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Review Article

# Unearthing the Potential Fungal Bioactive Secondary Metabolites from the Red Sea: A Comprehensive Review

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## ABSTRACT

The Red Sea represents a potential ecosystem with very rich biodiversity in the production of unique natural compounds. Recently, fungal secondary metabolites have been a major domain of research in the meadow of natural compounds with special emphasis on fungal strains isolated from marine ecosystems. More than 150 interesting secondary metabolites going with different classes of natural compounds had been reported with potential biological actions as cytotoxic activity with emphasis on the application of different approaches for example OSMAC ( one strain many compounds ) approach. The current review presents a comprehensive report for fungal secondary metabolites isolated from the Red Sea ecosystems either as endophytes from marine invertebrates (for example corals and sponges) and plants for example (algae and mangroves) or as free-living strains collected from sea sediments from different locations of Red Sea. Different databases had been utilized including the EKB (Egyptian Knowledge Bank), SciFinder, and MarinLit. In no doubt, the richness of published data directs to the marine fungi's medicinal potential. It will continue to be challenging to incorporate marine fungus into traditional therapy. The clinical environment demonstration of therapeutic activity is a fundamental task for medical research. For the profit of patients all through the world, it is to be wished that this significant barrier will be removed in the years to come.

**Keywords:** *Red Sea; Fungal endophytes; Biological activity; Natural products; OSMAC.*

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## 1. Introduction

The creation of new drugs may benefit from the abundant supplies of bioactive secondary metabolites found in marine habitats, thousands of outstanding novel bioactive molecules have been identified from different marine resources **[1]**, many of them acting as drug leads in the course of discovery of anti-cancer, antimicrobial, immunosuppressive, anti-biofilm, anti-inflammatory drug candidates, among others **[2]**.

Research in the field of Sea bioactive secondary compounds, mainly from marine invertebrates, has been confronted with many obstacles, mainly, the scarcity of the organisms, and the limitations of collections of endangered species added to the very low yield of active metabolites **[3]**. Although the chemical synthesis of interesting metabolites can provide a solution to these obstacles, however, in many cases, it is not the ideal solution. Endosymbionts could be regarded as an important alleviation of these obstacles, taking into consideration the cross interaction between the biosynthetic pathways between the host and the endosymbionts, where in many cases the host organism is not the actual

producer of the metabolite of interest, or at least the symbiotic micro-organism can provide the host with valuable chemical defense means with interesting biological activities **[4]**.

As a result of their potential to create a huge variety of bioactive secondary metabolites, marine-derived fungi have drawn a lot of attention for drug discovery during the past 20 years **[5]**. with thousands of interesting secondary metabolites being identified revealing potential biological and pharmacological properties **[6, 7]**. Anthraquinones, terpenes, peptides, and steroids are the interesting molecules yielded from marine-derived fungi **[8-11]**.

The Red Sea has a distinctive maritime ecosystem with numerous varied coral reefs displaying high variety along its almost 2,000-kilometer length and nearly 16 degrees of latitude **[12]**. The Red Sea is home to a wide variety of species that have yet to be properly characterized and categorized. This biodiversity has inspired chemists and others to investigate the connections and interactions between corals and other species and to create new marine biotechnology applications, such as the potential future discovery of novel medications, enzymes, and nutraceuticals from cultivable marine microbes **[13]**.

Hundreds of outstanding molecules had been isolated from the Red Sea marine ecosystems, including, but not limited to, terpenes, alkaloids, depsipeptides, macrolides, polyacetylenes, polyketides sterols, steroidal glycosides among others **[2, 14-17]**.

In this report, bioactive secondary metabolites isolated from the Red Sea-derived fungi spanning the period from 2000 to 2022 have been highlighted with emphasis on the interesting biological activities of the identified metabolites. Many databases were screened in writing this manuscript, including scifinder®, Egyptian knowledge bank "EKB", and MarinLit®, in addition to relevant review articles **[14, 18-21]**.

## 2. Chemical and Biological Review of Red Sea-Derived Fungal Endophytes

### 2.1. *Aspergillus* sp

Chemical analysis of the extract of ethyl acetate of the culture broth of *A. versicolor* isolated from the internal parts of the green algae *Halimeda opuntia* collected from Ras Muhamed (South Sinai) resulted in the isolation of the six anthraquinone derivatives (**1-6**), isocoumarin (**7)** and sesterterpene derivative (**8**). The isolated compounds were identified as Isorhodoptilometrin-1-methyl ether; 3-(2-Hydroxypropyl)-1-methyl ether-6,8-dihydroxy-9,10-anthraquinone (**1**), Emodin (**2),** Methyl-emodin(**3**), Evariquinone **(4)**, 7-Hydroxyemodin 6,8-methyl ether **(5),** Arugosin C **(6), Sider** in **(7)** and Variculanol **(8).** Compounds **1** and **7** showed adequate antimicrobial activity against B. subtilis, whereas compounds 2 and 3 showed moderate selective inhibitory action against HCV protease with $IC_{50}$ 22.2 and 40.2 $\mu g$/mL **[22]**.

The fungus taken from the Red Sea sponge *Spongia officinalis* was recognized as *A. versicolor* and yielded 8 known microbial polyketide secondary metabolites as in the example of (–)-Curvularin (**9**) and DKPs (Cyclodipeptides) or as compounds **10–15**. (–)-Curvularin (**9**) is the fungal metabolite originally isolated from *Penicillium sp* **[23]**. Instead, the DKPs **10–15** were selected before from diverse microbial sources and identified as Cyclo(L-Pro-LIle) (**10**), Cyclo(L-Tyr-L-Pro) (**11**), Cyclo(L-Phe-LPro) (**12**), Cyclo(L-Phe-4-hydroxy-L-Pro) (**13**), Cyclo(L-Try-L-Phe) (**14**) [20, 24, 25], and the cyclic Tetrapeptide cyclo-(phenylalanyl-prolyl-leucyl-prolyl) (**15**), which was selected before from *Pseudoalteromonas sp* **[26]**. Moreover, 2-Methyl-L-arginine (**16**) is a well-

known Streptomyces metabolite **[20]**.

