Review

Journal of the Brazilian Chemical Society

https://dx.doi.org/10.21577/0103-5053.20240032

J. Braz. Chem. Soc. **2024**, *35*, 8, e-20240032, 1-23

Antimicrobial Potential of Soil/Sediment Mangrove Associated Fungi: A Review

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Mangroves are highly productive ecosystems that support a diverse range of plant, animal, and microorganism species, especially fungi. This ecosystem is characterized as a transition zone between sea and land which is interesting because this environment can be considered an extreme environment due to the peculiar characteristics that it can exhibit, which is interesting for the establishment of diverse fungal species with great biotechnological potential, these habitats are relevant for the bioprospecting of interesting secondary-metabolite-producing fungi. Fungi play an essential role in maintaining this environment and also represent a rich source of structurally diverse antimicrobial compounds. This review summarizes antibacterial, antifungal, and antiviral chemicals produced by soil/sediment-derived mangrove fungi from 1990 to 2022.

Keywords: mangrove fungi, fungi from mangrove soil, fungi from mangrove sediment, fungal metabolites, biological activity

1. Introduction

Mangrove ecosystems support a diverse range of plant and animal species, as well as microorganisms, particularly fungi.[1] Mangroves are important targets for bioprospecting because of the constant interactions between these organisms and their biochemical adaptations required for life in this environment. They are coastal ecosystems known to be transition zones between marine and terrestrial environments.[2] From an ecological point of view, these ecosystems have interesting characteristics. Because they can present high temperatures, high levels of salinity, high pH, high organic matter concentrations, low aeration, and high humidity.[3]

Mangrove forests can be found in tropical and subtropical regions. The water temperatures in these areas can exceed 24 ºC during the hottest months, and the annual precipitation can exceed 1250 mm. This ecosystem currently covers an area of approximately 181,000 km^2 on the planet, with the largest formations found in Bangladesh, Brazil, Indonesia, India, and Thailand.[1,4,5] They can still withstand a wide range of sediment types brought by marine currents, changes in temperature, nutrients, salinity, and oxygen levels, as well as intermittent flooding and tidal level variation, resulting in the formation of unique microbial communities and high rates of biomass production,[6,7] as illustrated in Figure 1.

The unique characteristics of the mangrove environment make them interesting for the bioprospecting of organisms of interest, in addition, this ecosystem plays an important role in supporting and protecting life in the coastal zone, being essential for the support of both, marine and terrestrial life, resulting in a potential field for discovering new molecules of interest. However, regarding conserving this environment, at least 35% of these forests worldwide have been destroyed in recent decades by anthropogenic actions. Unfortunately, effective official

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Editor handled this article: Hector Henrique F. Koolen (Associate)

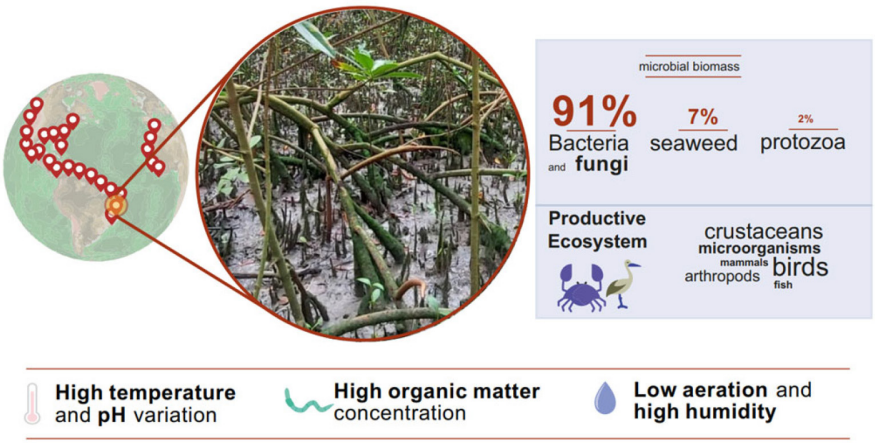


Figure 1. Main characteristics of mangrove areas.

policies or strategies to fully protect these ecosystems are rare.

Regarding the conservation of this environment, prospecting organisms of biotechnological interest may be one alternative to stimulate conservation actions from governments, since the discovery and application of compounds of natural origins are important not only from the point of view of social and economic development but mainly from an environmental point of view, since producing organisms need a healthy ecosystem to maintain their ecological niche, so that they are available in nature, since the lack of a healthy ecosystem can cause the loss of biodiversity and consequently the loss of several useful compounds, many of them unknown.

In this case, conservation strategies for these environments are relevant as they fit into the United Nations' 17 sustainable development goals (climate actions, life below water, and life on land), being appropriate for conserving mangrove areas and producing organisms, such as fungi.

The microbial biomass found in mangroves accounts for approximately 1.2% of the total organisms. Bacteria and fungi account for 91.0% of total microbial biomass in mangroves, with algae (7.0%) and protozoa (2.0%).[3,8,9] These fungal communities are known as "manglicolous fungi," and they consist primarily of marine fungi and a small group of terrestrial fungi. These fungi can be saprophytic, parasitic, symbiotic, or other, depending on their ecological role.[10]

Fungi are essential to the survival of this ecosystem. They participate in the synthesis of enzymes required for the decomposition of organic matter in this environment, converting it into nutrients available for its metabolism or that of other organisms, as well as allowing subsequent colonization by bacteria and yeasts to supplement the decomposition process, thereby contributing to the cycling and flow of nutrients to higher trophic levels.[5,10,11]

Furthermore, these microorganisms are a rich source of secondary metabolites that are of direct or indirect interest to humans, such as alkaloids, flavonoids, terpenoids, enzymes, peptides, and polyketides, which many of these natural products have significant biological and biotechnological applications.[12-16]

The mangrove environment is an important target for bioprospection of secondary metabolite-producing fungi because it contributes to the development of several fungal species with potential biotechnological applications. After all, fungal secondary metabolites are typically produced in response to biotic or abiotic environmental influences. The organisms present in these areas are expected to be sources of unusual compounds due to the mangrove's unique characteristics.[17,18]

The vast biodiversity of these mangrove habitats has piqued the interest of various researchers worldwide, who are interested in microbial variety and potential biotechnological uses.[19-22] Swart's investigations, published in 1958,[23] provided the first study on fungal diversity in mangrove soils. However, research on new compounds from fungi associated with mangrove areas began in 1989 with the publication of Poch and Gloer's work,[24] which described the isolation of new lactones from extracts of the liquid culture medium of the fungus *Helicascus kanaloanus* (ATCC 18591) isolated from the submerged roots of the species *Rhizophora mangle* in a mangrove swamp of Hawaii, USA.

Currently, research on the secondary metabolites of fungi associated with mangroves has grown significantly. Blunt, Carroll, and collaborators[25-29] emphasized the increasing number of new metabolites described in recent years, with approximately 710 new compounds reported between 2013 and 2018, the majority of which came from endophytic microbial species identified in mangrove plants.

Furthermore, Chen *et al*.[8] pointed out that throughout the last thirty years (1989-2020) around 451 research reported the discovery of roughly 1387 novel molecular structures synthesized by fungi associated with mangroves, the vast majority of which are discovered in endophytic fungi. In this case, 79% of the total compounds reported (1090 molecular structures) were produced by approximately 250 strains.

In addition to a high number of metabolites from endophytic species, 142 and 58 compounds isolated from soils and sediments fungi were reported, respectively, thus highlighting the genera that have the highest occurrence, mainly *Penicillium* and *Aspergillus*, followed by *Eurotium*, *Trichoderma*, *Fusarium*, *Lasiodiplodia theobromae*, and *Cladosporium*.

Endophytic fungi have stood out in these investigations, producing the majority of the chemical substances of fungal origin found in mangroves identified so far in the literature. These compounds were employed for the production of antibiotics, antivirals, and medicines having anticancer, cytotoxic, and anti-inflammatory properties, as well as biosurfactants and enzymes of industrial relevance.[30-32]

Fungi isolated from mangrove soils and sediments have also become essential research topics. This group has a high biological diversity and is a source of unusual secondary metabolites.[33,34] Even considering that there are still few studies involving such microorganisms collected in mangrove soils, the success of the research reinforces their importance, making this group an interesting target for investigations into its biological diversity and, as a result, for the bioprospection of natural products of fungal origin, leading to the discovery of new drugs and employment in biotechnological applications.

Although the existence of published studies, and reviews on natural products derived from fungi associated with mangrove environments are still limited in the literature, particularly those dealing with fungi isolated from soils or sediments. Due to the fact that the great majority report metabolites from endophytic species. Jakubczyk and Dussart[35] highlighted natural products of fungal origin with antimicrobial activity but did not identify isolated mangrove species. Cadamuro *et al*.[15] reported on compounds with antimicrobial activity isolated only from endophytic fungi from mangrove areas.

Ancheeva *et al*.[36] systematically described the compounds isolated from microorganisms associated with mangrove areas, highlighting a section for fungi isolated from soil or sediment. However, this study only reports compounds having cytotoxic action and compounds with lipid-reducing activity, with a table-based overview of additional biological activities from 2014 to 2018. In this context, we propose to broaden our understanding of the previously discussed topic by focusing on the literature that describes the study of fungi isolated from soil or sediments to describe the source of isolation and reported metabolites between 1991 and 2022, highlighting antimicrobial activities, and potential applications.

In this paper, we highlight research that focuses on the isolation of manglicolous fungi, in which fungi of the genus *Penicillium* and *Aspergillus* stand out as the main producers of antimicrobial compounds, as can be summarized in Table 1.

2. Research Methodology

Extensive research was developed in PubMed, Scopus, Web of Science, Google Scholar, Springer, Wiley, and Mendeley databases using different combinations of the following sentences: “Mangrove fungi”, “marine fungi”, “fungi from mangrove soil”, “fungi from mangrove sediment”, and “secondary metabolites”.

3. Antimicrobial Activity of Manglicolous Fungi Metabolites

From the research done by Poch and Gloer,[37] studies focusing on fungi from soil or sediment from mangrove environments and their generated secondary metabolites and biological activity started in 1991. The study demonstrated the isolation and antibacterial activity of

Table 1. Summary of research on fungi associated with mangrove soil/sediments and antimicrobial activities

Number of researches						
Genus						
Penicillium	*Aspergillus*	*Eurotium*	*Trichoderma*	*Fusarium*	*Lasiodiplodia*	*Cladosporium*
15	6	1	2	2	2	1
Number of compounds						
Activity						
Anti-bacterial		Antifungal		Antiviral		
39		12		30		

two novel depsidones produced by the fungus *Preussia aurantiaca* (ATCC 14745): auranticin A and auranticin B (Figure 2). Auranticin A was found to be more active against the microorganisms tested, with biological activity against *Bacillus subtilis* and *Staphylococcus aureus* at 5 and 50 μg *per* disc, respectively.[37]

Table 2 shows the results of the antimicrobial activities of substances isolated from these microorganisms (different genera and species) over the years.

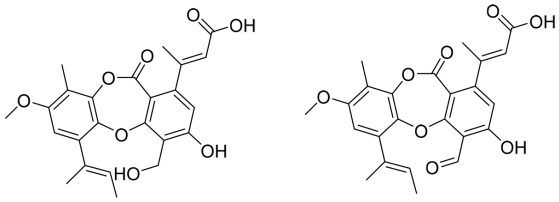


Figure 2. Structures of auranticin A and auranticin B isolated from *P. aurantiaca* (ATCC 14745).

