhibitory effects on the nitric oxide (NO)	Jiang et al.[44]
Sclerazaphilone G **(53)**	$C_{23}H_{29}O_5$	Inhibitory effects on the nitric oxide (NO)	Jiang et al.[44]

	Sclerazaphilone H **(54)**	$C_{21}H_{28}ClO_6$		Jiang et al.[44]
	Sclerazaphilone I **(55)**	$C_{23}H_{30}ClO_7$		Jiang et al.[44], Zhao et al.[42]
	Sclerotioramine **(56)**	$C_{21}H_{24}NClO_4$		Wu et al.[27]
	Sclerotiorin **(57)**	$C_{21}H_{23}ClO_5$	Strong antifouling activity against the larval settlement of barnacle *Balanus amphitrite*	Wang et at. [30]
	Sclerotiorin A **(58)**	$C_{23}H_{29}ClO_4$		Jia et al.[29]
	Sclerotiorin B **(59)**	$C_{23}H_{29}ClO_4$	Strong phytotoxicity against the development of plumule and radicle.	Jia et al.[29]
	Sclerotiorin C **(60)**	$C_{23}H_{30}O_4$		Jia et al.[29]
	Sclerotiorin D **(61)**	$C_{26}H_{32}NClO_6$	Anti-inflammatory (inhibit NO production: 2.7 mM)	Jia et al.[29]
	Sclerotiorin E **(62)**	$C_{46}H_{54}N_2Cl_2O_8$	Moderate bioactivity against H1N1 virus, better inhibition of LPS-induced NO release from RAW264.7 without obvious cytotoxicity	Jia et al.[29]
	Pencolide **(63)**	$C_9H_9NO_4$	Antimicrobial activity	Lucas et al.[23]
Meroterpenoids	Peniscmeroterpenoid A **(64)**	$C_{26}H_{32}O_{10}$	Inhibition of nitric oxide (NO) production	Zhao et al. [43]
	Peniscmeroterpenoid B **(65)**	$C_{27}H_{39}O_8$		Zhao et al. [43]
	Peniscmeroterpenoid C **(66)**	$C_{26}H_{36}O_8$		Zhao et al. [43]
	Peniscmeroterpenoid D **(67)**	$C_{27}H_{37}O_8$	Pro-inflammatory mediators and the iNOS enzyme's protein expression	Zhao et al. [43]
	Peniscmeroterpenoid E **(68)**	$C_{24}H_{31}O_6$		Zhao et al. [43]
	Peniscmeroterpenoid F **(69)**	$C_{26}H_{34}O_7$		Zhao et al. [43]
	Peniscmeroterpenoid G **(70)**	$C_{26}H_{36}O_8$		Zhao et al. [43]
	Peniscmeroterpenoid H **(71)**	$C_{26}H_{32}O_8$	LPS-stimulated RAW 264.7: inhibition of NO generation and anti-inflammatory action	Zhao et al. [43] Jiang et al. [44]
	Peniscmeroterpenoid I **(72)**	$C_{26}H_{35}O_9$		Zhao et al. [43] Jiang et al. [44]
	Peniscmeroterpenoid J **(73)**	$C_{27}H_{40}O_9$		Zhao et al. [43]

				Jiang et al. [44]
	Peniscmeroterpenoid K **(74)**	$C_{26}H_{34}O_8$		Zhao et al. [43]
				Jiang et al. [44]
	Peniscmeroterpenoid L **(75)**	$C_{27}H_{38}O_8$	Anti-inflammatory activity	Zhao et al. [43]
				Jiang et al. [44]
	Peniscmeroterpenoid M **(76)**	$C_{26}H_{34}O_8$		Zhao et al. [43]
				Jiang et al. [44]
	Peniscmeroterpenoid N **(77)**	$C_{26}H_{34}O_8$		Zhao et al. [43]
				Jiang et al. [44]
Polyketides	Sclerketide A **(78)**	$C_{21}H_{21}O_5$		Liu et al.[46]
	Sclerketide B **(79)**	$C_{22}H_{26}ClO_5$	Inhibitory effect against the production of NO	Liu et al.[46]
	Sclerketide C **(80)**	$C_{26}H_{33}NClO_6$	Inhibitory effect against the production of NO	Liu et al.[46]
	Sclerketide D **(81)**	$C_{21}H_{21}O_6$	Inhibitory effect against the production of NO	Liu et al.[46]
Peptides	Penisclerotiorin A **(82)**	$C_{18}H_{24}O_6$	Notable inhibitory effects against nitric oxide production	Zhao et al. [41]
	Penidepsidone A **(83)**	$C_{16}H_{14}O_5$	Notable inhibitory effects against nitric oxide production	Zhao et al. [15]
	Diaporthein C **(84)**	$C_{20}H_{28}O_5$	Notable inhibitory effects against nitric oxide production	Zhao et al. [15]
Furan derivatives	(2*S*,3*S*,5*S*)-2-allyl-3-hydroxy-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran **(85)**	$C_{10}H_{19}O_3$	*α*-glucosidase inhibitory activity	Jing et al.[28]
	(2*S*,3*S*,5*S*)-2-(2-hydroxyethyl)-3-hydroxy-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran **(86)**	$C_{10}H_{21}O_4$	*α*-glucosidase inhibitory activity and anti-inflammatory	Jing et al.[28]

5. Biotechnological Potential of *Penicillium sclerotiorum*

Industrial exploration of secondary metabolites requires thorough understanding of regulatory genes, biosynthetic enzymes, and genetic foundations. This knowledge forms the basis for metabolic engineering tactics that maximize the production of desired natural products while maintaining financial sustainability.[49] Moreover, these biosynthetic enzymes are essential to many biotechnological activities. Nielsen et al. presented an excellent work on the worldwide investigation of clusters of biosynthetic genes in *Penicillium* species.[50] Interestingly, study of 24 *Penicillium* genomes showed that there were further unrealized possibilities for this species to produce secondary metabolites than anticipated.[51]

