Review

Stachybotrys chartarum—A Hidden Treasure: Secondary Metabolites, Bioactivities, and Biotechnological Relevance

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Abstract: Fungi are renowned as a fountainhead of bio-metabolites that could be employed for producing novel therapeutic agents, as well as enzymes with wide biotechnological and industrial applications. Stachybotrys chartarum (black mold) (Stachybtoriaceae) is a toxigenic fungus that is commonly found in damp environments. This fungus has the capacity to produce various classes of bio-metabolites with unrivaled structural features, including cyclosporins, cochlioquinones, atra- nones, trichothecones, dolabellanes, phenylspirodromanes, xanthones, and isoindoline and chromene derivatives. Moreover, it is a source of various enzymes that could have variable biotechnological and industrial relevance. The current review highlights the formerly published data on S. chartarum, including its metabolites and their bioactivities, as well as industrial and biotechnological relevance dated from 1973 to the beginning of 2022. In this work, 215 metabolites have been listed and 138 references have been cited.

Keywords: fungi; Stachybotrys chartarum; Stachybotriaceae; metabolites; phenylspirodromanes; bioactivity; biotechnology

1. Introduction

Fungi are found predominantly in all environments and have substantial roles in preserving eco-balance, diversity, and sustainability [1–3]. They have demonstrated a wide array of industrial and biotechnological potentials [1,4–6]. Additionally, they are an important source of metabolites with unique chemical skeletons that have the potential for discovering drugs of clinical relevance [7–12]. This was evident by many reported fungi-derived drugs that are in use, for example camptothecin, cyclosporin, paclitaxel, torreyanic acid, compactin, vincristine, lovastatin, and cytarabine [13–15]. Additionally, they are a pool of new scaffolds, which can be further modified to achieve the needed action [16]. Many of these metabolites can be obtained in considerable amounts and at a feasible cost through fermentation utilizing genetically modified or wild type fungi [15]. Regardless of the remarkable advancement in discovering drugs that provide treatment for most ailments, epidemics, and infections, novel drugs are requested to counter the reported resistance of some diseases and infections to the existing drugs [17–19]. Despite the biodiversity of the fungi kingdom, only a limited number of fungi have been explored for their capacity to produce bioactive metabolites.
Stachybotrys chartarum (black mold) (Stachybotriaceae, S. atra or S. alternans) is a toxigenic fungus that is widely present in the indoor air of buildings or homes which have water damage or sustained flooding from roofs, broken pipes, floor or wall leaks, and condensation. *S. chartarum* a hydrophilic fungus, needing wet conditions for maintaining and initiating its growth. It is also found on gypsum, cellulose-based ceiling tiles, fiberglass, wallpaper, paper products, natural fiber carpets, insulated pipes paper covering, wood and wood paneling, and organic debris, as well as soil, grains, and litter [20,21]. *S. chartarum* is one of the most common pathogenic indoor fungi that is capable of producing mycotoxins, having life-threatening health impacts [21]. Several reports stated that the exposure to this fungus or its mycotoxins through contaminated indoor air and construction material causes severe fungi-mediated sick building illnesses and even human death [20–22]. The common symptoms of this illness are fatigue, chest tightness, mucosal irritation, and headache [20]. It can also cause respiratory disorders that range from cough and congestion to more dangerous syndromes including bronchiectasis, alveolitis, and pulmonary fibrosis [23]. It was also found that exposure to this fungus has been related to infants’ pulmonary hemorrhage outbreaks [24]. Further, the exposure to *S. chartarum* in damp environments exceeds the threshold of sensitization in susceptible people [25]. This fungus causes stachybotryotoxicosis in horses and other animals [26]. The fungus’ biosynthesized macrocyclic trichothecenes are considered one of the most powerful inhibitors for protein synthesis. Additionally, it produces biometabolites (e.g. atranones and spirodrimanes), protein factors (e.g. stachylysin and hemolysin), immunosuppressive agents, and proteinases (e.g. serine proteases) that are attributed to pulmonary destruction, hemosiderosis, and hemorrhage [27–29]. Most of the reported studies on *S. chartarum* highlighted its pathogenic influences on humans and animals [21,30–32].

Surveying the literature revealed no review article that shed light on the positive impact of this important fungus. Therefore, this work reviewed the published studies on this fungus, particularly its metabolites and their bioactivities. In addition, the reported research on *S. chartarum*, including biotechnological and industrial applications, as well as nanoparticles’ preparation, have been reviewed. The reported studies from 1973 to the beginning of 2022 are cited. For the reported metabolites, molecular weights and formulae, classes, places, hosts, and bioactivities were recorded, and their structures were also illustrated. Further, the pathways for biosynthesis of the main metabolites were discussed. The aim of this work is to draw the attention of chemists, biologists, and phytochemistry and fungi-interested researchers to these interesting metabolite producing fungus. Additionally, it highlights the possible utilization of these metabolites as drug leads that could change the research direction regarding this fungus. The data for this work were gathered via computer searches in various databases (Web of Knowledge, PubMed, and SCOPUS), scientific websites (Science Direct and Google Scholar), and publishers (Wiley Online Library, Taylor & Francis, JACS, Springer, Bentham, and Thieme).

2. *S. chartarum* Enzymes and Their Possible Applications

Fungi possess diverse digestive-enzyme batteries. They can utilize agro-industrial wastes by yielding diverse enzyme types, such as xylanases, cellulases, amylases, laccases, and pectinases. These enzymes play a substantial ecological role in lignin-cellulosic materials’ decomposition and can be utilized in various biotechnological applications. In this work, the reported research on *S. chartarum* enzymes and their possible biotechnological and industrial applications have been discussed.

Polythene wastes are adversely affecting the environment due to strong reluctance towards degradation [33]. Biodegradation is one of the favorable solutions for conquering this problem [34]. *S. chartarum* was found to possess degradation potential for biodegradable and low-density polythene [34].

Andersen et al. also reported that the indoor strain of *S. chartarum* had no or little xylanolytic and cellulolytic potentials in the AZCL (Azurine-cross-linked) assay [35]. On the
contrary, it exhibited amylolytic and cellulolytic potential [36,37] and had a lignocellulose complex-degrading enzymes system [28].

Kordula et al. purified and characterized stachyrase A (chymotrypsin-like serine protease) from *S. chartarum* that had wide substrate specificity and hydrolyzed various physiologically potential proteins, protease inhibitors, and collagen in the lung [38].

2.1. Laccases

Enzymes’ oxidizing phenols have diversified applications in various industries, including paper and wood pulp delignification, textile (dye and stain bleaching), and biosensors. Laccases are phenol oxidases that can oxidize several aromatic compounds [4,39,40]. Fungal laccases have a crucial role in developing the fruiting body, as well as in lignin degradation [41]. Some laccases are produced upon exposure to phenolic substances.

Mander et al. purified a laccase enzyme from *S. chartarum* and its gene was separated and expressed in *Trichoderma reesei*, *Aspergillus niger*, and *A. nidulans*. This enzyme oxidized the artificial substrate ABTS (2,2-azino-di-(3-ethylbenzthiazolinsulfonate) [42]. Further, Janssen et al. stated that the insertion of the peptide sequences IERSAPATAPPP, YGYLPSR, SLLNATK, KASAPAL, and CKASAPALC inserted in the C-terminal of *S. chartarum* laccase by recombinant DNA tools resulted in laccase-peptide fusions that selectively targeted carotenoid stains and displayed enhanced bleaching potential on stained fabrics [43]. This suggested that the modification of certain enzymes could improve their activity, suggesting a new area of research in this fungus.

2.2. Mannanases

Mannans are constituents of hemicellulose that are found in plants, some algae, microorganisms, and tremella [44]. They include gluco-, galacto-, and galactoglucomannan as well as linear mannan [45]. They have diverse applications, for example KG (konjac glucomannan) and LBG (locust bean gum, galactomannan) are commonly utilized for chronic diseases and obesity prevention and viscosity-boosting food additives, respectively [46,47]. Mannans’ degradation is accomplished by various GHs (glycoside hydrolases) such as β-mannanase, β-mannosidase, β-glucosidase, acetyl-mannan-esterase, and α-galactosidase producing manno-oligosaccharides [48]. The later were utilized as prebiotics that enhance immune responses and modulate gut microbiota [49]. Yang et al. identified two β-mannanase genes (*s331* and *s16942*) from *S. chartarum* that were expressed in *Aspergillus niger* with high protein titers and activities [50].

2.3. β-Glucanases

β-Glucans comprise glucose polymers heterogeneous group, including lichenan (β-1,4-1,3-glucan), cellulose (β-1,4-glucan), β-1,3(4)-glucan, and laminarin (β-1,3-glucan). Their hydrolysis is catalyzed by various kinds of β-glucanases, such as lichenases, cellulases, laminarinases, and β-1,3(4)-glucanases [51]. Lichenases are produced by various microorganisms, including fungi and bacteria, and have remarkable applications in detergent, food, feed, brewing, and wine industries as well as biodiesel and bioethanol production [51]. The expression of the gene *Cel12A* isolated from rotting cellulose rag-associated *S. chartarum* by Picart et al. was triggered by rice straw than 0.1% glucose or 1% lactose [52,53]. The resulting enzyme *Cel12A* (GH12 family) had a lichenase potential. It also exhibited high potential towards barley mixed glucans and lichenan and low effectiveness on cellulose. Hence, *Cel12A* could have potential applications in various industries [53].

r-ScEG12, a recombinant glucanase gene from *S. chartarum*, belonging to GH12 (glycosyl hydrolase family12), was purified and expressed in *Pichia pastoris* [54]. It was found that Mn2+ and Cu2+ (%inhibition 50.97 and 71.64%, respectively) prohibited its activity, while Ca2+ and Na+ enhanced the activity. This proved the capacity of *S. chartarum* to secrete endoglucanases that could be beneficial for industrial use [54].

Xylanase is the principal enzyme accountable for hemicellulose hydrolysis. The *xya6205a* gene obtained from *S. chartarum* was expressed in *A. niger*. The obtained xylanase
had optimum potential at 5.8 pH and 50°C temperature and maintained 83% activity after 18 h in the alkaline buffer [55].

2.4. Fucoidanases and Alginate Lyases

Alginate and fucoidan are polysaccharides found in brown seaweed that have wide potential applications because of their diversified bioactivities. Alginate lyases are polysaccharide lyases that hydrolyze alginate by cleaving the glycosidic bond to produce oligoalginates, which have a substantial role in feed, food, nutraceutical, biofuel, and pharmaceutical industries [56]. In addition, they possess film-formation, emulsifying, gelling, and plant-growth promoting capacities [57]. Fucoidan showed antioxidant, anticoagulant, antiviral, anticancer, anti-inflammatory, and immunomodulatory capacities [56,58]. In spite of these beneficial bioactivities, fucoidan molecules possess structural variation, high molecular weight, and viscous nature that limit their therapeutic and pharmaceutical applications, however, low molecular-weight fucoidan-derived oligosaccharides have a wide potential for applications [59]. Fucoidanases are accountable for fucoidan hydrolysis to fucooligosaccharides and are a substantial tool for fucoidan structural characterization [59]. It is noteworthy that S. chartarum was found to have fucoidanase and alginate lyases producing potential [60].

3. Secondary Metabolites from S. chartarum

Reported data displayed that S. chartarum is rich with various types of metabolites with diverse structural characteristics, including phenylspirodrimanes, trichotheccenes, isodolone derivatives, atranones, dolabellane diterpenoids, xanthones, chromenes, cochliquinones, and cyclosporins. Here, they are classified according to their chemical classes. Furthermore, it was detected that some reported compounds having the same molecular formulae and chemical structures were given different nomenclature (e.g., stachartin A/stachybotrysin (13), arthproliferin E/stachybotrin E (31), stachybotrysin/stachybotramide (32)). Besides, some metabolites with different structures had the same names. Some formerly reported metabolites were also separated recently as new ones, e.g., atranone Q (180) and stachatranone C (187), reported in 2019 by Yang et al. [61] and isolated as new metabolites in 2020 by Qin et al. [62], which may be due to improper literature search. Herein, the separated metabolites from S. chartarum and their bioactivities, as well as their biosynthesis and structure/activity relation, have been highlighted.

3.1. Phenylspirodrimanes

Phenylspirodrimanes are an uncommon class of meroterpenoids (terpenylphenol) reported from Stachybotrys genus. Structurally, they are featured by the fusion of spirocyclic drimane with a phenyl moiety via spirofuran ring. They are created from farnesyl-diphosphate and orsellinic acid via ilicicolin B intermediate [63]. Their dimers are derivatives with various structural scaffolds that are produced from two monomers’ dimerization through C-C or C-N linkage with or without an alkyl chain. These metabolites are designated as the most dominant and characteristic kind of mycotoxins in this genus [64]. Various phenylspirodrimanes have been purified and characterized from S. chartarum utilizing diverse chromatographic and spectral tools (Table 1). Their bioactivities were assessed using different bioassays that were discussed in this work.
Table 1. List of compounds isolated from *Stachybotrys chartarum*.

| Compound Name                  | Mol. Wt. | Mol. Formula     | Host (Part, Family)                        | Place                                | Ref.  |
|--------------------------------|----------|------------------|-------------------------------------------|--------------------------------------|-------|
| Stachybotrydial (1)            | 386      | C_{23}H_{30}O_{5} | Cultured                                  | -                                    | [65]  |
| K-76 (2)                       | 402      | C_{25}H_{31}O_{6} | Cultured                                  | -                                    | [65]  |
| Mer-NF5003E (3)                | 388      | C_{23}H_{32}O_{5} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                   | [66]  |
| Stachybotrysin B (4)           | 430      | C_{25}H_{34}O_{6} | Cultured                                  | -                                    | [67]  |
| Mer-NF5003B (5)                | 404      | C_{23}H_{32}O_{6} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                   | [66]  |
| Stachybotrysin C (6)           | 446      | C_{25}H_{34}O_{7} | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [68]  |
| Stachybotrysin D (7)           | 488      | C_{27}H_{36}O_{8} | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [68]  |
| Stachyboside A (8)             | 550      | C_{29}H_{42}O_{10} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                   | [66]  |
| Stachyboside B (9)             | 566      | C_{29}H_{42}O_{11} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                   | [66]  |
| Stachybotrysin D (10)          | 468      | C_{23}H_{32}O_{6}S | Cultured                                  | -                                    | [67]  |
| Stachybotrysin E (11)          | 428      | C_{25}H_{32}O_{6} | Cultured                                  | -                                    | [67]  |
| F1839-1 (12)                   | 372      | C_{23}H_{32}O_{4} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                   | [66]  |
| Stachybotrysin A (13)          | 414      | C_{25}H_{34}O_{5} | Cultured                                  | -                                    | [67]  |
| Stachybochartin A = Stachybotrysin (14) | 428 | C_{26}H_{50}O_{5} | Cultured                                  | Soil sample                          | Datun tin mine tailings area, Yunnan, China | [67]  |
| Stachybochartin G (15)         | 388      | C_{23}H_{32}O_{5} | *Pinellia ternata* (rhizomes, Araceae)     | Nanjing, Jiangsu, China              | [70]  |
| Stachybotrysin F (16)          | 428      | C_{26}H_{56}O_{5} | Cultured                                  | -                                    | [67]  |
| Stachybotrysin G (17)          | 428      | C_{26}H_{56}O_{5} | Cultured                                  | -                                    | [67]  |
| Stachybotrysin H (18)          | 444      | C_{26}H_{56}O_{5} | Cultured                                  | -                                    | [71]  |
| Stachybotrysin I (19)          | 444      | C_{26}H_{56}O_{5} | Cultured                                  | -                                    | [71]  |
| Stachybotrylactone = Stachybotrolide (20) | 386 | C_{23}H_{50}O_{5} | Cultured                                  | East Dongting Lake, Hunan, China     | [65]  |

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Table 1. Cont.