Table 2. Antimicrobial activity of manglicolous fungi isolated from soil or sediment

Species	Source	Major compounds	Antimicrobial activity microorganism	Potency	Reference
Penicillium sp. MA-37	soil	7-*o*-acetylsecopenicillide C (**1**)	*Micrococcus luteus* *Escherichia coli*	MIC 64.0 μg mL^{-1} 16.0 μg mL^{-1}	38
		iso-monodictyphenone (**2**)	*Aeromonas hydrophilia*	8.0 μg mL^{-1}	39
Penicillium sp. ML226	sediment	penicitrinol J (**3**) penicitrinol K (**4**)	*Staphylococcus aureus*	inhibition zone 10 mm 9 mm	40
Penicillium bilaiae MA-267	soil	penicibilaene A (**5**) penicibilaene B (**6**)	*Colletotrichum gloeosporioides*	MIC 1.0 μg mL^{-1} 0.125 μg mL^{-1}	41
Penicillium simplicissimum MA-332	soil	penicisimpin A (**7**)	*Escherichia coli* *Pseudomonas aeruginosa* *Vibrio parahaemolyticus* *Vibrio harveyi* *Colletotrichum gloeosprioides*	MIC 4.0 μg mL^{-1}	42
		simpterpenoid A (**8**)	influenza neuraminidase *Physalospora piricola*	IC_{50} 8.1 nM MIC 64.0 μg mL^{-1}	43
Penicillium janthinellum HK1-6	soil	penicilones B-D (**9-11**)	Methicillin-resistant *Staphylococcus aureus*	MIC 3.1-6.2 μg mL^{-1}	44
		penicilone G (**12**) penicilone H (**13**)	*Staphylococcus aureus* *Enterococcus faecalis* *Enterococcus faecium* *Escherichia coli*	MIC 3.1-50.0 μg mL^{-1}	45
		penijanthinone A (**14**)	Methicillin-resistant *Staphylococcus aureus*	MIC 3.1 μg mL^{-1}	45
Penicillium sp. HK1-22	soil	peninaphones A-C (**15-17**)	*Staphylococcus aureus*	MIC 12.5-50.0 μg mL^{-1}	46
		peninaphone C (**17**)	*Rhizoctonia solani*	–	46
Penicillium pinophilum SCAU037	soil	sch725680 (**18**)	*Mycobacterium smegmatis* *Staphylococcus aureus*	IC_{50} 23.5 μM 2.6 μM	47
Penicillium ludwigii SCSIO 41408	sediment	adametizine C (**19**) adametizine A (**20**) DC1149B (**21**) outovirin B (**22**) pretrichodermamide E (**23**)	*Erysipelothrix rhusiopathiae* WH13013 *Streptococcus suis* SC19	MIC 50.0-100.0 μg mL^{-1}	48
		adametizine A (**20**)	*Botrytis cinerea* *Septoria nodorum* Berk	MIC 25.0 μg mL^{-1}	48

Table 2. Antimicrobial activity of manglicolous fungi isolated from soil or sediment (cont.)

Species	Source	Major compounds	Antimicrobial activity microorganism	Potency	Reference
Penicillium camemberti OUCMDZ-1492	soil	3-deoxo-4b-deoxypaxilline (**24**) 4a-demethylpaspaline-4a-carboxylic acid (**25**) 4a-demethylpaspaline-3,4,4a-triol (**26**) 9,10-diisopentenylpaxilline (**27**) (6*S*,7*R*,10*E*,14*E*)-16-(1*H*-indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol (**28**) emindole SB (**29**) 21-isopentenylpaxilline (**30**) paspaline (**31**) paxilline (**32**)	H_1N_1	IC_{50} 28.3 μM 38.9 μM 32.2 μM 73.3 μM 34.1 μM 26.2 μM 6.6 μM 77.9 μM 17.7 μM	49
Penicillium sp. OUCMDZ-4736	sediment	(−)-1,2,4,5-tetrahydroxy-7-((2*R*)-2-hydroxypropyl) anthracene-9,10-dione (**33**) methyl 6,8-dihydroxy-3-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**34**)	HBV	dose dependent	50
Penicillium sp. IMB17-046	sediment	trypilepyrazinol (**35**)	HIV-1 HCV	IC_{50} 4.6 μM 7.7 μM	51
		(+)-neocitreoviridin (**36**)	IAV	IC_{50} 3.6 μM	51
		3β-hydroxyergosta-8,14,24(28)-trien-7-one (**37**)	HIV-1 IAV	IC_{50} 3.5 μM 0.5 μM	51
		trypilepyrazinol (**35**) (+)-neocitreoviridin (**36**)	*Helicobacter pylori*	MIC 1.0-16.0 μg mL^{-1}	51
Penicillium raistrickii IMB17-034	sediment	raistrickindole A (**38**) raistrickin (**39**) sclerotigenin (**40**)	HCV	EC_{50} 5.7 μM 7.0 μM 5.8 μM	52
Aspergillus versicolor HDN1009	soil	5-epi-asperdichrome (**41**)	*Vibrio parahemolyticus* *Bacillus subtilis* *Mycobacterium phlei* *Pseudomonas aeruginosa* *Candida albicans*	MIC 100-> 200 μM	22
Aspergillus ochraceus MA-15	soil	asperochrin A (**42**) chlorohydroaspyrone A (**43**) chlorohydroaspyrone B (**44**) chlorohydroasperlactone A (**45**) penicillic acid (**46**) (*R*)-7-hydroxymellein (**47**)	*Aeromonas hydrophilia* *Vibrio anguillarum* *Vibrio harveyi*	MIC 0.5-64.0 μg mL^{-1}	53
Aspergillus sp. DM94	soil	asperpyrone A (**48**) aurasperone A (**49**) aurasperone F (**50**) aurasperone B (**51**)	*Helicobacter pylori* G27 *Helicobacter pylori* HP159	MIC 4.0-16.0 μg mL^{-1}	54
Aspergillus terreus SCAU011	sediment	asperbutenolide D (**52**) (+)-3',3'-di-(dimethylallyl)-butyrolactone II (**53**) aspernolide E (**54**) terrusnolide A (**55**)	*Staphylococcus aureus*	IC_{50} 17.4-36.6 μM	55
Aspergillus terreus Gwq-48	soil	isoaspulvinone E (**56**) aspulvinone E (**57**) puvic acid (**58**)	H_1N_1	IC_{50} 32.3 μg mL^{-1} 56.9 μg mL^{-1} 29.1 μg mL^{-1}	56
Aspergillus taichungensis ZHN-7-07	soil	aspergilazine A (**59**)	H_1N_1	dose dependent	57

Table 2. Antimicrobial activity of manglicolous fungi isolated from soil or sediment (cont.)

Species	Source	Major compounds	Antimicrobial activity microorganism	Potency	Reference
Eurotium rubrum MA-150	soil	dihydroxyisoechinulin A (**60**)	*Vibrio alginolyticus*	MIC 16.0 μg mL^{-1}	58
Trichoderma sp. NPK2	sediment	crude extracts	*Bacillus subtilis* *Vibrio cholerae*	MIC 200.0 μg mL^{-1}	59
			Staphylococcus aureus *Bacillus cereus*	MIC 150.0 μg mL^{-1}	59
			Escherichia coli	MIC 125.0 μg mL^{-1}	59
			Vibrio parahaemolyticus *Vibrio harveyi*	MIC 200.0 μg mL^{-1} 150.0 μg mL^{-1}	59
Trichoderma sp. T-4-1	solo	trichodimerol (**61**) demethyltrichodimerol (**62**)	H_1N_1	IC_{50} 0.5 μg mL^{-1} 0.9 μg mL^{-1}	60
Fusarium solani H915	sediment	fusariumester B (**63**)	*Pestalotiopsis theae*	MIC 50.0 μg *per* disk	61
		hymeglusin (**64**) equisetin (**65**)	*Pestalotiopsis theae* *Colletotrichum gloeosporioides*	MIC 25.0 μg *per* disk	61
Fusarium solani H918	sediment	hymeglusin (**64**)	*Pestalotiopsis theae*	ED_{50} 55 μM	62
Lasiodiplodia theobromae M4.2-2	sediment	(+)-(*R*)-de-*O*-methyl-lasiodiplodin (**66**)	*Staphylococcus aureus* *Enterococcus faecium*	MIC 25.0 μg mL^{-1}	63
Lasiodiplodia theobromae NSTRU-PN1.4	soil	(3*R*,4*R*)-4-acetyl-3-methyl-2(3*H*)-dihydrofuranone (**67**)	*Cryptococcus neoformans*	MIC 200.0 μg mL^{-1}	64
Cladosporium sp. PJX-41	soil	oxoglyantrypine (**68**) norquinadoline A (**69**) deoxynortryptoquivaline (**70**) deoxytryptoquivaline (**71**) tryptoquivaline (**72**) quinadoline B (**73**)	H_1N_1	IC_{50} 85 μM 82 μM 87 μM 85 μM 89 μM 82 μM	65

MIC: minimum inhibitory concentration; IC_{50}: 50.0% inhibitory concentration; ED_{50}: 50.0% effective dose; H_1N_1: influenza A virus; HBV: anti-hepatitis B virus; HCV: hepatitis C virus; IAV: influenza A virus; HIV-1: human immunodeficiency virus.

3.1. Genus *Penicillium*

Fungi of the genus *Penicillium* are one of the most diverse genera of fungi, capable of growing in a wide range of environments. Because of their high adaptability, they are regarded as major sources of secondary metabolites of interest, which may have a variety of actions, including powerful antibacterial activity. For example, the discovery of penicillin produced by *Penicillium notatum*, one of the most powerful antibiotics that ever existed.[66]

In this context, Zhang *et al*.[38] isolated the fungus *Penicillium* sp. MA-37 from the rhizosphere soil of *Bruguiera gymnorrhiza* on Hainan Island, China. The research resulted in the production of distinct compounds from the same fungus when grown in various ways (static and shaken fermentation modes). The microorganism was able to biosynthesize six meroterpenoid derivatives, including three new compounds: 4,25-dehydrominiolutelide B, 4,25-dehydro 22-deoxyminiolutelide B, and isominiolutelide A, in addition to three already known compounds: berkeleyacetal A, berkeleyacetal B, and 22-epoxyberkeleydione, when cultivated in static fermentation mode. However, when cultivated in shaken fermentation mode, chemical analyses led to the identification of three novel diphenyl derivatives, $\Delta^{1',3'}$-1'-dehydroxypenicillide, 7-*O*-acetylsecopenicillide C (**1**), and hydroxytenellic acid B, in addition to five related derivatives, including as 6-[2-hydroxy-6-(hydroxymethyl)-4-methylphenoxy]-2-methoxy-3-(1-methoxy-3-methylbutyl) benzoic acid, penicillide, secopenicillide C, dehydroisopenicillide, 3'-*O*-methyldehydroisopenicillide.

