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Exploring *Aspergillus ochraceopetaliformis*: Biosynthesis, chemical diversity, and pharmacological potential of its secondary metabolites

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ABSTRACT

The *Aspergillus* genus is one of the most widespread fungal genera with significant pharmaceutical, industrial, and agricultural importance. *Aspergillus ochraceopetaliformis,* a member of this genius, is known for producing a diverse class of bioactive metabolites. These metabolites include pyran derivatives, cyclopentenones, lactones, anthraquinones, polyketides, sesquiterpenoids, alkaloids, biphenyl ethers, isocoumarins, cyclopeptides, and other secondary metabolites with distinct biological activities. Despite the potential of this fungus, there is lacking comprehensive review of its metabolites, biosynthesis pathway, and biological properties. The aim of this work is to provide a thorough overview of chemical diversity, biological activities, and biosynthetic pathways of the reported metabolites from *A. ochraceopetaliformis* in the period from 2016 to November 2024. The reported results highlight the untapped potential of *A. ochraceopetaliformis* metabolites that could encourage further research into their mechanisms of action and therapeutic uses in developing novel drug leads for various disorders.

INTRODUCTION

Fungi represent one of the most prevalent kingdoms of organisms on earth with more than 12,000 reported species. The updated estimate of the number of undiscovered species falls within the range of 2.2 to 3.8 million [1,2]. These microorganisms have vast and varied economic and ecological impacts, ranging from the manufacture of life-saving pharmaceuticals and the fermentation industry [3,4] to human and animal infections, as well as mycotoxin-induced poisoning of crops, livestock, and food [5].

The *Aspergillus* genus is considered the most widespread fungal genus worldwide with more than 330 accepted species [6]. These species are widely found in different natural habitats and play crucial roles in the decomposition of organic materials, while some species produce a variety of mycotoxins that lead to destructive rots in agricultural and food products [7]. These species can produce a variety of secondary metabolites, including terpenoids, alkaloids, glycosides, peptides, polyketides, and steroids. These metabolites possess

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Table 1. List of pyran derivatives isolated from *Aspergillus ochraceopetaliformis.*

Compound name	M. wt.	Mol. formula	Strain, host, and location	Ref.
Ochraceopone A (**1**)	450	$C_{23}H_{30}O_9$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
Ochraceopone B (**2**)	436	$C_{22}H_{28}O_9$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
Ochraceopone C (**3**)	420	$C_{22}H_{28}O_8$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
Ochraceopone D (**4**)	418	$C_{22}H_{26}O_8$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
Ochraceopone E (**5**)	390	$C_{22}H_{30}O_6$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
Isoasteltoxin (**6**)	418	$C_{23}H_{30}O_7$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
Asteltoxin (**7**)	418	$C_{23}H_{30}O_7$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[8]
	-	-	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Asteltoxin B (**8**)	434	$C_{23}H_{30}O_8$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[23]
	-	-	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Asteltoxin C (**9**)	404	$C_{22}H_{28}O_7$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Asteltoxin G (**10**)	334	$C_{18}H_{22}O_6$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Ochratoxin A (**11**)	403	$C_{20}H_{18}ClNO_6$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Ochratoxin A methyl ester (**12**)	417	$C_{21}H_{20}ClNO_6$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Ochratoxin A_1 (**13**)	507	$C_{24}H_{26}ClNO_9$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Ochratoxin B (**14**)	369	$C_{20}H_{19}NO_6$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Ochratoxin B methyl ester (**15**)	383	$C_{21}H_{21}NO_6$	*A. ochraceopetaliformis, Reniochalina* sp. (sponge, Axinellidae), Xisha Islands in the South China Sea	[9]
Ochraceopyronide (**16**)	244	$C_{10}H_{12}O_7$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[10]
Asperochrapyran (**17**)	216	$C_{10}H_{16}O_5$	*A. ochraceopetaliformis, Anthurium brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Asperochralactone D (**18**)	216	$C_{10}H_{16}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
3,5-Dimethylpyrone (**19**)	140	$C_7H_8O_3$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
(5*S*,6*R*,8*S*,9*R*)-8,9-Dihydroxy-8,9-deoxyaspyrone (**20**)	216	$C_9H_{14}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Aspyronol (**21**)	216	$C_{10}H_{16}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Dihydroaspyrone (**22**)	186	$C_9H_{14}O_4$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Aspyrone (**23**)	184	$C_9H_{12}O_4$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Phomapyrone C (**24**)	182	$C_{10}H_{14}O_3$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]

promising activities such as ovicidal, antifungal, cytotoxic, antibacterial, nematicidal, radical scavenging, and insect growth-regulating properties [14–22]. Some of them have potential applications in the medicinal and agricultural sectors. For example, lovastatin and simvastatin, well-known cholesterol-lowering medications, were biosynthesized and synthetically derived from *Aspergillus terreus*, respectively. They have been shown to promote HMG-CoA reductase inhibition and are utilized in clinical settings for treating cardiovascular disease and hypercholesterolemia [23].

Some species such as *Aspergillus sclerotiorum* and *Aspergillus ochraceus* are of economic importance because of their role in the biochemical transformation of phenazines, steroids, and alkaloids [15,19,24]. Besides, *Aspergillus melleus* and *Aspergillus ochraceus* are potential producers of proteolytic enzymes and various bio-metabolites [15,19,24]. On the other hand, *A. ochraceus* and *A. sclerotiorum* have been reported as human and animal pathogens that cause antromycosis, onychomycosis, allergic bronchopulmonary aspergillosis, and otomycosis in humans, as well as mycotic placentitis in the cow [24].

Unlike other *Aspergillus* species, *Aspergillus ochraceopetaliformis* Bat. & Maia, a rarely studied fungus, has not yet been recognized as a well-known human pathogen. It had been identified to cause infection of a healthy woman's toenails that had been treated effectively by ciclopiroxolamine plus terbinafine [24,25]. *Aspergillus ochraceopetaliformis* was identified as a soft-rot fungus that degrades archeological wood at the Al-Aqsa Mosque [7]. Recently, it was isolated from *Setipinna phasa* (Shukti) dried fish [26]. Ngo *et al.* noted that *A. ochraceopetaliformis* produced high levels of exopolysaccharide (9.89 g/l) that are major contributors to significant physical, chemical, and aesthetical alterations and leaching of elements from glass surfaces [27]. On the other hand, this fungus produces diverse classes of secondary metabolites: pyran derivatives, cyclopentenones, lactones, polyketides, anthraquinones, biphenyl ethers, sesquiterpenoids, alkaloids, isocoumarins, and cyclopeptides with significant pharmacological properties.

Despite many studies investigating various *Aspergillus* species, there is a lack of review that combines the pharmacological properties, mechanism of actions, and biosynthesis pathways of *A. ochraceopetaliformis* metabolites.

Therefore, the current review aims to provide a comprehensive discussion of *A. ochraceopetaliformis*, including its secondary metabolites and their biological properties. Additionally, the biosynthetic pathways of these metabolites were highlighted. These compounds were classified based on their chemical skeletons. This work is the first to thoroughly discuss the biosynthetic pathways and bio-activities of *A. ochraceopetaliformis* metabolites, highlighting this species' potential as a source of new bioactive compounds, particularly for the treatment of viral infections, inflammation, and cancer.

SEARCH METHODOLOGY

A literature search using databases, including PubMed, Scopus, Web of Science, and Google Scholar was done to compile all reported studies on *A. ochraceopetaliformis*, its secondary metabolites, and biological activities. The search employed keywords such as "*Aspergillus ochraceopetaliformis* + secondary metabolites" OR "*Aspergillus ochraceopetaliformis* + biosynthetic

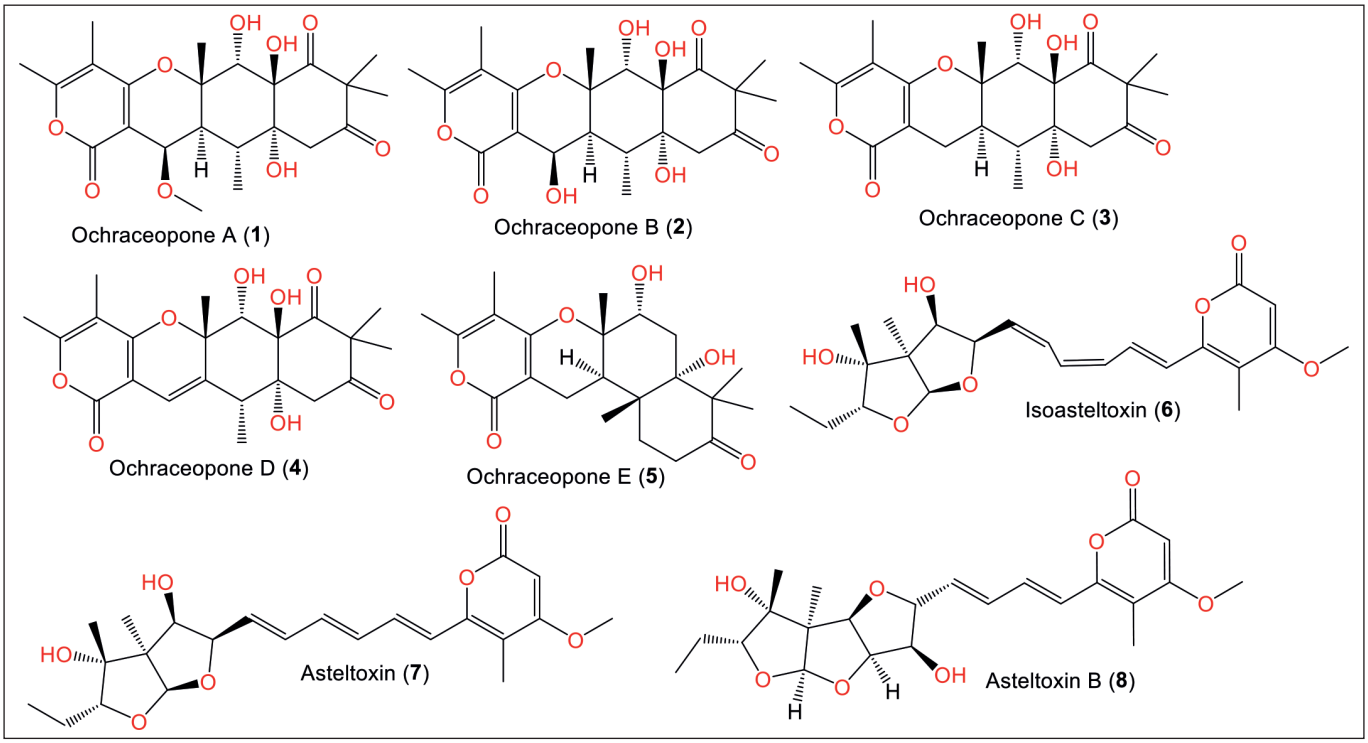

Figure 1. Chemical structures of pyrones derivatives (**1**–**8**) reported from *Aspergillus ochraceopetaliformis*.

pathways", "*Aspergillus ochraceopetaliformis* + biological activities". The studies reported on isolation, identification, biosynthesis, and biological properties of *A. ochraceopetaliformis* metabolites were included, while publications unrelated to these areas on *A. ochraceopetaliformis* were excluded.