Fractionation of the ethyl acetate extract of the endophyte *A. flavipes* culture broth DY001 selected from the internal parts of the Red Sea tunicate *Didemnum sp.* resulted in the isolation of two diketopiprazine alkaloids (**17-18**) and two Isocoumarin derivatives (**19-20**). The isolated compounds were identified as Asperopiprazines A and B (**17-18**), +-Citreoisocoumarin (**19**), and (-)-6,8-di-O-methylcitreoisocoumarin (**20**). Compounds **17-20** were evaluated for their antimicrobial as well as cytotoxic activities, where compounds **17-18** revealed adequate antibacterial action against *E.coli* and *S.aureas*, whereas compounds **17-20** showed potent to adequate cytotoxic action against HCT-116 cancer cell lines that have $IC_{50}$ values 15.1, 16.2, 19.3, 17.2 $\mu$M, respectively together with moderate activity against MDA-MB-113 cell lines and no activity against Hela cell lines, suggesting selectivity against human colon cancer cell lines **[27]**. Marine sediments from the Canyons of Dahab, Red Sea had yielded the fungus *A. falconensis*, and chromatographic examination of the ethyl acetate extract of its solid rice fermentation media had yielded 11 azaphilone derivatives (**21-29**). Interestingly, applying the OSMAC approach (One strain with many compounds) resulted in the diversity of the isolated compounds, where the fungal strain was fermented on Rice medium supplied with either 3.5% NaCl or 3.5% NaBr. NaCl supplied medium had resulted in the isolation of new chlorinated derivative Falconensins O and P (**21-22**), together with the identified Falconensins (**23-24)** A, M, N, and H, respectively, on the other hand NaBr enriched media had given rise to in the isolation of two new brominated derivatives Falconensin Q (2**5)** and Falconensin R (**26**), and the new non-halogenated Falconensin S (**27**) together with the known derivatives Falconensin K (**28**) and Falconensin I (**29**). Compounds 2**1**, 2**3**–2**7**, and **29** were tested for their ability to reduce inflammation in a triple-negative cell line of breast cancer. were estimated for their anti-inflammatory action on the triple-negative breast cancer cell line NF-kB-MDA-MB-231 revealing potent to moderate anti-inflammatory activity, with Falconensin Q (**25)** being the most potent showing $IC_{50}$ 11.9 $\mu$M without cytotoxicity **[28]**. The same research group had informed additional metabolites from the same fungal strain *A. falconensis* cultivated on solid rice medium with the addition of salts 3.5 % NaCl or $(NH_4)_2SO_4$, where eight diverse polyketides had been isolated from the NaCl-containing medium including the new dibenoxepin derivative Aurgosin O (**30**) and the new Isocoumarin 2-(8-Hydroxy-6-methoxyisochromen-3′-yl) acetic acid (**31**) along with the six known polyketides Arugosin C (**32**), Dichlorodiaportin (**33**), Desmethyldiaportinol (**34**), Question (**35**), Diorcinol (**36**), and 4-Hydroxybenzaldehyde (**37**). On the other hand, the $(NH_4)_2 SO_4$-containing medium had directed the fungal strain to produce additional metabolites namely, Sulochrin (**38**), Monochlorosulochrin (**39**) and Dihydrogeodin (**40**). Isolated compounds **30-40** has been evaluated for their cytotoxicity using human DNA topoisomerase II (TOP-2), *in silico* (molecular modelling) utilizing matrix metalloproteinase 13 (MMP-13), and human cyclin-dependent kinase 2 (CDK-2) where compounds **36-39** revealed significant stability and activity within the active pocket of CDK-2, *in vitro* cytotoxic assay using mouse lymphoma cell lines compound **38** showed potent cytotoxicity at $IC_{50}$ of 5.1$\mu$M **[29]**.

The calcium chelating complex Coumamarin (**41**) along with 4 known compounds Diorcinol (**42**), Violaceol I (**43**), and Hydroxysydonic acid (**44**) were selected from the methanolic extract of *A. sydowii* fungus ASTI derived from a sample of marine water taken from Tiran Island, the Red Sea. Compound **41** represents the first calcium

coumarin complex to be isolated from nature, showing potent antibacterial activity against *Bacillus subtilis* with no cytotoxicity against the cell line of human cervix carcinoma (KB-3-1) **[30]**.

Orfali et al. reported an unprecedented cytochalasan alkaloid, Asporychalasin (**45**) from the rice fermentation medium of *A.oryzae* isolated from marine sediment from the Red Sea, Jeddah. Compound **45** revealed a unique 6/6/11 tricyclic nucleus and the 14,16,18-trimethylated Cycloundecane ring C not known for the previously isolated Cytochalasan. Compound **45** was assessed contrary to a board of cancer cell lines, where it revealed cytotoxicity against cancer cells A549, MCF-7 & and HepG2 with $IC_{50}$ 8.8, 7.4 & and 8.3 $\mu g$/mL **[31]**.

The same research group had stated the isolation and identification of two illudalane sesquiterpenes **46-47** from the same fungal strain *A.oryzae*. The compounds were identified as Asperorlactone (**46)** and Echinolactone D (**47)**. two identified pyrones, 4-(hydroxymethyl)-5-hydroxy-2*H*-pyran-2-one (**48**) and its acetate (**49)**. Compound**s 46** and **47** exhibited small cytotoxic actions against A-549 cancer cell lines. It is noteworthy to mention that this was the first report for illualane type sesquiterpenes from Ascomycetes **[32]**.

Elissawy et al. stated the isolation and identification of secondary compounds from the derived fungus *Aspergillus sp*. AV-2 is isolated from the fresh leaves of *Aviceenia marina* collected from Hurghada, the Red Sea. The chemical investigation had headed to the isolation of 15 compounds, along with one novel Phenylpyridazine derivative compound (**50**), Peroxy-pernylated benzaldhyde derivative Dioxoauroglaucine (**51),** among the known derivatives Tetrahydroauroglaucin (**52**), Isotetrahydroauroglaucin (**53**), Flavoglaucin (**54**), Isodihydroauroglaucin (**55**), 2-(2,3-epoxy-1,3,5-heptatrienyl)-6-hydroxy-5-(3-methyl-2-butenyl)benzaldehyde(**56**), Parahydroxybenzaldehyde (**57**) together with the known Indole-diketopiprazine derivatives Echinulin (**58**), Neoechinulin B (**59**), Isoechinulin B (**60**), Variecolorin J (**61**) Neoechinulin E (**62**), Cryptoechinulin B (**63**), Cryptoechinulin D (**64**). Isolated compounds were evaluated for their cytotoxicity against Caco-2 cell lines, where Isodihydroauroglaucin (**55)** showed potent activity with an $IC_{50}$ value of 2.87 $\mu$M **[33] (Fig. 1.).**

### 2.2. *Alternaria sp*

Inquiry of the fungal ethyl acetate extract of endophyte *Alternaria* sp. LV52 isolated from the Red Sea algae internal tissue *Cystoseira tamariscifolia* gained from Nabq-bay, had run to the isolation and identification of five polyketide compounds (**65-69**), identified as Alternariol (**65**), Alternariol-9-methyl ether (**66**), Altertoxin I (**67**), Altertoxin II (**68**) and Tenuazonic acid (**69**). The isolated compounds had been evaluated for their antimicrobial activities, where compound **69 (**Tenuazonic acid) displayed significant antibacterial activity against *P. aeruginosa*, on the other hand, the other compounds (**65-68**) displayed weak activities. **[34]**.

Another strain of *Alternaria* had been reported by Hawas et al., where they investigated the culture broth of *A. alternata* selected from the oft-coral *Litophyton arboretum* gained from the Gulf of Suez, the Red Sea. The authors isolated Alternariol-9-methyl ether-3-O-sulphate (**70**), Alternariol-9-methyl ether (**71**), Alternariol (**72**), Maculosin (**11**) and Maculosin-5 (**104**). The selected compounds were assessed for their antiviral, antimicrobial, and cytotoxic activities, where **70** and **71** showed less antiviral activity against HCV protease with $IC_{50}$ 52, 32, and 12

*μg*/mL, respectively, indicating the importance of free hydroxyl groups for the potent activity. Instead, compound **70** presented potent antibacterial activity against *B. cereus*, whereas compounds **71** and **72** showed moderate activity against *B. megaterium* **[35] (Fig. 2.)**.