Ecotoxicity and antibacterial experiments were performed in order to assess the potential of the fungus's

compounds. In the brine shrimp lethality studies, compound 3'-*O*-methyldehydroisopenicillide, was found to be active, with an median lethal dose (LD_{50}) of 72.6 μM, comparable to the positive control (colchicine, LD_{50} of 71.1 μM) while compounds $\Delta^{1',3'}$-1'-dehydroxypenicillide, penicillide, and berkeleyacetal B were also active in the test with LD_{50} values of 135.9, 158.5, and 160.0 μM, respectively, which may mischaracterize them as prospective therapeutic candidates. Compound **1**, on the other hand, demonstrated activity against the microorganisms *Micrococcus luteus* and *Escherichia coli*, with MIC values of 64.0 and 16.0 μg mL^{-1}, respectively, demonstrating significant bioactive potential when compared to the other compounds examined. However, the minimum inhibitory concentration (MIC) values are still higher than the reference values of the drug used as a positive control in the experiments (chloromycetin, MIC of 4.0 μg mL^{-1} for both bacteria).[38]

Further research using the fungus *Penicillium* sp. MA-37, cultivated in shaken fermentation mode, resulted in the isolation of one new benzophenone, iso-monodictyphenone (**2**), two new diphenyl ether derivatives, penikellides A and B, together with two known analogs, monodictyphenone and 6-[2-hydroxy-6-(hydroxymethyl)-4-methylphenoxy]-2-methoxy-3-(1-methoxy-3-methylbutyl) benzoic acid.

Furthermore, when tested for ecotoxicity against *Artemia salina*, the compounds iso-monodictyphenone (**2**), and penikellides (A-B) exhibited activity with LD_{50} values of 25.3, 14.2, and 39.2 μM, respectively, while colchicine, the standard drug used as a positive control, showed an LD_{50} of 1.2 μM. Because of the low toxicity of the compounds studied, these results suggest that they are promising candidates for drug development. In contrast, only compound **2** exhibited moderate antimicrobial activity against *Aeromonas hydrophilia* with a MIC value of 8.0 μg mL^{-1}, when compared to the positive control chloromycetin (MIC value of 4.0 μg mL^{-1}).[39] The compounds produced by *Penicillium* sp. MA-37 can be observed in Figure 3.

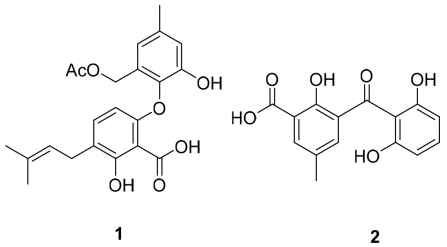


Figure 3. Chemical structures of active compounds 7-*O*-acetylsecopenicillide C (**1**) and iso-monodictyphenone (**2**) isolated from *Penicillium* sp. (MA-37).

Another study[40] identified four novel citrinin compounds from extracts of the fungus *Penicillium* sp. ML226 isolated from sediments in the Chinese Fu Gong mangrove area. Chemical investigations led to the isolation of two new citrinin dimers, penicitrinone E and penicitrinol J (**3**) and two new citrinin monomer derivatives, penicitrinol K (**4**) and citrinolactone D, in addition to six known compounds, penicitrinone A, penicitrinone B, citrinolactone B, citrinin, 2,3,4-trimethyl-5,7-dihydroxy-2,3-dihydrobenzofuran, and phenol A.[40] However, biological assays showed that compounds **3** and **4** exhibited weak activity against *S. aureus* CMCC26003 with inhibition zones of 10 and 9 mm in diameter, respectively, compared to the positive control, gentamicin (inhibition zone of 18 mm in diameter).[40] The chemical structures of compounds produced by *Penicillium* sp. ML226 can be observed in Figure 4.

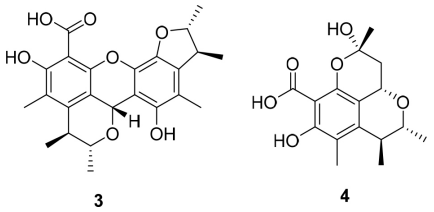


Figure 4. Active compounds, penicitrinol J (**3**) and K (**4**), isolated from *Penicillium* sp. (ML-226).

Interestingly, another species of *Penicillium* was isolated from the rhizospheric soil of the mangrove plant *Lumnitzera racemosa* and later identified as *Penicillium bilaiae* MA-267. Meng *et al*.[41] investigated the extracts of this fungus, resulting in the isolation of two new sesquiterpenes with tricyclo [6.3.1.$0^{1,5}$] dodecane skeletons, identified as penicibilaene A (**5**) and penicibilaene B (**6**). This is attractive because the fungus could be used as a biological agent to boost plant development. However, there are few investigations on its secondary metabolites in the literature. This led the researchers to investigate the antimicrobial activity of the isolated molecules.

Compounds **5** and **6** were tested against human- and aquapathogenic microbes, but they did not display potent activity against these strains (MIC > 64.0 μg mL^{-1}). However, the investigated substances demonstrated antifungal activity against the phytopathogenic fungus identified as *Colletotrichum gloeosporioides*, with MIC values of 1.0 and 0.125 μg mL^{-1} for compounds **5** and **6**, respectively. In the bioassays, compound **6** was determined to be more effective than the positive control (zeocin, with MIC of 0.25 μg mL^{-1}). Moreover, in a possible relation between biological activity and chemical structure, acetylation of 4-OH (compound **6**) likely enhanced the activity, which highlights the fungus's potential for the development of antifungal drugs.[41] Figure 5 shows the new sesquiterpenes produced by *Penicillium bilaiae* MA-267.

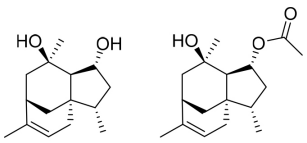


Figure 5. Structures of the compounds, penicibilaene A (**5**) and penicibilaene B (**6**), isolated from *Penicillium bilaiae* (MA-267)

Xu *et al.*[42] also investigated the chemical and biological properties of extracts of the fungus identified as *Penicillium simplicissimum* MA-332 (isolated from the rhizospheric soil of the mangrove *Bruguiera sexangula* var. *rhynchopetala* collected on Hainan Island, China). As a result, three novel dihydroisocoumarin derivatives known as penicisimpins A (**7**), and B-C were isolated and identified. When the antimicrobial potential of the isolated compounds was evaluated, the results revealed that the compounds demonstrated a broad spectrum of bactericidal and antifungal activity against the strains tested, with compound **7** exhibiting the highest activity against the strains *E. coli*, *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus*, *Vibrio harveyi*, and *Colletotrichum gloeosprioides*, with MIC values of 4.0 μg mL^{-1}.

However, the brine shrimp lethality experiments revealed that this compound is active, with an LD_{50} value of 7.7 μg mL^{-1}, when compared to the positive control used in the test (colchicine, LD_{50} 16.5 μg mL^{-1}), which may not be an appropriate choice for antimicrobial product development. Moreover, small differences in the molecular structures of the compounds change their antimicrobial properties. Whereas, the methyl group in C-7 increases activity (penicisimpin A *vs*. B), while the double bond in C-11 decreases activity (penicisimpin A *vs*. C).[42]

Later research using extracts of *Penicillium simplicissimum* MA-332 resulted in the discovery of a novel meroterpenoid known as simpterpenoid A (**8**). This substance is an unusual tricyclic meroterpenoid with a highly substituted and unsaturated ring (ring C) and rare gem-propane-1,2-dione and methylformate groups. Aside from possessing an unusual chemical structure, compound **8** demonstrated high inhibitory effects against influenza neuraminidase with an half maximal inhibitory concentration (IC_{50}) value of 8.1 nM (oseltamivir was used as a positive control, which has an IC_{50} value of 3.2 nM) and weak antifungal activity against the plant-pathogenic fungi *Physalospora piricola* with a MIC of 64.0 μg mL^{-1}, when compared to the positive control used in the test (amphotericin B, with MIC value of 4.0 μg mL^{-1}).[43] The chemical structures of compounds produced by *Penicillium simplicissimum* MA-332 can be observed in Figure 6.

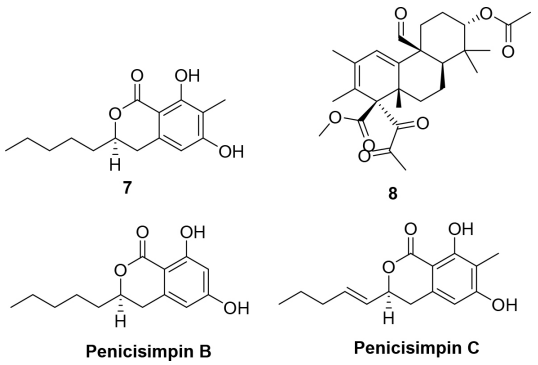


Figure 6. Chemical structure of the penicisimpin A (**7**), penicisimpin B, penicisimpin C and simpterpenoid A (**8**) isolated from *Penicillium simplicissimum* (MA-332).

Because pathogenic strains can develop resistance to commonly employed antibiotics, there is a clear need for research aimed at developing innovative antimicrobial treatments. Thus, fungal metabolites appear as potential alternatives to overcome this problem.[67,68] Based on this hypothesis, the fungus *Penicillium janthinellum* HK1-6 (isolated from the rhizospheric soil of the Dongzhaigang mangrove nature reserve, on Hainan Island, China) was studied because its extracts showed significant antibacterial activity against methicillin-resistant *S. aureus* (MRSA).[44]

The fractionation of the extracts led to the isolation of four new azaphilones, named penicilones A, B-D (**9-11**), as shown in Figure 7. These compounds belong to the polyketide class and are understood as fungal pigments with various molecular structures, characterized by having in their basic skeleton a bicyclic nucleus of oxygenated pyranoquinone and a center with quaternary carbon, and may be biologically active.[69,70]

When subjected to bioassays, compounds **9-11** displayed significant activity against all Gram-positive bacteria used in the test (*S. aureus*, ATCC 43300, ATCC 33591, ATCC 29213, ATCC 25923, *Enterococcus faecalis*, ATCC 51299, and *Enterococcus faecium*, ATCC 35667), with MIC values ranging from 3.1 to 12.5 μg mL^{-1}. Compounds **9-11** exhibited significant activity against both antibiotic-resistant strains, methicillin-resistant *S. aureus*, ATCC 43300, and ATCC 33591, with MIC values ranging from 3.1 to 6.2 μg mL^{-1}, inferring that the studied compounds may have the capacity to effectively overcome cross-antibiotic resistance.[44] These results also highlight the crucial importance of fungal metabolites as new therapeutic agents, supporting the hypothesis that fungi constitute a rich source of compounds of interest.