However, *Penicillium* fungi have been highly regarded for their pivotal involvement in biotechnological enzyme production.[52] This genus holds significant importance in the creation of crucial industrial products, including penicillin and statins. As highlighted by Chavez et al., penicillin serves as a rich source of enzymes, particularly xylanolytic enzymes.[53] The utilization of xylanases derived from *Penicillium* sp. has gained increasing prominence in various biotechnological applications. In addition to its exceptional capacity to generate new bioactive secondary metabolites, *P. sclerotiorum* is also a valuable source of enzymes for biotransformation and biotechnological applications.[53] *P. sclerotiorum* is the source of a unique and innovative ß-D-glucosidase that hydrolyzes ginsenoside Rg1, as reported by Wei et al.[55] This particular ß-Glucosidase demonstrated the capacity to hydrolyze ginsenoside Rg1 at the C6-glucoside site, hence producing the uncommon ginsenoside F1. This ß-D-Glucosidase basically has the potential to be used in large-scale in vitro operations or in conjunction with *P. sclerotiorum* to conveniently produce the uncommon ginsenoside F1 from panaxatriol-type ginsenoside Rg1.[54]

Knob et al. described the production and characterization of β-xylosidases derived from *P. sclerotiorum.*[18] In recent decades, the utilization of β-xylosidases has become prevalent across various processing industries. This enzyme exhibited notable characteristics: it displayed strong susceptibility to inhibition by divalent cations and sensitivity to denaturing agents like SDS and EDTA.[18] Activation was found when thiol-containing reducing agents were present. Such distinctive properties render this enzyme particularly intriguing for various biotechnological applications in industries related to animal feed, juice, and wine.[18]

Furthermore, Knob et al. achieved the purification of *P. sclerotiorum's* β-xylosidase and established homogeneity using a quick and economical method.[56] Structural analysis revealed its dimeric nature, with a native molecular mass estimated at 144 kDa. Moreover, the enzyme was identified as a glycoprotein, comprising a substantial 56.4% carbohydrate content. This report describes the characterization and purification of a β-xylosidase derived from *P. sclerotiorum*, highlighting its potential uses in a range of biotechnological processes in sectors including wine, juice, and animal feed.[56] The properties of β-xylosidase also make it an attractive option for use in the animal feed sector. Numerous investigations have demonstrated that include β-xylosidases in diets enhances feed's nutritional content and enhances animal performance.[57] Furthermore, this enzyme stops the growth of pollutants caused by microorganisms when used in industrial processes at low pH and temperatures of about 60°C.[57]

As described by Knob et al. two xylanases that were recovered from the pure culture filtrate of *P. sclerotiorum* through a quick and effective purification procedure using ion-exchange and molecular exclusion chromatography.[58] Xylanases I and II were purified to homogeneity, with estimated molecular weight of 23.9 kDa and 33.1 kDa, respectively, assessed through sodium dodecyl sulfate-polyacrylamide gel electrophoresis.[58] β-mercaptoethanol and dithio-treito were shown to be reducing agents that cause xylanase activities to increase.[58] Xylanase I hydrolyzed oat spelt xylan, releasing xylobiose and larger xylo-oligosaccharides, while xylanase II produced xylo-oligosaccharides up to xylotriose, displaying a decreasing polymerization degree. These characterized xylanases exhibit compelling traits for diverse biotechnological applications, particularly within the feed and food industries.[59] The utilization of xylanases has proliferated across multiple processing industries encompassing pulp and paper, food, and textiles.[59] The most efficient inducers of xylanase activity were found to be wheat bran and oat spelts xylan when *P. sclerotiorum* was cultured in a submerged environment.[60] Furthermore, xylanases show great promise for enhancing the economical synthesis of important chemicals such as ethanol and xylitol.[61]

P. sclerotiorum holds incredible promise in producing novel bioactive secondary metabolites, yet this area remains relatively underexplored. There are plenty of research opportunities in this field due to its unexplored surface. Recently, a handful of bioactive compounds unearthed from *P. sclerotiorum* have revealed compelling potential for various industrial applications.

6. Conclusion:

The exploration of *penicillium sclerotiorum* reveals an amazing array of possible applications that highlight both its unique morphological characteristics and its vast secondary metabolite diversity. This filamentous fungus not only inhabits diverse environments but also exhibits a prolific capacity to synthesize a wide range of bioactive compounds. The extensive list of secondary metabolites, spanning alkaloids, azaphilones, steroids, and meroterpenoids, underlines its remarkable biotechnological potential. Further investigation is needed into how environmental factors influence the fungus secondary metabolite production.

Moreover, *P. sclerotiorum* produces a variety of enzymes, it presents an interesting option for industrial use. Enzymes such as ß-D-glucosidase, β-xylosidases, and xylanases present opportunities for a range of industries, including animal feed, beverages, and medicines. The profound biotechnological significance of *P. sclerotiorum*, both in its enzyme production and diverse secondary metabolites, underscores the necessity for continued research. Further exploration into its genetic foundations, regulatory mechanisms, and environmental influences holds immense promise for unlocking its full potential in pharmaceuticals, food technology, and other industrial applications.

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Israt Jahan- Conceptualization, Data curation, Writing - original draft, Yihan Wang, Ping Li, Sarfaraz Hussain, Jiayi Song- review & editing. Yan Jian: Conceptualization, Project administration, Funding acquisition, Writing - review & editing.