| Compound Name | Mol. Wt. | Mol. Formula | Host (Part, Family) | Place | Ref. |
|---------------|----------|--------------|---------------------|-------|------|
| Stachybotrylactone acetate | 428 | C_{25}H_{32}O_{6} | Cultured Mud | - | [65,67] |
| Stachybotrane A | 386 | C_{23}H_{30}O_{5} | Mud Pinellia ternata (rhizomes, Araceae) | East Dongting Lake, Hunan, China | [72] |
| Stachybotrane B | 428 | C_{25}H_{32}O_{6} | Mud Pinellia ternata (rhizomes, Araceae) | East Dongting Lake, Hunan, China | [72] |
| 2α-Hydroxystachybotrylactone | 402 | C_{23}H_{30}O_{6} | Cultured Mud | - | [65] |
| Stachybochartin E | 444 | C_{25}H_{32}O_{7} | Pinellia ternata (rhizomes, Araceae) | Nanjing, Jiangsu, China | [70] |
| 2α-Acetoxy stachybotrylactone acetate | 486 | C_{27}H_{34}O_{8} | Cultured | - | [65] |
| Stachybotrane C | 402 | C_{23}H_{30}O_{6} | Mud | East Dongting Lake, Hunan, China | [72] |
| Stachybotractone B = Stachartin B | 386 | C_{23}H_{30}O_{5} | Cultured Soil sample Himerometra magnipinna (Crinoids, Himerometridae) | - | [67] |
| Stachybotrylactam | 385 | C_{23}H_{31}NO_{4} | Cultured Niphates recondita (Sponge, Niphatidae) | - | [68] |
| Stachybotrylactam acetate | 427 | C_{25}H_{33}NO_{5} | Cultured Niphates recondita (Sponge, Niphatidae) | - | [68] |
| Arthproliferin E = Stachybotrin E | 399 | C_{24}H_{33}NO_{4} | Cultured Sinularia sp. (Soft coral, Alcyoniidae) | Yongxing Island, South Chian Sea, China | [73] |
| Compound Name                  | Mol. Wt. | Mol. Formula | Host (Part, Family)                                                                 | Place                                                                                   | Ref. |
|--------------------------------|----------|--------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------|
| Stachybotrin = Stachybotramide (32) | 429      | C_{25}H_{35}NO_{5} | *Sinularia* sp. (Soft coral, Alcyoniidae)                                           | Yongxing Island, South Chian Sea, China                                                 | [73] |
|                                |          |              | *Pinellia ternata* (rhizomes, Araceae)                                              | Nanjing, Jiangsu, China                                                                | [70] |
|                                |          |              | Cultured                                                                             | -                                                                                        |      |
|                                |          |              | *Niphates recondita* (Sponge, Niphatidae)                                           | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China                           | [74] |
|                                |          |              | Mud                                                                                  | East Dongting Lake, Hunan, China                                                      | [72] |
| Stachybochartin F (33)         | 471      | C_{27}H_{37}NO_{6} | *Pinellia ternata* (rhizomes, Araceae)                                              | Nanjing, Jiangsu, China                                                                | [70] |
| Stachybotrin D (34)            | 441      | C_{26}H_{35}NO_{5} | *Xestospongia testudinaris* (Sponge, Petrosiidae)                                   | Xisha Island, China                                                                   | [66] |
| Stachybotrysam E (35)          | 471      | C_{27}H_{37}NO_{6} | Cultured                                                                             | -                                                                                        | [76] |
| K-76-1 (36)                    | 515      | C_{28}H_{37}NO_{8} | Soil                                                                                 | Himalaya, India                                                                       | [77] |
|                                |          |              | *Xestospongia testudinaris* (Sponge, Petrosiidae)                                   | Xisha Island, China                                                                   | [66] |
| K-76-2 (37)                    | 487      | C_{27}H_{37}NO_{7} | Soil                                                                                 | Himalaya, India                                                                       | [77] |
| Stachybotrin E (38)            | 529      | C_{29}H_{39}NO_{8} | *Xestospongia testudinaris* (Sponge, Petrosiidae)                                   | Xisha Island, China                                                                   | [66] |
| Stachybotrin F (39)            | 529      | C_{29}H_{39}NO_{8} | *Xestospongia testudinaris* (Sponge, Petrosiidae)                                   | Xisha Island, China                                                                   | [66] |
| Chartarlactam A (40)           | 399      | C_{23}H_{20}NO_{5} | *Niphates recondita* (Sponge, Niphatidae)                                           | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China                          | [74] |
|                                |          |              | Soil sample                                                                          | Datun tin mine tailings area, Yunnan, China                                           | [69] |
| Chartarlactam B (41)           | 485      | C_{28}H_{39}NO_{6} | *Niphates recondita* (Sponge, Niphatidae)                                           | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China                          | [74] |
| Chartarlactam C (42)           | 401      | C_{23}H_{33}NO_{5} | *Niphates recondita* (Sponge, Niphatidae)                                           | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China                          | [74] |
| Chartarlactam D (43)           | 563      | C_{30}H_{45}NO_{9} | *Niphates recondita* (Sponge, Niphatidae)                                           | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China                          | [74] |
| Chartarlactam E (44)           | 383      | C_{23}H_{29}NO_{4} | *Niphates recondita* (Sponge, Niphatidae)                                           | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China                          | [74] |
|                                |          |              | *Sinularia* sp. (Soft coral, Alcyoniidae)                                           | Yongxing Island, South Chian Sea, China                                               | [73] |
| Stachartin C (45)              | 499      | C_{29}H_{41}NO_{6} | Soil sample                                                                          | Datun tin mine tailings area, Yunnan, China                                           | [69] |
| Stachartin D (46)              | 513      | C_{30}H_{43}NO_{6} | Soil sample                                                                          | Datun tin mine tailings area, Yunnan, China                                           | [69] |
| Stachybonoid E (47)            | 457      | C_{26}H_{35}NO_{6} | *Himerometra magnipinna* (Crinoids, Himerometridae)                                | Zhanjiang Mangrove National Nature Reserve, Guangdong, China                         | [68] |
| Compound Name                  | Mol. Wt. | Mol. Formula | Host (Part, Family)                  | Place                                           | Ref.     |
|-------------------------------|----------|--------------|-------------------------------------|------------------------------------------------|----------|
| Stachybonoid F (48)           | 485      | C_{28}H_{39}NO_{6} | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [68]     |
| Stachatin E (49)              | 547      | C_{33}H_{41}NO_{6} | Soil sample                         | Datun tin mine tailings area, Yunnan, China     | [69]     |
| N-(2-Benzeneacetonic acid)    | 533      | C_{32}H_{39}NO_{6} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| F1839-A (51)                  | 401      | C_{23}H_{31}NO_{5} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| Chartarlactam I (52)          | 401      | C_{23}H_{31}NO_{5} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| Chartarlactam J (53)          | 401      | C_{23}H_{31}NO_{5} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| Chartarlactam K (54)          | 443      | C_{25}H_{33}NO_{6} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| Chartarlactam M (55)          | 385      | C_{23}H_{31}NO_{4} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| Chartarlactam P (56)          | 401      | C_{23}H_{31}NO_{5} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| F1839-E (57)                  | 445      | C_{25}H_{35}NO_{6} | *Niphates recondita* (Sponge, Niphatidae) | Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China | [74]     |
| Stachybotrane D (58)          | 445      | C_{25}H_{35}NO_{6} | Mud                                | East Dongting Lake, Hunan, China                | [72]     |
| K-76-3 (59)                   | 487      | C_{27}H_{37}NO_{7} | Soil                               | Himalaya, India                                 | [77]     |
| K-76-4 (60)                   | 501      | C_{28}H_{39}NO_{7} | Soil                               | Himalaya, India                                 | [77]     |
| K-76-5 (61)                   | 515      | C_{29}H_{41}NO_{7} | Soil                               | Himalaya, India                                 | [77]     |
| K-76-6 (62)                   | 515      | C_{29}H_{41}NO_{7} | Soil                               | Himalaya, India                                 | [77]     |
| K-76-7 (63)                   | 549      | C_{32}H_{39}NO_{7} | Soil                               | Himalaya, India                                 | [77]     |
Table 1. Cont.

| Compound Name                          | Mol. Wt. | Mol. Formula | Host (Part, Family)                      | Place                                                                 | Ref. |
|----------------------------------------|----------|--------------|------------------------------------------|----------------------------------------------------------------------|------|
| 2α-Acetoxystachybotrylactam acetate   | 485      | C_{27}H_{35}NO_{7} | Cultured                                | -                                                                    | [65] |
|                                        |          |              | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          |      |
|                                        |          |              | *Sinularia sp.* (Soft coral, Alcyoniidae)| Yongxing Island, South Chian Sea, China                              |      |
| Chartarlactam F                        | 385      | C_{23}H_{31}NO_{4} | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          | [74] |
|                                        |          |              | *Sinularia sp.* (Soft coral, Alcyoniidae)| Yongxing Island, South Chian Sea, China                              | [73] |
| Chartarlactam G                        | 385      | C_{23}H_{31}NO_{4} | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          | [74] |
| Chartarlactam H                        | 429      | C_{25}H_{35}NO_{5} | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          | [74] |
| Chartarlactam N                        | 429      | C_{25}H_{35}NO_{5} | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          | [74] |
| Chartarlactam O                        | 385      | C_{23}H_{31}NO_{4} | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          | [74] |
| Chartarlactam L                        | 766      | C_{46}H_{58}N_{2}O_{8} | *Niphates recondita* (Sponge, Niphatidae)| Coral reef near Weizhou Island, Beibuwan Bay, Guangxi, China          | [74] |
| Bistachybotrysin A                     | 774      | C_{46}H_{62}O_{10} | Cultured                                | -                                                                    | [79] |
| Bistachybotrysin B                     | 816      | C_{48}H_{64}O_{11} | Cultured                                | -                                                                    | [79] |
| Bistachybotrysin C                     | 790      | C_{46}H_{62}O_{11} | Cultured                                | -                                                                    | [79] |
| Bistachybotrysin D                     | 772      | C_{47}H_{64}O_{9}  | Cultured                                | -                                                                    | [80] |
| Bistachybotrysin E                     | 772      | C_{47}H_{64}O_{9}  | Cultured                                | -                                                                    | [80] |
| Bistachybotrysin F                     | 800      | C_{48}H_{64}O_{10} | Cultured                                | -                                                                    | [81] |
| Bistachybotrysin G                     | 774      | C_{46}H_{62}O_{10} | Cultured                                | -                                                                    | [81] |
| Bistachybotrysin H                     | 816      | C_{48}H_{64}O_{11} | Cultured                                | -                                                                    | [81] |
| Bistachybotrysin I                     | 788      | C_{47}H_{64}O_{10} | Cultured                                | -                                                                    | [81] |
Table 1. Cont.

| Compound Name            | Mol. Wt. | Mol. Formula | Host (Part, Family) | Place                                      | Ref.          |
|--------------------------|----------|--------------|---------------------|--------------------------------------------|---------------|
| Bistachybotrysin J (82)  | 816      | C₄₀H₆₆O₁₁    | Cultured            |                                            | [81]          |
| Bistachybotrysin K (83)  | 758      | C₄₆H₂₂O₉     | Cultured            |                                            | [82]          |
| Bistachybotrysin L (84)  | 772      | C₄₇H₆₄O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin M (85)  | 772      | C₄₇H₆₄O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin N (86)  | 772      | C₄₇H₆₄O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin O (87)  | 772      | C₄₇H₆₄O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin P (88)  | 814      | C₄₀H₆₆O₁₀    | Cultured            |                                            | [83]          |
| Bistachybotrysin Q (89)  | 814      | C₄₀H₆₆O₁₀    | Cultured            |                                            | [83]          |
| Bistachybotrysin R (90)  | 854      | C₃₂H₇₀O₁₀    | Cultured            |                                            | [83]          |
| Bistachybotrysin S (91)  | 854      | C₃₂H₇₀O₁₀    | Cultured            |                                            | [83]          |
| Bistachybotrysin T (92)  | 798      | C₄₀H₆₆O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin U (93)  | 756      | C₄₆H₆₀O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin V (94)  | 758      | C₄₆H₆₂O₉    | Cultured            |                                            | [83]          |
| Bistachybotrysin W (95)  | 832      | C₄₈H₆₄O₁₂   | Cultured            |                                            | [84]          |
| Bistachybotrysin X (96)  | 832      | C₄₈H₆₄O₁₂   | Cultured            |                                            | [84]          |
| Bistachybotrysin Y (97)  | 874      | C₄₉H₆₂O₁₃   | Cultured            |                                            | [84]          |
| Chartarolide A (98)      | 772      | C₄₄H₄₉O₁₀Cl  | Niphates sp. (Sponge, Niphatidae) | Near coral reef, Beibuwan Bay, GuangXi, China | [85]          |
| Chartarolide B (99)      | 772      | C₄₄H₄₉O₁₀Cl  | Niphates sp. (Sponge, Niphatidae) | Near coral reef, Beibuwan Bay, GuangXi, China | [85]          |
| Chartarolide C (100)     | 771      | C₄₄H₄₉O₁₀Cl  | Niphates sp. (Sponge, Niphatidae) | Near coral reef, Beibuwan Bay, GuangXi, China | [85]          |
| Chartarlactam Q (101)    | 753      | C₄₆H₅₉NO₈   | Cultured            |                                            | [86]          |
| Chartarlactam R (102)    | 797      | C₄₆H₅₉NO₈   | Cultured            |                                            | [86]          |
| Chartarlactam S (103)    | 771      | C₄₆H₅₉NO₈   | Cultured            |                                            | [86]          |
| Chartarlactam T (104)    | 855      | C₄₆H₅₉NO₈   | Cultured            |                                            | [86]          |
| Stachybochartin A (105)  | 774      | C₄₆H₆₂O₁₀   | Pinellia ternata (Rhizomes, Araceae) | Nanjing, Jiangsu, China                     | [70]          |
| Stachybochartin B (106)  | 844      | C₅₀H₆₈O₁₁   | Pinellia ternata (Rhizomes, Araceae) | Nanjing, Jiangsu, China                     | [70]          |
| Stachybochartin C (107)  | 772      | C₄₇H₆₄O₉    | Pinellia ternata (Rhizomes, Araceae) | Nanjing, Jiangsu, China                     | [70]          |
Table 1. Cont.

| Compound Name          | Mol. Wt. | Mol. Formula | Host (Part, Family)                              | Place                                              | Ref.          |
|------------------------|----------|--------------|--------------------------------------------------|----------------------------------------------------|---------------|
| Stachybochartin D (108) | 858      | C_{50}H_{66}O_{12} | *Pinellia ternata* (Rhizomes, Araceae)           | Nanjing, Jiangsu, China                            | [70]          |
| Stachyin B (109)       | 755      | C_{46}H_{61}NO_{8} | Cultured                                         | -                                                  | [86]          |
| Stachartone A (110)    | 758      | C_{46}H_{62}O_{8} | Soil sample                                      | Datun tin mine tailings area, Yunnan, China       | [87]          |
| Stachartarin A (111)   | 758      | C_{46}H_{62}O_{8} | Soil sample                                      | Datun tin mine tailings area, Yunnan, China       | [88]          |
| Stachartarin B (112)   | 772      | C_{47}H_{64}O_{8} | Soil sample                                      | Datun tin mine tailings area, Yunnan, China       | [89]          |
| Stachybocin E (113)    | 824      | C_{50}H_{68}N_{2}O_{8} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                               | [66]          |
| Stachybocin F (114)    | 838      | C_{51}H_{70}N_{2}O_{8} | *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                               | [66]          |
| 12,13-Epoxytrichothe-9-ene (115) | 234 | C_{15}H_{22}O_{2} | Cultured                                         | -                                                  | [90, 91]      |
| 2,4,12-Trihydroxyapotrichothecene (116) | 268 | C_{15}H_{24}O_{4} | *Niphates recondita* (Sponge, Niphatidae)       | Inner coral reef, Beibuwan Bay, Guangxi, China    | [92]          |
| Chartarene A (117)     | 398      | C_{21}H_{34}O_{7} | *Niphates recondita* (Sponge, Niphatidae)       | Inner coral reef, Beibuwan Bay, Guangxi, China    | [92]          |
| Chartarene B (118)     | 282      | C_{16}H_{26}O_{4} | *Niphates recondita* (Sponge, Niphatidae)       | Inner coral reef, Beibuwan Bay, Guangxi, China    | [92]          |
| Chartarene C (119)     | 264      | C_{16}H_{24}O_{3} | *Niphates recondita* (Sponge, Niphatidae)       | Inner coral reef, Beibuwan Bay, Guangxi, China    | [92]          |
| Trichodermol (120)     | 250      | C_{15}H_{22}O_{3} | Air and surface samples                          | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [93]          |
| Verrucarol (121)       | 266      | C_{15}H_{22}O_{4} | Cultured                                         | -                                                  | [65, 91, 94]  |
|                        |          |              | Straw                                            | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses | [95]          |
| Trichodermin (122)     | 292      | C_{17}H_{24}O_{4} | Air and surface samples                          | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [93]          |
| Isotrichoverrol B (123) | 420     | C_{23}H_{32}O_{7} | *Niphates recondita* (Sponge, Niphatidae)       | Inner coral reef, Beibuwan Bay, Guangxi, China    | [92]          |
| Verrol (124)           | 362      | C_{21}H_{30}O_{5} | Air and surface samples                          | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [93]          |
|                        |          |              | *Niphates recondita* (Sponge, Niphatidae)       | Inner coral reef, Beibuwan Bay, Guangxi, China    | [92]          |
| Trichoverrol (125)     | 434      | C_{24}H_{34}O_{7} | Cultured                                         | -                                                  | [65]          |
| Trichoverrol A (126)   | 434      | C_{24}H_{34}O_{7} | Dead animals                                      | Various parts of Hungary and Czechoslovakia       | [96]          |
|                        |          |              | Egyptian paddy grains                           | Egypt                                              | [97]          |
| Compound Name | Mol. Wt. | Mol. Formula | Host (Part, Family) | Place | Ref. |
|---------------|---------|--------------|---------------------|-------|-----|
| Trichoverrol B (127) | 434 | C_{24}H_{34}O_{7} | Dead animals | Various parts of Hungary and Czechoslovakia | [96] |
| Trichodermadienediol B (128) | 404 | C_{23}H_{32}O_{6} | Niphates recondita (Sponge, Niphatidae) | Inner coral reef, Beibuwan Bay, Guangxi, China | [92] |
| Roridin L-2 (129) | 544 | C_{30}H_{40}O_{9} | Cultured | - | [65,94,98] |
| | | | Air and surface samples | | [93] |
| | | | Niphates recondita (Sponge, Niphatidae) | Inner coral reef, Beibuwan Bay, Guangxi, China | [92] |
| Chartarene D (130) | 512 | C_{29}H_{36}O_{8} | Niphates recondita (Sponge, Niphatidae) | Inner coral reef, Beibuwan Bay, Guangxi, China | [92] |
| Verrucarin J (131) | 484 | C_{27}H_{32}O_{8} | Cultured | - | [91] |
| | | | Straw | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses | [95] |
| | | | Dead animals | Various parts of Hungary and Czechoslovakia Egypt | [96,99] |
| | | | Egyptian paddy grains | Egyptian | [97] |
| Roridin A (132) | 532 | C_{29}H_{40}O_{9} | Cultured | - | [91] |
| Roridin D (133) | 530 | C_{29}H_{38}O_{9} | Cultured | - | [91] |
| Roridin E (134) | 514 | C_{29}H_{36}O_{8} | Cultured | - | [65,91,94] |
| | | | Straw | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses | [95] |
| | | | Dead animals | Various parts of Hungary and Czechoslovakia Egypt | [96,99] |
| | | | Egyptian paddy grains | Egyptian | [97] |
| Isororidin E (135) | 514 | C_{29}H_{38}O_{8} | Cultured | | [65] |
| Epiroridin E (136) | 514 | C_{29}H_{38}O_{8} | Cultured | | [65] |
| Epiisororidin E (137) | 514 | C_{29}H_{38}O_{8} | Cultured | - | [65] |
| Roridin H (138) | 512 | C_{29}H_{36}O_{8} | Cultured | - | [91] |
| Muconomycin B (139) | 484 | C_{27}H_{32}O_{8} | Niphates recondita (Sponge, Niphatidae) | Inner coral reef, Beibuwan Bay, Guangxi, China | [92] |
| Satratoxin F (140) | 542 | C_{29}H_{34}O_{10} | Cultured | | [90] |
| | | | Straw | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses | [95,100] |
| | | | Dead animals | Various parts of Hungary and Czechoslovakia Egypt | [96] |
| | | | Egyptian paddy grains | Egyptian | [97] |
| Compound Name   | Mol. Wt. | Mol. Formula | Host (Part, Family)                                                                 | Place                                                                                   | Ref. |
|-----------------|----------|--------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------|
|                | -        |              | Air and surface samples                                                              | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [93] |
| Sinularia sp. (Soft coral, Alcyoniidae) |          |              | Air and surface samples                                                              | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [73] |
| Isosatratoxin F (141) | 542      | C_{29}H_{34}O_{10} | Air and surface samples                                                              | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [93] |
| Sratotoxin G (142) | 544      | C_{29}H_{36}O_{10} | Cultured                                                                             | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses             | [65,90,98] |
| -               | -        |              | Straw                                                                               | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses             | [95,100] |
| -               | -        |              | Dead animals                                                                         | Various parts of Hungary and Czechoslovakia                                            | [96,99] |
| -               | -        |              | Egyptian paddy grains                                                                | Egypt                                                                                  | [97] |
| -               | -        |              | Bedding Straw of a Sheep Flock with Fatal Stachybotryotoxicosis                      | Hungary                                                                                | [101] |
| -               | -        |              | Air and surface samples                                                              | Finland                                                                                 | [102] |
| -               | -        |              | Indoor Air from a Water-Damaged building                                              | Sartorius, Goettingen, Germany                                                        | [103] |
| -               | -        |              | Niphates recondita (Sponge, Niphatidae)                                              | Inner coral reef, Beibuwan Bay, Guangxi, China                                        | [92] |
| Isosatratoxin G (143) | 544      | C_{29}H_{36}O_{10} | Air and surface samples                                                              | Homes enrolled in a case-control study of pulmonary hemosiderosis in infants, Cleveland, Ohio, USA | [93] |
| Sratotoxin H (144) | 528      | C_{29}H_{36}O_{9} | Cultured                                                                             | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses             | [65,75,91] |
| -               | -        |              | Straw                                                                               | Hungarian village of Jaszapati from a field case of mycotoxicosis in horses             | [75,95] |
| -               | -        |              | Dead animals                                                                         | Various parts of Hungary and Czechoslovakia                                            | [96,99] |
| -               | -        |              | Egyptian paddy grains                                                                | Egypt                                                                                  | [97] |
| -               | -        |              | Bedding Straw of a Sheep Flock with Fatal Stachybotryotoxicosis                      | Finland                                                                                 | [102] |
| -               | -        |              | Indoor Air from a Water-Damaged building                                              | Sartorius, Goettingen, Germany                                                        | [103] |
| -               | -        |              | Sinularia sp. (Soft coral, Alcyoniidae)                                              | Yongxing Island, South Chian Sea, China                                                | [73] |
| -               | -        |              | Niphates recondita (Sponge, Niphatidae)                                              | Inner coral reef, Beibuwan Bay, Guangxi, China                                        | [92] |
## Table 1. Cont.