Halogenated metabolites frequently prove to be remarkable biological agents, capable of displaying antimicrobial, antiviral, antiparasitic, antioxidant, anti-inflammatory, and antitumor activities.[71] Guided by the

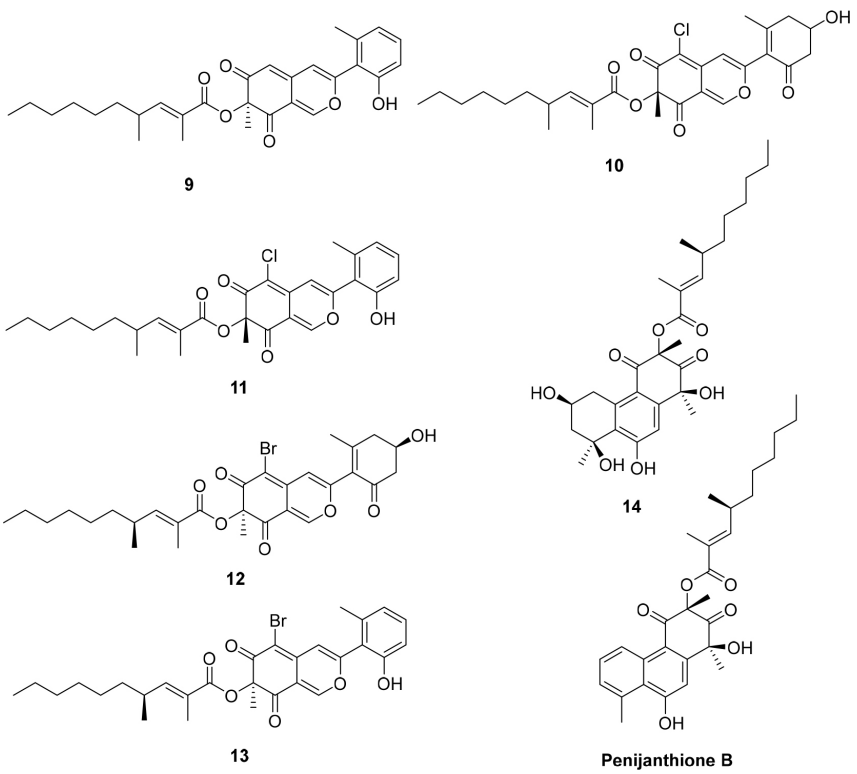


Figure 7. Chemical structures of penicilones B (**9**), C (**10**), D (**11**), G (**12**), H (**13**), penijanthinone A (**14**), and penijanthinone B isolated from *Penicillium janthinellum* (HK1-6).

detection of halogenated metabolites with significant biological activity (penicillones C-D (**10-11**) from extracts of the fungus *Penicillium janthinellum* HK1-6),[44] Chen *et al*.[45] reevaluated the potential previously mentioned fungus, which was cultivated in potato dextrose broth supplemented with 30 mg L^{-1} of NaBr, resulting in a distinct metabolic profile, allowing the identification and isolation of two new brominated azaphilones, penicillones G and H (**12-13**), and two new structurally related tricyclic polyketides, penijanthinones A (**14**) and B, together with the known penicilones A and B (Figure 7).[45]

According to previous reports of the biological activities of penicilones B-D,[44] the isolated compounds were subjected to antimicrobial activity assays against the bacteria *S. aureus* (ATCC 43300, ATCC 33591, ATCC 29213, ATCC 25923), *E. faecalis* (ATCC 51299), *E. faecium* (ATCC 35667), and *E. coli* (ATCC 25922). This demonstrated that compounds **12** and **13** exhibit activity against the tested gram-positive bacteria with MIC values ranging from 3.13 to 50 μg mL^{-1}, while compounds **13** and **14**, in turn, showed high activity against methicillin-resistant *S. aureus* ATCC 33591 with a MIC value of 3.1 μg mL^{-1}, a value close to the MIC of the positive control used in the assay (vancomycin, 1.6 μg mL^{-1}).

Compound **14** also displayed moderate antibacterial activities against *S. aureus* (ATCC 43300, ATCC 33591, and ATCC 29213), *E. faecalis* (ATCC 51299), and *E. faecium* (ATCC 35667) with MIC values ranging from 3.1 to 25.0 μg mL^{-1}.

Furthermore, regarding a possible relationship between chemical structure and biological activity, aromatization in the C ring plays diverse roles in the compounds' bactericidal activities. In the case of compound **13**, aromatization increases the inhibitory effect of the molecule, with a MIC from 3.1 to > 50.0 μg mL^{-1}. In the case of penijanthinone B, additional aromatization significantly decreases the inhibitory potency of the molecule, with a MIC > 50.0 μg mL^{-1} for tested microorganisms. These results highlight the fungal potential for the development of efficient drugs, particularly against microorganisms resistant to reference drug.[45]

In addition to azaphilones and polyketides, the studied strain has also demonstrated a diverse secondary metabolism. Zheng *et al*.[72] isolated prenylated indole alkaloids from the extracts of the fungus *Penicillium janthinellum* HK1-6, including a new prenylated indole alkaloid named paraherquamide J, the known compounds paraherquamide K, the latter of which was isolated in this study for the first time as a natural product, paraherquamide A, paraherquamide E, and SB200437. Considering the ability of this fungus to biosynthesize compounds with potential biological

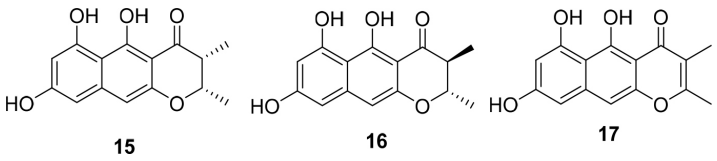


Figure 8. Chemical structures of peninaphones A (**15**) B (**16**), and C (**17**) *Penicillium* sp. (HK1-22).

activities, the prenylated indole alkaloids under study did not affect the bacteria *S. aureus* (ATCC 43300, ATCC 33591, ATCC 29213, ATCC 25923), *E. faecalis* (ATCC 51299), *E. faecium* (ATCC 35667), and *E. coli* (ATCC 25922). They were also proven to be inactive in inhibitory experiments against topoisomerase I (topo I) and brine shrimp lethality tests.[72]

Another strain, *Penicillium* sp. HK1-22, isolated from mangrove rhizospheric soil in the Dongzhaigang nature reserve on Hainan Island, provided intriguing preliminary results since extracts exhibited bactericidal activity. Fractionation studies of the fungal extract led to the isolation and identification of three new monomeric naphtho-γ-pyrones, peninaphones A-C (**15-17**), as shown in Figure 8, along with two known bis-naphtho-γ-pyrones.[46]

The bactericidal effect of the isolated compounds was evaluated against the strains *S. aureu*s (ATCC 43300, 33591, 29213, and 25923), *E. faecalis* (ATCC 51299), *E. faecium* (ATCC 35667), and *E. coli* (ATCC 25922), indicating that compounds **15-17** have activity against *S. aureus* strains with MIC values ranging from 12.5 to 50 μg mL^{-1}. Besides, compound **17** also exhibited antifungal potential, particularly against *Rhizoctonia solani*.[46]

Despite much of the research focusing on endophytic species, the fungal diversity present in the soils and sediments of mangrove areas has proven to be a rich source of secondary metabolites. He *et al.*[47] demonstrated that the fungus *Penicillium pinophilum* SCAU037, isolated from the rhizospheric soil of *Rhizophora stylosa* from Techeng Island, China, was capable of biosynthesizing five new funicone derivatives, pinophilones A-E, along with 18 biosynthetically related analogs: dihydrovermistatin, vermistatin, penisimplicissin, 2"-epihydroxydihydrovermistatin, 5'-*O*-methyldihydrovermistatin, methoxyvermistatin, hydroxyvermistatin, 6-demethylvermistatin, 6-demethylpenisimplicissin, 3-*O*-methylfunicone, penicidone D, penicidone C, isopenicillide, penicillide, 3'-*O*-methyldehydroisopenicillide, pinophilin G, pinophilin B, and Sch725680 (**18**).

The interesting fact is that the novel compounds reported were inactive when subjected to the proposed biological assays. Only compound **18** (Figure 9) was active against *Mycobacterium smegmatis* (ATCC 607) and *S. aureus* (ATCC 25923), with IC_{50} values of 23.5 and 2.6 μM, respectively. In addition, compounds penicidone C, penicillide, and compound **18** also exhibited significant inhibitory activity against α-glucosidase with IC_{50} values of 51.9, 78.4, and 33.8 μM, respectively. On the other hand, the scientists reported for the first time that the dihydrofuran moiety in funicone derivatives reported was also isolated for the first time from nature.[47] Proving the relevance of the biological and metabolic diversity of this environment.

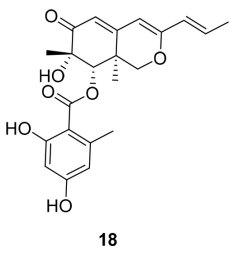


Figure 9. Chemical structure of Sch 725680 isolated from *Penicillium pinophilum* (SCAU037).

The fungus *Penicillium ludwigii* SCSIO 41408 has also demonstrated antagonistic properties against fungi and bacteria. Cai *et al.*[48] reported a new trithiodiketopiperazine derivative, adametizine C (**19**), along with five dithiodiketopiperazines: adametizine A (**20**), DC1149B (**21**), outovirin B (**22**), pretrichodermamide E (**23**), and peniciadametizine A. Compounds **19-23** exhibited weak antibacterial activity against *Erysipelothrix rhusiopathiae* WH13013 and *Streptococcus suis* SC19, with MIC values ranging from 50.0-100.0 μg mL^{-1}, when compared to the positive control (cephalosporin, MIC value of 0.8 μg mL^{-1}). Compound **20** also displayed moderate fungicidal activity against *Botrytis cinerea* and *Septoria nodorum* Berk, with a MIC value of 25.0 μg mL^{-1}, whereas the positive control, cycloheximide, had a MIC value of 6.2 μg mL^{-1}.[48] All compounds discussed above can be observed in Figure 10.

Penicillium camemberti OUCMDZ-1492 is another interesting species. The fungus was obtained from the soil of the Wenchang mangrove natural reserve region in China, and it proved to be an intriguing candidate in the quest for new antiviral chemicals. The investigations of the fungal extracts led to the identification of six new indole-diterpenoids, 3-deoxo-4b-deoxypaxilline (**24**), 4a-demethylpaspaline-4a-carboxylic acid (**25**),

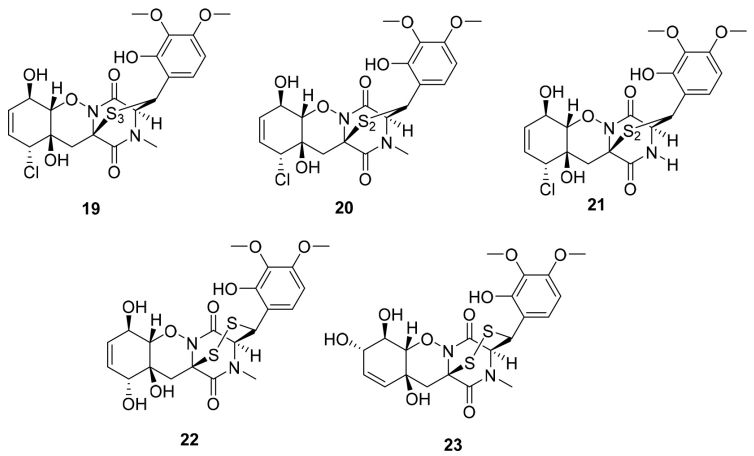


Figure 10. Isolated compounds, **19, 20, 21, 22, 23,** from *Penicillium ludwigi* (SCSIO 41408) with antimicrobial potential.