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Figure 1: Structures form Azaphilones group of compounds **(1-12)** isolated from *Penicillium sclerotiorum.*

Figure 2: Structures form Azaphilones group of compounds **(13-27)** isolated from *Penicillium sclerotiorum.*

Figure 3: Structures form Azaphilones group of compounds **(28-39)** isolated from *Penicillium sclerotiorum.*

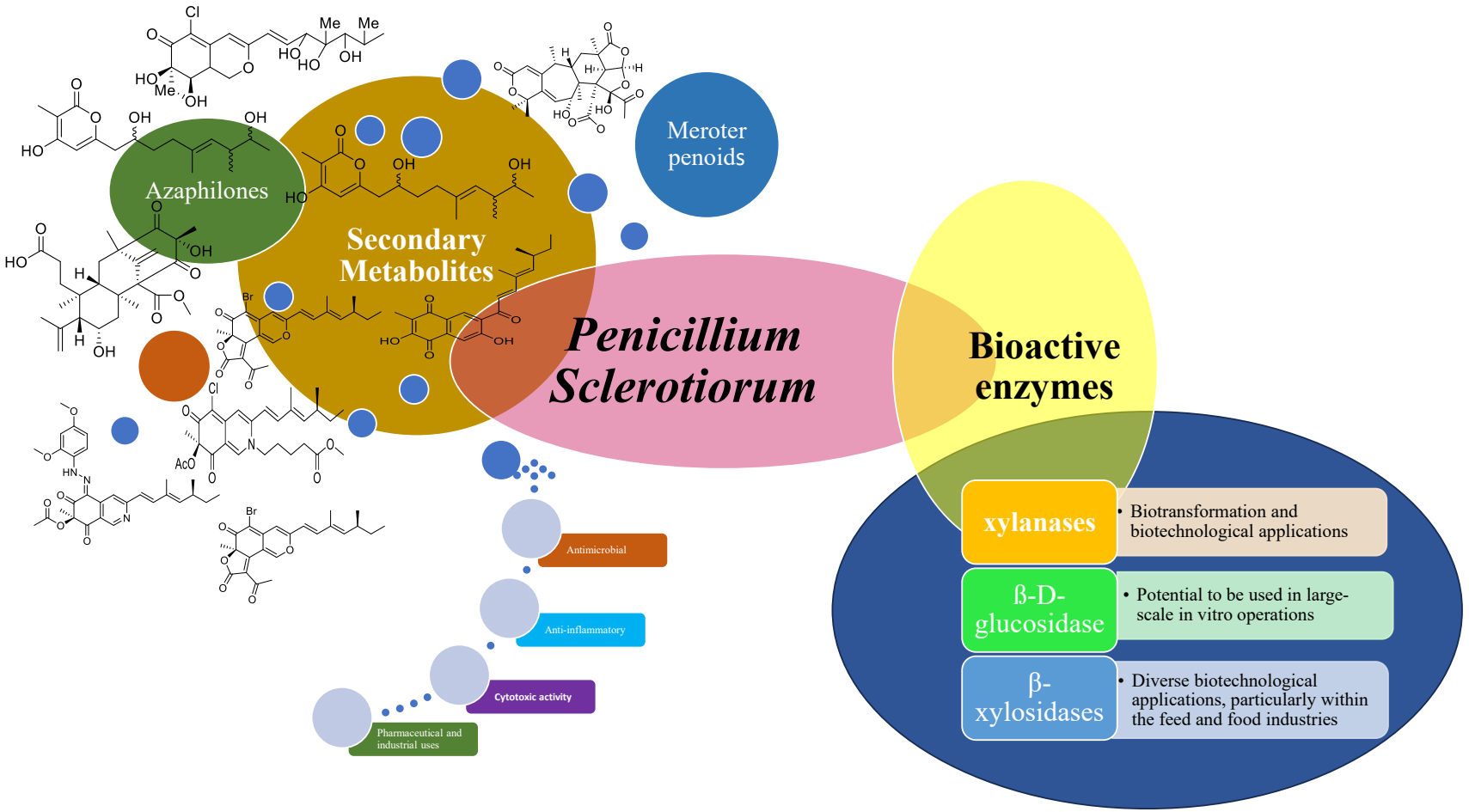
Figure 4: Structures form Azaphilones group of compounds **(40-52)** isolated from *Penicillium sclerotiorum.*

Figure 5: Structures form Azaphilones group of compounds **(53-63)** isolated from *Penicillium sclerotiorum.*

Figure 6: Structures form meroterpenoids group of compounds **(64-77)** isolated from *Penicillium sclerotiorum.*

Figure 7: Structures form Polyketides, Peptides and Furan derivatives isolated from *Penicillium sclerotiorum.*