ASPERGILLUS OCHRACEOPETALIFORMIS METABOLITES AND THEIR BIOACTIVITIES

Pyran derivatives

α-Pyrone mero-sesquiterpenoids have an angular tetracyclic skeleton, consisting of α-pyrone and highly oxygenated trans-decalin substructures. These compounds have been previously reported from *Penicillium* and *Aspergillus* species [28].

Wang *et al*. separated new α-pyrone mero-sesquiterpenoids: ochraceopones A-E (**1**–**5**) and isoasteltoxin (**6**), along with **7** and **8** from the ethyl acetate (EtOAc) extract of nutrient-deprived medium of Antarctic soil-derived *A. ochraceopetaliformis* SCSIO-05702 collected near the Great Wall station using SiO_2/Sephadex LH-20 CC/high-performance liquid chromatography (HPLC) [8] (Table 1).

Ochraceopones A–D (**1**–**4**) are α-pyrone mero-sesquiterpenoids, having a tetracyclic linear carbon skeleton that differs at position 6, possessing CH-OCH_3, CH-OH, and CH_2, respectively (Fig. 1). The C-7 methine and C-6 oxymethine in **2** are replaced by C-6-C7 double bond in **4** [8]. Their 6R/7S/8S/9R/10R/11R, 12R/6R/7S/8S/9R/10R/11R/12R, 7R/8S/9R/10R/11R/12R, and 8S/9R/10R/11R/12R configurations, respectively, were assigned based on nuclear overhauser effect spectroscopy (NOESY)/CD/Xray analyses.

Compound **5** is 7R/8S/9R/11S/12R configured and has different connectivity of decalin unit from **3**. Compound **6** possesses α-pyrone and 2,8-dioxabicyclo[3.3.0]octane units as **7** with Z-geometry of C-12-C-11 double bond. Compounds **1**–**5** are proposed to be generated via mevalonate/polyketide pathways. *Trans*-farnesyl pyrophosphate (FPP) is formed through a mevalonate pathway that combines with malonyl-CoA and acetyl-CoA to produce an intermediate A (Fig. 2). The tetracyclic core is formed from this intermediate through epoxidation, polyene cyclization, and retro-aldol/aldol rearrangement. Compounds **1**–**5** are created through oxidation, epoxidation, cyclization, retro-aldol/aldol rearrangement, dehydration, and methylation [8]. Compounds **1**–**8** were tested for anti-H1N1 and H3N2 activities. Compounds **6** and **7** displayed powerful antiviral capacities against the H3N2 and H1N1 influenza viruses (IC_{50}s 0.66/0.23 and 0.84/0.54 μM, respectively) with anti-H1N1 selectivity indexes (SIs) 2.35 and 0.44, respectively, compared to Tamiflu (IC_{50}s 18.5 and 16.9 nM, respectively) in the cytopathic effect inhibition

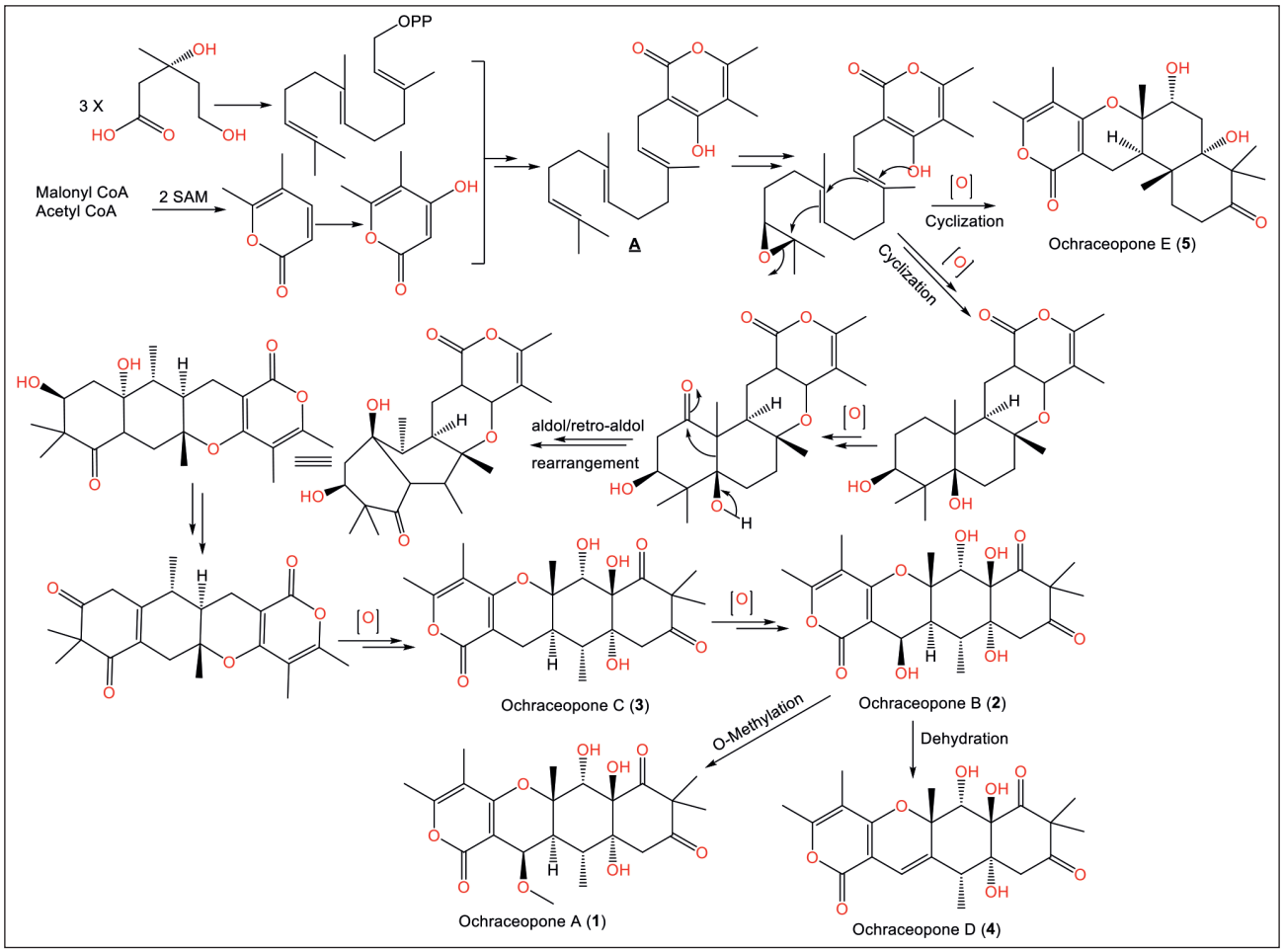

Figure 2. Biosynthetic pathways of ochraceopones A–E (**1**–**5**) [8].

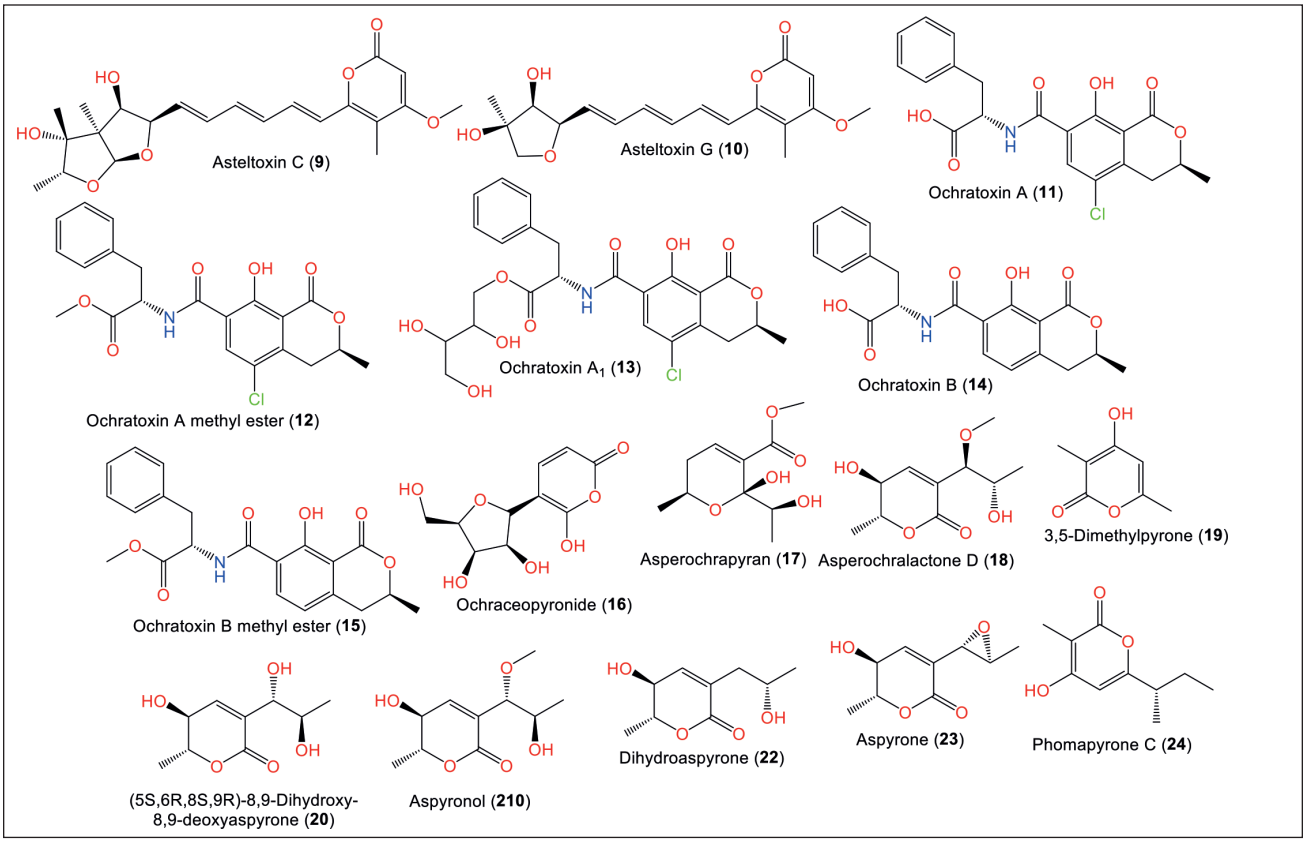

Figure 3. Chemical structures of pyrone derivatives (**9**–**24**) reported from *Aspergillus ochraceopetaliformis*.