4a-demethylpaspaline-3,4,4a-triol (**26**), 2'-hydroxypaxilline, 9,10-diisopentenylpaxilline (**27**), (6*S*,7*R*,10*E*,14*E*)-16-(1*H*-indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol (**28**) as well as five known analogues, emindole SB (**29**), 21-isopentenylpaxilline (**30**), paspaline (**31**), paxilline (**32**), and dehydroxypaxilline (Figure 11).[49]

Compared with the positive control (ribavirin,

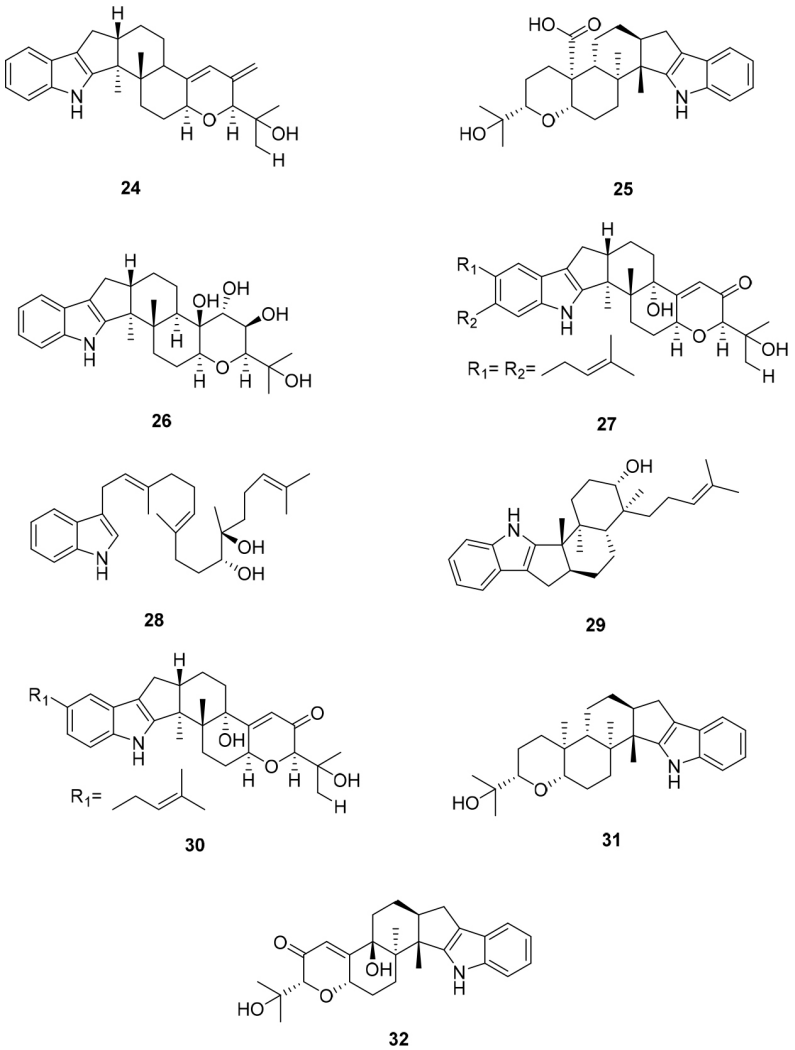


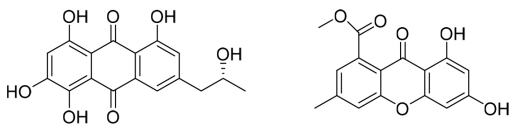
Figure 11. Isolated compounds, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, from *Penicillium camemberti* (OUCMDZ-1492).

IC_{50} 113.1 μM), compounds **24-26** and **27-32** were highly active against the influenza A (H_1N_1) virus with IC_{50} values equal to 28.3, 38.9, 32.2, 73.3, 34.1, 26.2, 6.6, 77.9, and 17.7 μM, respectively, highlighting compound **30** as the most effective in bioassays, even more effective than the positive control used in the assay. Also, the results indicate that 3-oxo, 4b-hydroxy, and 9-isopentenyl substitutions tend to enhance the anti-H_1N_1 activity of the hexacyclic indole-diterpenoid.[49]

Penicillium camemberti OUCMDZ-1492's metabolic capacity was investigated. Continuing research resulted in the identification of a new indole-diterpenoid derivative, secopaxilline A, but the chemical lacked antiviral activity. In line with previous results, certain indole-diterpenoids generated by the strain under study have shown substantial antiviral efficacy against the H_1N_1 virus.[49] Given that, secopaxilline A is an indole-diterpenoid with an indole section with a carbon-nitrogen bond cleavage skeleton, this leads to the notion that the indole portion of indole-diterpenoids is a key nucleus for the activity against the H_1N_1 virus.[73]

Extreme settings have become critical for the isolation of microorganisms of interest, as environmental circumstances have a substantial impact on the generation and discovery of new microbial metabolites.[74]

The fungus *Penicillium* sp. OUCMDZ-4736, isolated from the sediments of the mangrove plant *Acanthus ilicifolius* in Wenchang, China, produced three new anthraquinone derivatives, only when cultivated in an acid medium (pH equal to 2.5), in which the fractionation studies of the extracts led to the isolation of (−)-1,2,4,5-tetrahydroxy-7-((2*R*)-2-hydroxypropyl) anthracene-9,10-dione (**33**), methyl 3,4,8-trihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate, and methyl 6,8-dihydroxy-3-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**34**, Figure 12).[50]



33 **34**

Figure 12. Chemical substances, (−)-1,2,4,5-tetrahydroxy-7-((2*R*)-2-hydroxypropyl) anthracene-9,10-dione (**33**) and methyl 6,8-dihydroxy-3-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**34**) isolated from *Penicillium* sp. (OUCMDZ-4736).

Antiviral assays revealed that compounds **33** and **34** had anti-HBV (anti-hepatitis B virus) action that was dose-dependent and more effective than the standard medicine used, lamivudine (3TC). Furthermore, when compared to 3TC's (13.0% inhibition potential), compound **33** demonstrated a higher proportion of inhibition equal to 17.0% at a concentration of 20 μM, indicating that such a compound may have anti-hepatitis B virus capability. Furthermore, such findings demonstrate for the first time research with anthraquinone compounds with anti-HBV activity.[50]

Due to the increasing emergence of strains resistant to traditional medications, the search for and development of new antiviral treatments is essential, beyond resistant strains, one of the biggest challenges regarding antiviral treatments is the lack of antiviral medicines commercially available, this situation was in evidence due to the recent coronavirus (COVID-19) pandemic, so researches focusing on the development of new antiviral treatments are necessary, particularly those with a broad viral spectrum that perform diverse mechanisms of inhibition against viruses, concerning the current scenario of emergence of new viral diseases [75]

Recently, Li *et al*.[51] isolated the fungus *Penicillium* sp. IMB17-046, which proved to be an excellent candidate for the development of new antiviral agents. The fungus produced compounds with broad-spectrum antiviral activities. Chemical studies of the fungal extracts led to the isolation and identification of a new pyrazine derivative, trypilepyrazinol (**35**), a new α-pyrone polyketide, (+)-neocitreoviridin (**36**), and a new ergostane-type sterol, 3β-hydroxyergosta-8,14,24(28)-trien-7-one (**37**), together with the known compounds epiisocitreoviridinol, citreoviripyrone B, kigelin, 3β-hydroxyergosta-8,24(28)-dien-7-one, and (22*E*,24*R*)-24-methyl-5α-cholesta-7,22-dien-3β,5,6β-triol.[51]

Biological assays revealed that compound **35** inhibited HIV-1 (human immunodeficiency virus) and HCV (hepatitis C virus) with IC_{50} values of 4.6 ± 0.3 and 7.7 ± 0.2 μM, respectively. When compared to the utilized positive control (ribavirin, with IC_{50} value of 15.4 ± 0.9 μM), compound **36** was demonstrated to be highly active against IAV (influenza A virus), with IC_{50} value of 3.6 ± 0.2, while compound **37** was found to be active against HIV-1 with an IC_{50} of 3.5 ± 0.8 μM and highly active against IAV with an IC_{50} of 0.5 ± 0.02 μM, which is 300 times greater than ribavirin (IC_{50} 15.4 ± 0.9 μM).[51]

Furthermore, compounds **35** and **36** exhibited antimicrobial activity against clinical isolates of *Helicobacter pylori* (strains G27 and 159) with MIC values between 1-16 μg mL^{-1} and were considered inactive against strains of *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *Klebsiella pneumoniae* with MICs > 128.0 μg mL^{-1}. Natural products containing a pyrazine moiety are uncommon, in this context, compound **35** is the first example of a natural product from this group that demonstrates a broad spectrum of antiviral activities and antibacterial activity

against *H. pylori*.[51] All compounds discussed above can be observed in Figure 13.

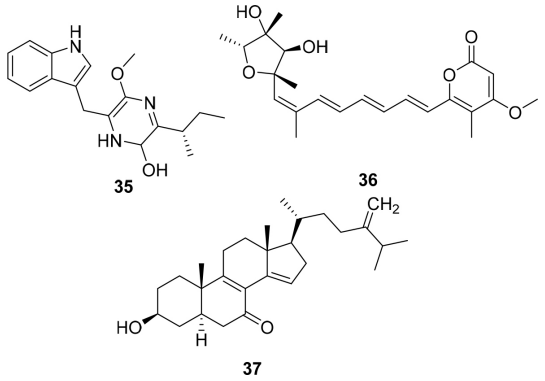


Figure 13. Isolated compounds, trypilepyrazinol (**35**), (+)-neocitreoviridin (**36**), and 3β-hydroxyergosta-8,14,24(28)-trien-7-one (**37**), from *Penicillium* sp. (IMB17-046).

For antiviral agents, the fungus *Penicillium raistrickii* IMB17-034 (isolated from marine sediments collected in a mangrove swamp in Sanya, China) has emerged as a promising candidate in the search for secondary metabolites with therapeutic potential. The strain produced raistrickindole A (**38**), a new indole diketopiperazine alkaloid, and raistrickin (**39**), a new benzodiazepine, as well as two related alkaloids, haenamindole, and sclerotigenin (**40**).[52]

Biological experiments revealed that compounds **38**, **39**, and **40** (Figure 14) had anti-HCV (against hepatitis C virus) action with EC_{50} values of 5.7 ± 1.5, 7.0 ± 2.4, and 5.8 ± 1.1 μM, respectively. Although the evaluated compounds showed lower inhibitory activity than the positive control (VX-950, (half-maximal effective concentration) (EC_{50}) 0.05 ± 0.03 μM), they demonstrated anti-HCV activity comparable to most natural products (NPs) with anti-HCV potential reported in the literature. All compounds have also been shown to have minor antibacterial properties against pathogenic strains *S. aureus*, *E. faecalis*, *E. coli*, and *P. aeruginosa* (values of MIC > 128.0 μg mL^{-1}). It is worth noting that structural compound **38** has an unusual pyrazino[1',2':2,3]-[1,2]oxazino[6,5-*b*]indole tetraheterocyclic ring system, considered rare in nature. This improves the variety of known indole alkaloids and allows for the advancement of research into novel antiviral agents.[52]

3.2. Genus *Aspergillus*

The genus *Aspergillus* encompasses hundreds of highly aerobic fungal species, present in a variety of oxygen-rich environments. Among these species, several can thrive in nutrient-deficient environments essential for their growth. While some species are economically relevant, others can occur as pathogens. Additionally, the *Aspergillus* genus produces numerous compounds that exhibit interesting biological properties.[76]

Notably, the fungus *Aspergillus versicolor* HDN1009 is an interesting producer of diverse xanthones. Yu *et al.*[22] employed a bioassay-guided fractionation method of fungal extracts and ultra-performance liquid chromatography mass spectrometry (UPLC-MS) in order to obtain new xanthones. As a result, 5-epi-asperdichrome (**41**), a new tetrahydroxanthone dimer with antibacterial action, was isolated and characterized (Figure 15). The biological studies reported that the studied compound exhibited weak antimicrobial activity against *Vibrio parahemolyticus*, *B. subtilis*, *Mycobacterium phlei*, *P. aeruginosa*, and *Candida albicans* with MIC values ranging from 100.0 to 200.0 μM, when compared to the positive control for bacteria (ciprofloxacin, MIC ranging from 0.391 to 1.56 μM) and for *C. albicans* (nystatin, MIC value of 3.13 μM).[22]

Remarkably, the fungus identified as *Aspergillus ochraceus* MA-15, isolated from the rhizospheric soil of the mangrove plant *Bruguiera gymnorrhiza* Hainan Island, China, proved to be interesting from a metabolic standpoint. Since then, chemical investigations of fungal extracts have resulted in the isolation and identification of three novel polyketides named asperochrin A (**42**), asperochrins B-C in addition to the compounds previously reported in the literature: (±)-botryoisocoumarin A, isolated as a racemic mixture, chlorohydroaspyrones A-B (**43** and **44**), dihydroaspyrone, aspyronol, chlorohydro-asperlactone A (**45**) chlorohydroasperlactone B, penicillic acid (**46**), 5(6)-dihydropenicillic acid, (3*R*,4*S*)-4-hydroxy-mellein, (3*R*,4*R*)-4-hydroxymellein, and (*R*)-7-hydroxy-mellein (**47**).[53]

Aspergillus species are known to be exceptional producers of secondary metabolites with pharmacological

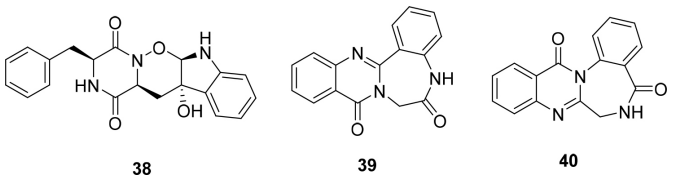


Figure 14. Chemical structures of the isolated compounds raistrickindole A (**38**), raistrickin (**39**), and sclerotigenin (**40**) from *Penicillium raistrickii* (IMB17-034).