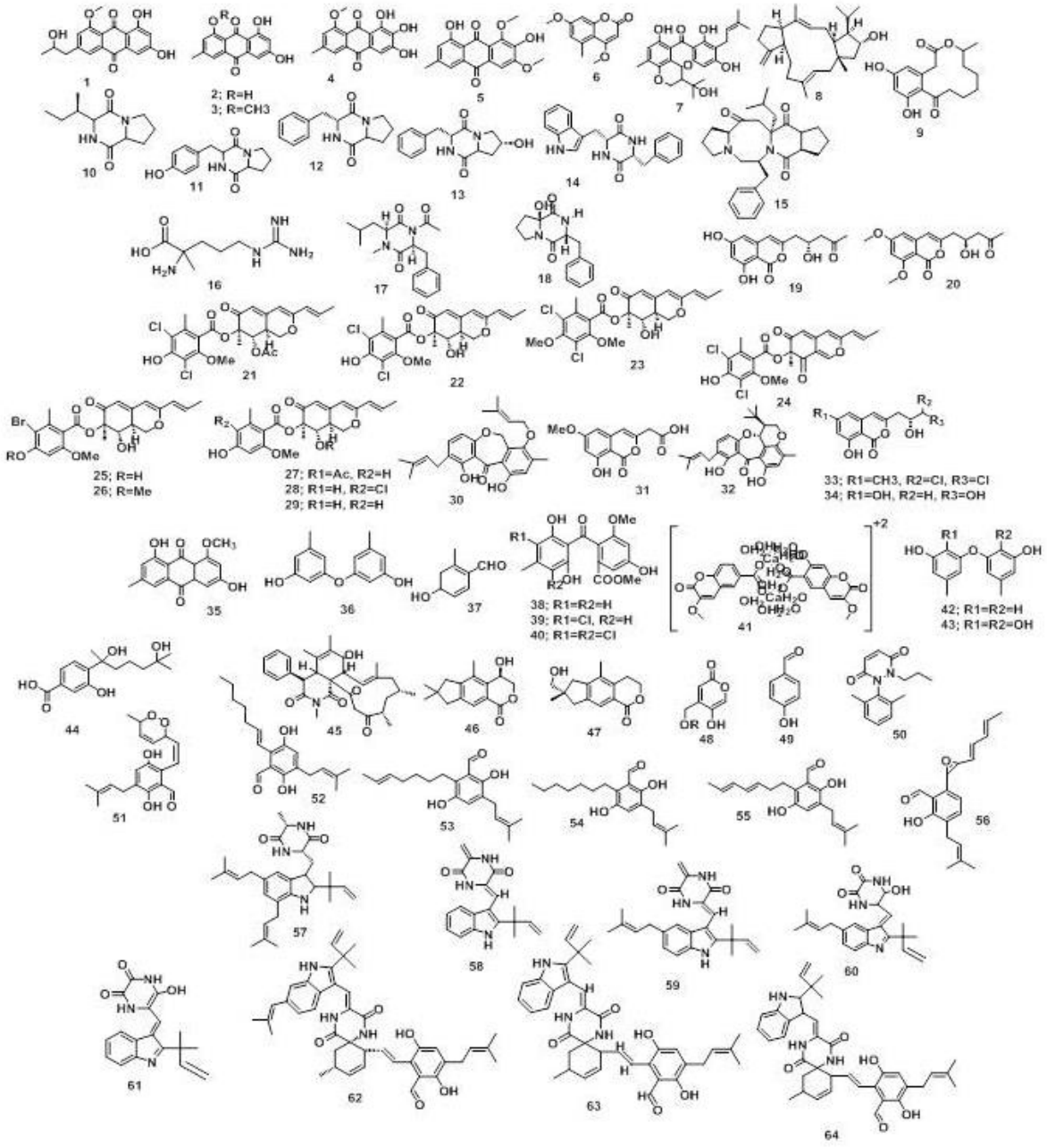


**Fig. 1.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of *Aspergillus* sp

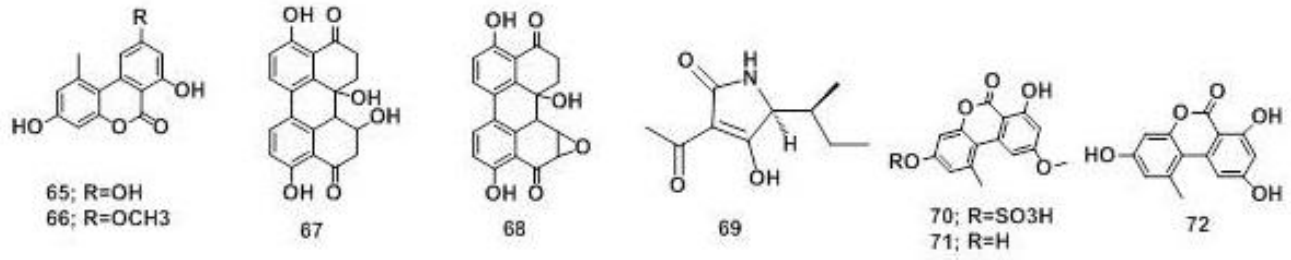


**Fig. 2.** illustrates the chemical structures of the secondary metabolites isolated from different Red Sea strains of *Alternaria sp*

### 2.3. *Cladosporium sp*

Gesner et al. had conveyed the isolation of two diastereoisomeric hexapeptide lactones, namely, Pandagolide 1a (**73**) and Pandagolide 1 (**74**), together with Isocladospolide B (**75**) from the marine-derived fungal endophyte *Cladosporium sp* ethyl acetate extract selected from the internal parts of the Red Sea sponge Niphates rowii gained from the Gulf of Aqaba, Red Sea. Differentiation between **73** and **74** was mainly based on Riguera's method and circular dichroism **[36] (Fig. 3.)**.

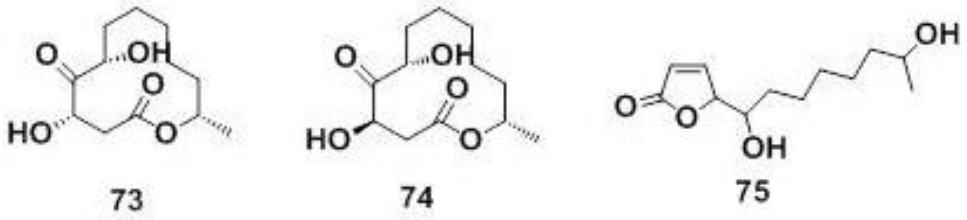


**Fig. 3.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of *Cladosporium* sp

### 2.4. *Chrysosporium sp*

Le Goff et al. studied the effect of different culture media on the assembly and yield of secondary metabolites from the endophytic fungus *C. lobatum* TM-237-S5 secluded from the internal tissues of the Sponge *Acanthella cavernosa* gained from the Gulf of Aqaba, the Red Sea. The authors applied a recent technique in the cultivation enhancing the yield of secondary metabolites from the culture media through pairing solid-state extraction (SSF/SSE) and solid-state fermentation with XAD Amberlite resin, applying different culture media including potato dextrose agar (PDA), potato dextrose broth (PB), marine broth (MB) and marine agar (MA). PDA revealed the most suitable medium in terms of the quantity and quality of the produced metabolites. Ten phenalenone derivatives had been isolated (**76-85**), the isolated compounds were identified as Peniciphenalenin D (**76**), Isoconiolactone (**77**), Coniolactone (**78**), (-)-Peniciphenalenin F (**79**), (+)-8-Hydroxyscleroderolide (**80**), (-)-7,8-Dihydro-3,6-dihydroxy-1,7,7,8-tetramethyl-5H-furo-[2',3':5,6] Naphtho[1,8-bc]furan-5-one (**81**), (+)-Scleroderolide (**82**), (+)-8-Hydroxyslerodin (**83**), Coniosclerodin (**84**), (+)-Sclerodin (**85**). It is noteworthy that the SSF/SSE technique represents a very valuable, recent, and eco-friendly technique in microbial cultivation with high recovery of the secondary metabolites while minimizing the use of solvents **[37] (Fig. 4.)**.