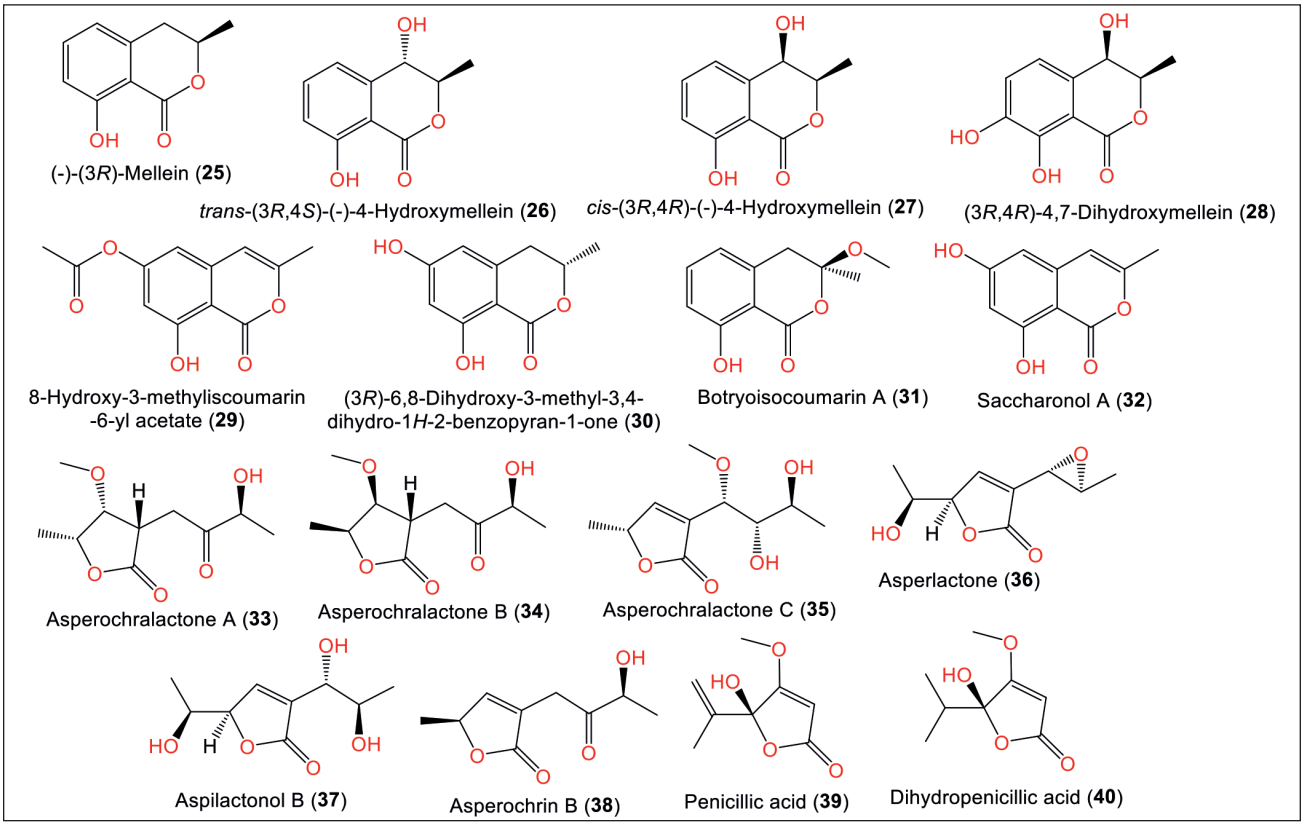

Figure 4. Chemical structures of isocoumarin derivatives (**25**–**32**) and lactones (**33**–**40**) reported from *Aspergillus ochraceopetaliformis*.

Table 2. List of isocoumarins and lactones isolated from *Aspergillus ochraceopetaliformis*.

Compound name/chemical class	M. wt.	Mol. formula	Strain, host, and location	Ref.
Isocoumarins				
(-)-(3*R*)-Mellein (**25**)	178	$C_{10}H_{10}O_3$	*A. ochraceopetaliformis, Anthurium brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
trans-(3*R*,4*S*)-(-)-4-Hydroxymellein (**26**)	194	$C_{10}H_{10}O_4$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
	-	-	*A. ochraceopetaliformis* SCSIO 41020, *Hypnea pannosa* (Alga, Cystocloniaceae), South China Sea, Luhuitou, Sanya, Hainan, China	[29]
cis-(3*R*,4*R*)-(-)-4-Hydroxymellein (**27**)	194	$C_{10}H_{10}O_4$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
	-	-	*A. ochraceopetaliformis* SCSIO 41020, *H. pannosa* (Alga, Cystocloniaceae), South China Sea, Luhuitou, Sanya, Hainan, China	[29]
(3*R*,4*R*)-4,7-Dihydroxymellein (**28**)	210	$C_{10}H_{10}O_5$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
8-Hydroxy-3-methyliscoumarin-6-yl acetate (**29**)	234	$C_{12}H_{10}O_5$	*A. ochraceopetaliformis, Tethya wilhelma* (Sponge, Tethyidae), Nanao Island, Shantou, Guangdong, China	[30]
(3*R*)-6,8-Dihydroxy-3-methyl- 3,4-dihydro-1*H*-2-benzopyran-1-one (**30**)	194	$C_{10}H_{10}O_4$	*A. ochraceopetaliformis, T. wilhelma* (Sponge, Tethyidae), Nanao Island, Shantou, Guangdong, China	[30]
Botryoisocoumarin A (**31**)	208	$C_{11}H_{12}O_4$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Saccharonol A (**32**)	192	$C_{10}H_8O_4$	*A. ochraceopetaliformis* SCSIO 41020, *H. pannosa* (Alga, Cystocloniaceae), South China Sea, Luhuitou, Sanya, Hainan, China	[29]
Lactones				
Asperochralactone A (**33**)	216	$C_{10}H_{16}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Asperochralactone B (**34**)	216	$C_{10}H_{16}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Asperochralactone C (**35**)	216	$C_{10}H_{16}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Asperlactone (**36**)	184	$C_9H_{12}O_4$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Aspilactonol B (**37**)	202	$C_9H_{14}O_5$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Asperochrin B (**38**)	184	$C_9H_{12}O_4$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Dihydropenicillic acid (**39**)	172	$C_8H_{12}O_4$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Penicillic acid (**40**)	170	$C_8H_{10}O_4$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[26]

assay. These findings suggested that the polyene chain Δ^{11} double bond geometry contributes to the anti-H1N1 efficacy [8].

Compounds **10** and **13** are new trienic α-pyrone and ochratoxin derivatives, respectively, that were reported from *Reniochalina* sp. sponge-associated *A. ochraceopetaliformis* collected from the Xisha Islands/South China Sea, in addition to **7**–**9**, **11**, **12**, **14,** and **15** using silica gel column chromatography/ODS/HPLC [9]. Compound **10** has a pyrone-triene core attached to a substituted tetrahydrofuran moiety. While **13** (α_D-57.5) was like **11** ($[\alpha]_D$-66) with an additional butane-1,2,3,4-tetraol (Fig. 3).

Compounds **13**–**15** displayed a notable reduction in the tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) induced lipopolysaccharide (LPS) expression in human monocytic cell line (THP-1) cells (%inhibition 67.7%, 72.8%, and 72.9% for TNF-α and 74.4%, 91.6%, and 89.7%, respectively, for IL-6) without cytotoxicity after 24 hours treatment [9]

Mitani *et al.* identified compound **7** as a potential inhibitor of mitochondrial Adenosine triphosphate (ATP) synthase and extracellular vesicles (EVs) [31]. It suppressed EV secretion without causing mitochondrial damage by reducing ATP levels and triggering 5' adenosine monophosphate-activated protein kinase-mediated mechanistic target of rapamycin C1 inactivation, leading to nuclear translocation of microphthalmia/transcription factor E transcription factors and enhancing lysosomal gene expression and activation. It revealed increased lysosomes and reduced multivesicular bodies (MVBs) and EV levels, highlighting **7** as a novel EV inhibitor that influences MVB dynamics [31].

Asmaey *et al.* identified **16** as a rare and new α-pyrone-C-glycoside derivative from *A. ochraceopetaliformis* collected from Giza province/Egypt. This compound was assigned as 6-OH-2-pyrone-5-C-lyxofuranoside, which has 6-OH-*a*-

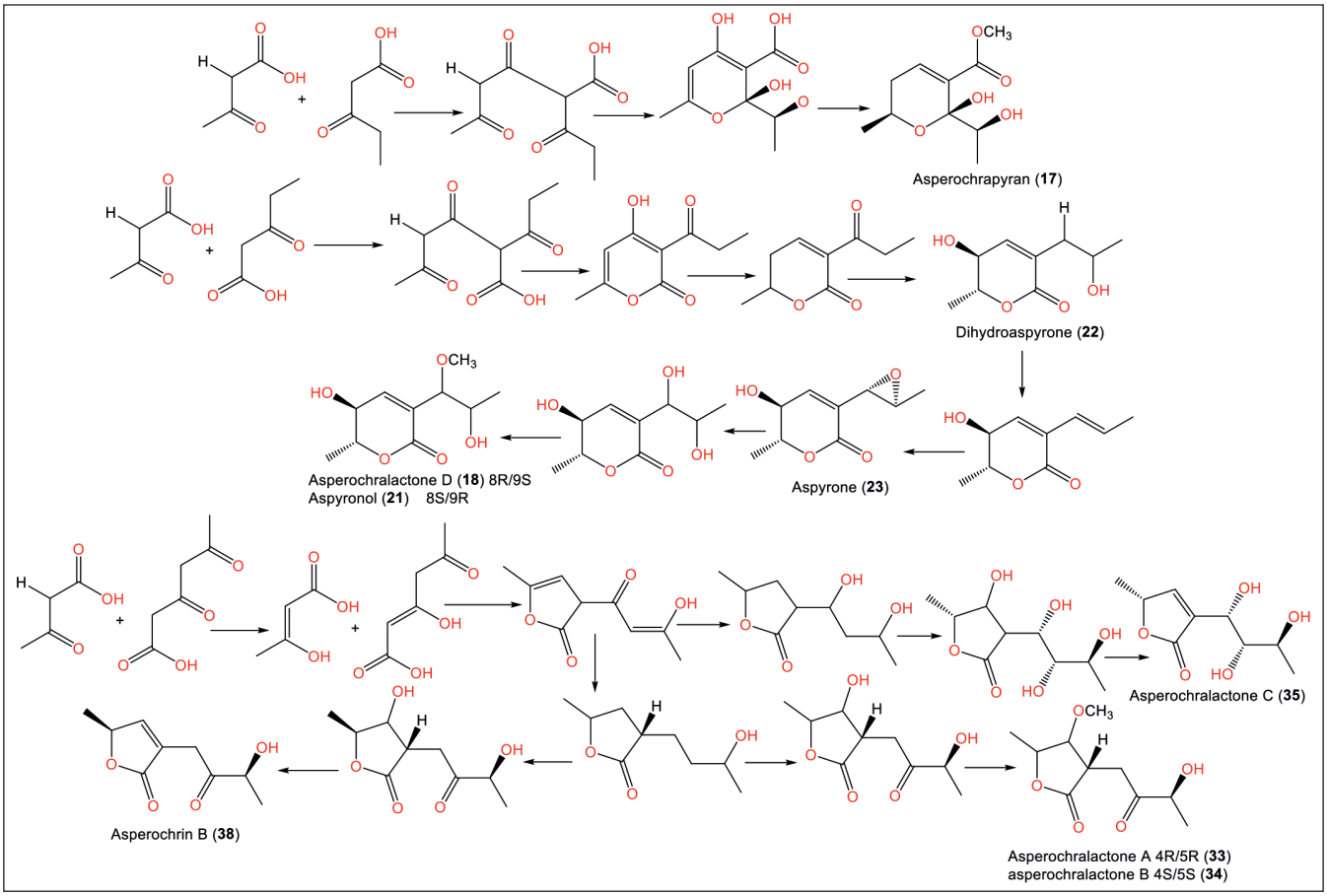

Figure 5. Biosynthetic pathways of **17**, **18**, **21**–**23**, **33**–**35,** and **38** [11].