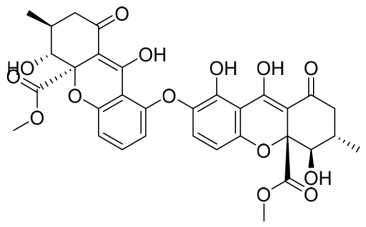


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Figure 15. Chemical structure of 5-epi-asperdichrome (**41**) isolated from *Aspergillus versicolor* (HDN1009).

potential. As a result, the bactericidal and ecotoxicological activities of the substances produced by the strain in issue were evaluated. Fortunately, none of the studied compounds exhibited potent brine shrimp lethality. On the other hand, compounds **42**, **43**, **44**, **45**, **46**, and **47** demonstrated activity against the aquatic bacterial strains *A. hydrophilia*, *Vibrio anguillarum*, and *V. harveyi*, with MIC values ranging from 0.5 to 64.0 μg mL^{-1}.

In addition, based on the results, in a possible relationship between molecular structure and biological activity, it is suggested that the amount of hydroxyl groups in chemical structures influences the biological potential of the molecules, with the highest activities being performed by those with the most amount of OH groups. The structural differences also suggest variations in the biological potency of compounds **46** and 5(6)-dihydropenicillic acid. Compound **46** was demonstrated to be more active against the strains *A. hydrophilia* and *V. harveyi* (MIC 1.0 and 0.5 μg mL^{-1}, respectively) than 5(6)-dihydropenicillic acid, also the compound was found to be highly active when compared to the positive control used in the assay (chloramphenicol, MIC 4.0, and 8.0 μg mL^{-1}, respectively). Therefore, such a difference can be explained due to the double bond at the terminal carbon C-6(7).[53] All compounds discussed above can be observed in Figure 16.

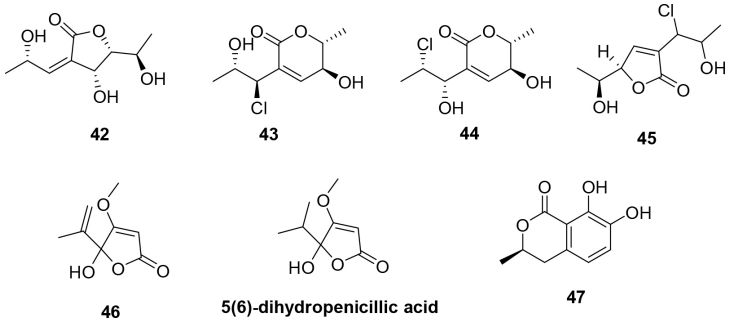
The extract of the fungus *Aspergillus* sp. DM94, isolated from the rhizospheric soil of *Bruguiera gymnorrhiza* (L.) Poir, was found to be a rich source of pyrones. From the fungal extract, it was possible to isolate three (6-benzyl-4-oxo-1,4-dihydropyridin-3-yl)- carboxamides, two 6-benzyl-4-oxo-1,4-dihydropyrones, four pyrano[2,3-*b*] pyrroles, three bicoumarins, and eight naphto-γ-pyrones.[54]

Pyrones are heterocyclic compounds with a six-membered unsaturated ring with the presence of a ketone function and an oxygen atom in the ring. Such compounds exist in the form of two isomers, α-pyrones, and γ-pyrones, they can demonstrate a range of biological activities.[77,78]

Gou *et al*.[54] evaluated the antimicrobial potential of the isolated molecules against *H. pylori* strains G27 and one clinical isolate, strain HP159. *H. pylori* is a Gram-negative bacterium that infects about 50% of the world's population. In general, those infected suffer progressive chronic stomach inflammation, which can lead to the development of peptic ulcers, gastric atrophy, and gastric intestinal metaplasia, which can lead to the development of gastric cancer or lymphoma. Additionally, these microorganisms may exhibit resistance to antibiotics used in the infection treatment.[79]

Thus, according to the assays, the naphto-γ-pyrones, compounds **48** (asperpyrone A), **49** (aurasperone A), **50** (aurasperone F), and **51** (aurasperone B) exhibited activity against the evaluated strains, with MIC values ranging from 4 to16 μg mL^{-1}. The authors suggest that the hydroxyl group in the C-8 position in the lower unit is crucial for its anti-*H. pylori* activity. Furthermore, compound **49** showed synergistic activity with the antibiotics amoxicillin, clarithromycin, or metronidazole, which reduces the antibiotic dosage required for treatment.[54] This implies the compound's potential for the development of new agents, regarding the resistance of microorganisms. All naphto-γ-pyrones discussed above can be observed in Figure 17.

Another strain identified as *Aspergillus* sp. DM29, isolated from the rhizospheric soil of the mangrove *Aegiceras corniculatum*, in Thailand, was studied due to the extracts demonstrating strong α-glucosidase inhibitory effects and weak antibacterial activity against *S. aureus*. The fractionation of the extract led to the isolation of two unusual naturally Diels-Alder additive steroids,



42 43 44 45

46 5(6)-dihydropenicillic acid 47

Figure 16. Metabolites asperochrin A (**42**), chlorohydroaspyrone A (**43**), chlorohydroaspyrone B (**44**), chlorohydroasperlactone A (**45**), penicillic acid (**46**), 5(6)-dihydropenicillic acid, and hydroxymellein (**47**) produced by *Aspergillus ochraceus* (MA-15).

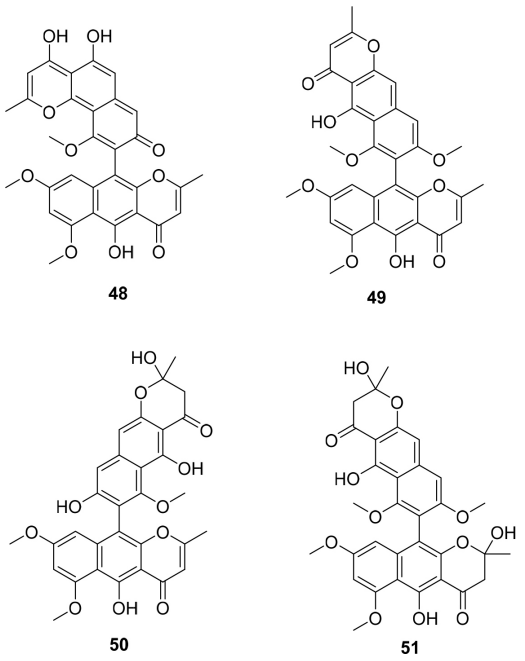


Figure 17. Isolated substances, asperpyrone A (**48**), aurasperone A (**49**), aurasperone F (**50**), and aurasperone B (**51**) isolated from *Aspergillus* sp. (DM94).

ergosterdiacids A and B, both of which have an unusual 6/6/6/6/5 pentacyclic steroidal system.[80]

Chemically, steroids are complex organic molecules that have a basic tetracyclic structure. Depending on the functional groups attached to their structure, these molecules can perform different activities in living organisms. Such molecules are fundamental components of the plasma membranes in eukaryotic organisms, primarily acting on the cellular processes associated with the structure of the cell membrane, in addition to their signaling and regulatory roles.[81]

In this sense, the isolated compounds were studied to elucidate their biological role. It was reported that the isolated compounds did not have the same action as the crude extract, which may be explained by the molecular synergism phenomenon. However, they exhibited high activity against *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MptpB) with IC_{50} values of 15.1 and 30.1 μM, respectively, when compared to the positive control used in the assay (oleanolic acid, IC_{50} = 22.7 μM). In addition, the compounds exhibited potent anti-inflammatory activity according to the *in vitro* inhibitory assay of nitric oxide (NO) effects at IC_{50} concentrations of 4.5 and 3.6 μM, respectively.[80]

Furthermore, Bao *et al.*[55] reported the identification of a new aromatic butenolide analog, named asperbutenolide D (**52**), together with other known analogs, (+)-3',3'-di-(dimethylallyl)-butyrolactone II (**53**), aspernolide E (**54**), and terrusnolide A (**55**), as shown in Figure 18, from extracts of the fungus *Aspergillus terreus* SCAU011, isolated from the rhizospheric sediments of the mangrove *Rhizophora stylosa* in Techeng Island, China. However, the molecules exhibited weak antimicrobial activity against *S. aureus* ATCC25923 with IC_{50} values ranging from 17.4 to 36.6 μM, when compared to the positive control (penicillin, IC_{50} of 0.13 μM).[55]

Considering the need for new antiviral molecules, researchers investigated the potential of isoaspulvinone E (**56**), aspulvinone E (**57**), and pubic acid (**58**) compounds produced by the fungus *Aspergillus terreus* Gwq-48, as shown in Figure 19, isolated from mangrove rhizosphere soil collected from the coast of Fujian province, China. The isolated compounds prove to be interesting candidates against the influenza A (H_1N_1) virus, showing antiviral activity with IC_{50} equal to 32.3, 56.9, and 29.1 μg mL^{-1} for compounds **56-58**, respectively. Which highlights the fungal potential for the development of active natural products capable of preventing viral infections.[56]

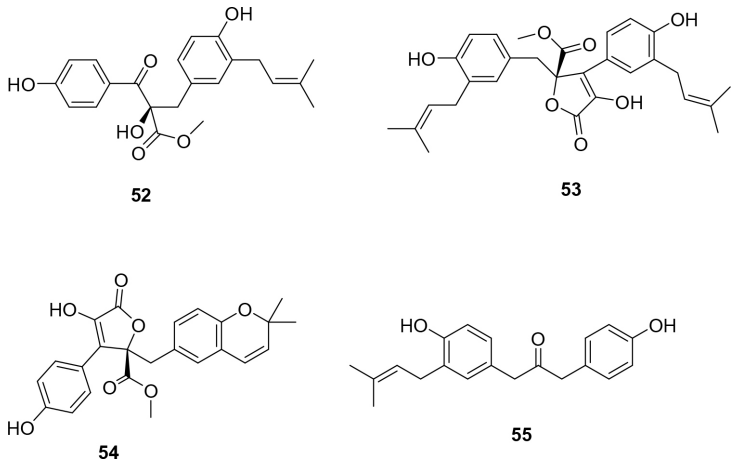


Figure 18. Metabolites, asperbutenolide D (**52**), (+)-3',3'-di-(dimethylallyl)-butyrolactone II (**53**), aspernolide E (**54**), and terrusnolide A (**55**) isolated from *Aspergillus terreus* (SCAU011).