| Compound Name                  | Mol. Wt. | Mol. Formula       | Host (Part, Family)                                      | Place                                      | Ref.                 |
|-------------------------------|----------|--------------------|----------------------------------------------------------|--------------------------------------------|----------------------|
| Satratoxin H diacetate (145)  | 612      | C_{33}H_{40}O_{11} | Cultured                                                 | -                                          | [91]                 |
| Mytoxin A (146)               | 544      | C_{29}H_{56}O_{10} | *Niphates recondita* (Sponge, Niphatidae)               | Inner coral reef, Beibuwan Bay, Guangxi, China | [92]                 |
| Chartarutine A (147)          | 403      | C_{23}H_{33}NO_{5} | *Niphates* sp. (Sponge, Niphatidae)                     | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine B (148)          | 369      | C_{22}H_{31}NO_{3} | *Niphates* sp. (Sponge, Niphatidae) Cultured            | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine C (149)          | 449      | C_{23}H_{33}NO_{8}S| *Niphates* sp. (Sponge, Niphatidae) Cultured            | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine D (150)          | 448      | C_{23}H_{32}N_{2}O_{5}S| *Niphates* sp. (Sponge, Niphatidae) | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine E (151)          | 401      | C_{23}H_{31}NO_{5} | *Niphates* sp. (Sponge, Niphatidae)                     | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine F (152)          | 401      | C_{23}H_{31}NO_{5} | *Niphates* sp. (Sponge, Niphatidae)                     | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine G (153)          | 367      | C_{23}H_{29}NO_{3} | *Niphates* sp. (Sponge, Niphatidae)                     | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Chartarutine H (154)          | 367      | C_{23}H_{29}NO_{3} | *Niphates* sp. (Sponge, Niphatidae)                     | Near coral reef, Beibuwan Bay, Guangxi, China | [104]               |
| Stachybotrin G (155)          | 503      | C_{27}H_{39}N_{2}O_{5}S| *Xestospongia testudinaris* (Sponge, Petrosiidae) | Xisha Island, China                     | [105]               |
| Stachybotrysam A (156)        | 413      | C_{25}H_{35}NO_{4} | Cultured                                                 | -                                          | [76]                 |
| Stachybotrysam B (157)        | 493      | C_{25}H_{35}NO_{5}S| Cultured                                                 | -                                          | [76]                 |
| Stachybotrysam C (158)        | 535      | C_{27}H_{37}NO_{5}S| Cultured                                                 | -                                          | [76]                 |
| Stachybotrysam D (159)        | 611      | C_{29}H_{41}NO_{11}S| Cultured                                                 | -                                          | [76]                 |
| Atranone A (160)              | 416      | C_{24}H_{32}O_{6}  | Cultured                                                 | -                                          | [75,106]             |
| Methylatranone A (161)        | 430      | C_{25}H_{34}O_{6}  | Cultured *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve in Guangdong, China | [107] [108] |
| Atranone B (162)              | 446      | C_{25}H_{34}O_{7}  | Cultured *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [62,75,106] [108] |
| Methylatranone B (163)        | 460      | C_{26}H_{36}O_{7}  | *Himerometra magnipinna* (Crinoids, Himerometridae)      | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108]               |
| 22-Epimer-methylatranone B (164) | 460 | C_{26}H_{36}O_{7}  | *Himerometra magnipinna* (Crinoids, Himerometridae)      | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108]               |
| Compound Name | Mol. Wt. | Mol. Formula | Host (Part, Family) | Place | Ref. |
|---------------|----------|--------------|---------------------|-------|-----|
| Atranone C (165) | 416 | C\(_{24}\)H\(_{32}\)O\(_{6}\) | Cultured | - | [75,106] |
| Methylatranone C (166) | 430 | C\(_{25}\)H\(_{34}\)O\(_{6}\) | Cultured | - | [107] |
| Atranone D (167) | 386 | C\(_{24}\)H\(_{34}\)O\(_{4}\) | Cultured | - | [106] |
| Atranone E (168) | 386 | C\(_{24}\)H\(_{34}\)O\(_{4}\) | Cultured | - | [106] |
| Atranone F (169) | 432 | C\(_{24}\)H\(_{32}\)O\(_{7}\) | Cultured | - | [106] |
| Atranone G (170) | 462 | C\(_{25}\)H\(_{34}\)O\(_{8}\) | Cultured | - | [106] |
| Atranone H (171) | 432 | C\(_{24}\)H\(_{32}\)O\(_{7}\) | Cultured | - | [107] |
| Atranone I (172) | 432 | C\(_{24}\)H\(_{32}\)O\(_{7}\) | Cultured | - | [107] |
| Atranone J (173) | 404 | C\(_{23}\)H\(_{32}\)O\(_{6}\) | Cultured | - | [107] |
| Atranone K (174) | 448 | C\(_{24}\)H\(_{32}\)O\(_{8}\) | Cultured | - | [107] |
| Atranone L (175) | 478 | C\(_{26}\)H\(_{38}\)O\(_{8}\) | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108] |
| Atranone M (176) | 476 | C\(_{26}\)H\(_{36}\)O\(_{8}\) | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108] |
| Atranone N (177) | 462 | C\(_{26}\)H\(_{38}\)O\(_{7}\) | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108] |
| Atranone O (178) | 480 | C\(_{25}\)H\(_{36}\)O\(_{9}\) | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108] |
| Atranone P (179) | 404 | C\(_{23}\)H\(_{32}\)O\(_{6}\) | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [108] |
| Atranone Q (180) | 390 | C\(_{23}\)H\(_{34}\)O\(_{5}\) | *Sarcophyton subviride* (Coral, Alcyoniidae) | Xisha Island, South China Sea, China | [61] |
| Atranone R (181) | 450 | C\(_{25}\)H\(_{38}\)O\(_{7}\) | *Sarcophyton subviride* (Coral, Alcyoniidae) | Xisha Island, South China Sea, China | [61] |
| Atranone S (182) | 402 | C\(_{24}\)H\(_{34}\)O\(_{5}\) | *Sarcophyton subviride* (Coral, Alcyoniidae) | Xisha Island, South China Sea, China | [61] |
| Atranone T (183) | 432 | C\(_{24}\)H\(_{32}\)O\(_{7}\) | Cultured | - | [62] |
| Atranone U (184) | 446 | C\(_{25}\)H\(_{34}\)O\(_{7}\) | Cultured | - | [62] |
| Stachatranone A (185) | 318 | C\(_{20}\)H\(_{30}\)O\(_{3}\) | *Sarcophyton subviride* (Coral, Alcyoniidae) | Xisha Island, South China Sea, China | [61] |
Table 1. Cont.

| Compound Name | Mol. Wt. | Mol. Formula | Host (Part, Family) | Place | Ref. |
|---------------|----------|--------------|---------------------|-------|------|
| Stachatranone B (186) | 334 | C_{20}H_{30}O_{4} | *Sarcophyton subviride* (Coral, Alcyoniidae) | Xisha Island, South China Sea, China | [61] |
| Stachatranone C (187) | 334 | C_{20}H_{30}O_{4} | *Sarcophyton subviride* (Coral, Alcyoniidae) | Xisha Island, South China Sea, China | [61] |
| - | - | - | Cultured | - | [62] |
| 6α-Hydroxydolabella-3E,7E,12-trien-14-one (189) | 302 | C_{20}H_{30}O_{2} | Cultured | - | [106] |
| (1S,3R*,4R*,6S*,11S*)-3,4-Epoxy-6-hydroxydolabella-7E,12-dien-14-one (188) | 318 | C_{20}H_{30}O_{3} | Cultured | - | [106] |
| Arthproliferin B (191) | 360 | C_{22}H_{32}O_{4} | *Sinularia* sp. (Soft coral, Alcyoniidae) | Yongxing Island, South China Sea, China | [73] |
| Arthproliferin C (192) | 388 | C_{23}H_{32}O_{5} | *Sinularia* sp. (Soft coral, Alcyoniidae) | Yongxing Island, South China Sea, China | [73] |
| Stachybotrychromene A (193) | 354 | C_{23}H_{30}O_{3} | Cultured | - | [64] |
| Stachybotrychromene B (194) | 412 | C_{25}H_{32}O_{5} | Cultured | - | [64] |
| Stachybotrychromene C (195) | 368 | C_{23}H_{28}O_{4} | Cultured | - | [64] |
| Stachybonoid A (196) | 460 | C_{26}H_{36}O_{7} | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [68] |
| Stachybonoid B (197) | 446 | C_{25}H_{34}O_{7} | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [68] |
| Stachybonoid C (198) | 388 | C_{23}H_{32}O_{5} | *Himerometra magnipinna* (Crinoids, Himerometridae) | Zhanjiang Mangrove National Nature Reserve, Guangdong, China | [68] |
| Epi-cochlioquinone A (199) | 532 | C_{30}H_{44}O_{8} | Cultured | - | [109] |
| 11-O-Methyl-epicochlioquinone A (200) | 546 | C_{31}H_{46}O_{8} | Cultured | - | [109] |
| Arthproliferin D (201) | 358 | C_{20}H_{22}O_{6} | *Sinularia* sp. (Soft coral, Alcyoniidae) | Yongxing Island, South China Sea, China | [73] |
| Pestaxanthone (202) | 358 | C_{20}H_{22}O_{6} | *Sinularia* sp. (Soft coral, Alcyoniidae) | Yongxing Island, South China Sea, China | [73] |
| Prenxanthone (203) | 340 | C_{20}H_{20}O_{5} | *Sinularia* sp. (Soft coral, Alcyoniidae) | Yongxing Island, South China Sea, China | [73] |
| Staprexanthone A (204) | 394 | C_{24}H_{29}O_{5} | Root of an unidentified mangrove plant | Fujian, China | [110] |
| Compound Name | Mol. Wt. | Mol. Formula | Host (Part, Family) | Place | Ref. |
|---------------|----------|--------------|---------------------|-------|------|
| Staprexanthone B (205) | 392 | C_{25}H_{28}O_{4} | Root of an unidentified mangrove plant | Fujian, China | [110] |
| Staprexanthone C (206) | 392 | C_{25}H_{28}O_{4} | Root of an unidentified mangrove plant | Fujian, China | [110] |
| Staprexanthone D (207) | 392 | C_{25}H_{28}O_{4} | Root of an unidentified mangrove plant | Fujian, China | [110] |
| Staprexanthone E (208) | 392 | C_{25}H_{28}O_{4} | Root of an unidentified mangrove plant | Fujian, China | [110] |
| Cyclosporin A (209) | 1202 | C_{62}H_{111}N_{11}O_{12} | Soil | Hahajima Island Tokyo, Japan | [111] |
| FR901459 A (210) | 1218 | C_{62}H_{111}N_{11}O_{13} | Soil | Hahajima Island Tokyo, Japan | [111] |
| Arthproliferin A (211) | 407 | C_{25}H_{29}NO_{4} | Sinularia sp. (Soft coral, Alcyoniidae) | Yongxing Island, South Chian Sea, China | [73] |
| 5-[(2-Methoxyphenoxo)methyl]-1,3-oxazolidin-2-one (212) | 223 | C_{11}H_{13}NO_{4} | Black mold | Uzbekistan | [112] |
| Cyclopentanone oxime (213) | 99 | C_{4}H_{6}NO | Black mold | Uzbekistan | [113] |
| BR-011 (214) | 372 | C_{23}H_{32}O_{4} | Niphates sp. (Sponge, Niphatidae) | Near coral reef, Beibuwan Bay, GuangXi, China | [104] |
| β-Sitosterol (215) | 414 | C_{29}H_{50}O | Black mold | Uzbekistan | [112] |
Various illnesses are featured by unregulated and persistent angiogenesis [77,114]. The agents that inhibit angiogenesis have a substantial role in various diseases such as metastasis, cancer, hemangioma, arthritis, and ocular diseases [114]. Angiogenesis is a complicated multicellular process in which specified receptors and their ligands have a considerable role. It was reported that Tie2 receptor (tyrosine kinase receptor) and its ligands have an important function in angiogenesis [77,115].

Compounds 4, 6, 10, 11, 13, 16, and 17 are new phenylspirodrimane derivatives that were isolated by Zhao et al. along with 3, 12, 14, 21, and 28 from S. chartarum CGMCC-3.5365 by using SiO₂, RP, and HPLC. Their structures and configurations were established by spectral analyses, as well as X-ray, ECD (electronic circular dichroism), calculated ECD, and optical rotation. Stachybotrysin D (10) is an alcoholic O-sulfating derivative, whereas stachybotrysins F and G (16 and 17) have isobenzo-tetrahydrofuran moiety with a C-8’-attached acetonyl group. Their antiviral potential versus HIV-1 virus and influenza A virus (IAV) was estimated. Compounds 4, 11, 13, and 17 displayed weak anti-HIV capacity (IC₅₀ range 18.1–35.7 µM) compared to efavirenz (IC₅₀ 4.0 nM), however 11, 13, 14, 16, 17, and 21 possessed inhibitory effectiveness versus IAV (IC₅₀ range 12.4–45.6 µM) relative to ribavirion (IC₅₀ 2.0 nM). In the cytotoxicity MTT assay, 12, 13, and 17 revealed weak potential versus HepG2 cell (IC₅₀ 18.4, 24.7, and 24.6 µM, respectively) in comparison to paclitaxel (IC₅₀ 6.3 nM), besides, 12 was weakly active versus BGC823 and NCI-H460 cell lines (IC₅₀ 21.9 and 15.8 µM, respectively) [67]. These metabolites are terpenoid-polyketide hybrids that were proposed to be originated from ilicicolin B, which was established to be biosynthesized from farnesyldiphosphate and orsellinic acid (Scheme 1).