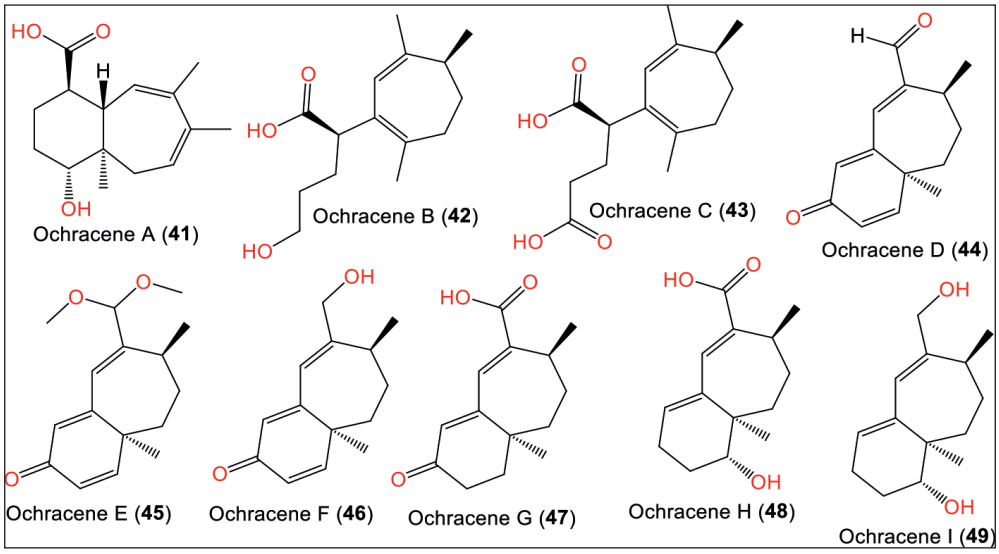

Figure 6. Chemical structures of sesquiterpenoids (**41**–**49**) reported from *Aspergillus ochraceopetaliformis*.

pyrone with C-5-linked pentofuranoside moiety. Compound **16** exhibited weak antimicrobial potential versus different microbes [10].

Hu *et al.* [11] reported that *Anthurium brownii*-harboring *A. ochraceopetaliformis* EtOAc extract possessed marked anti-inflammatory capacity by suppressing elastase release and superoxide anion production (%inhibition 107% and 103 %, respectively; Conc. 10 µg/ml) [11]. Its bio-guided separation led to the identification of new pyran derivatives: **17** and **18**, along with **20**–**23**. Compounds **17** and **18**'s 2R/6S/9S and

Table 3. List of sesquiterpenoids and cyclopentanones isolated from *Aspergillus ochraceopetaliformis*.

Compound name/chemical class	M. wt.	Mol. formula	Strain, host, and location	Ref.
Sesquiterpenoid derivatives				
Ochracene A (**41**)	250	$C_{15}H_{22}O_3$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene B (**42**)	252	$C_{15}H_{24}O_3$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene C (**43**)	266	$C_{15}H_{22}O_4$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene D (**44**)	216	$C_{14}H_{16}O_2$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene E (**45**)	262	$C_{16}H_{22}O_3$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene F (**46**)	218	$C_{14}H_{18}O_2$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene G (**47**)	234	$C_{14}H_{18}O_3$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene H (**48**)	236	$C_{14}H_{20}O_3$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Ochracene I (**49**)	222	$C_{14}H_{22}O_2$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
Cyclopentanones				
Aspernone A (**50**)	270	$C_{14}H_{22}O_5$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Aspernone B (**51**)	284	$C_{15}H_{24}O_5$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Aspernone C (**52**)	300	$C_{15}H_{24}O_6$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Aspernone D (**53**)	256	$C_{13}H_{20}O_5$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Aspernone E (**54**)	170	$C_8H_{10}O_4$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Methyl-3-(3-oxocyclopent-1-en-1-yl) propanoate (**55**)	168	$C_9H_{12}O_3$	*A. ochraceopetaliformis, Tethya wilhelma* (Sponge, Tethyidae), Nanao Island, Shantou, Guangdong, China	[30]
(+) Ochrathinol A (**56**)	170	$C_8H_{10}O_2S$	*A. ochraceopetaliformis* SCSIO 05702, soil, the Great Wall station (Chinese Ant arctic station), China	[32]
(–) Ochrathinol A (**57**)	170	$C_8H_{10}O_2S$	*A. ochraceopetaliformis* SCSIO 05702, soil, the Great Wall station (Chinese Ant arctic station), China	[32]
(+) Ochrathinol B (**58**)	170	$C_8H_{10}O_2S$	*A. ochraceopetaliformis* SCSIO 05702, soil, the Great Wall station (Chinese Ant arctic station), China	[32]
(–) Ochrathinol B (**59**)	170	$C_8H_{10}O_2S$	*A. ochraceopetaliformis* SCSIO 05702, soil, the Great Wall station (Chinese Ant arctic station), China	[33]

5S/6R/8R/9S configurations, respectively, were assigned based on electronic circular dichroism (ECD) analysis. Compound **23** revealed anti-inflammatory potential (% inhibition 29%, Conc. 10 µM) by inhibiting the formation of superoxide anion in neutrophils stimulated by N-formyl-L-methionyl-L-leucylL-phenylalanine [11].

Isocoumarins

Compound **25** was reported to have anti-inflammation potential through inhibition of elastase release and superoxide anion production (% inhibition 34 % and 26 %, respectively) [11]. Compounds **26**–**28** were reported by Wang *et al.* from a nutrient-rich agitated fermentation medium of SCSIO-05702 strain [12]. Compounds **26** and **27** were found to suppress LPS-caused nitric oxide (NO) production and lessened TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) levels in RAW 264.7 macrophages in the cell counting kit-8 (CCK-8) assay [29]. The new isocoumarin, **29** and its related analog **30** were separated from *Tethya wilhelma*-harboring *A. ochraceopetaliformis* collected from Nanao Island/ Shantou/Guangdong Province (Fig. 4). Compound **29** demonstrated cytotoxic efficacy on the B16 cell line (IC_{50} 72.5 µM) in the MTT assay [30].

Lactones

Asperochralactones A–C (**33**–**35**), in addition to compounds **36**–**39** were obtained from *A. ochraceopetaliformis* associated with *A. brownii* leaves. Compounds **33**–**35** are new polyketides γ-lactone moiety that have 3S/4R/5R/9S, 3S/4S/5S/9S, 5R/7S/8S/9S, and 5S/6R/8R/9S, respectively (Table 2) [11].

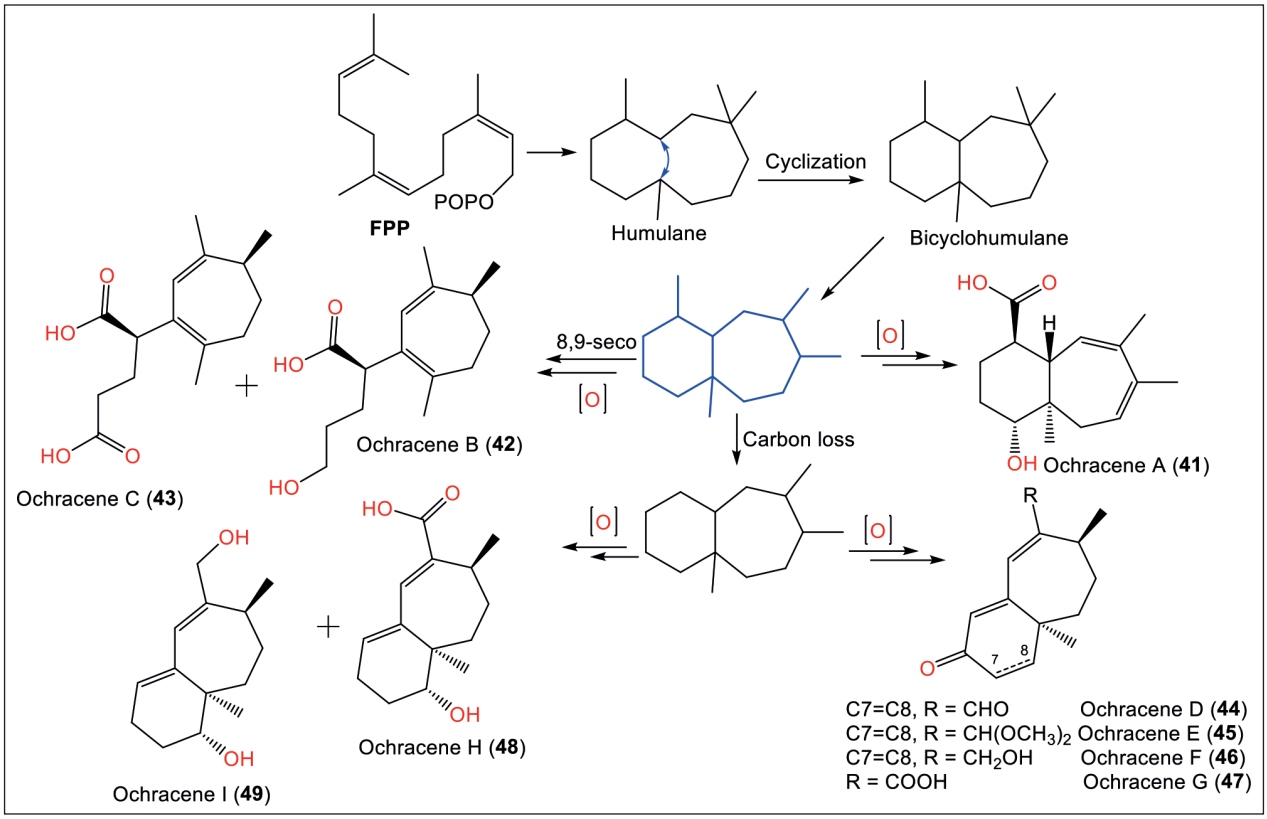

Figure 7. Biosynthetic pathways of ochracene A−I (**41**–**49**) from humulane [12].