Figure 8: The biotechnological potential of *Penicillium sclerotiorum.*



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411 **Graphical Abstract**

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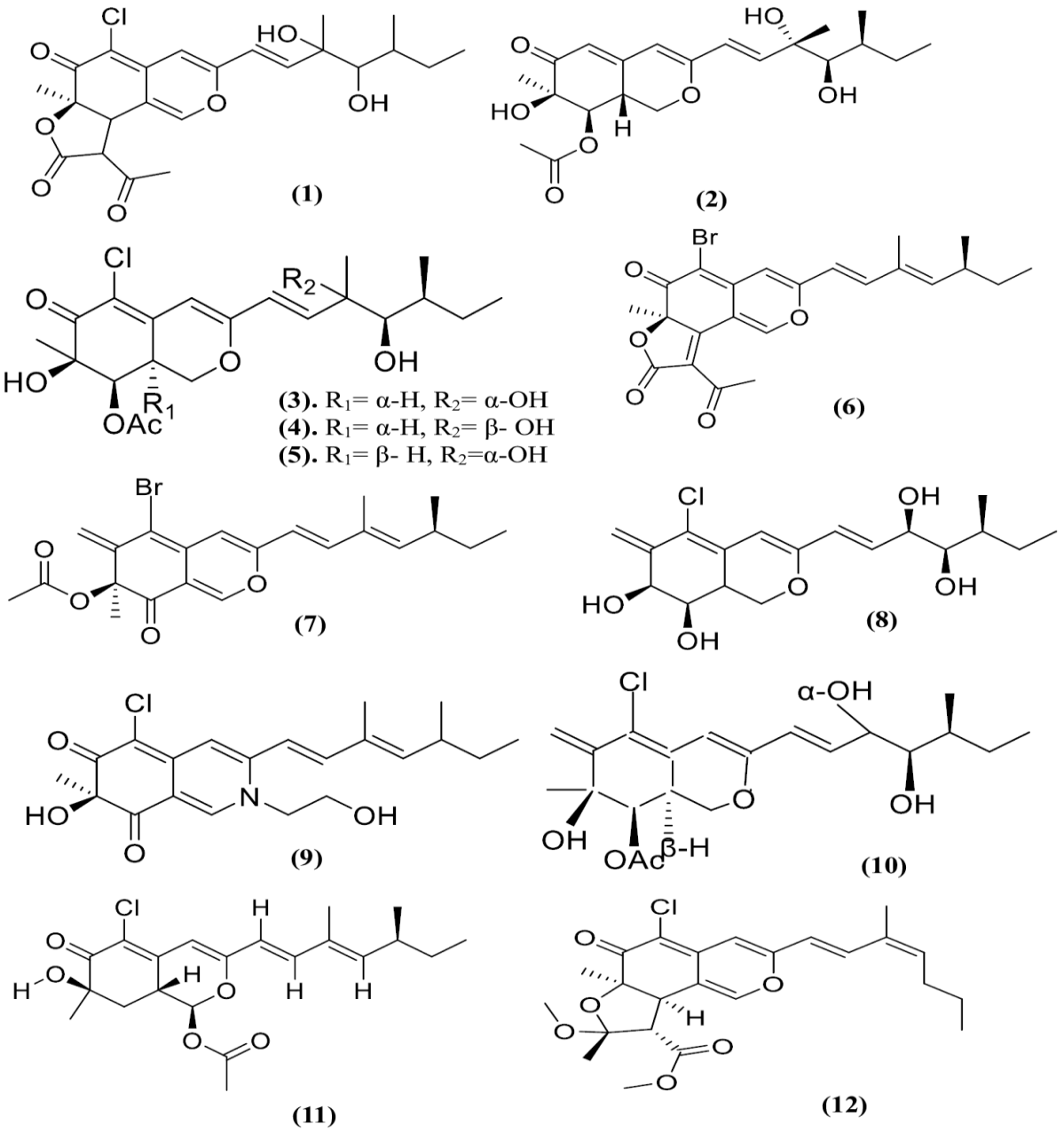
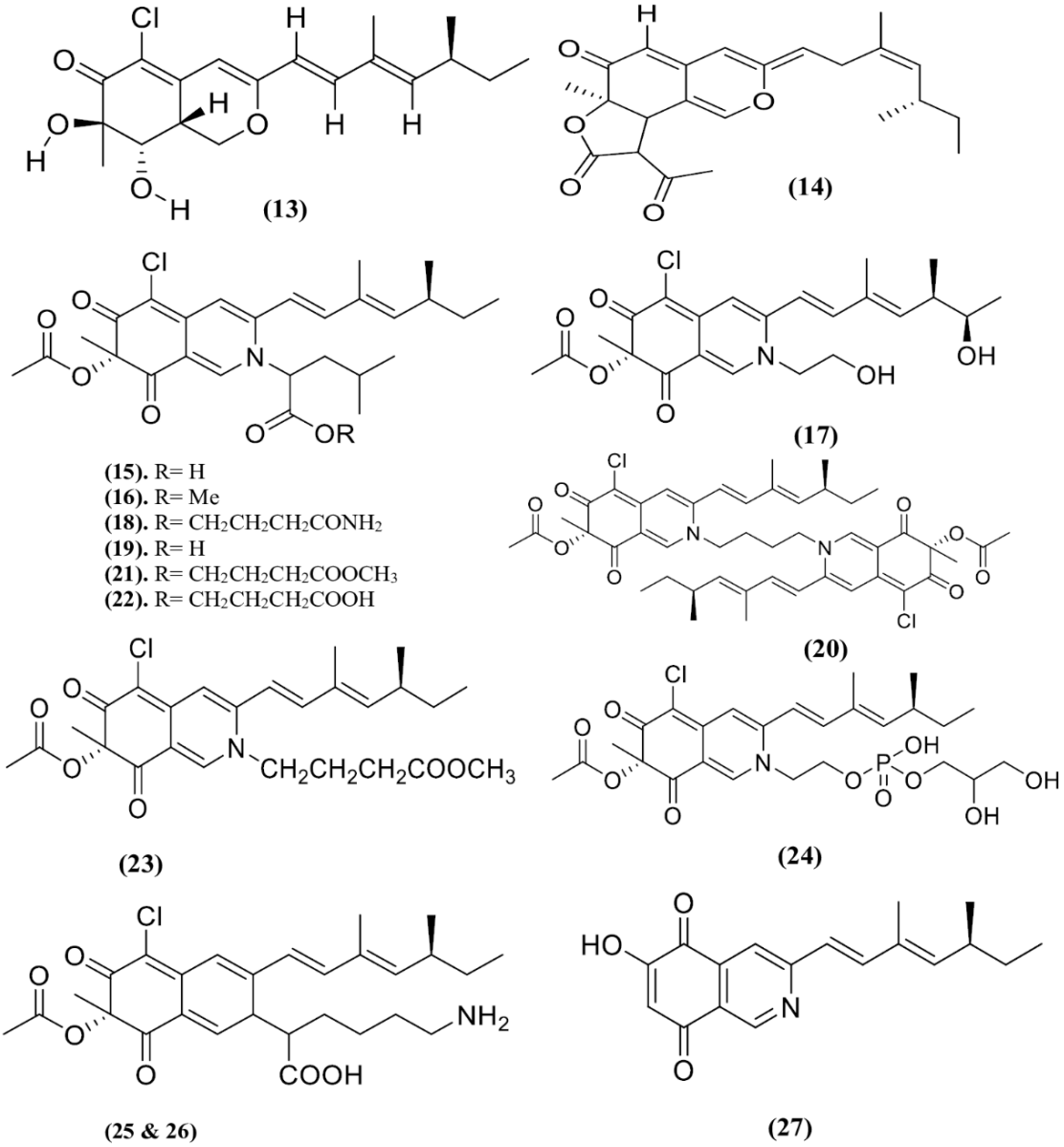