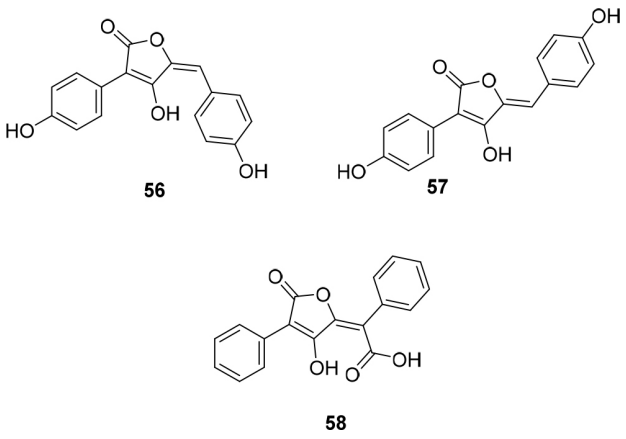


Figure 19. Compounds isoaspulvinone E (**56**), aspulvinone E (**57**), and puvic acid (**58**) isolated from *Aspergillus terreus* (Gwq48).

Another species, *Aspergillus taichungensis* ZHN-7-07, was studied to investigate if it could produce compounds with antiviral activity against the influenza A (H_1N_1) virus. In addition to the already-known substance brevianamide F, the fungus was able to produce a novel compound named aspergilazine A (**59**), as shown in Figure 20. However, antiviral activity testing revealed that compound **59** exhibited weak activity, inhibiting 34.1% of the tested cells at a concentration of 50.0 μg mL^{-1}.[57]

Fungi of the genus Eurotium, a teleomorph of *Aspergillus*, are known producers of tryptophan-derived alkaloids with

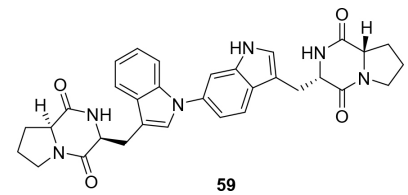


Figure 20. Structure of aspergilazine A (**59**) isolated from *Aspergillus taichungensis* (ZHN-7-07).

diverse biological activities. The researchers isolated the fungus *Eurotium rubrum* MA-150 from the rhizosphere soil of a mangrove ecosystem on the coast of Thailand's Andaman Sea. The extracts resulted in the isolation and identification of three new isoechinulin-type indolediketopiperazine alkaloids, known as rubrumazines A-C, together with 13 related known analogues neoechinulin A, isoechinulin A, variecolorin G, dehydroechinulin, variecolorin E, dihydroxyisoechinulin A (**60**), variecolorin L, echinulin, tardioxopiperazine, L-alanyl-L-tryptophan anhydride, neoechinulin E, variecolortide B, and variecolortide C (Figure 21).[58]

Only compound **60** demonstrated antibacterial action against the bacterium *Vibrio alginolyticus*, with a MIC value of 16.0 μg mL^{-1} (the MIC for the positive control, chloromycetin, is 4.0 μg mL^{-1}). Ecotoxicity tests on saline brine shrimp revealed that rubrumazine B, dehydroechinulin, and neoechinulin E had very high

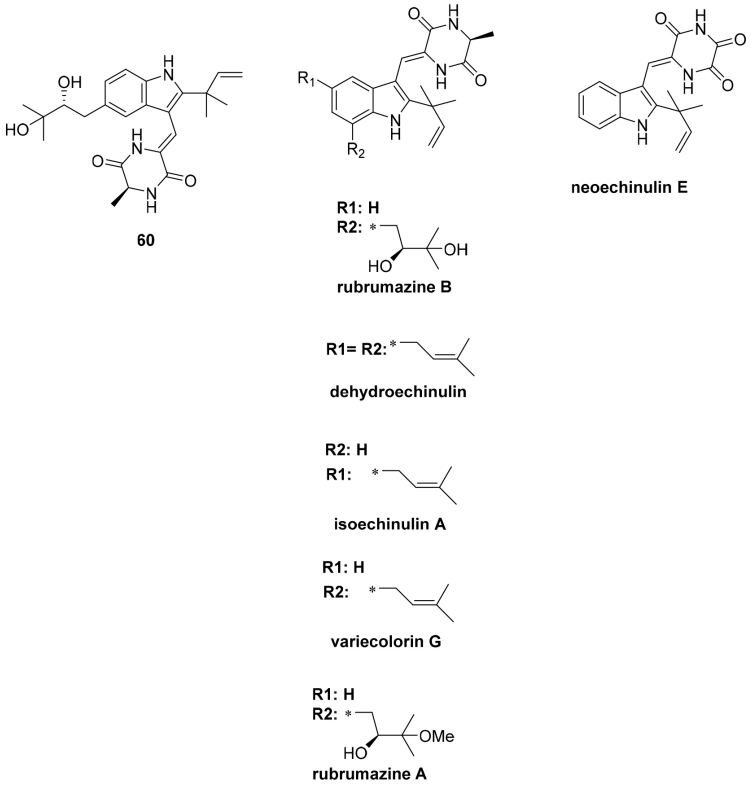


Figure 21. Chemical substances, dihydroxyisoechinulin A (**60**), rubrumazine A, rubrumazine B, dehydroechinulin, isoechinulin A, variecolorin G, and neoechinulin E isolated from *Eurotium rubrum* MA-150.

activity, with LD_{50} values of 2.43, 3.53, and 3.93 μM, respectively, which was significantly higher than the positive control used in the test (colchicine, LD_{50} of 19.40 μM).

Compounds' biological activity can also be influenced by substituent groups. Prenyl groups affect the variation of biological activity exhibited by most different types of molecules.[82] Because of the greater number of prenyl groups in the molecule, compound dehydroechinulin has a higher LD_{50} (3.5 μM) than compounds isoechinulin A and, variecolorin G (LD_{50} 11.7 and 22.0 μM, respectively). Furthermore, replacing OMe with OH in C-23 increased the activity of compound rubrumazine B (LD_{50} 2.4 μM) as compared to compound rubrumazine A (LD_{50} 29.8 μM).[58]

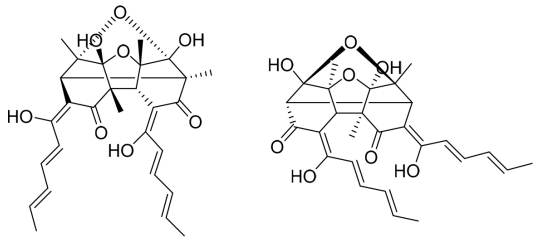
3.4. Genus *Trichoderma*

The genus *Trichoderma* is extremely important for biotechnological progress, particularly in the agricultural sector. This genus of fungi can be isolated from a variety of substrates, particularly soils. These fungi have the potential to be used as biological controls as well as well-known plant growth biostimulators. Furthermore, they include secondary metabolites with antibacterial activity against phytopathogens, making them essential candidates for technological advancement.[83-85]

Considering the unique properties of Trichoderma species, Narendran and Kathiresan[59] found extracts from the fungus *Trichoderma* sp. NPK2 with antioxidant and antibacterial action against human and fish diseases. The bioassays revealed that its extracts had antimicrobial activity against *B. subtilis* and *Vibrio cholerae* with MIC values of 200.0 μg mL^{-1}, as well as activity against *S. aureus* and *Bacillus cereus* with MIC values of 150.0 μg mL^{-1} and activity against *E. coli* with MIC of 125.0 μg mL^{-1}. The fungal extract was also active against the fish pathogens *V. parahaemolyticus* and *V. harveyi* with MIC values of 200.0 and 150.0 μg mL^{-1}, respectively.[59]

These findings suggest that the extracts of this fungus contain promising antibacterial agents, implying that more study on the separation and purification of metabolites is required to get new and efficient secondary metabolites for the development of effective antimicrobials.

Furthermore, the fungus *Trichoderma* sp. T-4-1, isolated from soil from Shenzhen Mangrove Reserve, Guangdong Province, China, is a good producer of antiviral agents. Huang *et al*.[60] reported the isolation of a new sesquiterpene, isocyclonerodiol oxide, in addition to 15 previously identified compounds, epicyclonerodiol oxide, cyclonerodiol oxide, 5-hydroxyepicyclonerodiol oxide, cyclonerodiol D, lignoren, trichoderiol A, trichoderiol C, chrysopyrone A, Nb-acetyltryptamine, linoleic acid, *n*-tetratriacint-20,23-dienoic acid, ergosterol, 1-linoleoylglycerol, trichodimerol (**61**), and demethyltrichodimerol (**62**), as shown in Figure 22, from fungal extracts. Interestingly, compounds **61** and **62** stood out in terms of antiviral activity against Influenza A (H_1N_1) with IC_{50} values equal to 0.52 ± 0.13 and 0.95 ± 0.36 μg mL^{-1}, respectively.[60]



61 **62**

Figure 22. Chemical substances, trichodimerol (**61**) and demethyltrichodimerol (**62**) isolated from *Trichoderma* sp. T-4-1.

3.5. Genus *Fusarium*

Fusarium is found in a wide range of ecosystems around the world, from the most extreme to the least severe. Because of their capacity to appear as phytopathogens, some species in this genus are economically relevant. They end up harming many agricultural products and may even impair human and animal health as a result of the mycotoxins they produce. In contrast, *Fusarium* species have been demonstrated to be significant producers of secondary metabolites of interest, many of which have distinct chemical and biological properties.[86,87]

The fungus *Fusarium solani* H915, isolated from the sediments of the Zhangjiangkou Mangrove National Nature Reserve, Fujian, China, has been demonstrated to produce new alkenoic acid, fusaridioic acid A, three new bis-alkenoic acid esters, namely, fusariumester A1, A2, and B (**63**), together with three metabolites already described, L660282, hymeglusin (**64**) and equisetin (**65**), all isolated from the culture medium extract (Figure 23).[61]

Antifungal susceptibility tests were performed to evaluate the biological potential of the isolated compounds. Compound **63** demonstrated moderate activity against *Pestalotiopsis theae* with a MIC value of 50 μg *per* disk, while compounds **64** and **65** demonstrated higher activity against *P. theae* and *C. gloeosporioides*, with MIC values of 25 μg *per* disk. Although the chemicals are biologically active, their toxicity must be considered. In this case, toxicity tests with zebrafish embryos revealed that compound **65** exhibited strong anti-proliferative effects, resulting in the death of embryos with an EC_{50} value of 0.12 μM after 48 h of testing, but the mortality rate in 96 h

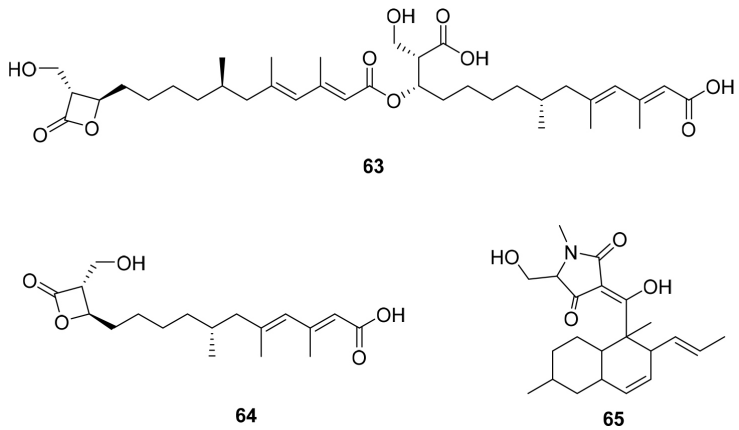


Figure 23. Compounds, fusariumester B (**63**), hymeglusin (**64**), and equisetin (**65**) isolated from *Fusarium solani* H915.