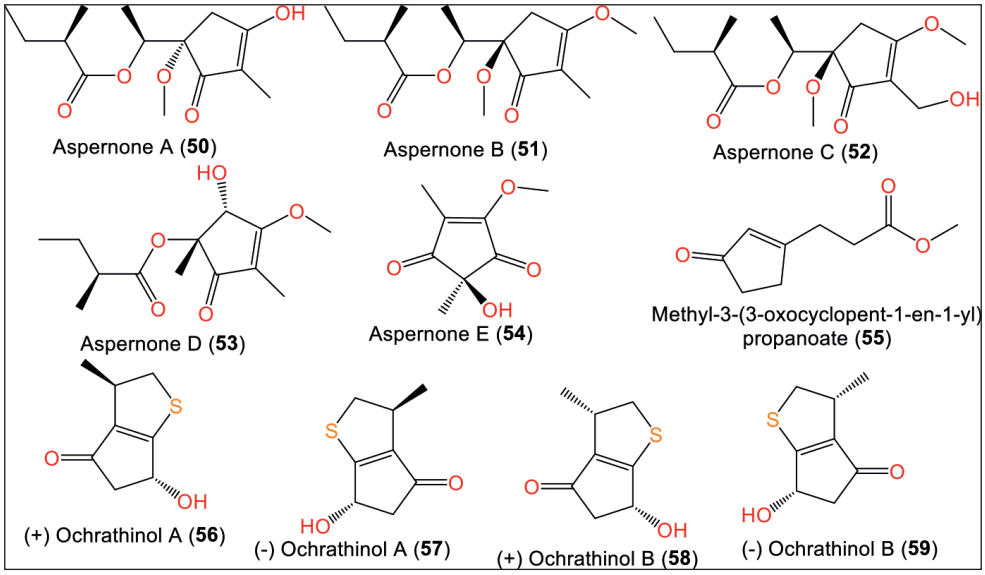

Figure 8. Chemical structures of cyclopentanones (**50**–**59**) reported from *Aspergillus ochraceopetaliformis*.

Their anti-inflammation test using fMLP-stimulated human neutrophils revealed that **36** inhibited superoxide anion formation (Conc. 10 µM; % inhibition 30%); however, compounds **36**, **37,** and **39** displayed elastase release inhibitory capacities (25%, 38% and 25%, respectively). Also, compounds **36** and **39** were cytotoxic against the HepG2 cancer cell line (IC_{50}s 42.9 and 32.9 µM, respectively) [11]. Compounds **17**, **18**, **20**, **21**, **23**, **33**–**35,** and **38** have 3-oxobutanoic acid with 3-oxopentanoic or 3,5-dioxohexanoic acid that were proposed to be biosynthesized via polyketide synthase (PKS) pathway through series of reactions, involving cyclization, condenation, decarbonation, dehydration, methylation, reduction, and oxidation [11] (Fig. 5).

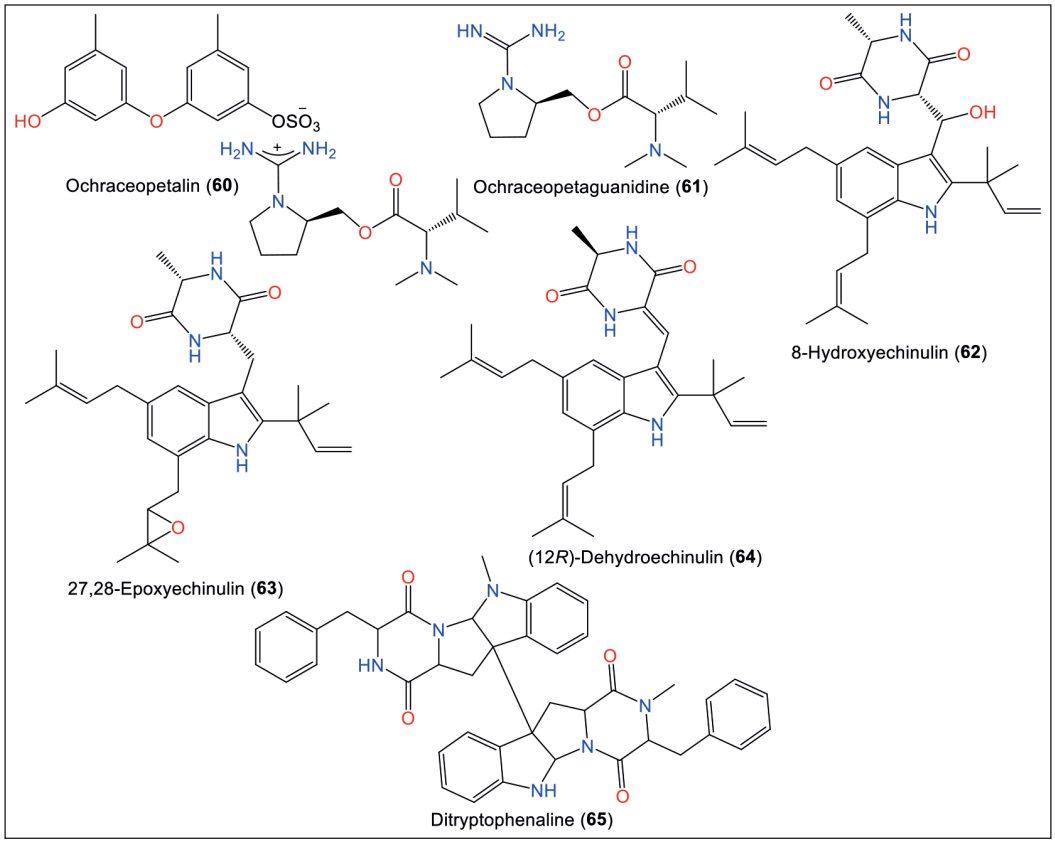

Figure 9. Chemical structures of alkaloids (**60**–**65**) reported from *Aspergillus ochraceopetaliformis*.

Sesquiterpenoids

Humulane-type sesquiterpenoids, a rare class of compounds with a distinctive 11-membered ring were reported from mushrooms, plants, and liverworts, while they are uncommonly found in actinomycetes or fungi [33]. A study by Wang *et al.* reported that the culture condition greatly affected the type of biosynthesized metabolites. Changing the static fermentation of *A. ochraceopetaliformis* SCSIO 05702 in a limited-nutrient culture medium to a nutrient-rich culture with agitated fermentation resulted in the production of **41**–**49**, new humulane sesquiterpenoids that were separated using SiO_2/reversed phase-18 column chromatography (RP-18 CC)/HPLC and elucidated based on spectral/ECD analyzes and Mosher's method. These compounds possess unprecedented carbon frameworks with ring cleavage, methyl migration, and carbon loss (Fig. 6, Table 3). The 9S/12S, 9S/12S, and 8R configurations for **44**/**45, 46**/**49,** and **48**/**49** were assured based on specific rotation, ECD, and Mosher's method, respectively. For instance, **42** and **43** belong to 8,9-seco-humulane sesquiterpenoids.

Compounds **42** and **43** exhibited inhibitory effectiveness on NO formation induced by LPS in RAW 264.7 mouse macrophage cell lines (IC_{50}s 14.6 and 18.3 µM, respectively), compared to dexamethasone (IC_{50} 2.5 µM) in cell culture and viability assay [12]. These compounds possessed no antiviral or cytotoxic activities (up to 100 µM) [12].

Biosynthetically, compounds **41**–**49** are generated from the humulane skeleton. This skeleton is obtained from the enzymatic cyclization of FPP (Fig. 7). A 6/7 carbon ring framework is formed by a bond between C-9 and C-4. Consequently, **41**–**49** are produced via a sequence of reactions, including methyl migration, oxidation, ring cleavage, and carbon loss [12].

Cyclopentenones

From sponge-derived SCSIO 41018 strain, aspernones A–E (**50**–**54**), new cyclopentenone analogs that differ in configuration and side chain were identified using spectral/ECD/Xray analyzes (Fig. 8). Compounds **50**–**54** feature 3,5-dihydroxy-cyclopentenone skeleton, while **54** has hydroxylated C-2 and methyl at C-4. Their configurations were assigned as 5S/6S/21R, 5R/2`R, 5R/2`R, 4R/5R and 2S, respectively, based on ECD and Xray analyzes [13].

Compounds **56**–**59** are undescribed sulfur-containing racemates that were separated from Antarctic soil-derived *A. ochraceopetaliformis* SCSIO 05702 by SiO_2/Sephadex LH-20 CC/HPLC/Chiral HPLC and elucidated by spectral/chiral-phase HPLC/X-ray analyses and quantum ECD calculations [32]. These enantiomers were separated by HPLC with FLM chiral-ND (2)-RH chiral column into (+) A (**56**), (–) A (**57**), (+) B (**58**), and (–) B (**59**). These compounds feature a novel 3-methylhexahydro-2*H*-cyclopenta [*b*]thiophene framework with 3R/7R, 3S/7S, 3S/7R, and 3R/7S configurations,

Table 4. List of alkaloids and peptides isolated from *Aspergillus ochraceopetaliformis*.

Compound name/chemical class	M. wt.	Mol. formula	Strain, host, and location	Ref.
Alkaloids				
Ochraceopetalin (**60**)	581	$C_{27}H_{41}N_4O_8S$	*A. ochraceopetaliformis* FJ120, sea sediment, Jeju-do, Korea	[34]
Ochraceopetaguanidine (**61**)	270	$C_{13}H_{26}N_4O_2$	*A. ochraceopetaliformis* FJ120, sea sediment, Jeju-do, Korea	[34]
8-Hydroxyechinulin (**62**)	477	$C_{29}H_{39}N_3O_3$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[35]
27,28-Epoxyechinulin (**63**)	477	$C_{29}H_{39}N_3O_3$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[35]
(12*R*)-Dehydroechinulin (**64**)	459	$C_{29}H_{37}N_3O_2$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[35]
Ditryptophenaline (**65**)	692	$C_{42}H_{40}N_6O_4$	*Aspergillus ochraceopetaliformis* MN083316, soft coral, Ein El-Sukhna-Zafarana Rd 65 KM, Red Sea, Egypt	[36]
Mactanamide (**66**)	340	$C_{19}H_{20}N_2O_4$	*A. ochraceopetaliformis* DSW-2, sea water, Dongshan Island, Fujian, China,	[37]
Cyclo-(L-Pro-L-Tyr) (**67**)	260	$C_{14}H_{16}N_2O_3$	*A. ochraceopetaliformis* DSW-2, sea water, Dongshan Island, Fujian, China,	[37]
Dizinchydroxyneoaspergillin (**68**)	1084	$C_{48}H_{76}N_8O_{12}Zn_2$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Wasabidienone-E (**69**)	311	$C_{16}H_{25}NO_5$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Ferrineoaspergillin (**70**)	837	$C_{36}H_{57}FeN_6O_6^{2+}$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Deoxy-β-Hydroxyneoaspergillic acid (**71**)	224	$C_{12}H_{20}N_2O_2$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Hydroxyneoaspergillic acid (**72**)	240	$C_{12}H_{20}N_2O_3$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
3,6-Diisobutyl-2(1*H*)-pyrazinone (**73**)	208	$C_{12}H_{20}N_2O$	*A. ochraceopetaliformis* SCSIO 41018, sponge, China	[13]
Ochracid A (**74**)	209	$C_{10}H_{11}NO_4$	*A. ochraceopetaliformis* SCSIO 05702, soil, the Great Wall station (Chinese Ant arctic station), China	[32]
Ochracid B (**75**)	223	$C_{11}H_{13}NO_4$	*A. ochraceopetaliformis* SCSIO 05702, soil, the Great Wall station (Chinese Ant arctic station), China	[32]
Peptides				
FJ120DPA (**76**)	734	$C_{38}H_{50}N_6O_9$	*A. ochraceopetaliformis* FJ120, sea sediment, the coast of Jeju-do, Korea	[38]
FJ120DPB (**77**)	752	$C_{38}H_{52}N_6O_{10}$	*A. ochraceopetaliformis* FJ120, sea sediment, the coast of Jeju-do, Korea	[38]
Sclerotiotide B (**78**)	406	$C_{21}H_{34}N_4O_4$	*A. ochraceopetaliformis* DSW-2, sea water, Dongshan Island, Fujian, China,	[37]
Sclerotiotide F (**79**)	420	$C_{21}H_{32}N_4O_5$	*A. ochraceopetaliformis* DSW-2, sea water, Dongshan Island, Fujian, China,	[37]
Sclerotiotide M (**80**)	440	$C_{21}H_{36}N_4O_6$	*A. ochraceopetaliformis* DSW-2, sea water, Dongshan Island, Fujian, China,	[37]