Scheme 1. Biosynthetic pathways of compounds 3, 4, 6, 10–13, 21, and 28 from ilicicolin B [67].
On the other side, 14, 16, and 17 featured an additional C3 chain bound to the phenolic unit, revealing their origin from a non-orsellinic acid precursor (Scheme 2). It was suggested that they had a polyketone precursor (1a) derived from an acetyl-CoA (starter) and 5 malonyl-CoA (extenders). The polyketone farnesylation, oxidation, and decarboxylation yield 1b. The latter undergoes several enzymatic cyclization to afford 14 and subsequent oxidation and non-stereoselective cyclization to form 16 and 17 [67].

Scheme 2. Biosynthetic pathway of 14, 16, and 17 [67].

Further, new phenylspirodrimanes; stachybotrysins H and I (18 and 19) and stachybotrin E (31) along with stachybotrylactam (29) were separated from S. chartarum CGMCC-3.5365 mycelia and filtrate EtOAc extract by SiO₂ CC and HPLC that were established by NMR and ECD analyses, as well as optical rotation [71]. They have 2R/3S/5S/8R/9R/10S/8'R, 2R/3S/5S/8R/9R/10S/8'S, and 3R/5S/8R/9R/10S configurations, respectively. Kv1.3 (voltage-gated K channel) controls both non-excitable and excitable cell membrane potential and has a remarkable contribution in Ca²⁺ signaling regulation [116]. It has been signaled as a pronounced target for remedial intervention, particularly for multiple sclerosis, type 1 diabetes, psoriasis, and autoimmune disorders [116]. Compounds 18 and 19 possessed Kv1.3 inhibitory effectiveness (IC₅₀ 13.4 and 10.9 μM, respectively) compared to clofazamine (IC₅₀ 2.01 μM) and PAP-1 (5-(4-phenoxybutoxy)psoralen, IC₅₀ 13.4 and 10.9 μM, respectively) in the Kv1.3 FLIPR (fluorometric imaging plate reader) thallium flux assay using CHO-Kv1.3 stable cell line [71].

Seven novel K-76 (2) derivatives, K-76-1 (36), K-76-2 (37), K-76-3 (59), K-76-4 (60), K-76-5 (61), K-76-6 (62), and k-76-7 (63), were purified from ethyl-methyl-ketone extract by flash SiO₂ CC and HPLC and elucidated by NMR and MS spectroscopic tools (Figure 1). They are drimane sesquiterpenoids having phenylspirodrimane moiety linked with an α,β-unsaturated γ-lactam ring. They differed in the hydroxylation at C-2 and the nature of the N-linked substituent of the γ-lactam ring [77]. These metabolites were assessed for their potency to prohibit the ATP ³²P incorporation into the Tie2 intracellular tyrosine kinase portion in the auto-phosphorylation reaction. All metabolites notably prohibited Tie2 kinase receptor (IC₅₀ ranging from 0.025 to 0.146 mM), where 60 was the most powerful one (IC₅₀ 0.025 mM) [77].

From the wetland strain, new phenylspirodrimanes, stachybotranes A–D (22, 23, 27, and 58) and formerly reported 20, 21, 24, 25, and 32, were purified by RP-18 and Sephadex
CC and HPLC and assigned via spectroscopic, X-ray, and CD analyses. Compounds 22/23 and 27/58 had 3R,5S,8S,9R,10S and 2R,3S,5S,8S,9R,10S configurations, respectively (Figure 2). Compounds 21, 22, and 23 were moderately cytotoxic (IC\(_{50}\) ranging from 9.23 to 31.22 µM) versus A-549, SMMC-7721, MCF-7, SW-480, and HL-60 in the MTT assay compared to cisplatin (IC\(_{50}\) 1.25–17.63 µM). The structure/activity relation demonstrated that the lactone groups had a positive influence on cytotoxicity compared with the lactam ring [72].

![Figure 1. Structures of phenylspirodrimane derivatives (1–12) reported from S. chartarum.](image)

The new phenylspirodrimanes; stachybonoids D–F (7, 47, and 48), in addition to stachybotrysin C (6), stachybotrylactone (20), and stachartin B (28), were separated using HPLC and SiO\(_2\) and Sephadex LH-20 CC and characterized based on spectral, X-ray, and ECD. These metabolites shared the same 2S,3S,8S,10S-configurations. Their inhibition capacity versus LPS-boosted NO production in RAW264.7 cells was estimated in the Griess assay. It was found that 6, 20, and 48 displayed moderate inhibition of NO production (IC\(_{50}\)
27.2, 17.9, and 52.5 μM, respectively) compared to indomethacin (IC$_{50}$ 37.5 μM), while 7, 47, and 28 were inactive [68]. Zhang et al. assumed that these metabolites are generated from the addition reaction of farnesyl diphosphate and orsellinic acid to produce an intermediate ilicicolin B (Scheme 3). After that, the epoxidation of the prenyl group terminal olefinic bond takes place and the aromatic OH group reacts with C2 of the prenyl group. This is followed by a series of reactions, including cyclization, addition, oxidation, and acetylation, to produce 6, 7, 20, 28, 47, and 48 [68].

Figure 2. Structures of phenylspirodrimane derivatives (13–26) reported from S. chartarum.
From *Xestospongia testudinaris*-associated *S. chartarum*, the new derivatives, stachybosides A (8) and B (9), stachybotrins D-F (34, 38, and 39), and stachybocins E (113) and F (114), along with 3, 5, 12, 36, and 51, were separated (Figure 3) and elucidated using spectroscopic tools and their configuration was estimated based on alpha D, modified Mosher’s and Marfey’s methods, and chemical hydrolysis. Compound 34 was like 36, except the side chain on the N-atom was replaced by an acetonyl group and had 3R/5S/8R/9R/10S configuration, whilst 38 and 39 are methylated derivatives 36 having the same alpha D but differing in the position of the methyl group. Besides, 113 and 114 are dimers that were structurally like 34 except for the replacement of the acetonyl moiety at nitrogen with two and three methylenes, respectively.

On the other side, 8 and 9 have glycosylated hydroxymethyl moiety instead of the hydroxymethyl group in 3, whereas 9, a 2-OH congener of 8, has 2R/3S/5S/8R/9R/0S configuration. Compound 34 prohibited HIV-1 replication towards 5 NNRTI-resistant and wild-type HIV-1 strains by targeting reverse transcriptase (EC₅₀ 6.2–23.8 µM) compared to nevirapine (EC₅₀ 0.023–51.9 µM) in the luciferase assay system [66] (Table 2).

**Scheme 3.** Biosynthetic pathway of 6, 7, 20, 28, 47, and 48 [68].
Figure 3. Structures of phenylspirodrimane derivatives (27–38) reported from *S. chartarum*. 

On the other side, 8 and 9 have glycosylated hydroxymethyl moiety instead of the hydroxymethyl group in 3, whereas 9, a 2-OH congener of 8, has 2R/3S/5S/8R/9R/0S conformation. Compound 34 prohibited HIV-1 replication towards 5 NNRTI-resistant and wild-type HIV-1 strains by targeting reverse transcriptase (EC 50 6.2–23.8 μM) compared to nevirapine (EC50 0.023–51.9 μM) in the luciferase assay system [66] (Table 2).
Table 2. List of biological activities of compounds isolated from *Stachybotrys chartarum*.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|-------------------------------|--------------------|------------------|------|
| Stachybotrysin B (4) | Anti-HIV-1 virus | Luciferase/VSV-G | 19.2 µM (IC₅₀) | Efavirenz 4.0 nM (IC₅₀) | [67] |
| Stachybotrysin C (6) | Antiinflammatory | Griess assay/RAW264.7 cells/ LPS-induced NO production inhibition | 27.2 µM (IC₅₀) | Indomethacin 37.5 µM (IC₅₀) | [68] |
| Stachybotrysin E (11) | Anti-HIV-1 virus | Luciferase/VSV-G | 20.5 µM (IC₅₀) | Efavirenz 4.0 nM (IC₅₀) | [67] |
| | Anti-influenza A virus | Luciferase/VSV-G | 45.6 µM (IC₅₀) | Ribavirion 2.0 nM (IC₅₀) | [67] |
| | Cytotoxicity | MTT/HepG2 | 36.2 µM (IC₅₀) | Paclitaxel 6.3 nM (IC₅₀) | [67] |
| F1839-I (12) | Anti-HIV-1 virus | Luciferase/VSV-G | 15.6 µM (IC₅₀) | Efavirenz 4.0 nM (IC₅₀) | [67] |
| | Cytotoxicity | MTT/NCI-H460 | 15.8 µM (IC₅₀) | Paclitaxel 1.0 nM (IC₅₀) | [67] |
| | | MTT/BGC823 | 21.9 µM (IC₅₀) | Paclitaxel 0.8 nM (IC₅₀) | [67] |
| | | MTT/Baoy | 41.5 µM (IC₅₀) | Paclitaxel 0.4 nM (IC₅₀) | [67] |
| | | MTT/HepG2 | 18.4 µM (IC₅₀) | Paclitaxel 6.3 nM (IC₅₀) | [67] |
| Stachybotrysin A (13) | Anti-HIV-1 virus | Luciferase/VSV-G | 19.6 µM (IC₅₀) | Efavirenz 4.0 nM (IC₅₀) | [67] |
| | Anti-influenza A virus | Luciferase/VSV-G | 12.4 µM (IC₅₀) | Ribavirion 2.0 nM (IC₅₀) | [67] |
| | Cytotoxicity | MTT/Baoy | 29.8 µM (IC₅₀) | Paclitaxel 0.4 nM (IC₅₀) | [67] |
| | | MTT/HepG2 | 24.7 µM (IC₅₀) | Paclitaxel 6.3 nM (IC₅₀) | [67] |
| Stachartin A = Stachybotrysin (14) | Anti-influenza A virus | Luciferase/VSV-G | 18.7 µM (IC₅₀) | Ribavirion 2.0 nM (IC₅₀) | [67] |
| | Cytotoxicity | MTT/HepG2 | 34.0 µM (IC₅₀) | Paclitaxel 6.3 nM (IC₅₀) | [67] |
| Stachybochartin G (15) | Cytotoxicity | MTT/MDA-MB231 | 5.6 µM (IC₅₀) | Doxorubicin 1.0 µM (IC₅₀) | [70] |
| | | MTT/U2-OS | 4.5 µM (IC₅₀) | Doxorubicin 1.2 µM (IC₅₀) | [70] |
| Stachybotrysin F (16) | Anti-HIV-1 virus | Luciferase/VSV-G | 35.7 µM (IC₅₀) | Efavirenz 4.0 nM (IC₅₀) | [67] |
| | Anti-influenza A virus | Luciferase/VSV-G | 14.6 µM (IC₅₀) | Ribavirion 2.0 nM (IC₅₀) | [67] |
| | Cytotoxicity | MTT/HCT116 | 48.5 µM (IC₅₀) | Paclitaxel 1.0 nM (IC₅₀) | [67] |
| | | MTT/NCI-H460 | 41.2 µM (IC₅₀) | Paclitaxel 1.0 nM (IC₅₀) | [67] |
| | | MTT/BGC823 | 41.7 µM (IC₅₀) | Paclitaxel 0.8 nM (IC₅₀) | [67] |
| | | MTT/Baoy | 30.6 µM (IC₅₀) | Paclitaxel 0.4 nM (IC₅₀) | [67] |
| | | MTT/HepG2 | 28.4 µM (IC₅₀) | Paclitaxel 6.3 nM (IC₅₀) | [67] |
| Stachybotrysin G (17) | Anti-HIV-1 virus | Luciferase/VSV-G | 18.1 µM (IC₅₀) | Efavirenz 4.0 nM (IC₅₀) | [67] |
| | Anti-influenza A virus | Luciferase/VSV-G | 23.4 µM (IC₅₀) | Ribavirion 2.0 nM (IC₅₀) | [67] |
| | Cytotoxicity | MTT/HCT116 | 44.6 µM (IC₅₀) | Paclitaxel 1.0 nM (IC₅₀) | [67] |
| | | MTT/NCI-H460 | 26.9 µM (IC₅₀) | Paclitaxel 1.0 nM (IC₅₀) | [67] |
| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|------------------------------|--------------------|------------------|------|
| MTT/BGC823    |                     |                              | 31.6 µM (IC₅₀)     | Paclitaxel 0.8 nM (IC₅₀) | [67] |
| MTT/Baoy      |                     |                              | 56.9 µM (IC₅₀)     | Paclitaxel 0.4 nM (IC₅₀) | [67] |
| MTT/HepG2     |                     |                              | 24.6 µM (IC₅₀)     | Paclitaxel 6.3 nM (IC₅₀) | [67] |
| Stachybotrysin H (18) | Potassium channel inhibition | Kv1.3 FLIPR thallium flux /CHO-Kv1.3 | 13.4 µM (IC₅₀) | -Clofazamine 2.01 µM (IC₅₀) | [71] |
| Stachybotrysin I (19) | Potassium channel inhibition | Kv1.3 FLIPR thallium flux /CHO-Kv1.3 | 10.9 µM (IC₅₀) | -Clofazamine 2.01 µM (IC₅₀) | [71] |
| Stachybotrylactone = Stachybotrolide (20) | Antiinflammatory | Griess assay /RAW264.7 cells / LPS-induced NO production inhibition | 17.9 µM (IC₅₀) | Indomethacin 37.5 µM (IC₅₀) | [68] |
| Stachybotrylactone acetate (21) | Cytotoxicity | MTT/HL-60, MTT/SMMC-7721, MTT/A-549, MTT/MCF-7, MTT/SW480, Luciferase/VSV-G | 11.44 µM (IC₅₀), 23.31 µM (IC₅₀), 22.84 µM (IC₅₀), 18.20 µM (IC₅₀), 17.28 µM (IC₅₀), 18.9 µM (IC₅₀) | Cisplatin 1.25 µM (IC₅₀), Cisplatin 7.77 µM (IC₅₀), Cisplatin 6.12 µM (IC₅₀), Cisplatin 17.63 µM (IC₅₀), Cisplatin 14.58 µM (IC₅₀), Ribavirin 2.0 nM (IC₅₀) | [72] |
| Stachybotrane A (22) | Cytotoxicity | MTT/HL-60, MTT/SMMC-7721, MTT/A-549, MTT/MCF-7 | 9.23 µM (IC₅₀), 19.67 µM (IC₅₀), 31.22 µM (IC₅₀), 18.74 µM (IC₅₀) | Cisplatin 1.25 µM (IC₅₀), Cisplatin 7.77 µM (IC₅₀), Cisplatin 6.12 µM (IC₅₀), Cisplatin 17.63 µM (IC₅₀) | [72] |
| Stachybotrane B (23) | Cytotoxicity | MTT/HL-60, MTT/SMMC-7721, MTT/MCF-7 | 15.08 µM (IC₅₀), 24.90 µM (IC₅₀), 29.34 µM (IC₅₀), 31.03 µM (IC₅₀) | Cisplatin 1.25 µM (IC₅₀), Cisplatin 7.77 µM (IC₅₀), Cisplatin 17.63 µM (IC₅₀), Cisplatin 14.58 µM (IC₅₀) | [72] |
| K-76-1 (36) | Tyrosine kinase inhibition | Radiometry/³³P | >0.2 mM (IC₅₀) | - | [77] |
| K-76-2 (37) | Tyrosine kinase inhibition | Radiometry/³³P | >0.031 mM (IC₅₀) | - | [77] |
| K-76-3 (38) | | | | | |
| Stachybonoid F (48) | Antiinflammatory | Griess assay /RAW264.7 cells / LPS-induced NO production inhibition | 52.5 µM (IC₅₀) | Indomethacin 37.5 µM (IC₅₀) | [68] |
| Stachybochartin G (51) | Cytotoxicity | MTT/MDA-MB231, MTT/U2-OS | 4.5 µM (IC₅₀), 5.6 µM (IC₅₀) | Cisplatin 11.3 µM (IC₅₀), Cisplatin 1.0 µM (IC₅₀), Cisplatin 5.9 µM (IC₅₀), Cisplatin 1.2 µM (IC₅₀) | [70] |
Table 2. Cont.