### 2.5. *Epicoccum sp*

Chemical investigation of the fungal endophyte *E. nigrum* M13 was derived from the internal tissues of the seagrass *Thalassia hemprichii* gained from Hurghada, The Red Sea, which led to in the selection and identification of six secondary metabolites namely, the cyclic tripeptide epicotripeptin **86** together with the cyclic dipeptides Cyclo(L-pro-L-val) **87,** cyclo (L-pro-L-Ileu) **88,** Cyclo (L-pro-L-tyr) **89,** Cyclo (L-pro-L-phe) **90** and the Acetamide N-(2-phenyl ethyl acetamide) **91.** Isolated compounds were established for their antimicrobial activity, where compound **89** revealed potent antibacterial action against gram-negative bacteria with a MIC value of 2.5 $\mu g$/mL towards *S. aureus*, similarly, compounds **89** and **90** exposed moderate activity with MIC of 10 $\mu g$/mL. Compounds **86, 88,** and **89** showed selective moderate biofilm inhibitory activity against biofilm-forming gram-positive isolates with no activity against gram-negative strains **[38] (Fig. 5.)**.

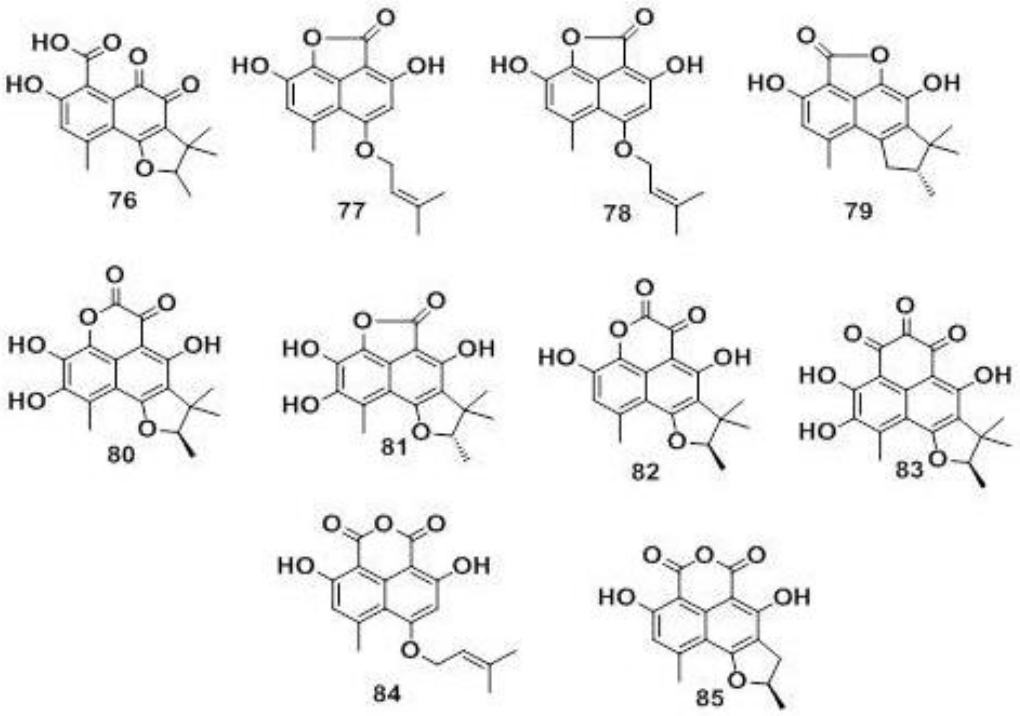


**Fig. 4.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of *Chrysosporium* sp

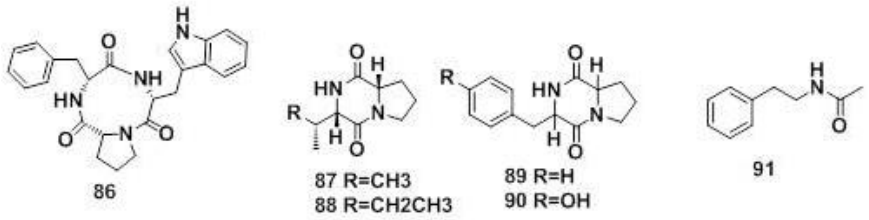


**Fig. 5.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of *Epicoccum* sp

### 2.6. *Fusarium sp.*

Two new highly oxygenated pyridine

alkaloids (**92-93**) had been obtained from the fermentation broth's ethyl acetate extract of the fungal endophyte *Fusarium sp*. selected from the internal parts of the Red Sea sponge *Suberea mollis*. The alkaloids were identified as Fusaripyridine A (**92**) and B (**93**), the isolated compounds revealed an extraordinary 1,4-bis(2-hydroxy-1,2-dihydropyridin-2-yl)butane-2,3-dione backbone first reported in Nature. Compounds **94** and **11** were assessed for their antimicrobial effects against a board of gram-positive and gram-negative bacteria in addition to pathogenic fungi, where they showed effective choosy antifungal activity against *C. albicans* with MIC value 8 $\mu$M for both compounds, Moreover both compounds showed no cytotoxicity on Hela cell lines **[39]**.

The Endophytic fungal strain, *F. equiseti* was selected from the internal part of the brown alga *Padina pavonica*, from the Red Sea. The extract of the liquid culture was assessed for its inhibition NS3-NS4A protease of hepatitis C virus (HCV) revealing high level inhibition ($IC_{50}$ 27.0 $\mu g$/mL); Bioassay directed fractionation of the ethyl acetate extract of the fungus culture broth discovered seven identified metabolites (**94-99**) known as Cyclo-L-Ala-L-Leu **(94),** Cyclo(L-Tyr-L-Pro) **(11),** Cordycepi (3'-Deoxyadenosine; 9- cordyceposidoadenosine; Adenine cordyceposide) **(95),** Ara-A (Adenosine; spongouridine; Adenine 9-N-βarabinofuranoside) **(96),** Chrysophanol (1,8-Trihydroxy-3-methylanthraquinone) **(97)**, ω-Hydroxyemodin (1,3,8-Trihydroxy-6-hydroxymethylanthraquinone) **(98),** Communiol D **(99)**. Using positive control HCV NS3 protease inhibitor 2, the selected compounds from the EtOAc extract were examined for their inhibition efficacy against HCV PR. These isolated substances have shown some powerful anti-HCV NS3-NS4A protease activity with $IC_{50}$ values from 10.7 to 58.3 $\mu g$/mL, related to their EtOAc extract with $IC_{50}$ value of 27 $\mu g$/mL. Compounds **94** and **95** showed the most potent inhibitory effect with $IC_{50}$ values of 18.20 and 10.7 $\mu g$/ml, respectively, while Adenosine compounds **95** and **96** exhibited mild inhibitory with an $IC_{50}$ value of 24.5 and 22.3 $\mu g$/mL, respectively. Compounds 82, **97,** and **99** were quiet with no activity as inhibitors of HCV PR as related to other components **[40]**.