411

412 **Figure 1:** Structures form Azaphilones group of compounds **(1-12)** isolated from *Penicillium*
413 *sclerotiorum.*



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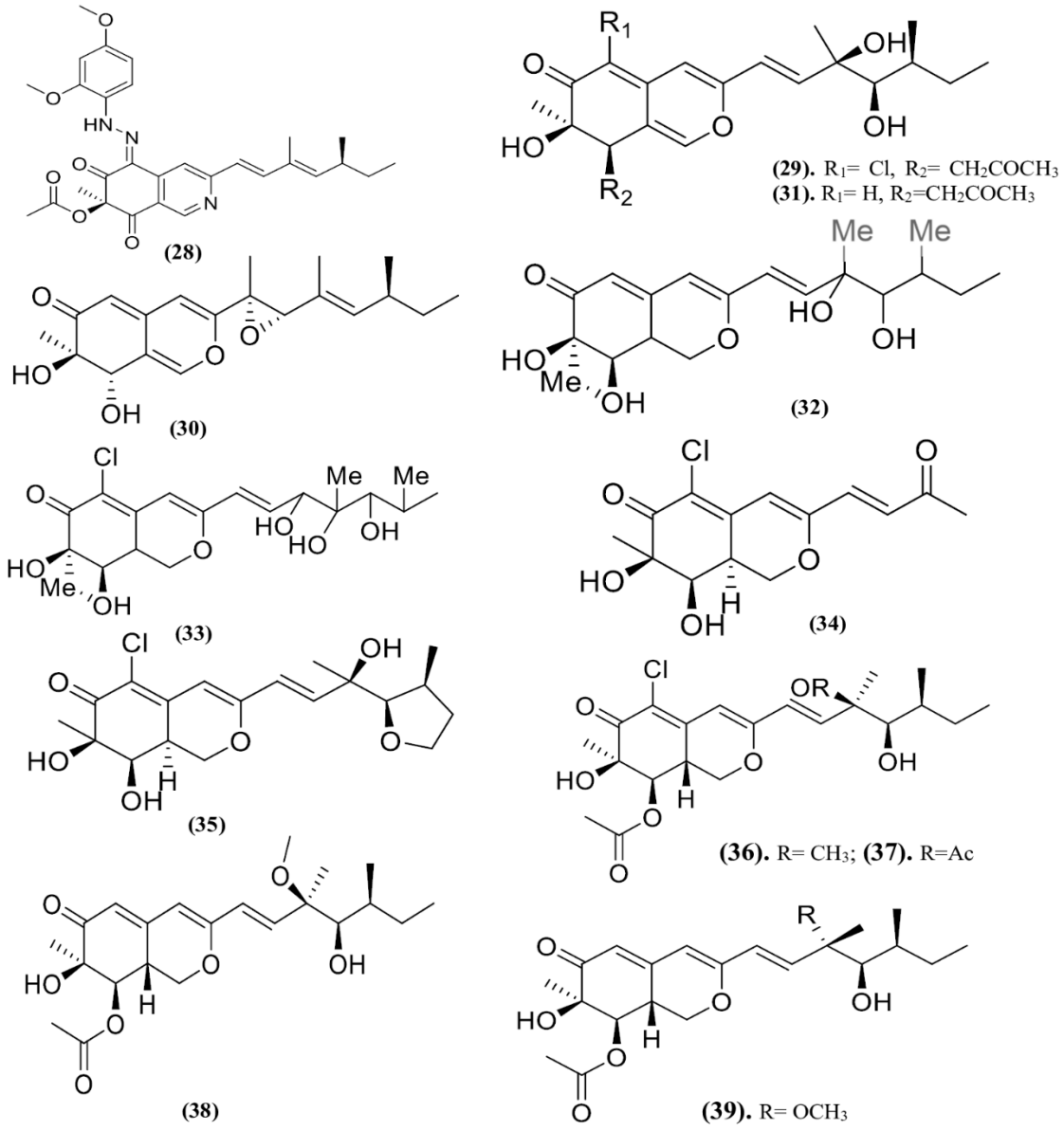
411 **Figure 2:** Structures form Azaphilones group of compounds **(13-27)** isolated from *Penicillium*
412 *sclerotiorum.*