respectively. The racemic mixture **56/57** repressed IL-6, IL-1β, and TNF-*α* release produced by LPS (Conc. 10 μM) and raised the unbalanced NADH/NAD+ ratio in RAW264.7 macrophages [33].

Alkaloids

In 2021, Park *et al.* isolated **60** from marine-derived *A. ochraceopetaliformis*, which is a novel sulfonated diphenyletheraminol-amino acid guanidinium salt, along with its component **61** [1-(aminoiminomethyl)-prolinol, N,N-dimethylvaline ester] that were identified by spectral/chemical methods (Fig. 9; Table 4) [34].

The salt nature of **60** was established by a set of pH-based degradation reactions. Compound **60** was proposed to originate from mixed-biogenetic salt produced from amino acid and polyketide pathways. Compound **60** had notable cytotoxic potential against A-549 and K-562 (IC_{50} 6.8 and 9.5 μM, respectively), while **60** was weakly active in comparison to doxorubicin (IC_{50} 0.90 and 0.72, respectively). On the other side, compounds **60** and **61** displayed no antimicrobial or sortase A (SrtA) inhibitory activities [34].

New diketopiperazine alkaloids: **62**–**64** were reported by Asmaey *et al.* from soil-derived *A. ochraceopetaliformis* that were assigned using spectral/Marfey's analyses and optical rotation measurement. These compounds showed antimicrobial properties against different bacterial and fungal strains [35]. From the EtOAc extract of reef coral-associated MN083316 strain, **65** was purified that revealed marked antioxidant and antimicrobial activities, in addition to cytotoxic capacity on HEPG2 and MCF-7 (IC_{50}s 7.6 and 5.8, respectively) [36]. Additionally, **66** and **67** were reported from seawater-derived stains that showed weak cytotoxic potential versus HPAC and BXPC-3 cell lines [37].

Compound **68** a new zinc complex dimer, along with **69**–**73** were separated by Guo *et al.* from sponge-associated SCSIO 41018 strain using SiO_2/Sephadex LH-20/RP-18 CC/HPLC and assigned by spectral/ECD/X-ray analyses [13]. Compound **68** was identified as a zinc complex of **72**, which has a Zn atom connected N-4 by a coordinate bond (Fig. 10). These compounds were assessed for their antimicrobial and cytotoxic activities. Compounds **68** and **72** demonstrated potent activities versus *Enterococcus faecalis* and *Acinetobacter baumannii* (minimum inhibitory concentrations [MICs] 0.9/0.45 and 0.9/0.45 μg/ml, respectively), compared to ampicillin and gentamicin (MICs 0.04 and 0.33 μg/ml, respectively). Further, **68** was moderately cytotoxic against

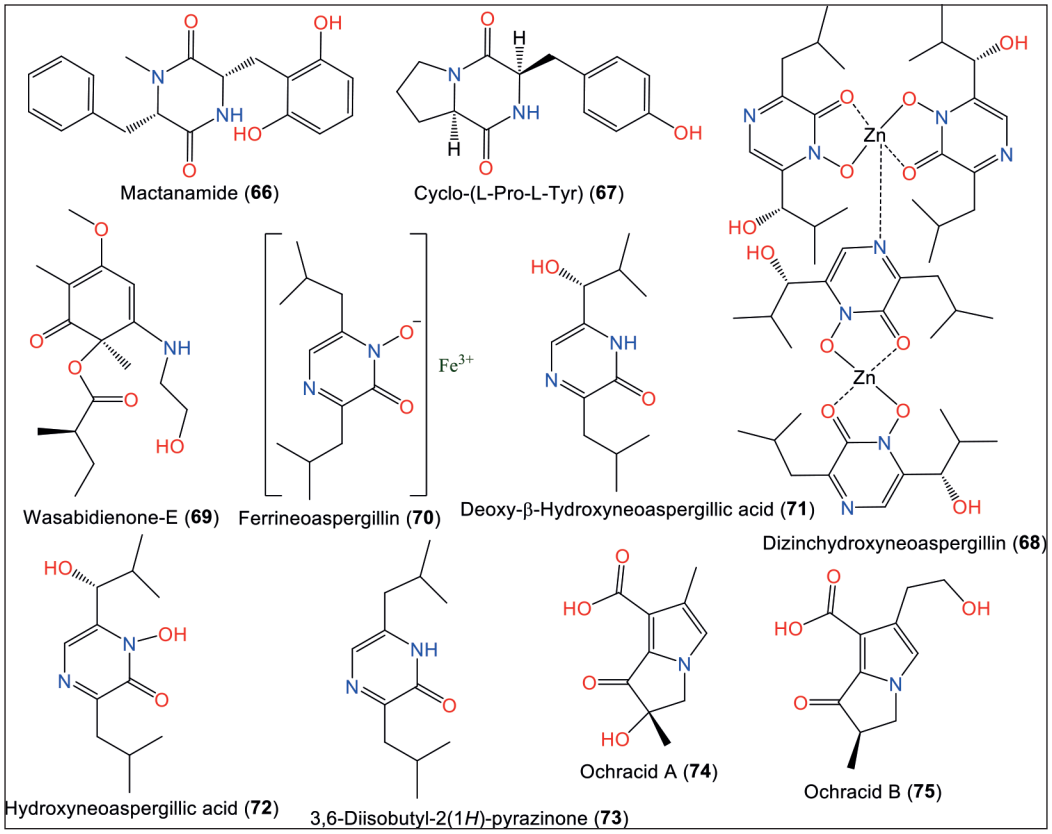

Figure 10. Chemical structures of alkaloids (**66**–**75**) reported from *Aspergillus ochraceopetaliformis*.

the SGC-7901, human BEL-7402, and K-562 cell lines (IC_{50}s 12.88–15.83 µM), compared to paclitaxel (0.76–1.44 µM) [13].

Unprecedented pyrrolizidine alkaloids: **74** and **75** were separated from SCSIO 05702 strain derived from Antarctic soil using SiO_2/Sephadex LH-20 CC/HPLC and elucidated by spectral/ECD/Xray analyses. These are bicyclic 7R-configured compounds with pyrrolidin-3-one containing $\Delta^{4,5}$ and $\Delta^{2,3}$ double bonds [33].

Peptides

Cyclopeptides are cyclic molecules produced from either non-proteinogenic or proteinogenic amino acids linked by peptide or amine bonds, which are reported from fungi, plants, bacteria, mammals, sponges, and algae [39,40]. These metabolites exhibited various biological activities, including antibacterial, insecticidal, cytotoxic, and anticancer properties [39,40].

Cyclohexadepsipeptide **76** and its linear derivative **77**, new metabolites were isolated from sea sediment-associated *A. ochraceopetaliformis* collected from the Jeju-do coast, Korea using SiO_2/Sephadex LH-20 CC/HPLC [38]. Their structures were assigned using HR LC/MS-MS/spectral tools and Marfey's method. Compound **76** has uncommon L-*N*-AcThr and D-Val units, whereas **77** was assigned as a *N*-AcThr and Ala ester linkage hydrolyzed derivative of **76** (Fig. 11). Compounds **76** and **77** had inhibition capacity for SrtA (IC_{50}s 131.9 and 77.0 µM, respectively), compared to berberine chloride (IC_{50} 104.3 µM) [38]; however, they were weakly active on isocitrate lyase (ICL). SrtA and ICL are prominent targets for developing anti-virulence medications that combat pathogenic microbes [38].

A novel cyclic tripeptide, **80**, in addition to **78** and **79** were isolated from the culture EtOAc extract of sea-water-derived *A. ochraceopetaliformis* using SiO_2/Sephadex LH-20 CC/HPLC [37]. Compound **80** consists of Ala, Orn, and Val amino acid residues with (E)-4,4-dimethoxy-1-one-2-butenyl side chain. Its 2S/6S/12S configuration was assured based on calculated nuclear magnetic resonance chemical shifts coupled with DP4$^+$ statistical method and optical rotation. Compounds **78** and **79** had selective anti-fungal properties against *Candida albicans* with (MICs 3.8 and 30 µM, respectively). On the other hand, **78**–**80** revealed weak cytotoxicity against BXPC-3 and HPAC cell lines in the CCK-8 assay [37].

Polyketides

Aspormisin A (**81**) a new linear polyketide and its related metabolite, **82** were obtained from SCSIO-41020 derived from *Hypnea pannosa* alga collected from the South China Sea/Hainan province/China. Compound **81** has a C-9 acetate group instead of C-9 OH in **82** (Fig. 12; Table 5).