The same research group had reported additional metabolites from *F.equiseti* applying the OSMAC approach using different culture media, the metabolites were identified as Cyclo-l-Ala-l-Leu (**95**), Cyclo(l-Pro-l-Val) (**100**), Uracil (**101**), Thymine (**102**), cyclic Tetrapeptidecyclo[Phenylalanyl-Pro-Leu-Pro] (**103**), 17-Demethyl-2,11-dideoxy-rhizoxin (**104**), Ergosterol peroxide (**105**), Ergostra-5,7-dien-3β-ol (**106**), β-Sitosterol 3-*O*-β-glucoside(**107**), Bis(2-ethylhexyl)phthalate (**108**), 5-Chloro-3,6-dihydroxy-2-methyl-1,4-benzoquinone (**109**), Griseoxanthone C (**110**). *F. equiseti* metabolites from the culture biomalt-peptone showed worthy inhibition of HCV protease with $IC_{50}$ range from 19 to 77 $\mu$M. The selected metabolites Griseoxanthone C (**110**) and Cyclo(l-Pro-l-Val) demonstrated strong anti-HCV NS3/4A protease activity, with $IC_{50}$ values of 19.8 and 23.2 $\mu$M, as opposed to its crude extract, which had an $IC_{50}$ of 56 $\mu g$/mL. The compounds 17-Demethyl-2,11-dideoxy-rhizoxin (**104**), 5-Chloro-3,6-dihydroxy-2-methyl-1,4-benzoquinone (**109**), and cyclic Tetrapeptidecyclo-[Phenylalanyl-pro-leu-pro] (**103**), exhibited a slight inhibition effect with $IC_{50}$ values of 29.4, 34.4, and 35.1 $\mu$M, correspondingly, while further compounds

**95**, **102**, **106** and **107** were quiet inactive for the inhibition of HCV PR as matched to other components **[41] (Fig. 6.)**.

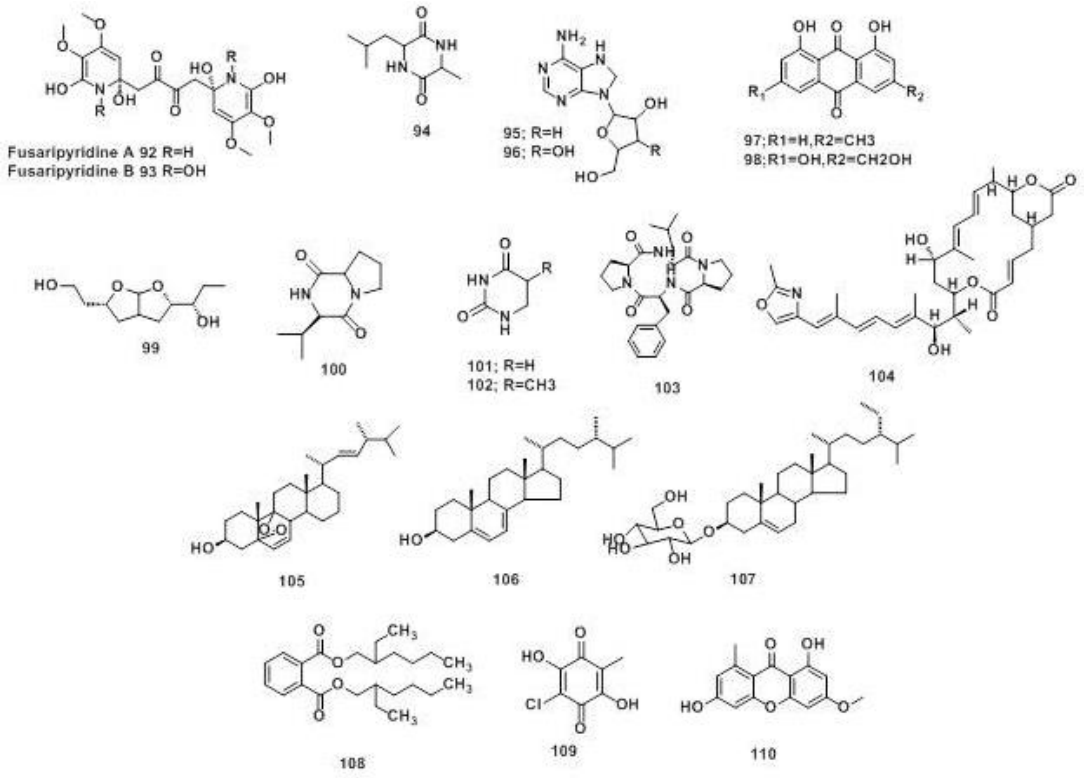


**Fig. 6.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of *Fusarium* sp.

### 2.7. *Penicillium sp.*

The endophyte *P.aculeatum* isolated from the red algae *Laurencia obtuse* from Suez Gulf, the Red Sea, had yielded two new Sulfonyl derivatives **111-112,** together with one sulfuated benzoic acid derivative (**113**), two steroidal compounds (**114-115**) and one dimeric Naphthopyrone (**116**). The isolated compounds were identified as Pensulfonoxy A and B (**111-112**), P-bromothiobenzoic acid **(113**), Ergosta-5,7,22-triol (**114**), Helvolic acid (**115**) and Fonsecinone A (**116**). Isolated compounds as well as the crude extract were assessed in comparison to a board of cancer cell lines. where compound **112** displayed effective cytotoxicity against MCF-7 and HCT 116 cell lines with $IC_{50}$ 2.18 and 6.12 $\mu$M, respectively, and compound **111** displayed moderate cytotoxicity against HCT 116 with $IC_{50}$ 5.23 $\mu$M **[42]**.

In an interesting study, Elhady et al. reported the therapeutic potential of the alkaloid Meleagrin (**117**) selected from the liquid culture ethyl acetate extract of the fungus *P. Chrysogynum* S003 derived from the sea sediment collected from the Red Sea, Saudia Arabia. The authors reported the potent protective effect of meleagrin against Bleomycin induced lung fibrosis in rats with the restoration of the antioxidant markers balance and activation of the antioxidant signaling pathways, moreover, it revealed the ability to decrease the release of pro-inflammatory cytokines and to delay the bleomycin-induced apoptosis **[43]**.

A new cerebroside, LAMA-1 (**118**), along with Kojic acid (**119**) had been selected and identified from the liquid culture ethyl acetate

extract broth of *P. chrysogynum* S003, resulting from deep-sea sediment collected from the Red Sea. The isolated compounds were verified for their cytotoxicity against a board of cancer cell lines including A-549, DU-145, MCF-7, and HepG-2 cell lines, where they revealed weak cytotoxic activity against all the tested cell lines **[44]**. Additional cerebrosides, namely, Penicillosides A and B (**122-123**), had been reported by Youssef et al. Compounds **122-123** were selected from the organic extract of the fungal endophyte *Penicillium sp.* isolated from the inner parts of the Red Sea tunicate *Didemnum sp.* **122** and **123** were assessed for their antimicrobial actions against a Gram-positive bacterium (*Staphylococcus aureus* ATCC 25923), a Gram-negative bacterium (*Escherichia coli* ATCC 25922), and yeast (Candida albicans ATCC 14053) using agar diffusion method. Accurately measured 0.1 ml (100 µg dissolved in DMSO) of each compound were inserted in the cups and then incubated at 37 °C for 24 h. The inhibition zones were measured and compared with the reference antibiotics and antifungal drugs; ampicillin, imipenem, and clotrimazole (each of 10 µg/disc giving 30, 30, and 40 mm inhibition zone respectively). Both compounds revealed no cytotoxicity when evaluated against Hela cancer cell lines **[45]**.