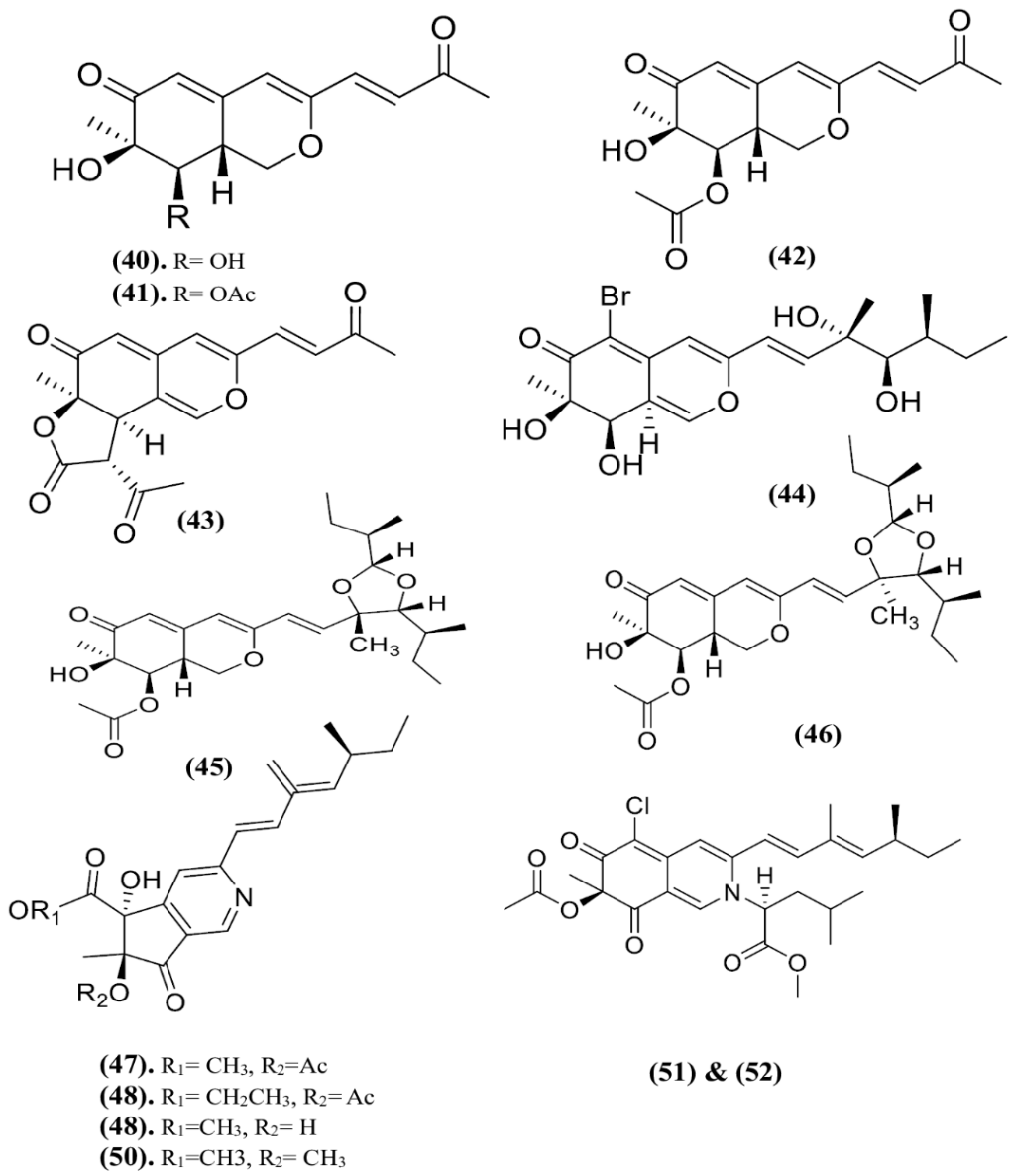


410

411 **Figure 3:** Structures form Azaphilones group of compounds **(18-39)** isolated from *Penicillium*