Compound **82** demonstrated a notable NO production inhibitory potential, compared to **81**, suggesting that the C-9 OH in **82** has a substantial role in the activity. Additionally, **82** effectively prohibited the *in vitro* and *in vivo* release of pro-

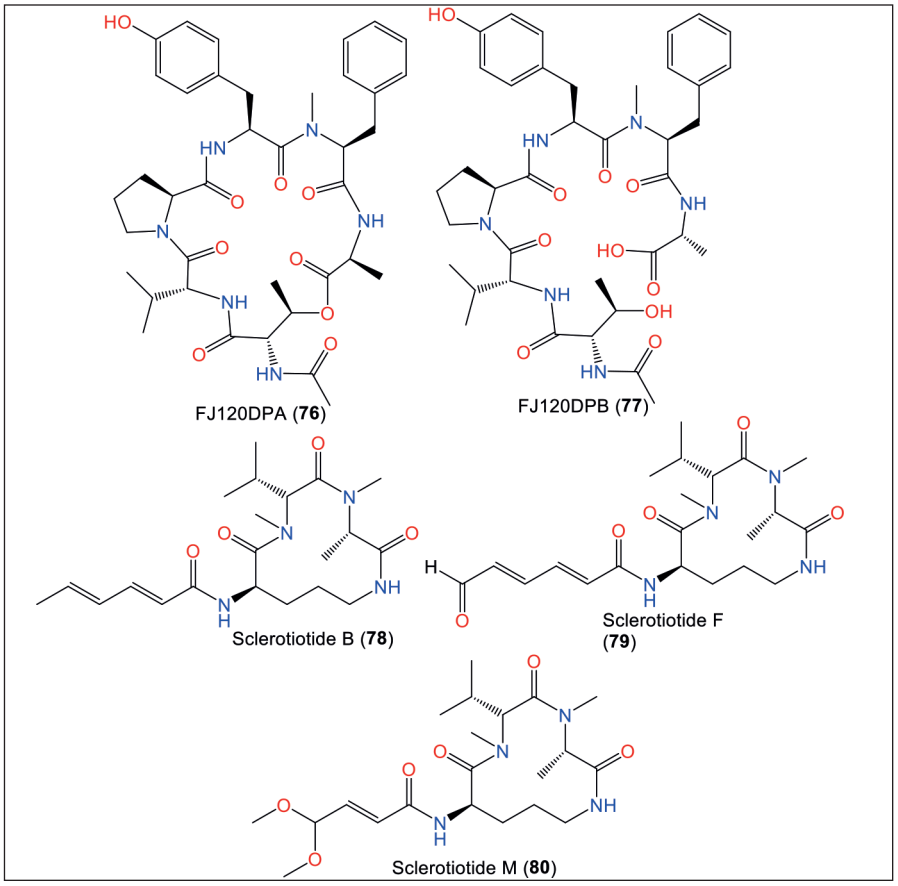

Figure 11. Chemical structures of peptides (**76**–**80**) reported from *Aspergillus ochraceopetaliformis*.

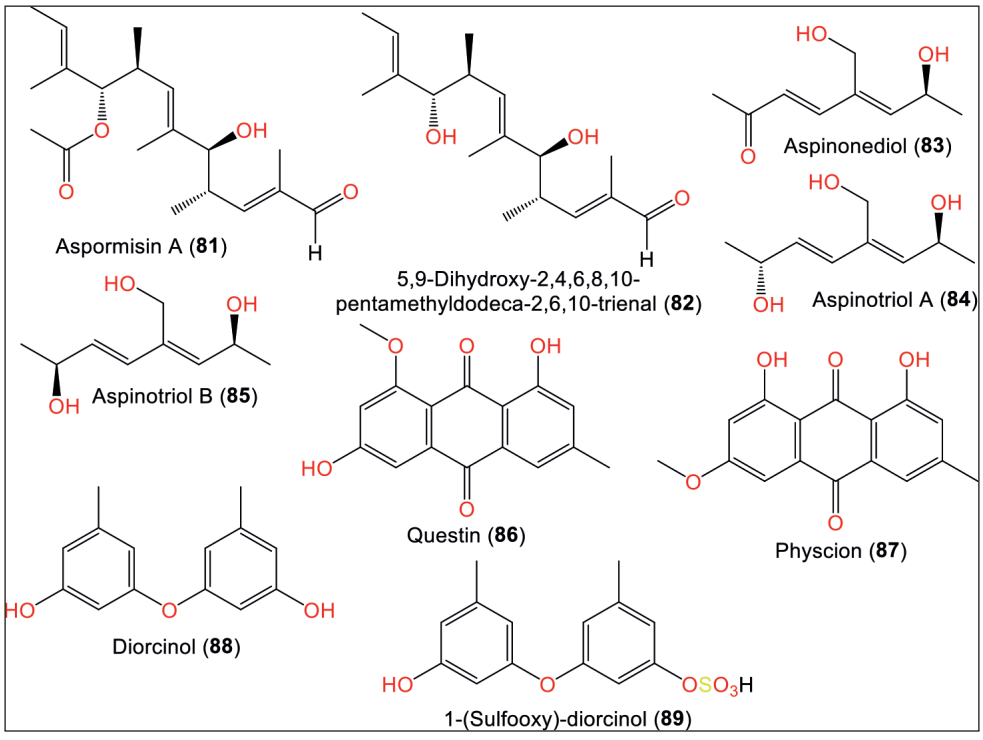

Figure 12. Chemical structures of polyketides (**81**–**85**), anthraquinones (**86** and **87**), and biphenyl ethers (**88** and **89**) reported from *Aspergillus ochraceopetaliformis*.

Table 5. List of polyketides, anthraquinones, diphenyl ethers, and other metabolites isolated from *Aspergillus ochraceopetaliformis.*

Compound name/chemical class	M. wt.	Mol. formula	Strain, host, and location	Ref.
Polyketides				
Aspormisin A (**81**)	322	$C_{19}H_{30}O_4$	*A. ochraceopetaliformis* SCSIO 41020, *Hypnea pannosa* (Alga, Cystocloniaceae), South China Sea, Luhuitou, Sanya, Hainan, China	[30]
5,9-Dihydroxy-2,4,6,8,10-pentamethyldodeca-2,6,10-trienal (**82**)	280	$C_{17}H_{28}O_3$	*A. ochraceopetaliformis* SCSIO 41020, *H. pannosa* (Alga, Cystocloniaceae), South China Sea, Luhuitou, Sanya, Hainan, China	[29]
Aspinonediol (**83**)	170	$C_9H_{14}O_3$	*A. ochraceopetaliformis, Anthurium brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Aspinotriol A (**84**)	172	$C_9H_{16}O_3$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Aspinotriol B (**85**)	172	$C_9H_{16}O_3$	*A. ochraceopetaliformis, A. brownii* (leaves, Araceae), Botanic Conservation Center, Pingtung, Taiwan	[11]
Anthraquinones				
Questin (**86**)	284	$C_{16}H_{12}O_5$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[10]
Physcion (**87**)	284	$C_{16}H_{12}O_5$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[10]
Diphenyl ethers				
Diorcinol (**88**)	230	$C_{14}H_{14}O_3$	*A. ochraceopetaliformis* FJ120, sea sediment, Jeju-do, Korea	[34]
1-(Sulfooxy)-diorcinol (**89**)	310	$C_{14}H_{14}O_6S$	*A. ochraceopetaliformis* FJ120, sea sediment, Jeju-do, Korea	[34]
Other metabolites				
O-Hydroxybenzoic acid (**90**)	138	$C_7H_6O_3$	*A. ochraceopetaliformis, Tethya wilhelma* (Sponge, Tethyidae), Nanao Island, Shantou, Guangdong, China	[30]
P-Hydroxy-phenylacetic acid methyl ester (**91**)	166	$C_9H_{10}O_3$	*A. ochraceopetaliformis, T. wilhelma* (Sponge, Tethyidae), Nanao Island, Shantou, Guangdong, China	[30]
2-(4-Hydroxyphenethyl) acetate (**92**)	180	$C_{10}H_{12}O_3$	*A. ochraceopetaliformis, T. wilhelma* (Sponge, Tethyidae), Nanao Island, Shantou, Guangdong, China	[30]
Isotorachrysone-6-O-α-D-ribofuranoside (**93**)	378	$C_{19}H_{22}O_8$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[10]
Stachyline B (**94**)	236	$C_{13}H_{16}O_4$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
2-Hydroxydiplopterol (**95**)	444	$C_{30}H_{52}O_2$	*A. ochraceopetaliformis* ASAI, soil, Giza, Egypt	[10]
2-ene-Glycyrrhetinic acid (**96**)	452	$C_{30}H_{44}O_3$	*A. ochraceopetaliformis* ATCC 12066, cultured, China	[42]
(*E*)-Methyl-5-methylhexa-3,5-dienoate (**97**)	140	$C_8H_{12}O_2$	*A. ochraceopetaliformis* SCSIO 05702, soil, near the Great Wall station (Chinese Antarctic station), China	[12]
(+)-(9*R*,10*E*,12*E*)-9-Methoxyoctadecadienoic acid (**98**)	310	$C_{19}H_{34}O_3$	*A. ochraceopetaliformis* SCSIO 41020, *H. pannosa* (Alga, Cystocloniaceae), South China Sea, Luhuitou, Sanya, Hainan, China	[30]

inflammatory cytokines (IL-6, MCP-1, and TNF-α) caused by LPS [29]. Hu *et al.* [11] reported the isolation of pentaketides **83**–**85**, which were formerly separated from *Aspergillus ostianus* 01F313 cultured with bromine-modified artificial seawater [41].

Anthraquinones and biphenyl ethers

The anthraquinones, **86** and **87** reported by [10] had weak capacities versus different Gram-positive and -negative bacteria and fungi strains [10]. Park *et al*. [34] reported biphenyl ethers: **88** and its new sulfonated derivative **89** from marine sponge-derived strain. Compound **88** was reported from other *Aspergillus* species such as *Aspergillus nidulans*, *Aspergillus versicolor,* and *Aspergillus tennesseensis*. These compounds displayed no antimicrobial and SrtA and ICL inhibitory activity [34].

Other metabolites

Compounds **90**–**92** were examined for antimicrobial and cytotoxic activities. Compound **92** displayed cytotoxic potential versus B16 (IC_{50} 1.0 µM) in the MTT assay, whereas **91** exhibited weak antimicrobial activity against *Bacillus subtilis*, *Micrococcus luteus,* and *Staphylococcus aureus* (MICs 128 µg/ml) in the microporous plate method [30]. The biphenyl glycoside: **93** and triterpene **95** exhibited powerful antifungal and antibacterial properties (MICs 0.09–0.87 mg/ml) in the agar dilution technique [10] (Fig. 13). From the SCSIO-05702 strain, **94** and **97** were identified [12]. Additionally, **96** was obtained from glycyrrhetinic acid biotransformation using *A. ochraceopetaliformis* ATCC-12066 which has a C-2 and C-3 double bond, instead of the 3-OH group in glycyrrhetinic acid [42].