The fungal strain *Penicillium sp.* MMA had been cultured from the internal tissues of the soft coral *Sarcophyton sp*. of the fungus ethyl acetate extract had led to the selection of the quinoline alkaloid veridicatol **124**, the tricyclic diketopiperazine alkaloid Aurantiomide C **125,** along with the sesquiterpene Aspterric acid **126**. The isolated compounds had been subjected to variable biological screening. The antimicrobial evaluation revealed that compound **126** was the most effective against *B. subtilis* and *P. aeruginosa*. Regarding the antioxidant activity compound **125** showed the most potent activity with maximum DPPH scavenging activity (75%), meanwhile, both compounds **124** and **125** revealed potent cytotoxicity against MCF-7, HepG-2, and HCT 116 cancer cell lines **[46] (Fig. 7.)**.

### 2.8. *Scopulariopsis sp*

The *Scopulariopsis sp* fungal strain ST-F1 selected from the internal parts of the *Stylophora sp.* hard coral collected from the Gulf of Suez, the Red Sea, demonstrated to be a fertile home of various secondary metabolites. In two different reports, El-Naggar et al. described the isolation and identification of more than 40 compounds belonging to different classes of natural products including polyketides, sesquiterpenes, triterpenes, alkaloids, and depsipeptides. The authors applied the OSMAC approach changing the culture media with significant variation in the metabolic profiles between the rice and white beans culture media.

Utilizing rice media, 27 different natural products had been identified including eleven xanthones 12-Dimethoxypinselin (**127**), 12-O-acetyl-AGI-B4 (**128)**, AGI-B4(**129**), Huperxanthone C(**130**), Pinselin (**131**), Sydowinin B (**132**), 13- O-acetylsydowinin B(**133**), 2,11-dihydroxy-1-methoxycarbonyl-9-carboxylxanthone(**134**), Sydowinin A (**135**), 8-(methoxycarbonyl)- 1-hydroxy-9-oxo-9H-xanthene-3-carboxylic acid (**136**), Methyl-3,8-dihydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylate (**137**), in addition to five phenolic terpenoids including Sydowic acid (**138**), Sydonic acid (**139**), 11- Hydroxysydonic acid (**140**), 11,12-dihydroxysydonic acid (**141**), 1-Hydroxyboivinianic acid (**142**), one tri-phenolic derivative Rikuzenol (**143**), five nitrogenous compounds Scopulamide (**144**), Lumichrome (**145**), WIN 64821 (**146**), Scopularide A (**147**), and Scopularide B (**148**), and three polyketide derivatives Scopupyrone (**149**), Pyrenochaetic acid A (**150**), 7-Hydroxy-2,5-dimethylchromone

(**151**) **[47]**.

On the other hand using wheat beans as a culture media yielded 17 different natural products including 5 triterpenes 3β,7β,15α,24-Tetrahydroxyolean-12-ene-11,22-dione (**152**), 15α,22β,24-Trihydroxyolean-11,13-diene-3-one (**153**), 7β,15α,24-Trihydroxyolean-12-ene-3,11,22-trione (**154**), 15α,24-Dihydroxyolean-12-ene-3,11,22-trione (**155**) Soyasapogenol B (**156**), in addition to two sesquiterpenes 2E, 4E)-4′-Dihydrophaseic acid (**157**), (2Z, 4E)-4′-Dihydrophaseic acid (**158**), one naphtoquinone 6-Hydroxy-2,7-dimethyl-1,4-naphthoquinone (**159**), two chromenes 6-Hydroxy-2,2-dimethyl-2H chromene (**160**), Scoparone (**161**) in addition to the seven nitrogenous compounds 5-Methyluracil (**162**), 4-Hydroxy- 3-methoxy-2(1H)-quinolinone (**163**), 4 Hydroxyphenylgly oxylic acid amide (**164**), Indole-3-carboxaldehyde (**165**), Indole- 3-carboxylic acid (**166**), (1H-indol-3-yl) oxoacetamide (**167**) and N-acetyl-β-oxotryptamine (**168**) **[48] (Fig. 8.)**.