412 *sclerotiorum.*

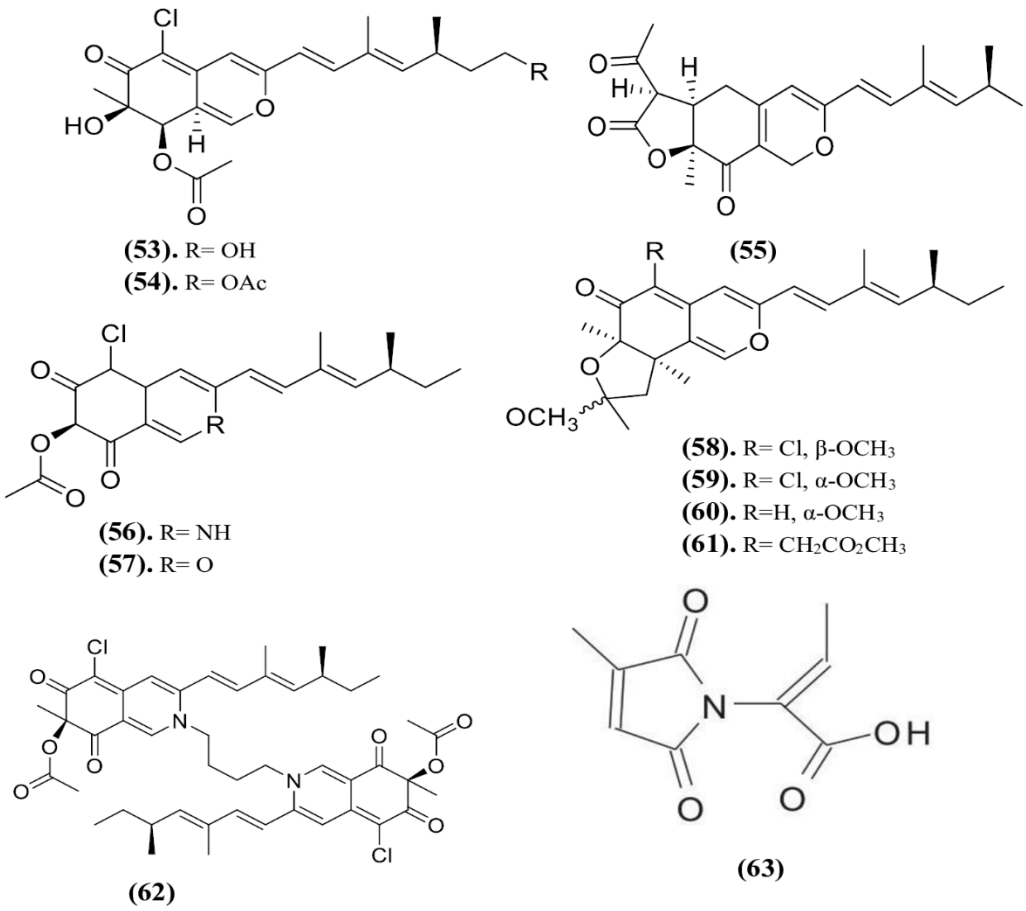
413



410

411 **Figure 4:** Structures form Azaphilones group of compounds **(40-52)** isolated from *Penicillium*

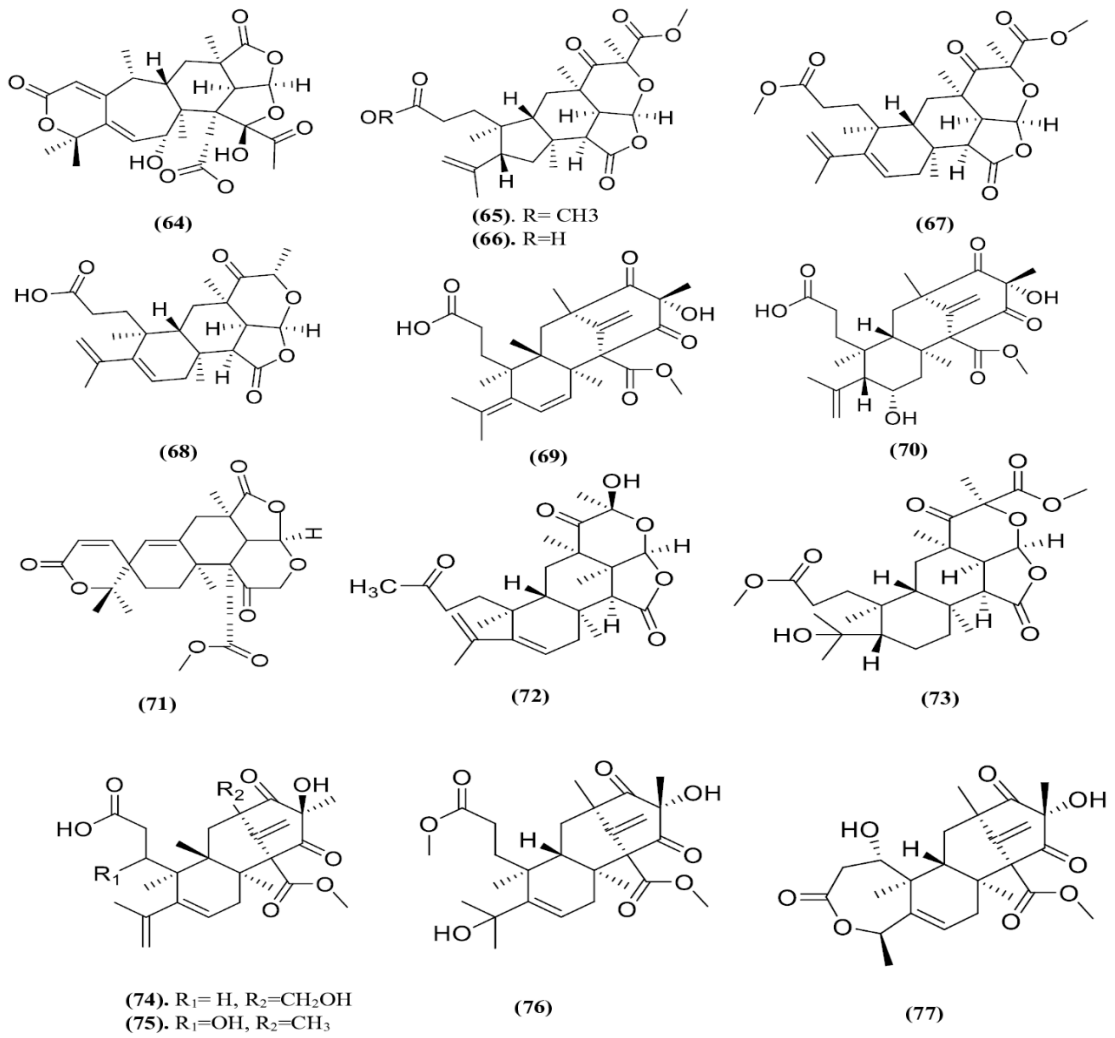
412 *sclerotiorum.*



410

411 **Figure 5:** Structures form Azaphilones group of compounds **(53-63)** isolated from *Penicillium*