| Compound Name       | Biological Activity               | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref.   |
|---------------------|-----------------------------------|-------------------------------|--------------------|------------------|--------|
| K-76-3 (59)         | Tyrosine kinase inhibition        | Radiometry/\(^{33}\)P        | >0.4 mM (IC\(_{50}\)) | -                | [77]   |
| K-76-4 (60)         | Tyrosine kinase inhibition        | Radiometry/\(^{33}\)P        | >0.025 mM (IC\(_{50}\)) | -                | [77]   |
| K-76-5 (61)         | Tyrosine kinase inhibition        | Radiometry/\(^{33}\)P        | >0.097 mM (IC\(_{50}\)) | -                | [77]   |
| K-76-6 (62)         | Tyrosine kinase inhibition        | Radiometry/\(^{33}\)P        | >0.146 mM (IC\(_{50}\)) | -                | [77]   |
| K-76-7 (63)         | Tyrosine kinase inhibition        | Radiometry/\(^{33}\)P        | >0.046 mM (IC\(_{50}\)) | -                | [77]   |
| Bistachybotrysin A (73) | Cytotoxicity                   | MTT/HCT116                    | 6.7 µM (IC\(_{50}\))  | Paclitaxel 0.0038 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/NCI-H460                  | 7.5 µM (IC\(_{50}\))  | Paclitaxel 0.0004 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/BGC823                    | 14.2 µM (IC\(_{50}\)) | Paclitaxel 0.002 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/Daoy                      | 2.8 µM (IC\(_{50}\))  | Paclitaxel 0.0002 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/HepG2                     | 11.9 µM (IC\(_{50}\)) | Paclitaxel 0.0102 µM (IC\(_{50}\)) | [79]   |
| Bistachybotrysin B (74) | Cytotoxicity                   | MTT/HCT116                    | 18.0 µM (IC\(_{50}\)) | Paclitaxel 0.0038 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/NCI-H460                  | 5.5 µM (IC\(_{50}\))  | Paclitaxel 0.0004 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/BGC823                    | 6.6 µM (IC\(_{50}\))  | Paclitaxel 0.002 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/Daoy                      | 4.2 µM (IC\(_{50}\))  | Paclitaxel 0.0002 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/HepG2                     | 19.3 µM (IC\(_{50}\)) | Paclitaxel 0.0102 µM (IC\(_{50}\)) | [79]   |
| Bistachybotrysin C (75) | Cytotoxicity                   | MTT/HCT116                    | 19.1 µM (IC\(_{50}\)) | Paclitaxel 0.0038 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/NCI-H460                  | 12.3 µM (IC\(_{50}\)) | Paclitaxel 0.0004 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/BGC823                    | 19.2 µM (IC\(_{50}\)) | Paclitaxel 0.002 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/Daoy                      | 14.6 µM (IC\(_{50}\)) | Paclitaxel 0.0002 µM (IC\(_{50}\)) | [79]   |
|                     |                                  | MTT/HepG2                     | 19.3 µM (IC\(_{50}\)) | Paclitaxel 0.0102 µM (IC\(_{50}\)) | [79]   |
| Bistachybotrysin D (76) | Cytotoxicity                   | MTT/HCT116                    | 6.8 µM (IC\(_{50}\))  | Paclitaxel 0.00381 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/NCI-H460                  | 14.7 µM (IC\(_{50}\)) | Paclitaxel 0.000384 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/BGC823                    | 11.4 µM (IC\(_{50}\)) | Paclitaxel 0.00197 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/Daoy                      | 11.6 µM (IC\(_{50}\)) | Paclitaxel 0.000187 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/HepG2                     | 7.5 µM (IC\(_{50}\))  | Paclitaxel 0.0102 µM (IC\(_{50}\)) | [80]   |
|                     | Antiinflammatory                 | LPS/BV2/NO production inhibition | 61.1% at 10.0 µM | Curcumin 67.6% at 10.0 µM | [80]   |
| Bistachybotrysin E (77) | Cytotoxicity                   | MTT/HCT116                    | 8.9 µM (IC\(_{50}\))  | Paclitaxel 0.00381 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/NCI-H460                  | 19.0 µM (IC\(_{50}\)) | Paclitaxel 0.000384 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/BGC823                    | 6.7 µM (IC\(_{50}\))  | Paclitaxel 0.00197 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/Daoy                      | 59.0 µM (IC\(_{50}\)) | Paclitaxel 0.000187 µM (IC\(_{50}\)) | [80]   |
|                     |                                  | MTT/HepG2                     | 12.4 µM (IC\(_{50}\)) | Paclitaxel 0.0102 µM (IC\(_{50}\)) | [80]   |
| Compound Name       | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------------|---------------------|-------------------------------|--------------------|------------------|------|
| Bistachybotrysin F (78) | Cytotoxicity       | MTT/HCT116                     | 22.8 µM (IC50)     | Taxol 0.00381 µM (IC50) | [81] |
|                     |                     | MTT/NCI-H460                   | 22.5 µM (IC50)     | Taxol 0.000384 µM (IC50) | [81] |
|                     |                     | MTT/BGC823                     | 18.3 µM (IC50)     | Taxol 0.00197 µM (IC50) | [81] |
|                     |                     | MTT/Daoy                       | 61.8 µM (IC50)     | Taxol 0.000187 µM (IC50) | [81] |
|                     |                     | MTT/HepG2                      | 18.3 µM (IC50)     | Taxol 0.0102 µM (IC50) | [81] |
|                     |                     | MTT/NCI-H460                   | 22.5 µM (IC50)     | Taxol 0.000384 µM (IC50) | [81] |
|                     |                     | MTT/BGC823                     | 10.6 µM (IC50)     | Taxol 0.00197 µM (IC50) | [81] |
|                     |                     | MTT/Daoy                       | 20.7 µM (IC50)     | Taxol 0.000187 µM (IC50) | [81] |
|                     |                     | MTT/HepG2                      | 18.4 µM (IC50)     | Taxol 0.0102 µM (IC50) | [81] |
|                     |                     | MTT/NCI-H460                   | 19.9 µM (IC50)     | Taxol 0.000384 µM (IC50) | [81] |
|                     |                     | MTT/BGC823                     | 17.2 µM (IC50)     | Taxol 0.00197 µM (IC50) | [81] |
|                     |                     | MTT/Daoy                       | 18.4 µM (IC50)     | Taxol 0.00187 µM (IC50) | [81] |
| Bistachybotrysin G (79) | Cytotoxicity       | MTT/HepG2                      | 22.7 µM (IC50)     | Taxol 0.0102 µM (IC50) | [81] |
| Bistachybotrysin H (80) | Cytotoxicity       | MTT/HCT116                     | 20.7 µM (IC50)     | Taxol 0.00381 µM (IC50) | [81] |
|                     |                     | MTT/NCI-H460                   | 10.6 µM (IC50)     | Taxol 0.000384 µM (IC50) | [81] |
|                     |                     | MTT/BGC823                     | 21.1 µM (IC50)     | Taxol 0.00197 µM (IC50) | [81] |
|                     |                     | MTT/Daoy                       | 20.7 µM (IC50)     | Taxol 0.000187 µM (IC50) | [81] |
|                     |                     | MTT/HepG2                      | 18.4 µM (IC50)     | Taxol 0.0102 µM (IC50) | [81] |
| Bistachybotrysin I (81) | Cytotoxicity       | MTT/HCT116                     | 9.1 µM (IC50)      | Taxol 0.00381 µM (IC50) | [81] |
|                     |                     | MTT/NCI-H460                   | 19.9 µM (IC50)     | Taxol 0.000384 µM (IC50) | [81] |
|                     |                     | MTT/BGC823                     | 17.2 µM (IC50)     | Taxol 0.00197 µM (IC50) | [81] |
|                     |                     | MTT/Daoy                       | 18.4 µM (IC50)     | Taxol 0.00187 µM (IC50) | [81] |
|                     |                     | MTT/HepG2                      | 21.4 µM (IC50)     | Taxol 0.0102 µM (IC50) | [81] |
| Bistachybotrysin J (82) | Cytotoxicity       | MTT/HCT116                     | 15.8 µM (IC50)     | Taxol 0.00381 µM (IC50) | [81] |
|                     |                     | MTT/NCI-H460                   | 20.4 µM (IC50)     | Taxol 0.000384 µM (IC50) | [81] |
|                     |                     | MTT/BGC823                     | 16.9 µM (IC50)     | Taxol 0.00197 µM (IC50) | [81] |
|                     |                     | MTT/Daoy                       | 25.4 µM (IC50)     | Taxol 0.00187 µM (IC50) | [81] |
|                     |                     | MTT/HepG2                      | 12.2 µM (IC50)     | Taxol 0.0102 µM (IC50) | [81] |
| Bistachybotrysin K (83) | Cytotoxicity       | MTT/HCT116                     | 3.4 µM (IC50)      | Paclitaxel 0.0038 µM (IC50) | [82] |
|                     |                     | MTT/NCI-H460                   | 4.7 µM (IC50)      | Paclitaxel 0.0004 µM (IC50) | [82] |
|                     |                     | MTT/BGC823                     | 3.3 µM (IC50)      | Paclitaxel 0.0002 µM (IC50) | [82] |
|                     |                     | MTT/Daoy                       | 1.1 µM (IC50)      | Paclitaxel 0.0002 µM (IC50) | [82] |
|                     |                     | MTT/HepG2                      | 4.3 µM (IC50)      | Paclitaxel 0.0102 µM (IC50) | [82] |
| Bistachybotrysin L (84) | Neuroprotective    | MTT/SK-N-SH                    | 0.15 % at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
|                     | Cytotoxicity       | MTT/HCT116                     | 10.6 µM (IC50)     | Paclitaxel 0.038 µM (IC50) | [83] |
|                     |                     | MTT/NCI-H460                   | 13.5 µM (IC50)     | Paclitaxel 0.004 µM (IC50) | [83] |
|                     |                     | MTT/BGC823                     | 22.3 µM (IC50)     | Paclitaxel 0.002 µM (IC50) | [83] |
|                     |                     | MTT/HepG2                      | 18.9 µM (IC50)     | Paclitaxel 0.0102 µM (IC50) | [83] |
|                     | Antiinflammatory   | LPS/BV2/NO production inhibition | 5.31% at 10.0 µM | Curcumin 67.6% at 10.0 µM | [83] |
| Compound Name   | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|----------------|---------------------|-------------------------------|-------------------|------------------|-----|
| Bistachybotrysin M (85) | Neuroprotective | MTT/SK-N-SH                     | 17.4 % at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
|                 | Cytotoxicity       | MTT/HCT116                      | 2.5 µM (IC₅₀)     | Paclitaxel 0.0038 µM (IC₅₀) | [83] |
|                 |                     | MTT/NCI-H460                    | 3.5 µM (IC₅₀)     | Paclitaxel 0.0004 µM (IC₅₀) | [83] |
|                 |                     | MTT/BGC823                      | 1.8 µM (IC₅₀)     | Paclitaxel 0.002 µM (IC₅₀) | [83] |
|                 |                     | MTT/Daoy                        | 2.4 µM (IC₅₀)     | Paclitaxel 0.0002 µM (IC₅₀) | [83] |
|                 |                     | MTT/HepG2                       | 2.2 µM (IC₅₀)     | Paclitaxel 0.0102 µM (IC₅₀) | [83] |
| Bistachybotrysin N (86) | Neuroprotective | MTT/SK-N-SH                     | 17.6 % at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
|                 | Cytotoxicity       | MTT/HCT116                      | 64.5 µM (IC₅₀)    | Paclitaxel 0.0038 µM (IC₅₀) | [83] |
|                 |                     | MTT/NCI-H460                    | 8.3 µM (IC₅₀)     | Paclitaxel 0.0004 µM (IC₅₀) | [83] |
|                 |                     | MTT/BGC823                      | 12.5 µM (IC₅₀)    | Paclitaxel 0.002 µM (IC₅₀) | [83] |
|                 |                     | MTT/Daoy                        | 61.4 µM (IC₅₀)    | Paclitaxel 0.0002 µM (IC₅₀) | [83] |
|                 |                     | MTT/HepG2                       | 56.1 µM (IC₅₀)    | Paclitaxel 0.0102 µM (IC₅₀) | [83] |
| Bistachybotrysin O (87) | Neuroprotective | MTT/SK-N-SH                     | 8.4 % at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
|                 | Cytotoxicity       | MTT/HCT116                      | 18.8 µM (IC₅₀)    | Paclitaxel 0.0038 µM (IC₅₀) | [83] |
|                 |                     | MTT/NCI-H460                    | 11.5 µM (IC₅₀)    | Paclitaxel 0.0004 µM (IC₅₀) | [83] |
|                 |                     | MTT/BGC823                      | 20.5 µM (IC₅₀)    | Paclitaxel 0.002 µM (IC₅₀) | [83] |
|                 |                     | MTT/Daoy                        | 10.7 µM (IC₅₀)    | Paclitaxel 0.0002 µM (IC₅₀) | [83] |
|                 |                     | MTT/HepG2                       | 20.1 µM (IC₅₀)    | Paclitaxel 0.0102 µM (IC₅₀) | [83] |
| Bistachybotrysin P (88) | Antiinflammatory | LPS/BV2/NO production inhibition | 12.9% at 10.0 µM | Curcumin 67.6% at 10.0 µM | [83] |
| Bistachybotrysin Q (89) | Antiinflammatory | LPS/BV2/NO production inhibition | 10.1% at 10.0 µM | Curcumin 67.6% at 10.0 µM | [83] |
|                 | Cytotoxicity       | MTT/HCT116                      | 18.5 µM (IC₅₀)    | Paclitaxel 0.038 µM (IC₅₀) | [83] |
|                 |                     | MTT/NCI-H460                    | 8.8 µM (IC₅₀)     | Paclitaxel 0.004 µM (IC₅₀) | [83] |
|                 |                     | MTT/BGC823                      | 55.4 µM (IC₅₀)    | Paclitaxel 0.002 µM (IC₅₀) | [83] |
|                 |                     | MTT/Daoy                        | 17.3 µM (IC₅₀)    | Paclitaxel 0.0002 µM (IC₅₀) | [83] |
|                 |                     | MTT/HepG2                       | 14.1 µM (IC₅₀)    | Paclitaxel 0.0102 µM (IC₅₀) | [83] |
| Bistachybotrysin R (90) | Cytotoxicity       | MTT/HCT116                      | 8.8 µM (IC₅₀)     | Paclitaxel 0.0038 µM (IC₅₀) | [83] |
|                 |                     | MTT/NCI-H460                    | 8.2 µM (IC₅₀)     | Paclitaxel 0.0004 µM (IC₅₀) | [83] |
|                 |                     | MTT/BGC823                      | 17.8 µM (IC₅₀)    | Paclitaxel 0.002 µM (IC₅₀) | [83] |
|                 |                     | MTT/Daoy                        | 13.1 µM (IC₅₀)    | Paclitaxel 0.0002 µM (IC₅₀) | [83] |
|                 |                     | MTT/HepG2                       | 9.4 µM (IC₅₀)     | Paclitaxel 0.0102 µM (IC₅₀) | [83] |
Table 2. Cont.