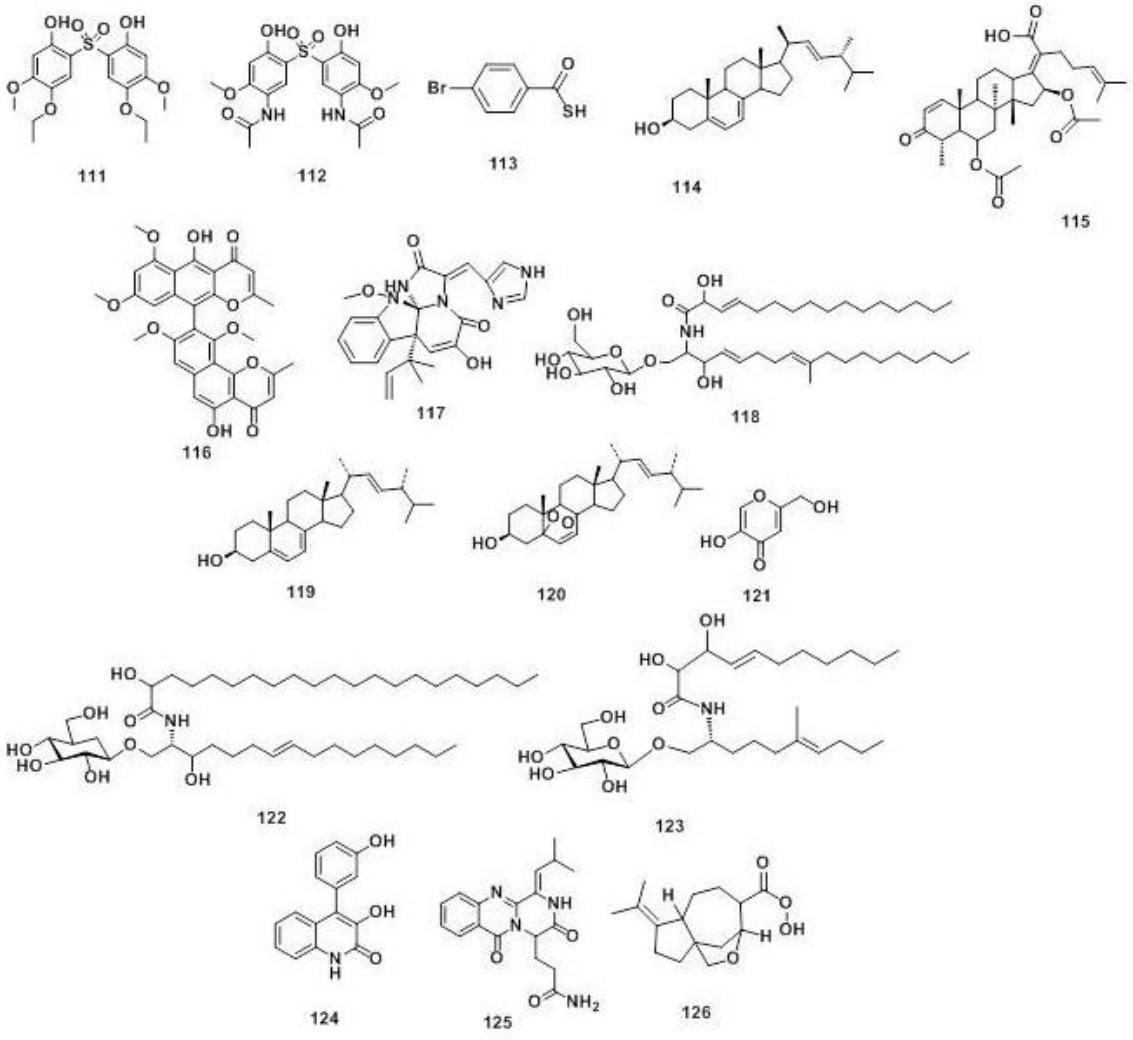


**Fig. 7.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of *Penicillium* sp

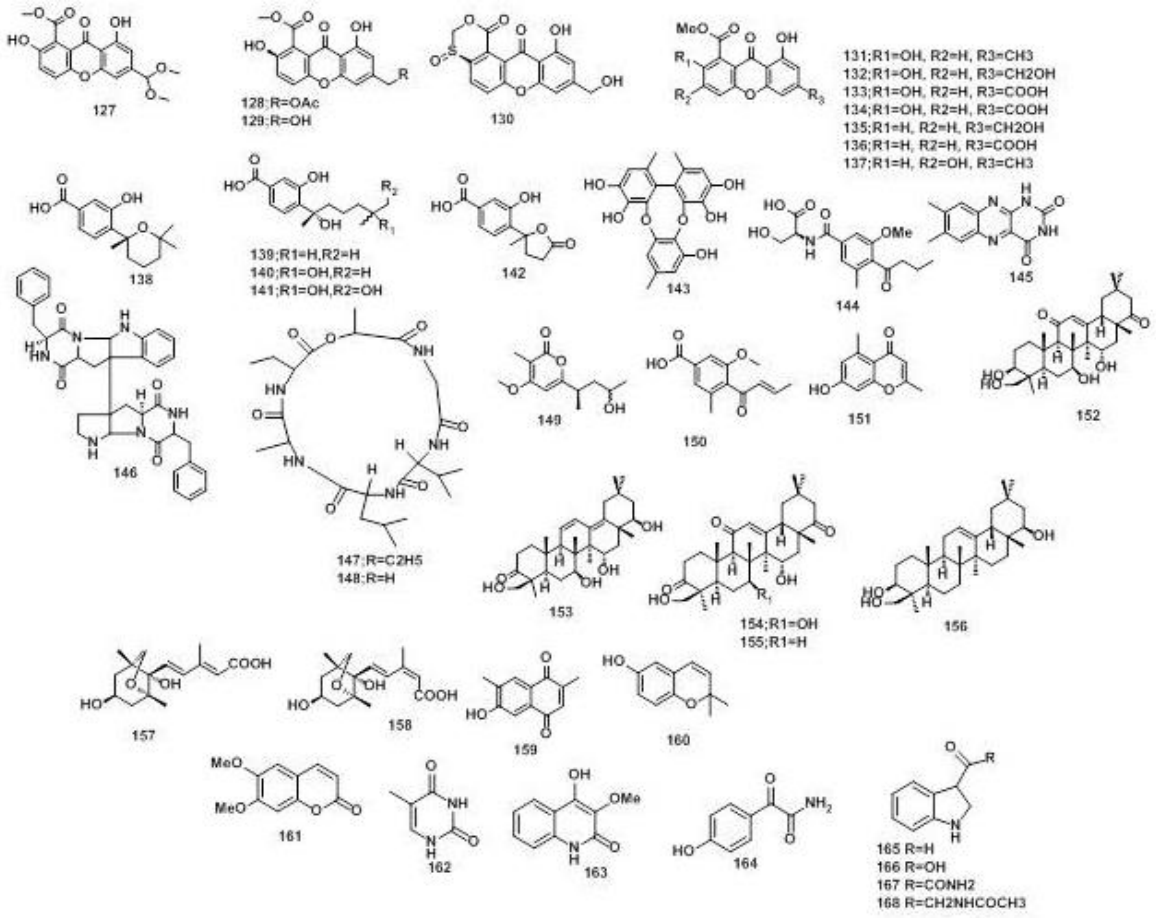


**Fig. 8.** illustrates the chemical structures of the secondary metabolites gained from different Red Sea strains of *Scopulariopsis sp*

### 2.9. Unidentified fungal sp

Nawar et al. informed the selection of two new benzofuranoids Deutromycols A & B (**169-170**) from a fungal endophyte isolated from the Red Sea submerged mangrove woods collected near El-Gouna, Hurghada. The Fungal strain in this report was not fully identified taxonomically due to lack of sporulation and was identified as a deuteromycete strain MF003 **[49] (Fig. 9.).**

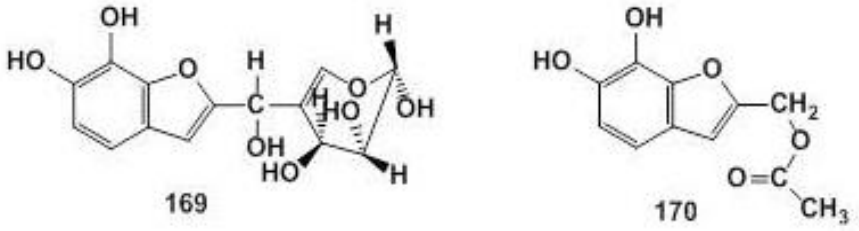


**Fig. 9.** illustrates the chemical structures of the isolated secondary metabolites from different Red Sea strains of Unidentified fungal sp

The summary of the biological activities of secondary metabolites isolated from Red Sea-derived fungi is shown in **Table 1.**

**Table 1. The biological activity of secondary metabolites isolated from Red sea derived fungi**

| Compound name | Biological activity | Reference control | Reference |
|---|---|---|---|
| Isorhodoptilometrin-1-methyl ether; 3-(2-Hydroxypropyl)-1-methyl ether-6,8-dihydroxy-9,10-anthraquinone (**1**) | adequate antimicrobial activity against B. subtilis | Soybean trypsin-chymotrypsin inhibitor | **[22]** |
| Emodin (**2)** | showed moderate selective inhibitory action against HCV protease with $IC_{50}$ 22.2 $\mu g$/mL. | Soybean trypsin-chymotrypsin inhibitor | **[22]** |
| Methyl-emodin **(3)** | showed moderate selective inhibitory action against HCV protease with $IC_{50}$ 40.2 $\mu g$/mL. | Soybean trypsin-chymotrypsin inhibitor | **[22]** |
| Siderin **(7)** | adequate antimicrobial activity against B. subtilis | Soybean trypsin-chymotrypsin inhibitor | **[22]** |
| Asperopiprazines A **(17)** | revealed adequate antibacterial action against *E.coli* and *S.aureas* potent to adequate cytotoxic action against HCT-116 cancer cell lines that have an $IC_{50}$ value of 15.1 $\mu$M | 5-Fluorouracil | **[27]** |
| Asperopiprazines B **(18)** | revealed adequate antibacterial action against *E.coli* and *S.aureas* potent to adequate cytotoxic action against HCT-116 cancer cell lines that have an $IC_{50}$ value of 16.2 $\mu$M | 5-Fluorouracil | **[27]** |
| +-Citreoisocoumarin (**19**) | potent to adequate cytotoxic action against HCT-116 cancer cell lines that have an $IC_{50}$ value of 19.3 $\mu$M | 5-Fluorouracil | **[27]** |
| (-)-6,8-di-O-methylcitreoisocoumarin (**20**) | potent to adequate cytotoxic action against HCT-116 cancer cell lines that have an $IC_{50}$ value of 17.2 $\mu$M | 5-Fluorouracil | **[27]** |
| Falconensins O **(21)** | potent to moderate anti-inflammatory activity | | **[28]** |
| Falconensins A **(23)** | potent to moderate anti-inflammatory activity | | **[28]** |
| Falconensin Q **(25)** | potent anti-inflammatory activity showing $IC_{50}$ 11.9 | | **[28]** |