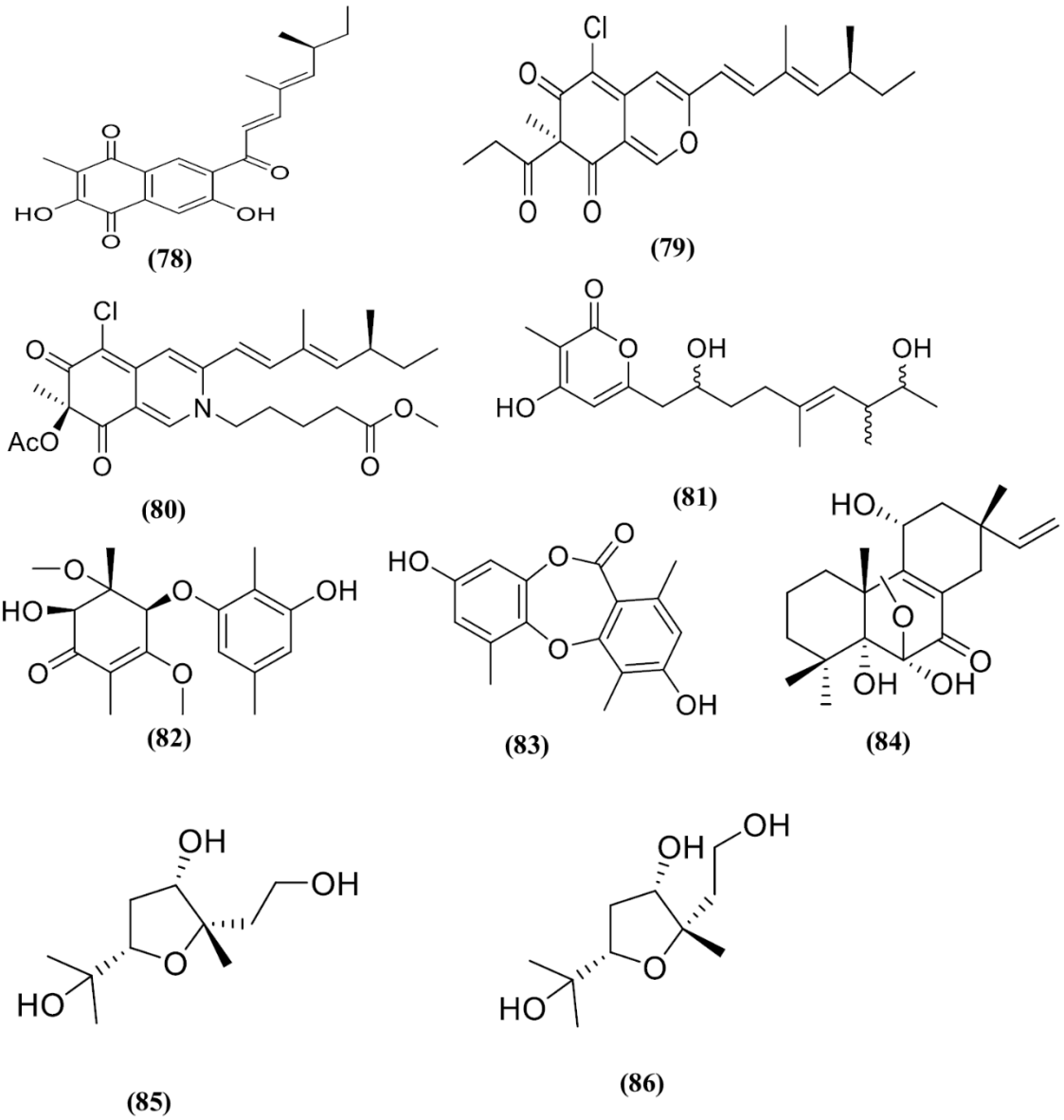
412 *sclerotiorum.*



410

411 **Figure 6:** Structures form meroterpenoids group of compounds **(64-77)** isolated from

412 *Penicillium sclerotiorum.*



410

411 **Figure 7:** Structures form Polyketides, Peptides and Furan derivatives isolated from *Penicillium*
412 *sclerotiorum.*

413

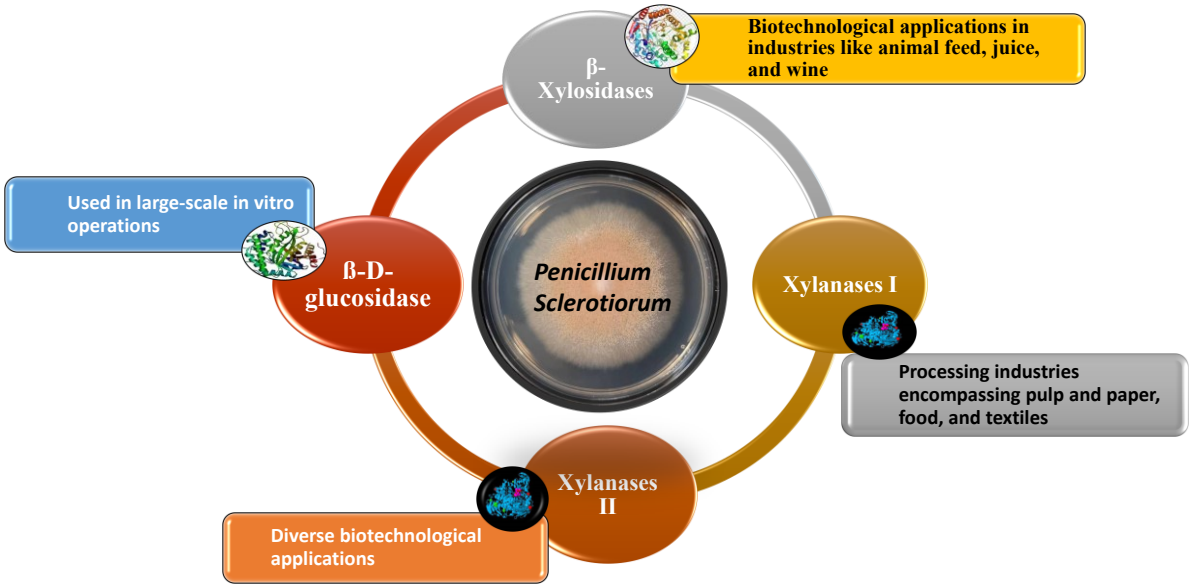


Figure 8: The biotechnological potential of *Penicillium sclerotiorum.*