is 100.0%, even at the lowest concentration of 0.625 μM, which may restrict this compound from being developed as an antifungal agent. Compound **64**, on the other hand, demonstrated lower cytotoxic activity, with practically all embryos alive after 48 h of testing, even at the maximum concentrations of 10 μM, which demonstrated enough antifungal activity while being less hazardous.[61]

Alternatively, the fungus *Fusarium solani* H918, isolated from mangrove sediments, is a considerable producer of antifungal agents. Investigations of the fermentative broth extracts resulted in the isolation and identification of eight polyketides, five new (fusarisolins A-E,) and three known, along with six phenolic compounds. Like the fungus *Fusarium solani* H915,[61] the lactone expressed by the fungus under study (compound **64**) exhibited high antifungal activity against the pathogenic tea fungus *P. theae*, with ED_{50} values equal to 55 ± 4.0 μM, showing greater activity than the positive control used in the assay (hexaconazole, ED_{50} = 68 ± 5.7 μM), which denotes its potential development as an agrochemical antifungal.[62]

Furthermore, fusarisolins A and B are two new 21-carbon polyketides with a rare β-lactone and γ-lactone unit, respectively, that have been reported for the first time in natural sources.[62]

3.6. *Lasiodiplodia theobromae*

Lasiodiplodia theobromae is a global, polyphagous, opportunistic fungus and phytopathogen with low pathogenic specificity that is found primarily in tropical and subtropical areas.[88] Despite its pathogenic potential, the fungus has been shown to produce a wide range of secondary metabolites, including phenolic compounds, fatty acids, terpenoids, steroids, and alkaloids, as well as enzymes of interest. These compounds offer intriguing biological features, such as antibacterial, anti-inflammatory, anticancer, and antioxidant activity, suggesting a high potential for use in a variety of technological areas.[89]

Umeokoli *et al.*[63] isolated the fungus *Lasiodiplodia theobromae*, strain M4.2-2, from mangrove sediments near Dongzhai Harbor in Hainan, China, according to the literature. Chemical studies of the extracts of the fungus, grown on solid rice medium, resulted in the isolation and identification of a new depsidone derivative botryorhodine I, together with the known compounds: botryorhodine D, 1*H*-dibenzo[b,e][1,4]dioxepin-11-one,3, 8-dihydroxy-4-(methoxymethyl)-1,6-dimethyl, simplicildone A, botryorhodine A, botryorhodine B, (+)-(*R*)-de-*O*-methyl-lasiodiplodin (**66**), (−)-(*R*)-nordinone, and (−)-(*R*)-mellein.

Biological studies, however, revealed that only compound **66** exhibited antimicrobial activity against *S. aureus* ATCC 29213, *S. aureus* ATCC 700699, and *E. faecium* ATCC 35667 with a MIC value of 25.0 μg mL^{-1}, whereas the other tested compounds did not show significant activity against the tested strains at concentration of 64.0 μg mL^{-1}.[63] Compound produced by *Lasiodiplodia theobromae* M4.2-2 can be observed in Figure 24.

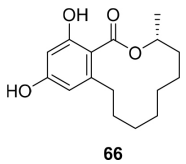
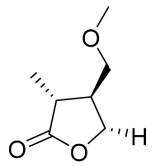


Figure 24. (+)-(*R*)-de-*O*-Methyl-lasiodiplodin (**66**) isolated from *Lasiodiplodia theobromae*, (M4.2-2).

The fungus *Lasiodiplodia theobromae* NSTRU-PN1.4, isolated from mangrove soil in Thailand's Nakhon Si Thammarat Province, was recently found to produce dimeric γ-lactone derivatives. Botryosphaerilactones A, B, and C, as well as the new botryosphaerilactones D and E, were identified through fractionation experiments, along with seven additional compounds previously reported in

the literature, (3*R*,4*S*,5*S*)-dihydro-4-(hydroxymethyl)-3,5-dimethyl-2(3*H*)-furanone, (3*R*,4*R*)-4-acetyl-3-methyl-2(3*H*)-dihydrofuranone (**67**), botryosphaeridione, (*R*)-(−)-mellein, *O*-methyl alboatrin, 4,5,6-trimethyl-2(1*H*)-pyrimidinone, and L-isoleucinamide.[64]

Compounds isolated in sufficient amount were subjected to antimicrobial testing, and compound **67** (Figure 25) demonstrated weak antifungal activity against *Cryptococcus neoformans* ATCC90113 with a MIC value of 200.0 μg mL^{-1}, when compared to the positive control (amphotericin B, MIC value of 0.27 μM). Furthermore, the chemical was tested for antimalarial (*Plasmodium falciparum*) and cytotoxic action (KB cell lines). It was, however, inactive in both experiments.[64]



67

Figure 25. Metabolite named (3*R*,4*R*)-4-acetyl-3-methyl-2(3*H*)-dihydrofuranone (**67**) isolated from *Lasiodiplodia theobromae* (NSTRU-PN1.4)

3.7. Genus *Cladosporium*

Cladosporium sp. PJX-41, on the other hand, resulted in the identification of antiviral alkaloids. Six new indole alkaloids, including 3-hydroxyglyantrypine, oxoglyantrypine a, and oxoglyantrypine b (**68**), cladoquinazoline, epi-cladoquinazoline, and norquinadoline A (**69**), were identified from the fungal extract, in addition to eight known quinazoline-containing indole alkaloids.[65]

Antiviral activity assays against the influenza A (H_1N_1) virus revealed that compounds **68**, **69**, **70** (deoxynortryptoquivaline), **71** (deoxytryptoquivaline), **72** (tryptoquivaline), and **73** (quinadoline B) exhibited antiviral activity comparable to the positive control (ribavirin, IC_{50} 87 μM) with IC_{50} values equal to 85, 82, 87, 85, 89, and 82 μM, respectively. In contrast, the other compounds exhibited weak antiviral activity with IC_{50} values ranging from 100- > 200 μM. This demonstrates relevant evidence regarding carbon skeletons to investigate and develop antiviral agents. In addition, it denotes the importance of research in the area, since the class of alkaloids reported is little known for species of *Cladosporium*.[65] All compounds discussed above can be observed in Figure 26.

4. Conclusions and Perspectives

In conclusion, this paper provides a thorough and up-to-date assessment of the antimicrobial properties of fungi isolated from mangroves. Mangrove ecosystems' great biodiversity has proven to be a promising source of microorganisms with distinct antimicrobial characteristics.

Mangrove-associated fungi have gained considerable attention as a rich source of structurally diverse secondary

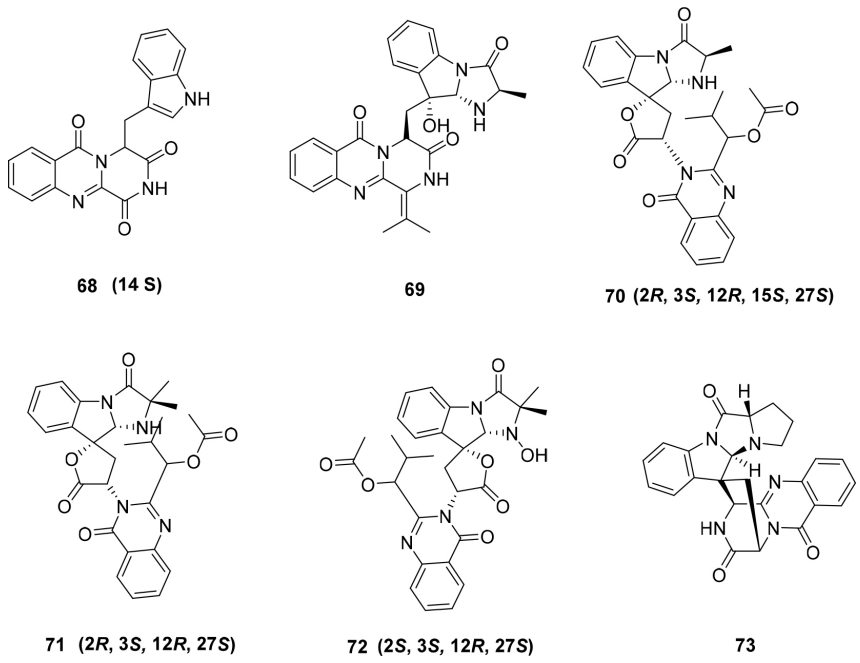


Figure 26. Six active compounds known as oxoglyantrypine b (**68**), norquinadoline A (**69**), deoxynortryptoquivaline (**70**), deoxytryptoquivaline (**71**), tryptoquivaline (**72**), and quinadoline B (**73**) isolated from *Cladosporium* sp. PJX-41.

metabolites, especially those isolated from soil and sediments, due to their unique ecological characteristics and diversity, with pronounced biological activities, including antibiotic-resistant bacteria, which could be utilized in the discovery of new drugs.

The fungal natural products reported in this paper were isolated from a diverse range of fungi species, mainly from *Penicillium* and *Aspergillus* species, demonstrating interesting pharmacological activities, some of them are potential clinical drug candidates, emphasizing the versatility of these microorganisms for producing different compounds with interesting potential antimicrobial application.

These findings not only give useful information for bioprospecting and the creation of new antimicrobial drugs but also emphasize the need to maintain mangrove habitats. The growing threat of habitat loss as a result of coastal development and climate change emphasizes the critical need to safeguard these natural ecosystems, not just to preserve biodiversity but also to continue to exploit their biotechnological potential.

Finally, this paper emphasizes the need to research and protect mangroves' enormous biological diversity, not only as a scientific resource but also as an essential component of our global ecology. Continuous collaboration between marine biologists, microbiologists, chemists, and healthcare specialists is required to translate these insights into real answers to today's antimicrobial concerns.

Acknowledgments

The authors are grateful to Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES, Financial Code 001) and IFMA for financial support. Antonio F. V. C. Braga thanks CAPES for her master's degree fellowship (process number: 88887.621336/2021-00), Antônio J. C. Filho thanks Foundation for Research and Scientific and Technological Development of Maranhão (FAPEMA - 06454/22) for financial support, and Edson R. Filho shows appreciation for National Council for Scientific and Technological Development (CNPq, 304867/2017-9) for financial support.

Author Contributions

Antonio F. V. C. Braga was responsible for the literature investigation, conceptualization, investigation, manual selection of articles, methodology, visualization, review, writing-original draft, and review; Marcelino S. Rosário, Jakson B. N. Gomes, Cristina A. Monteiro, and Flavia A. C. Farias were responsible for the writing-original draft and review; Antônio J. C. Filho and Edson. R. Filho designed the study and writing-review and editing. All authors have read and agreed to the published version of the manuscript.

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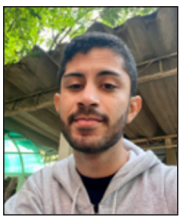

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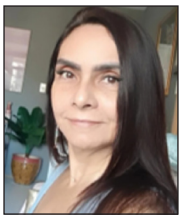

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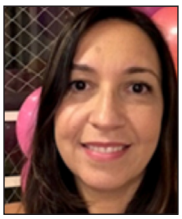

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Submitted: September 18, 2023
Published online: March 13, 2024