| Compound Name          | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|------------------------|---------------------|-------------------------------|--------------------|------------------|------|
| Bistachybotrysin S (91)| Neuroprotective     | MTT/SK-N-SH                   | 6.5% at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
|                        | Cytotoxicity        | MTT/HCT116                    | 8.0 µM (IC<sub>50</sub>) | Paclitaxel 0.0038 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/NCI-H460                  | 11.7 µM (IC<sub>50</sub>) | Paclitaxel 0.0004 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/BGC823                    | 8.7 µM (IC<sub>50</sub>) | Paclitaxel 0.002 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/Daoy                      | 11.8 µM (IC<sub>50</sub>) | Paclitaxel 0.0002 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/HepG2                     | 6.0 µM (IC<sub>50</sub>) | Paclitaxel 0.0102 µM (IC<sub>50</sub>) | [83] |
|                        | Antinflammatory     | LPS/BV2/NO production inhibition | 54.2% at 10.0 µM | Curcumin 67.6% at 10.0 µM | [83] |
| Bistachybotrysin T (92)| Neuroprotective     | MTT/SK-N-SH                   | 17.4% at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
| Bistachybotrysin U (93)| Neuroprotective     | MTT/SK-N-SH                   | 9.3% at 10.0 µM, ↑ cell viability | Resveratrol 16.1% at 10.0 µM, ↑ cell viability | [83] |
|                        | Cytotoxicity        | MTT/HCT116                    | 9.7 µM (IC<sub>50</sub>) | Paclitaxel 0.038 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/NCI-H460                  | 10.1 µM (IC<sub>50</sub>) | Paclitaxel 0.004 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/BGC823                    | 9.8 µM (IC<sub>50</sub>) | Paclitaxel 0.002 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/Daoy                      | 8.1 µM (IC<sub>50</sub>) | Paclitaxel 0.0002 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/HepG2                     | 9.4 µM (IC<sub>50</sub>) | Paclitaxel 0.0102 µM (IC<sub>50</sub>) | [83] |
| Bistachybotrysin V (94)| Cytotoxicity        | MTT/HCT116                    | 15.0 µM (IC<sub>50</sub>) | Paclitaxel 0.0038 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/NCI-H460                  | 10.9 µM (IC<sub>50</sub>) | Paclitaxel 0.0004 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/BGC823                    | 23.9 µM (IC<sub>50</sub>) | Paclitaxel 0.002 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/Daoy                      | 27.7 µM (IC<sub>50</sub>) | Paclitaxel 0.0002 µM (IC<sub>50</sub>) | [83] |
|                        |                     | MTT/HepG2                     | 12.9 µM (IC<sub>50</sub>) | Paclitaxel 0.0102 µM (IC<sub>50</sub>) | [83] |
| Bistachybotrysin W (95)| Cytotoxicity        | MTT/HCT116                    | 12.1 µM (IC<sub>50</sub>) | Paclitaxel 0.0038 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/NCI-H460                  | 11.5 µM (IC<sub>50</sub>) | Paclitaxel 0.0004 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/BGC823                    | 13.2 µM (IC<sub>50</sub>) | Paclitaxel 0.002 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/Daoy                      | 8.8 µM (IC<sub>50</sub>) | Paclitaxel 0.0002 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/HepG2                     | 7.0 µM (IC<sub>50</sub>) | Paclitaxel 0.0102 µM (IC<sub>50</sub>) | [84] |
| Bistachybotrysin X (96)| Cytotoxicity        | MTT/HCT116                    | 22.6 µM (IC<sub>50</sub>) | Paclitaxel 0.0038 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/NCI-H460                  | 10.8 µM (IC<sub>50</sub>) | Paclitaxel 0.0004 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/BGC823                    | 15.1 µM (IC<sub>50</sub>) | Paclitaxel 0.002 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/Daoy                      | 21.5 µM (IC<sub>50</sub>) | Paclitaxel 0.0002 µM (IC<sub>50</sub>) | [84] |
|                        |                     | MTT/HepG2                     | 11.5 µM (IC<sub>50</sub>) | Paclitaxel 0.0102 µM (IC<sub>50</sub>) | [84] |
| Compound Name                | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control                          | Ref. |
|------------------------------|---------------------|-------------------------------|--------------------|------------------------------------------|------|
| **Bistachybotrysin Y (97)**  | Cytotoxicity        | MTT/HCT116                    | 5.9 µM (IC$_{50}$) | Paclitaxel 0.0038 µM (IC$_{50}$) [84]     |      |
|                              |                     | MTT/NCI-H460                  | 13.0 µM (IC$_{50}$) | Paclitaxel 0.0004 µM (IC$_{50}$) [84]     |      |
|                              |                     | MTT/BGC823                    | 14.1 µM (IC$_{50}$) | Paclitaxel 0.002 µM (IC$_{50}$) [84]      |      |
|                              |                     | MTT/Daoy                      | 6.4 µM (IC$_{50}$)  | Paclitaxel 0.0002 µM (IC$_{50}$) [84]     |      |
|                              |                     | MTT/HepG2                     | 9.8 µM (IC$_{50}$)  | Paclitaxel 0.0102 µM (IC$_{50}$) [84]     |      |
| **Chartarolide A (98)**      | Cytotoxicity        | MTT/HCT-116                   | 1.9 µM (IC$_{50}$)  | Taxol 0.03 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/HepG2                     | 1.8 µM (IC$_{50}$)  | Taxol 0.02 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/BGC-823                   | 1.3 µM (IC$_{50}$)  | Taxol 0.001 µM (IC$_{50}$) [85]           |      |
|                              |                     | MTT/NCI-H1650                 | 5.5 µM (IC$_{50}$)  | Taxol 0.07 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/A2780                     | 1.5 µM (IC$_{50}$)  | Taxol 0.03 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/MCF-7                     | 1.4 µM (IC$_{50}$)  | Taxol 0.09 µM (IC$_{50}$) [85]            |      |
| Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | 2.6 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
|                              | Spectrophotometric/IGF1R | 6.8 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
|                              | Spectrophotometric/PDGFRb | 9.1 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
|                              | Spectrophotometric/TRKB | 8.0 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
| **Chartarolide B (99)**      | Cytotoxicity        | MTT/HCT-116                   | 2.3 µM (IC$_{50}$)  | Taxol 0.03 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/HepG2                     | 2.8 µM (IC$_{50}$)  | Taxol 0.02 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/BGC-823                   | 1.6 µM (IC$_{50}$)  | Taxol 0.001 µM (IC$_{50}$) [85]           |      |
|                              |                     | MTT/NCI-H1650                 | 4.8 µM (IC$_{50}$)  | Taxol 0.07 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/A2780                     | 3.2 µM (IC$_{50}$)  | Taxol 0.03 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/MCF-7                     | 3.8 µM (IC$_{50}$)  | Taxol 0.09 µM (IC$_{50}$) [85]            |      |
| Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | 4.9 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
|                              | Spectrophotometric/IGF1R | 8.4 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
|                              | Spectrophotometric/PDGFRb | 20.3 µM (IC$_{50}$)       | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
|                              | Spectrophotometric/TRKB | 11.3 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
| **Chartarolide C (100)**     | Cytotoxicity        | MTT/HCT-116                   | 7.8 µM (IC$_{50}$)  | Taxol 0.03 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/HepG2                     | 8.9 µM (IC$_{50}$)  | Taxol 0.02 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/BGC-823                   | 5.4 µM (IC$_{50}$)  | Taxol 0.001 µM (IC$_{50}$) [85]           |      |
|                              |                     | MTT/NCI-H1650                 | 11.3 µM (IC$_{50}$) | Taxol 0.07 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/A2780                     | 12.5 µM (IC$_{50}$) | Taxol 0.03 µM (IC$_{50}$) [85]            |      |
|                              |                     | MTT/MCF-7                     | 8.7 µM (IC$_{50}$)  | Taxol 0.09 µM (IC$_{50}$) [85]            |      |
| Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | 21.4 µM (IC$_{50}$)        | Satratoxin H <0.5 µM (IC$_{50}$) [85]   |                      |      |
| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|-------------------------------|--------------------|------------------|------|
| Chartarlactam Q (101) | Antibacterial | Broth microdilution / S. aureus ATCC 29213 | 8.0 µg/mL (MIC) | Chloramphenicol 1.0 µg/mL (MIC) | [86] |
| Chartarlactam R (102) | Antibacterial | Broth microdilution / S. aureus ATCC 29213 | 16.0 µg/mL (MIC) | Chloramphenicol 1.0 µg/mL (MIC) | [86] |
| Chartarlactam S (103) | Antibacterial | Broth microdilution / S. aureus ATCC 29213 | 4.0 µg/mL (MIC) | Chloramphenicol 1.0 µg/mL (MIC) | [86] |
| Stachybochartin A (105) | Cytotoxicity | MTT/MDA-MB231 | 21.7 µM (IC₅₀) | -Cisplatin 11.3 µM (IC₅₀) -Doxorubicin 1.0 µM (IC₅₀) -Cisplatin 5.9 µM (IC₅₀) -Doxorubicin 1.2 µM (IC₅₀) | [70] |
| Stachybochartin B (106) | Cytotoxicity | MTT/MDA-MB231 | 17.6 µM (IC₅₀) | -Cisplatin 11.3 µM (IC₅₀) -Doxorubicin 1.0 µM (IC₅₀) -Cisplatin 5.9 µM (IC₅₀) -Doxorubicin 1.2 µM (IC₅₀) | [70] |
| Stachybochartin C (107) | Cytotoxicity | MTT/MDA-MB231 | 11.6 µM (IC₅₀) | -Cisplatin 11.3 µM (IC₅₀) -Doxorubicin 1.0 µM (IC₅₀) -Cisplatin 5.9 µM (IC₅₀) -Doxorubicin 1.2 µM (IC₅₀) | [70] |
| Stachybochartin D (108) | Cytotoxicity | MTT/MDA-MB231 | 10.4 µM (IC₅₀) | -Cisplatin 11.3 µM (IC₅₀) -Doxorubicin 1.0 µM (IC₅₀) -Cisplatin 5.9 µM (IC₅₀) -Doxorubicin 1.2 µM (IC₅₀) | [70] |
| Stachyin B (109) | Antibacterial | Broth microdilution / S. aureus ATCC 29213 | 4.0 µg/mL (MIC) | Chloramphenicol 1.0 µg/mL (MIC) | [86] |
| 2,4,12-Trihydroxyapotrichothecene (116) | Cytotoxicity | MTT/HCT-116 | 0.87 µM (IC₅₀) | Taxol 0.03 µM (IC₅₀) | [92] |
| | | MTT/HepG2 | 0.69 µM (IC₅₀) | Taxol 0.01 µM (IC₅₀) | [92] |
| | | MTT/BGC-823 | 0.65 µM (IC₅₀) | Taxol 0.01 µM (IC₅₀) | [92] |
| | | MTT/NCI-H1650 | 0.84 µM (IC₅₀) | Taxol 0.04 µM (IC₅₀) | [92] |
| | | MTT/A2780 | 0.69 µM (IC₅₀) | Taxol 0.01 µM (IC₅₀) | [92] |
| | | | Tumor-related kinases inhibition | Spectophotometric / FGFR3 | 0.5 µM (IC₅₀) | [92] |
| Compound Name       | Biological Activity                  | Assay, Organism, or Cell Line | Biological Results | Positive Control                  | Ref. |
|---------------------|--------------------------------------|-------------------------------|--------------------|-----------------------------------|------|
| Chartarene A (117)  | Cytotoxicity                         | MTT/HCT-116                   | 3.39 µM (IC_{50})  | Taxol 0.03 µM (IC_{50})          | [92] |
|                     |                                      | MTT/HepG2                     | 3.95 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/BGC-823                   | 2.87 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/A2780                     | 2.38 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     | Tumor-related kinases inhibition     | Spectrophotometric/FGFR3      | 5.58 µM (IC_{50})  | Taxol 0.03 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/IGF1R      | 6.9 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/PDGFRb     | 10.4 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/TRKB       | 7.0 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/WT         | 12.9 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
| Chartarene B (118)  | Cytotoxicity                         | MTT/HCT-116                   | 5.58 µM (IC_{50})  | Taxol 0.03 µM (IC_{50})          | [92] |
|                     |                                      | MTT/HepG2                     | 6.9 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/BGC-823                   | 10.4 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/A2780                     | 7.0 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     | Tumor-related kinases inhibition     | Spectrophotometric/FGFR3      | 1.1 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/IGF1R      | 3.0 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/PDGFRb     | 5.3 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/TRKB       | 2.7 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/WT         | 6.3 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
| Chartarene C (119)  | Cytotoxicity                         | MTT/HCT-116                   | 0.74 µM (IC_{50})  | Taxol 0.03 µM (IC_{50})          | [92] |
|                     |                                      | MTT/HepG2                     | 2.09 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/NCI-H1650                 | 2.58 µM (IC_{50})  | Taxol 0.04 µM (IC_{50})          | [92] |
|                     |                                      | MTT/A2780                     | 2.07 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     | Tumor-related kinases inhibition     | Spectrophotometric/FGFR3      | 1.1 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/IGF1R      | 3.0 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/PDGFRb     | 5.3 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/TRKB       | 2.7 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/WT         | 6.3 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
| Trichodermol (120)  | Cytotoxicity                         | MTT/HCT-116                   | 7.22 µM (IC_{50})  | Taxol 0.03 µM (IC_{50})          | [92] |
|                     |                                      | MTT/HepG2                     | 3.69 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/BGC-823                   | 2.55 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | MTT/NCI-H1650                 | 2.68 µM (IC_{50})  | Taxol 0.04 µM (IC_{50})          | [92] |
|                     |                                      | MTT/A2780                     | 2.68 µM (IC_{50})  | Taxol 0.01 µM (IC_{50})          | [92] |
|                     | Tumor-related kinases inhibition     | Spectrophotometric/FGFR3      | 0.9 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/IGF1R      | 0.8 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/PDGFRb     | 3.1 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
|                     |                                      | Spectrophotometric/TRKB       | 1.8 µM (IC_{50})   | Taxol 0.01 µM (IC_{50})          | [92] |
| Compound Name              | Biological Activity                     | Assay, Organism, or Cell Line | Biological Results         | Positive Control          | Ref. |
|---------------------------|-----------------------------------------|-------------------------------|-----------------------------|---------------------------|------|
|                          |                                          | Spectrophotometric/WT         | 3.0 μM (IC₅₀)              | -                         | [92] |
| Isotrichoverrol B (123)   | Cytotoxicity                            | MTT/HCT-116                   | 3.48 μM (IC₅₀)             | Taxol 0.03 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/HepG2                     | 2.62 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/BGC-823                   | 2.64 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/NCI-H1650                 | 2.36 μM (IC₅₀)             | Taxol 0.04 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/A2780                     | 2.12 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           | Tumor-related kinases inhibition         | Spectrophotometric/FGFR3      | 24.0 μM (IC₅₀)             | -                         | [92] |
| Verrol (124)              | Cytotoxicity                            | MTT/HCT-116                   | 2.77 μM (IC₅₀)             | Taxol 0.03 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/HepG2                     | 1.45 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/BGC-823                   | 2.33 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/NCI-H1650                 | 2.68 μM (IC₅₀)             | Taxol 0.04 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/A2780                     | 2.00 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           | Tumor-related kinases inhibition         | Spectrophotometric/FGFR3      | 0.1 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/IGF1R      | 0.2 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/PDGFRb     | 0.7 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/TRKB       | 0.4 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/WT         | 0.9 μM (IC₅₀)              | -                         | [92] |
| Trichodermadienediol B (128) | Cytotoxicity                            | MTT/HCT-116                   | 1.65 μM (IC₅₀)             | Taxol 0.03 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/HepG2                     | 0.86 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/BGC-823                   | 0.81 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/NCI-H1650                 | 1.31 μM (IC₅₀)             | Taxol 0.04 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/A2780                     | 0.68 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           | Tumor-related kinases inhibition         | Spectrophotometric/FGFR3      | 0.5 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/IGF1R      | 0.7 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/PDGFRb     | 1.9 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/TRKB       | 1.0 μM (IC₅₀)              | -                         | [92] |
|                           |                                          | Spectrophotometric/WT         | 1.9 μM (IC₅₀)              | -                         | [92] |
| Roridin L-2 (129)         | Cytotoxicity                            | MTT/HCT-116                   | 1.73 μM (IC₅₀)             | Taxol 0.03 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/HepG2                     | 1.20 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/BGC-823                   | 1.81 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/NCI-H1650                 | 2.36 μM (IC₅₀)             | Taxol 0.04 μM (IC₅₀)      | [92] |
|                           |                                         | MTT/A2780                     | 1.61 μM (IC₅₀)             | Taxol 0.01 μM (IC₅₀)      | [92] |
| Compound Name       | Biological Activity                  | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------------|--------------------------------------|-------------------------------|--------------------|------------------|------|
| Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | 0.4 µM (IC₅₀) | -                  | [92]              |
|                     | Spectrophotometric/IGF1R            | 0.5 µM (IC₅₀) | -                  | [92]              |
|                     | Spectrophotometric/PDGFRb           | 2.3 µM (IC₅₀) | -                  | [92]              |
|                     | Spectrophotometric/TRKB             | 1.9 µM (IC₅₀) | -                  | [92]              |
|                     | Spectrophotometric/WT               | 1.7 µM (IC₅₀) | -                  | [92]              |
| Chartarene D (130)  | Cytotoxicity                         | MTT/HCT-116                  | 1.48 µM (IC₅₀)     | Taxol 0.03 µM (IC₅₀) | [92] |
|                     |                                     | MTT/HepG2                    | 0.90 µM (IC₅₀)     | Taxol 0.01 µM (IC₅₀) | [92] |
|                     |                                     | MTT/BGC-823                  | 0.68 µM (IC₅₀)     | Taxol 0.01 µM (IC₅₀) | [92] |
|                     |                                     | MTT/NCI-H1650                | 2.23 µM (IC₅₀)     | Taxol 0.04 µM (IC₅₀) | [92] |
|                     |                                     | MTT/A2780                    | 0.69 µM (IC₅₀)     | Taxol 0.01 µM (IC₅₀) | [92] |
|                     | Tumor-related kinases inhibition    | Spectrophotometric/FGFR3     | 0.1 µM (IC₅₀)      | -                | [92] |
|                     | Spectrophotometric/IGF1R            | 0.1 µM (IC₅₀)                | -                  | [92]              |
|                     | Spectrophotometric/PDGFRb           | 0.8 µM (IC₅₀)                | -                  | [92]              |
|                     | Spectrophotometric/TRKB             | 0.7 µM (IC₅₀)                | -                  | [92]              |
|                     | Spectrophotometric/WT               | 0.7 µM (IC₅₀)                | -                  | [92]              |
| Roridin E (134)     | Cytotoxicity                         | MTT/HCT-116                  | <0.01 µM (IC₅₀)    | Taxol 0.03 µM (IC₅₀) | [92] |
|                     |                                     | MTT/HepG2                    | <0.01 µM (IC₅₀)    | Taxol 0.01 µM (IC₅₀) | [92] |
|                     |                                     | MTT/BGC-823                  | <0.01 µM (IC₅₀)    | Taxol 0.01 µM (IC₅₀) | [92] |
|                     |                                     | MTT/NCI-H1650                | <0.01 µM (IC₅₀)    | Taxol 0.04 µM (IC₅₀) | [92] |
|                     |                                     | MTT/A2780                    | <0.01 µM (IC₅₀)    | Taxol 0.01 µM (IC₅₀) | [92] |
|                     | Tumor-related kinases inhibition    | Spectrophotometric/FGFR3     | 0.4 µM (IC₅₀)      | -                | [92] |
|                     | Spectrophotometric/IGF1R            | 0.4 µM (IC₅₀)                | -                  | [92]              |
|                     | Spectrophotometric/PDGFRb           | 1.4 µM (IC₅₀)                | -                  | [92]              |
|                     | Spectrophotometric/TRKB             | 1.0 µM (IC₅₀)                | -                  | [92]              |
|                     | Spectrophotometric/WT               | 2.1 µM (IC₅₀)                | -                  | [92]              |
| Muconomycin B (139) | Cytotoxicity                         | MTT/HCT-116                  | 1.32 µM (IC₅₀)     | Taxol 0.03 µM (IC₅₀) | [92] |
|                     |                                     | MTT/HepG2                    | 0.81 µM (IC₅₀)     | Taxol 0.01 µM (IC₅₀) | [92] |
|                     |                                     | MTT/BGC-823                  | 0.84 µM (IC₅₀)     | Taxol 0.01 µM (IC₅₀) | [92] |
|                     |                                     | MTT/NCI-H1650                | 0.86 µM (IC₅₀)     | Taxol 0.04 µM (IC₅₀) | [92] |
|                     |                                     | MTT/A2780                    | 0.68 µM (IC₅₀)     | Taxol 0.01 µM (IC₅₀) | [92] |
Table 2. Cont.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|-------------------------------|--------------------|------------------|------|
| Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | 0.3 µM (IC<sub>50</sub>) | - | [92] |
| | Spectrophotometric/IGF1R | 0.4 µM (IC<sub>50</sub>) | - | [92] |
| | Spectrophotometric/PDGFRb | 1.2 µM (IC<sub>50</sub>) | - | [92] |
| | Spectrophotometric/TRKB | 0.7 µM (IC<sub>50</sub>) | - | [92] |
| | Spectrophotometric/WT | 1.5 µM (IC<sub>50</sub>) | - | [92] |
| Satratoxin F (140) | Antibacterial | Serial dilution/Methicillin-resistant S. aureus ATCC 29213 | 39.0 µg/mL (MIC) | Ampicillin 10.0 µg/mL (MIC) | [73] |
| Satratoxin G (142) | Cytotoxicity | MTT/HCT-116 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.03 µM (IC<sub>50</sub>) | [92] |
| | | MTT/HepG2 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | | MTT/BGC-823 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | | MTT/NCI-H1650 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.04 µM (IC<sub>50</sub>) | [92] |
| | | MTT/A2780 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | 0.1 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/IGF1R | 0.1 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/PDGFRb | 0.5 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/TRKB | 0.2 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/WT | 0.9 µM (IC<sub>50</sub>) | - | [92] |
| Satratoxin H (144) | Cytotoxicity | MTT/HCT-116 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.03 µM (IC<sub>50</sub>) | [92] |
| | | MTT/HepG2 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | | MTT/BGC-823 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | | MTT/NCI-H1650 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.04 µM (IC<sub>50</sub>) | [92] |
| | | MTT/A2780 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | Tumor-related kinases inhibition | Spectrophotometric/FGFR3 | <0.1 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/IGF1R | <0.1 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/PDGFRb | <0.1 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/TRKB | <0.1 µM (IC<sub>50</sub>) | - | [92] |
| | | Spectrophotometric/WT | 0.1 µM (IC<sub>50</sub>) | - | [92] |
| Mytoxin A (146) | Cytotoxicity | MTT/HCT-116 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.03 µM (IC<sub>50</sub>) | [92] |
| | | MTT/HepG2 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | | MTT/BGC-823 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.01 µM (IC<sub>50</sub>) | [92] |
| | | MTT/NCI-H1650 | <0.01 µM (IC<sub>50</sub>) | Taxol 0.04 µM (IC<sub>50</sub>) | [92] |
| Compound Name          | Biological Activity          | Assay, Organism, or Cell Line     | Biological Results       | Positive Control          | Ref. |
|-----------------------|------------------------------|----------------------------------|--------------------------|---------------------------|------|
| Chartarutine A (147)  | Anti-HIV virus               | Luciferase/VSV-G                 | 74.00 μM (IC₅₀)          | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine B (148)  | Anti-HIV virus               | Luciferase/VSV-G                 | 4.90 μM (IC₅₀)           | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine C (149)  | Anti-HIV virus               | Luciferase/VSV-G                 | 24.00 μM (IC₅₀)          | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine D (150)  | Anti-HIV virus               | Luciferase/VSV-G                 | 51.76 μM (IC₅₀)          | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine E (151)  | Anti-HIV virus               | Luciferase/VSV-G                 | 40.70 μM (IC₅₀)          | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine F (152)  | Anti-HIV virus               | Luciferase/VSV-G                 | 18.63 μM (IC₅₀)          | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine G (153)  | Anti-HIV virus               | Luciferase/VSV-G                 | 5.57 μM (IC₅₀)           | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Chartarutine H (154)  | Anti-HIV virus               | Luciferase/VSV-G                 | 5.58 μM (IC₅₀)           | Efavirenz 0.65 μM (IC₅₀)  | [104]|
| Stachybotrysam A (156)| Anti-HIV virus               | Luciferase/293T cells            | 9.3 μM (IC₅₀)            | Efavirenz 2.0 nM (IC₅₀)   | [76] |
| Stachybotrysam B (157)| Anti-HIV virus               | Luciferase/293T cells            | 1.0 μM (IC₅₀)            | Efavirenz 2.0 nM (IC₅₀)   | [76] |
| Stachybotrysam C (158)| Anti-HIV virus               | Luciferase/293T cells            | 9.6 μM (IC₅₀)            | Efavirenz 2.0 nM (IC₅₀)   | [76] |
| Atranone Q (180)      | Cytotoxicity                 | MTT/MG-63                        | 8.6 μM (IC₅₀)            | 5-FU 10.4 μM (IC₅₀)       | [62] |
|                       |                              | Broth microdilution/S. aureus ATCC 43300 | 32.0 μg/mL (MIC)         | Vancomycin 0.5 μg/mL (MIC)| [61] |
|                       |                              | Broth microdilution/E. faecalis ATCC 29212 | 16.0 μg/mL (MIC)         | Vancomycin 0.5 μg/mL (MIC)| [61] |
|                       |                              | Broth microdilution/C. albicans ATCC 10231 | 8.0 μg/mL (MIC)          | Fluconazole 1.0 μg/mL (MIC)| [61] |
| Stachastranone B (186)| Antimicrobial                | Broth microdilution/A. baumannii ATCC 19606 | 16.0 μg/mL (MIC)         | Ceftriaxone 8 μg/mL (MIC) | [61] |
| Stachybotrychromene A (193)| Cytotoxicity             | Alamar Blue assay/HepG2          | 73.7 μM (IC₅₀)           | -                          | [64] |
| Stachybotrychromene B (194)| Cytotoxicity             | Alamar Blue assay/HepG2          | 28.2 μM (IC₅₀)           | -                          | [64] |
| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|-------------------------------|--------------------|-----------------|------|
| *Epi*-cochlioquinone A (199) | Human chemokine antagonist | CCR-5 | 4.0 µM (IC₅₀) | - | [109] |
| 11-O-Methyl-epi-cochlioquinone A (200) | Human chemokine antagonist | CCR-5 | 7.0 µM (IC₅₀) | - | [109] |
| Cyclosporin A (209) | Immunosuppressant | Lymphocyte murine inhibition/MLR | 9.9 ng/mL (IC₅₀) | - | [111] |
| | | Mitogen suppression/ConA | 21.9 ng/mL (IC₅₀) | - | [111] |
| | | Skin grafting, TGF-β/ | 19.0 day (Median survival time)/100 | Vehicle treated group (Olive oil) | [111] |
| | | radioimmunoprecipitation | mg/kg orally | | |
| FR901459 A (210) | Immunosuppressant | Lymphocyte murine inhibition/MLR | 26.8 ng/mL (IC₅₀) | - | [111] |
| | | Mitogen suppression/ConA | 50.1 ng/mL (IC₅₀) | - | [111] |
| | | Skin grafting, TGF-β/ | 10.0 day (Median survival time)/100 | Vehicle treated group (Olive oil) | [111] |
| | | radioimmunoprecipitation | mg/kg orally | | |
| Arthproliferin A (211) | Antibacterial | Serial dilution/Methicillin-resistant *S. aureus* ATCC 29213 | 78.0 µg/mL (MIC) | Ampicillin 10.0 µg/mL (MIC) | [73] |
| BR-011 (214) | Anti-HIV virus | Luciferase/VSV-G | 17.90 µM (IC₅₀) | Efavirenz 0.65 µM (IC₅₀) | [104] |
Yang et al. (2021) purified and characterized undescribed phenylspirodrimane derivatives, stachybotrolide (20), stachybotrylactam acetate (30), arthproliferin E (31), and formerly reported 32, 44, 51, 64, and 65 from Sinularia sp.-associated S. chartarum SCSIO4-1201 EtOAc extract (Figure 4). These metabolites were evaluated for their antimicrobial activity versus A. baumannii ATCC-19606, K. pneumonia ATCC-13883, E. coli ATCC-25922, A. hydrophila ATCC-7966, S. aureus ATCC-29213, and E. faecalis ATCC-29212 in the serial dilution technique using 96-well microtiter plates and for cytotoxicity against MDA-MB-231, C4-2B, MGC803, MDA-MB-468, and A549 cell lines in the CCK-4 assay. Compounds 30 and 31 showed weak inhibitory activity (MICs 325 and 125 µg/mL, respectively) towards methicillin-resistant S. aureus ATCC-29213 compared to ampicillin (MIC 10.0 µg/mL) and weak cytotoxic activity versus MDA-MB-231, C4-2B, MGC803, MDA-MB-468, and A549 [73].