| | | | |
|---|---|---|---|
| | $\mu$M without cytotoxicity | | |
| Falconensin S **(27)** | potent to moderate anti-inflammatory activity | | **[28]** |
| Falconensin I **(29)** | potent to moderate anti-inflammatory activity | | **[28]** |
| Diorcinol **(36)** | significant stability and activity within the active pocket of CDK-2 | depsipeptide kahalalide F | **[29]** |
| 4- Hydroxybenzaldehyde (**37**) | significant stability and activity within the active pocket of CDK-2 | depsipeptide kahalalide F | **[29]** |
| Sulochrin (**38**) | significant stability and activity within the active pocket of CDK-2<br>potent cytotoxicity against mouse lymphoma cell lines at $IC_{50}$ of 5.1$\mu$M | depsipeptide kahalalide F | **[29]** |
| Monochlorosulochrin (**39**) | significant stability and activity within the active pocket of CDK-2 | depsipeptide kahalalide F | **[29]** |
| Coumamarin (**41**) | potent antibacterial activity against *Bacillus subtilis* | | **[30]** |
| Asporychalasin (**45**) | revealed cytotoxicity against cancer cells A549, MCF-7 & HepG2 with $IC_{50}$ 8.8, 7.4 & 8.3 µg/mL | | **[31]** |
| Isodihydroauroglaucin (**55)** | potent activity with an $IC_{50}$ value of 2.87 $\mu$M | methotrexate | **[33]** |
| Tenuazonic acid ( **69** ) | antibacterial activity against *P. aeruginosa* | | **[34]** |
| Alternariol-9-methyl ether-3-O-sulphate (**70**) | potent antibacterial activity against *B. cereus* | virus C NS3 protease inhibitor 2 | **[35]** |
| Alternariol-9-methyl ether(**71**) | moderate activity against *B. megaterium*. | virus C NS3 protease inhibitor 2 | **[35]** |
| Alternariol (**72**) | moderate activity against *B. megaterium*. | virus C NS3 protease inhibitor 2 | **[35]** |
| epicotripeptin **(86)** | moderate biofilm inhibitory activity against biofilm-forming gram-positive isolates | Ciprofloxacin | **[38]** |
| cyclo (L-pro-L-Ileu) **(88)** | moderate biofilm inhibitory activity against biofilm-forming gram-positive isolates | Ciprofloxacin | **[38]** |
| Cyclo (L-pro-L-tyr) **(89)** | moderate biofilm inhibitory activity against biofilm-forming gram-positive isolates | Ciprofloxacin | **[38]** |
| Cyclo-L-Ala-L-Leu **(94)** | antifungal activity against *C. albicans* with MIC value 8 $\mu$M<br>potent inhibitory effect with $IC_{50}$ values of 18.20 $\mu g$/mL | Ketoconazole | **[39]** |

| | | | |
|---|---|---|---|
| Cordycepi (3'-Deoxyadenosine; 9- cordyceposidoadenosine; Adenine cordyceposide) **(95)** | potent inhibitory effect with $IC_{50}$ values of 18.20 $\mu g$/mL<br>mild inhibitory with an $IC_{50}$ value of 24.5 $\mu g$/mL | | **[40]** |
| Ara-A (Adenosine; spongouridine; Adenine 9-N-βarabinofuranoside) **(96)** | mild inhibitory with an $IC_{50}$ value of 22.3 $\mu g$/mL | | **[40]** |
| Griseoxanthone C (**110**) | strong anti-HCV NS3/4A protease activity, with IC50 values of 19.8 $\mu g/ml$ | | **[41]** |
| Pensulfonoxy A **(111)** | moderate cytotoxicity against HCT 116 with $IC_{50}$ 5.23 $\mu$M | paclitaxel | **[42]** |
| Pensulfonoxy B **(112)** | cytotoxicity against MCF-7 and HCT 116 cell lines with $IC_{50}$ 2.18 and 6.12 $\mu$M | paclitaxel | **[42]** |
| Aurantiomide C **(125)** | potent activity with maximum DPPH scavenging activity (75%)<br>potent cytotoxicity against MCF-7, HepG-2 and HCT 116 cancer cell lines with $IC_{50}$ $20.48 \pm 1.7$ , $23.94 \pm 1.8$ , $9.51 \pm 0.90$ $\mu g/ml$ | Doxorubicin | **[46]** |
| Aspterric acid **(126)** | effective against *B. subtilis* and *P. aeruginosa*<br>potent cytotoxicity against MCF-7, HepG-2 and HCT 116 cancer cell lines with $IC_{50}$ $31.67 \pm 2.5$ , $51.10 \pm 3.4$ , $26.71 \pm 2.1$ $\mu g/ml$ | Doxorubicin | **[46]** |

## Conclusion

A thorough literature review on the Red Sea fungal revealed that it produces a wide range of chemical components. The main groups of bioactive metabolites produced by marine fungi are flavonoids, alkaloids, phenolic acids, and triterpenoids. Marine fungus whole extracts, fractions, and isolated pure substances have exhibited a variety of biological and pharmacological effects. Therefore, marine fungus species might potentially produce promising aspirants for examination in medical trials.

Entire extracts or fractions rich in bioactive substances, such as polysaccharides or polyphenolics, may be applied topically or as therapy in the treatment of cancer and serious inflammatory diseases. Aspergillus sp., Penicillium sp., Fusarium sp., Epicoccum sp., Cladosporium sp., Alternaria sp., Scopulariopsis sp., and Chrysosporium sp. are the most studied species biologically, sendoff a large area for more studies on other species that have not yet been completely studied.

The current review contains widespread updated information on the pharmacology and phytochemistry of many marine fungal species, which may stand in the development and discovery of innovative drugs for the cure of various disorders. Without a doubt, the richness

of published data directs to the marine fungi's medicinal potential. The clinical efficacy of the marine fungal species is still uncertain, despite years of intensive research. It will continue to be challenging to incorporate marine fungus into traditional therapy.

This is a major hindrance not only to marine fungus species but also to many additional therapeutic marine creatures. The clinical environment demonstration of therapeutic activity is a fundamental task for medical research. For the profit of patients all through the world, it is to be wished that this significant barrier will be removed in the years to come.

**Declarations**

**Consent to publish**

All authors have read and agreed to the published version of the manuscript

**Ethics approval and consent to participate**

Not applicable

**Availability of data and material**

All data generated or analyzed during this study are included in this published article in the main manuscript.

**Competing interests**

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**Author contribution**

Conceptualization was performed by Abdel Nasser Singab, data preparation and collection of the draft was performed by Reem Elsheikh and Ahmed Elissawy, and revision of the first draft was performed by Ahmed Elissawy and Abdel Nasser Singab. All authors have read and approved the final manuscript.

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