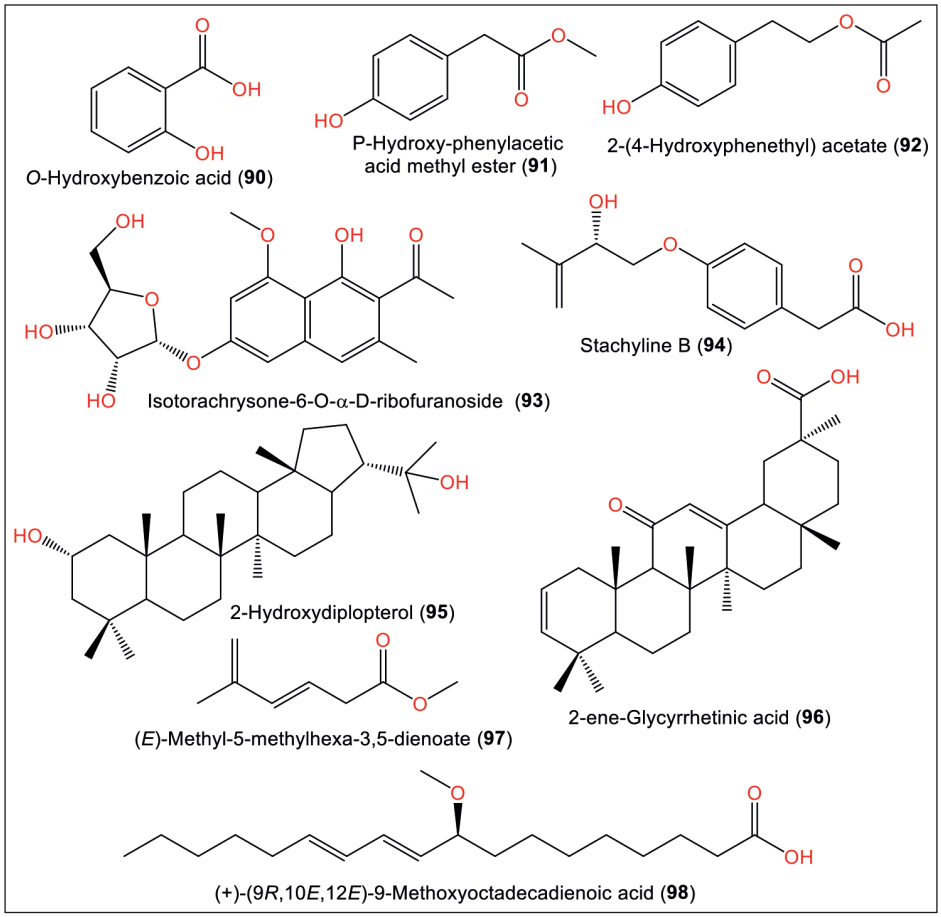

Figure 13. Chemical structures of other metabolites (**90**–**98**) reported from *Aspergillus ochraceopetaliformis*.

BIOLOGICAL ACTIVITIES OF *A. OCHRACEOPETALIFORMIS* EXTRACTS

Abd El-Rahman *et al.* reported that EtOAc extract of MN083316 strain obtained from coral reefs collected from Ein El-Sukhna/Red Sea/Egypt exhibited powerful cytotoxic potential versus Hep-G2 cell line (C_{50} 18.8 µg/ml) [36]. A study by Ramdass and Rampersad [43] revealed that *A. ochraceopetaliformis* isolated from Marac–Moruga mud volcano/South Trinidad possessed the broadest spectrum of oxidation against different tested substrates that completely decolorized methylene blue after 20 days. It was shown to be one of the strains with the highest oil tolerance and biosurfactant production [43]. Pattnaik *et al.* investigated the impact of *A. ochraceopetaliformis* SSP13 on reducing *Pseudomonas aeruginosa* PAO1's QS-regulated virulence factors and biofilm production. The extract was found to prohibit the synthesis of pyocyanin, exopolysaccharides, rhamnolipids, LasA protease, LasB elastase, and chitinase, as well as causing notable changes in *P. aeruginosa* PAO1 motility and biofilm development. In the gas chromatography-mass spectrometry (GC-MS) analysis, 3,5-di-tert butyl phenol, benzaldehyde, 4-ethoxy, 3-benzofuran carboxaldehyde, 2-methoxy, furan, 2,2′-methylenebis[5-methyl], and vermelone were the main bioactive components identified by GC-MS analysis that were linked to the extract quorum sensing attenuating potential by targeting some receptor proteins [44].

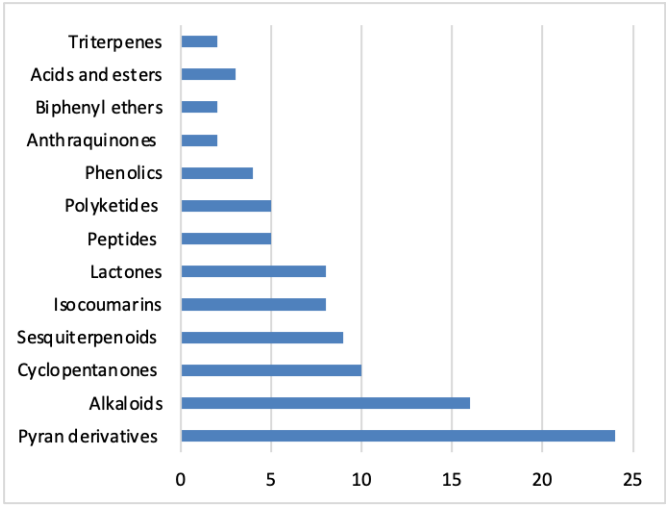

Figure 14. Different classes of compounds reported from *Aspergillus ochraceopetaliformis.*

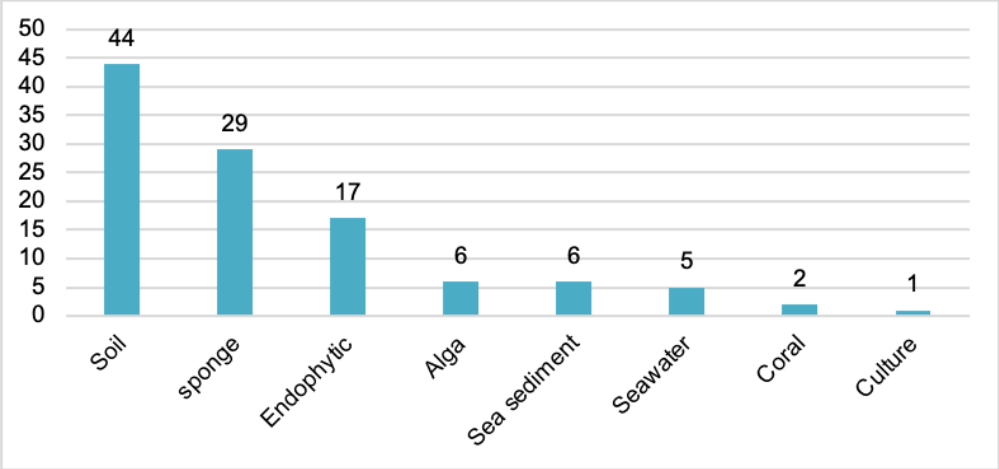

Figure 15. Number of metabolites reported from *Aspergillus ochraceopetaliformis* isolated from different sources.

DISCUSSION AND CONCLUSION

Aspergillus ochraceopetaliformis is a rich source of bioactive compounds with significant chemical diversity. The current review provides a thorough overview of *A. ochraceopetaliformis*, with a varied secondary metabolite profile. This review reveals that the Pyran derivatives represent the most abundant (24 compounds) metabolites, followed by alkaloids (16 compounds) and other classes such as cyclopentanones, lactones, sesquiterpenoids, and isocoumarins (Fig. 14). These metabolites were abundant through diverse environmental habitats, including soil, sponges, endophytes, algae, sea sediment, and seawater. The major number of metabolites were reported from soil-, sponges-, and endophytes-associated strains (Fig. 15).

Multiple studies have shown that the production of *A. ochraceopetaliformis* metabolites majorly driven by biosynthetic gene clusters (BGCs), which encode enzymes such as non-ribosomal peptide synthetases (NRPSs), polyketide synthases, and hybrid pathways [45,46]. Genomic analyses have identified a broad array of BGCs responsible for synthesizing bioactive compounds like diketopiperazines, ochratoxins, and meroterpenoids [47–49]. Recent epigenetic and transcriptomic research further indicates that gene expression within these clusters is regulated by DNA methylation and histone modifications, ultimately influencing metabolite production [50]. Further characterization of these biosynthetic pathways could offer valuable insights for metabolic engineering approaches aimed at producing biologically active high-value compounds.

Among the identified metabolites, lactones 36, 37, and 39 have shown inhibitory effects on superoxide anion production and elastase release. However, their precise molecular targets remain unknown, limiting our understanding of their anti-inflammatory mechanisms. Additionally, variability in culture conditions across studies poses a challenge for comparative analysis. For example, sesquiterpenoids such as ochracenes A–I were only produced in agitated, nutrient-rich fermentation environments, whereas pyran derivatives were obtained under nutrient-deprived conditions—demonstrating the strong impact of environmental factors on metabolite biosynthesis.

Future research should integrate omics-based profiling, molecular docking, and gene knockout techniques to identify specific targets and enhance the efficiency of metabolite production. Additionally, advancements in genetic engineering—particularly CRISPR/Cas-based pathway modifications—could significantly boost the production of valuable metabolites like alkaloids and diketopiperazines, increasing their pharmaceutical potential. Addressing these knowledge gaps will improve our understanding of the metabolites produced by *A. ochraceopetaliformis* and their therapeutic applications. In conclusion, *A. ochraceopetaliformis* is a promising source of bioactive compounds with notable biological activities, and further investigation may uncover new treatments for a variety of diseases.

LIST OF ABBREVIATIONS

A-549, human lung adenocarcinoma epithelial cell line; B16, mouse melanoma cell line; BEL-7042, human hepatocellular carcinoma cell line; BXPC-3, human pancreas adenocarcinoma cell line; CCK-8, cell counting kit-8; DU145, human prostate carcinoma cell line; ECD, electronic circular dichroism; EtOAc, ethyl acetate; EV, extracellular vesicles; fMLP, N-formyl-L-methionyl-L-leucyl-L-phenylalanine; GC-MS, gas chromatography mass spectrometry; HepG2, human hepatocellular liver carcinoma cell line; HeLa, human cervical epitheloid carcinoma cell line; HL-60, human promyelocytic leukemia cell line; HMEC-1, human microvascular endothelial cell line; HPAC, human pancreatic adenocarcinoma cell line; HPLC, high-performance liquid chromatography; HT-29, human colon cancer cell line; ICL, isocitrate lyase; IL-6, interleukin-6; K-562, human erythroleukemic cell line; LPS, lipopolysaccharide; MCF-7, human breast adenocarcinoma cell line; MCP-1, monocyte chemoattractant protein-1; MDA-MB-231, human breast cancer cell line; MIC, minimum inhibitory concentrations; MTT, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MVBs, multivesicular bodies; NO, nitric oxide; NOESY, nuclear overhauser

effect spectroscopy; RP-18 CC, reversed phase-18 column chromatography; SGC-7901, human gastric adenocarcinoma cell line; SrtA, sortase A; THP-1, human monocytic cell line; TNF-α, tumor necrosis factor alpha; U937, pro-monocytic, human myeloid leukaemia cell line.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

CONSENT FOR PUBLICATION

All authors have read and approved the final manuscript.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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