Figure 4. Structures of phenylspirodrimane derivatives (39–48) reported from S. chartarum.
Chemical investigation of the solid culture of the *S. chartarum* isolated from *Niphates recondita* using SiO$_2$ and ODS gel CC and HPLC resulted in the separation of sixteen new phenylspirodrimanes, chartarlactams A–P (40–44, 52–56, 65–69, and 72) along with 29, 30, 32, 50, 51, 57, 64, and 71 (Figure 5). Their structures and configuration were verified using spectral tools and single-crystal X-ray diffraction, respectively. This represented the first report of $8\beta$-CH$_3$ analogs, and 72 had a new framework that was formed by 40 dimerization.

![Chemical structures of phenylspirodrimane derivatives](image)

**Figure 5.** Structures of phenylspirodrimane derivatives (49–58) reported from *S. chartarum*.

The antihyperlipidemic effects of 29, 30, 40–44, 50–57, 65, 67, 69, 71, and 72 (Figure 6) in HepG2 cells were estimated utilizing a cell-based lipid accumulation assay. The results revealed that 43, 44, 50, 54, 65, 68, 69, and 72 (Conc. 10 $\mu$M) possessed significant lipid-lowering potential in HepG2 cells. Besides, 44, 50, 54, 65, and 69 displayed remarkable prohibition of intracellular TG (triglyceride) levels, whereas 43, 44, 50, 65, 68, and 72 dramatically lessened TC (total cholesterol). The structure–activity relation revealed that the 8$\alpha$-CH$_3$ analogs with alkyl N-substituted (e.g., 30, 32, 41, and 67) had weak potential, except 50, that has a benzene-propanoic acid substituent. In addition, the C-8$\gamma$-lactam carbonyl as in 65 and 69 boosted the inhibitory potential compared with 29 and 55, which have C-7$\gamma$-carbonyl. Compound 43, with a C-2$\gamma$-glucosyl moiety, possessed only inhibition on TC, whereas 54 selectively prohibited TG. The analogs with 2,3-diol had no activity, whereas C-3 acetoxy analogs (e.g., 54) had a selective inhibitory effect [74].
atetically lessened TC (total cholesterol). The structure–activity relation revealed that the 8α-CH₃ analogs with alkyl N-substituted (e.g., 30, 32, 41, and 67) had weak potential, except 50, that has a benzene-propanoic acid substituent. In addition, the C-8’ γ-lactam carbonyl as in 65 and 69 boosted the inhibitory potential compared with 29 and 55, which have C-7’ carbonyl. Compound 43, with a C-2’ glucosyl moiety, possessed only inhibition on TC, whereas 54 selectively prohibited TG. The analogs with 2,3-diol had no activity, whereas C-3 acetoxy analogs (e.g., 54) had a selective inhibitory effect [74].

Figure 6. Structures of phenylspirodrimane derivatives (59–66) reported from S. chartarum.

Zhao et al. reported the separation of three dimers: bistachybotrysins A–C (73–75) from S. chartarum CGMCC-3.5365 mycelia EtOAc extract by SiO₂ CC and HPLC that were assigned based on spectroscopic and ECD analyses. These metabolites are phenylspirodrimane dimers having [6,6,7,6]-tetracyclic scaffold with 6/7 oxygen heterocycle linkage and a central 2,10-dioxabicyclo[4.3.1]decan-7-ol core fused with two phenyl moieties (Figure 7).
Their in vitro cytotoxic potential versus HCT-116 (colorectal carcinoma), NCI-H460 (lung carcinoma, BGC823 (gastric carcinoma), Daoy (medulloblastoma), and HepG2 (liver carcinoma) in the MTT assay was assessed.

Compound 73 revealed powerful inhibitory capacity versus Daoy, HCT-116, and NCI-H460 (IC50S 2.8, 6.7, and 7.5 μM, respectively), whereas 74 had potent activity versus Daoy, NCI-H460, and BGC823 (IC50S 4.2, 5.5, and 6.6 μM, respectively). On the other side, 75 demonstrated weak cytotoxic effectiveness versus all cell lines. It was observed that 73 was more potent versus Daoy and HCT-116 than 74, while 74 possessed better influence versus BGC823 and NCI-H460 than 73, indicating that different substituents at C-3 might influence the selectivity towards tumor cell lines and substituent at 2'-OH might lessen the activity (Figure 8).
Further investigation is worth pursuing for 73 and 74 as new promising antitumor lead compounds [79]. They were postulated to be originated from farnesyl-diphosphate and orsellinic acid that give phenylspirodrimane monomer (Scheme 4). Then, a pinacol coupling reaction among the two CHO groups of 3 and 2 gives a vicinal-diol intermediate I. After that, one OH group of the 22,23'-diol moiety fuses further with the other CHO of 2 to produce II with a six-membered oxygen heterocyclic ring through acetalization intermolecularly. Subsequently, the dehydration of the mer-NF5003E (3) CH$_2$OH and hemiacetal OH groups yields 73 through 6/7 oxygen heterocyclic linkage. Further, 74 is resulted from bistachybotrysin A by selective acetylation, whereas 75 is generated from 5 and 2 through pinacol-coupling reaction, intermolecular acetalization, and dehydration [79].

Bistachybotrysins D (76) and E (77), stereoisomeric phenylspirodrimane dimers, have a central [6,5,6]-tricyclic carbon skeleton involving a cyclopentanone ring. Their structures were verified by extensive spectral analysis, and their configurations were established by ECD. Compound 76 demonstrated [6,5,6]-tricyclic carbon scaffold that dimerized through 3-(hydroxymethyl)cyclopentanone core C-C connected to one phenyl ring and fused to the other. Compound 77 has the same structure as 76 with 23S/23'S instead of 23R/23'R in 76. These metabolites (IC$_{50}$ ranged from 6.7 to 11.6 µM) had pronounced cytotoxic potential versus Daoy, HCT116, BGC823, and HepG2 cell lines. Besides, 76 possessed neural anti-inflammatory potential by prohibiting NO production in BV2 cells.

Figure 8. Structures of dimeric phenylspirodrimane derivatives (75–78) reported from *S. chartarum*. 
induced by LPS compared to curcumin (inhibitory rate 61.1 and 67.6%, respectively, at Conc. 10 \(\mu\)M) [80].

Scheme 4. Biosynthetic pathway of bistachybotrysins A–C (73–75) [79].

The monomers are biosynthesized from FPP (farnesyldiphosphate) and orsellinic acid by reduction, prenylation, and cyclization. Further, hydroxylation and oxidation form 3 and 1 that undergo a pinacol coupling reaction between the two aldehydic groups to produce I (vicinal diol intermediate) that is dehydrated by H-22 and OH-23' to yield II. Subsequently, the non-stereoselective aldol reaction of II gives a stereoisomer pair, and further O-methylation affords 76 and 77 (Scheme 5) [80].

Based on HPLC-UV/MS guided analyses, five new dimers, bistachybotrysins F–J (78–82), having cyclopentanone ring linkage were purified and characterized using SiO\(_2\)CC/HPLC and NMR/HRMS/ECD, respectively [81]. Compound 78 displayed the same structural features as 77 and 111. Besides, 78, 80, and 82 had 23'R/23'R configuration, whereas 79 and 81 possessed 23'S/23'S configuration (Figure 9).
Based on HPLC-UV/MS guided analyses, five new dimers, bistachybotrysins F–J (78–82), having cyclopentanone ring linkage were purified and characterized using SiO₂CC/HPLC and NMR/HRMS/ECD, respectively [81]. Compound 78 displayed the same structural features as 77 and 111. Besides, 78, 80, and 82 had 23R/23'R configuration, whereas 79 and 81 possessed 23S/23'S configuration (Figure 9).

**Scheme 5.** Biosynthetic pathway of bistachybotrysins D (76) and E (77) [80].

**Figure 9.** Structures of dimeric phenylspirodrimane derivatives (79–84) reported from *S. chartarum.*
Feng et al. postulated that bistachybotryins F–J (78–82) are generated from 1 and 3. They undergo a pinacol coupling reaction among the two CHO to yield a vicinal diol intermediate, subsequently, 110 and 111 are formed through dehydration and non-stereoselective aldol reaction. After that, the regioselective hydroxylation (C-2 or C-2') affords 78–80 and/or acetylation (OH-3' or OH-3). Further, 79 and 80 O-methylation produces 81 and 82, respectively (Scheme 6) [81]. Additionally, these metabolites were evaluated for cytotoxic potential versus HCT116, NCI-H460, BGC823, Daoy, and HepG2. It was found that 78 and 80–82 were moderately active (IC$_{50}$ 9.1–22.8 µM) versus HepG2, NCI-H460, BGC823, and HCT116 [81].

![Scheme 6. Biosynthetic pathway of bistachybotryins F–J (78–82) [81].](image)

Bistachybotrysin K (83) is a new phenylspirodrimane dimer with a central 6/7 oxygen heterocyclic core. It displayed potent cytotoxic capacity versus NCI-H460, HCT116, Daoy, BGC823, and HepG2 (IC$_{50}$ ranged from 1.1 to 4.7 mM) in the MTT assay, revealing its
potential as lead for promising anti-tumor [82]. Using SiO$_2$ CC and RP-HPLC, novel dimeric phenylspirodrimanes, bistachybotrysins L–V (84–94), were separated from the mycelia broth and extracts. Their structures and configurations were secured utilizing spectroscopic, X-ray, and ECD analyses (Figure 10).

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Compounds 84 and 85 are stereoisomeric dimers possessing an unusual [5,6]-spiroketal aromatic skeleton with a 2-methoxy-1,6-dioxaspiro[4,5]decane central core fused with 2 phenyl moieties. On the other side, 86–92 possess two linked-furan rings, whereas 93 and 94 featured a rare lactone/furan unit and one furan ring linkages, respectively (Figure 11). It is noteworthy that 91 and 92 selectively inhibited the proliferation of NCI-H460, HCT116, Daoy, BGC823, and HepG2 cell lines (IC$_{50}$ ranged from 1.8 to 11.8 μM) in the MTT assay.

Furthermore, 85, 86, and 92 (Conc. 10 μM) revealed potent neuroprotection potential versus glutamate-caused toxicity in SK-N-SH cells through raising cell viability (17.4, 17.6, and 17.4%, respectively), comparable to resveratrol (16.1% at Conc. 10 μM). Additionally, 91 possessed anti-inflammatory potential by repressing LPS-produced NO production in BV2 cells (inhibition rate 54.2% at Conc. 10 μM) relative to curcumin (67.6%) at the same concentration [83].

Liu et al. reported the separation of new phenylspirodrimane dimers, bistachybotrysins W–Y (95–97), having 6/7 oxygen heterocyclic unit using SiO$_2$ and Sephadex CC and HPLC that were characterized through spectroscopic and ECD analyses (Figure 12). Compounds 95 and 97 demonstrated selective cytotoxic potential versus HepG2, Daoy, and HCT116 cell lines (IC$_{50}$ ranged from 5.9–12.1 μM) [84].

Novel phenylspirodrimanes chartarolides A–C (98–100) were purified from S. chartarum isolated from Niphates recondite by SiO$_2$ and RP-18 CC and RP-HPLC and assigned relying on spectroscopic analyses, optical rotation, and TDDFT-ECD calculation. Compounds 98 and 99 possess mollicelin J and phenylspirodrimane linked via dioxabicyclononane core formation. These metabolites exerted notable prohibition versus HCT-116, BGC-823, HepG2, A2780, NCIH1650, and MCF7 (IC$_{50}$ ranged from 1.4 to 12.5 μM) in the MTT assay. Compound 99 (IC$_{50}$ 1.6–3.8 μM) had weaker potential than 98 (IC$_{50}$ 1.3–1.9 μM).
versus HCT-116, BGC-823, HepG2, A2780, and MCF7, revealing the direct influence of the
dioxabicyclononane moiety’s configuration on the activity. Additionally, they possessed
inhibitory effectiveness versus tumor-linked kinases, FGFR3, IGF1R, PDGFRb, and TrKB
(IC\textsubscript{50} 2.6–21.4 \mu M), compared to satratoxin H (IC\textsubscript{50} <0.5 \mu M) [85].

In 2020, Liu et al. purified new dimeric derivatives, chartarlactams Q–T (101–104), in
addition to 109 from the broth of a sponge-derived \textit{S. chartarum} WGC-25 C-6 using SiO\textsubscript{2}
and ODS CC and HPLC (Figure 13). Their structures and configurations were specified
by various spectral tools, along with ECD, optical rotation, and Mosher’s method. These
metabolites have two N–C linked phenylspirodrimane units without an alkyl chain.

![Figure 11. Structures of dimeric phenylspirodrimane derivatives (90–95) reported from \textit{S. chartarum}.](image-url)

Compounds 101–103 and 109 possessed inhibitory potential versus \textit{S. aureus} (MIC
8, 16, 4, and 4 \mu g/mL, respectively), compared with chloramphenicol (MIC 1.0 \mu g/mL).
Additionally, their anti-ZIKV virus capacity was assessed on ZIKV (African-lineage MR766
strain) infected A549 cells. It was found that 104 significantly prohibited NS5 and E protein
expression (conc. 10 \mu M), whereas 101–103 and 109 were inactive. Envelope (E) protein
in ZIKV virus has a remarkable role in membrane fusion and binding to target the host
cells receptors, whereas NS5 protein a ZIKV genome encoding non-structural proteins that
serves as template for the (+)ssRNA genomic RNA synthesis and viral polyprotein synthesis.
Hence, this metabolite prohibited ZIKV virus by multi-targets to block RNA replication and
viral entrance [86]. Biosynthetically, they are generated from 3 that undergoes nucleophilic
cyclization to give I (hemiacetal intermediate). The latter reacts by dehydroxylation with
various monomers (chartarlactam E (44), stachybotrylactam acetate (30), F1839-A (51),
F1839-A diacetate, and stachybotrylactam (29), respectively) to produce 101–104 and 109
(Scheme 7).
Figure 12. Structures of dimeric phenylspirodrimane derivatives (96–99) reported from *S. chartarum*.

Figure 13. Structures of dimeric phenylspirodrimane derivatives (100–104) reported from *S. chartarum*. 

Compounds 101–103 and 109 possessed inhibitory potential versus *S. aureus* (MIC 8, 16, 4, and 4 μg/mL, respectively), compared with chloramphenicol (MIC 1.0 μg/mL). Additionally, their anti-ZIKV virus capacity was assessed on ZIKV (African-lineage MR766 strain) infected A549 cells. It was found that 104 significantly prohibited NS5 and E protein expression (conc. 10 μM), whereas 101–103 and 109 were inactive. Envelope (E) protein in ZIKV virus has a remarkable role in membrane fusion and binding to target the host cells receptors, whereas NS5 protein a ZIKV genome encoding non-structural proteins that serves as template for the (+)ssRNA genomic RNA synthesis and viral polyprotein synthesis. Hence, this metabolite prohibited ZIKV virus by multi-targets to block RNA replication and viral entrance [86]. 

Biogenetically, they are generated from 3 that undergoes nucleophilic cyclization to give I (hemiacetal intermediate). The latter reacts by dehydroxylation with various monomers (chartarlactam E (44), stachybotrylactam acetate (30), F1839-A (51), F1839-A diacetate, and stachybotrylactam (29), respectively) to produce 101–104 and 109 (Scheme 7).
Scheme 7. Biosynthetic pathway of chartarlactams Q–T (101–104) and stachyin B (109) [86,88].
S. chartarum-associated with Pinellia ternata biosynthesized undescribed phenylspirodrimane derivatives, stachybochartins A (105), B (106), C (107), D (108), E (25), F (33), and G (51), that were separated using SiO\textsubscript{2} CC and RP-HPLC (Figure 14).

Figure 14. Structures of dimeric phenylspirodrimane derivatives (105–110) reported from S. chartarum.

Their assignments and configurations were accomplished through spectroscopic analysis as well as modified Mosher’s and ECD-calculations/ECD-exciton chirality methods. Compounds 105–108 are uncommon C–C coupled dimeric derivatives, where the monomeric units are C7’-C7”- (e.g., 105 and 106) and C5”-C8”-coupled (e.g., 107 and 108). On the other side, stachybochartin G (51) possessed a seco-bisabosqual framework with 3’S/6’R/7’S configuration. Further, their cytotoxic potential was assessed versus MDA-MB-231, MCF-7, and U-2OS cell lines in the MTT assay. It was found that 51 and 105–108 had cytotoxic potential versus U-2OS and MDA-MB-231 (IC\textsubscript{50}s 4.5–21.7 \textmu M). Besides, 51 and 107 demonstrated powerful anti-proliferation and anti-apoptosis effectiveness versus U-2OS cells, while all metabolites had no influence (IC\textsubscript{50} >50 \textmu M) versus MCF-7 cells [70].
These data may provide evidence for further research into the anticancer activities of these compounds.

A new phenylspirodrimane dimer, stachartarin A (111), was separated from tin mine tailings associated S. chartarum culture and elucidated by means of spectroscopic methods (Figure 15).

![Stachartarin A (111)](image)

![Stachartarin B (112)](image)

![Stachybacbon E (113)](image)

![Stachybacbon F (114)](image)

**Figure 15.** Structures of dimeric phenylspirodrimane derivatives (111–114) reported from *S. chartarum*.

It differed from stachartin B (28) by the absence of a lactone group in 28 and the existence of an oxymethylene and ketone carbonyl in 111. Compound 111 had (IC$_{50}$ >40 μM) no remarkable effectiveness versus MCF-7, HL-60, SMMC-7721, SW480, and A-549 cells in the MTT assay [88]. Ding et al. proposed that 111 is biosynthesized from two phenylspirodrimane derivative units through a reduction–oxidation reaction by C-C bond linkage among C-7′/C-8‴ and C-8′/C8‴, respectively, as illustrated in Scheme 8 [88].
3.2. Trichothecenes

Trichothecenes are sesquiterpenoid-related mycotoxins commonly produced by fungi. They possess a marked cytotoxic potential versus eukaryotic organisms through the prohibition of DNA and protein synthesis as well as mitochondrial electron transport system [92]. They have common structural features: 12,13-epoxide moiety, 9,10-double bond, and various ring oxygenation patterns [117]. Structurally, they involve three main groups: trichothecenes type A, having hydrogen, hydroxyl, or isovaleryl functionalities at C-8; trichothecenes type B, having a C-8 carbonyl group; and macrocyclic trichothecenes, having a cyclic di or tri-ester ring binding C-4 to C-15 [118,119]. Macrocyclic trichothecenes are the most powerful toxic group [120].

Bio-guided separation of the EtOAc fraction of *Niphates recondite*-associated *S. chartarum* using SiO$_2$ and RP-18 CC and HPLC afforded four new trichothecene-related sesquiterpenes, chartarenes A–D (117–119 and 130), and eleven known analogs, 116, 120, 123, 124, 128, 129, 134, 139, 142, 144, and 146, that were verified based on spectroscopic and X-ray analyses in addition to chemical methods [92] (Figures 16 and 17).

They were tested versus a panel of human cancer cell lines (e.g., HCT-116, HepG2, BGC-823, NCI-H1655, and A2780) in the MTT method. It is noteworthy that they had selective inhibitory influences versus all cell lines with 134, 142, 144, and 146 (IC$_{50}$ < 10 nM) having potent effectiveness (Figure 18). The structure–activity relation study demonstrated that this effect is related to the scaffolds and substitution pattern.

The apotrichothecene-related analogs, 117 with a C-12 sugar and without C-4 and C-2 hydroxy group (IC$_{50}$ 2.38–3.95 µM) or 118 with a C-2 methoxy group, had a weaker influence than that of the 2,4,12-trihydroxy analog, 116 (IC$_{50}$ 0.65–0.87 µM). On the other side, trichodermol-type analogs, having a macrocyclic ring alongside a tetrahydropyran ring (e.g., 142, 144, and 146), possessed remarkable potential; however, those without a tetrahydropyran-attached macrocyclic moiety (130 and 139) exhibited less cytotoxicity. Compounds 123, 124, 128, and 129 with a C-14 or C-4 linear moiety had reduced effects compared with 146. Additionally, their antitumor mechanism was investigated versus tumor growth-related tyrosine kinases (e.g., FGFR3 (fibroblast growth factor receptor 3), IGF1R (insulin-like growth factor 1 receptor), PDGFRb (β-type platelet-derived growth
factor receptor), and TRKB (tropomyosin receptor kinase B)). They were found to exert powerful inhibitory action, except for 117 and 123, having a weak activity (IC\textsubscript{50} > 20 µM). FGF signaling has a role in various disorders such as cancer, involving anti-apoptosis, proliferation, angiogenesis, drug resistance, and invasion. Therefore, targeting FGFR is a promising topic in the clinical oncology field [92].

Satratoxin G (142) and its biosynthetic precursor 129 were isolated from the culture acetonitrile extract using Michael–Miller SiO\textsubscript{2} CC and HPLC and characterized by ESI-CID (electrospray/ionization/collision-induced/dissociation). Compound 142 had a C-4 to C-15-linked cyclic ester ring, however, 129 possessed a C-4 extended carbon chain and no C-15-substituent. Satratoxin G was found to cause apoptosis of the nose and brain OSN (nasal-olfactory sensory neurons) of mice upon intranasal exposure [121]. Additionally, it induced apoptosis in PC-12 (neuronal cell model) through marked upregulation of p53, BAX, and
PKR [122]. In 2009, Islam et al. compared the neurotoxic potential of both metabolites in vivo and in vitro. The study revealed that 142 (conc. 10 to 25 ng/mL) caused PC-12 cells apoptotic death, while 129 (Conc. up to 1000 ng/mL) had no effect using Alamar blue, flow cytometry, and agarose DNA fragmentation assays. Similarly, 142 (dose 100 mg/kg/body weight, intra-nasal) produced remarkable OSN apoptosis and olfactory epithelium atrophy, whereas 129 showed no influence at the same dose. These results suggested that 129 had a weak potential to adversely affect health in comparison to 142 [98].

Figure 17. Structures of trichothecenes (128–138) reported from S. chartarum.
Satratoxin F (140) and satratoxin H (144) were separated by Yang et al. using RP-18 and HPLC CC. Compound 140 displayed moderate inhibitory activity against methicillin-resistant S. aureus ATCC-29213 (MIC 39 µg/mL) [73]. Besides, 140 (IC50s < 39 nM) displayed strong cytotoxic potential versus MDA-MB-231, C4-2B, MGC803, MDA-MB-468, and A549 cell lines in the CCK-4 assay [73].
3.3. Isoindoline derivatives

Mai et al. isolated 155 using SiO2 and C18 ODS CC of the mycelia EtOAc extract S. chartarum MXH-X73-associated with Xestospongia testudinaris that was characterized by HRESIMS, NMR, and X-ray. This metabolite is a cyclized iminoisoindoline, having farnesylated decahydropyrrolo[1,2-a][1,3]diazocine moiety (Figure 19).

![Figure 19. Structures of isoindoline derivatives (147–155) reported from S. chartarum.](image)

It had no cytotoxic (versus P388, A-549, HL-60, BEL-7402, and Hela cells), antiviral (versus HIV and H1N1), and antibacterial (versus M. phlei, S. aureus, Colibacillus sp., and Blastomyces albicans) potential [105]. Ma et al. proposed that 155 is generated through both mevalonate and polyketide pathways, with subsequent modifications, including amidation, cyclizing, and sulfation (Scheme 9).

Li et al. purified eight new derivatives: chartarutines A–H (147–154) from the mycelia EtOAc extract of Niphates sp.-associated S. chartarum using SiO2 and RP-18 CC and HPLC that were elucidated by spectroscopic tools, along with Mosher method and CD analysis. Compound 148 is 1′,11′-dehydroxy-10′,11′-ene derivative of 147, whereas 150 featured an isoindolimine unit instead of an isoindolamine unit in 149. Besides, 151/153 and 152/154 had pyrano-isoindolone rings linked to C5-C-3′ and C-3-C-3′, respectively. Compounds 147–154 revealed anti-HIV potential (IC50s 4.90–74.00 µM), whereas 148, 153, and 154 had the potent effectiveness (IC50 4.90–5.58 µM) in the luciferase assay with lower cell cytotoxicity (CC) than efavirenz (CC50 40 µM), suggesting their further investigation as lower cytotoxic anti-HIV candidates. The structure-activity relation indicated that the var-
iation in side chain directly influenced the inhibitory potential. The analogs having triene (153, 154) or diene (148) side-chain had more enhanced potential than vicinal diol analogs (147, 151, and 152), whereas the variation in scaffold (e.g., 148, 153, and 154) had no influence on the activity. Replacing 3-OH by sulfate (e.g., 149 and 150) reduced the activity [104].

Stachybotrysams A–D (156–159), new farnesylated isoindolinone derivatives, and new cyclized-farnesyl, stachybotrysam E (35), along with 148 were separated using SiO\textsubscript{2} CC and HPLC (Figure 20) and elucidated based on spectral data analysis and optical rotation. Compounds 156–158 featured prenylated isoindolinone core with N-linked side chain with (e.g., 157 and 158) or without (e.g., 156) C-4 sulphate moiety, whereas 159 has N/C-6″ linked glucose moiety. On the other side, 35 has a cyclized farnesyl moiety as chartarlactam N (68), except having N-linked butyric acid unit instead of the ethyl alcohol moiety. In the HIV-inhibition luciferase assay, 156–158 demonstrated promising inhibitory potential against HIV-1 virus (IC\textsubscript{50} 9.3, 1.0, and 9.6 \(\mu\text{M}\), respectively) compared to efavirenz (IC\textsubscript{50} 2.0 \(\mu\text{M}\)) using 293T cells. It was reported that the farnesyl chain cyclization reducing the effectiveness and the N-attached side chain, as well as sulphate moiety existence, could influence the activity [76].

![Scheme 9. Biosynthetic pathway of stachybotrin G (155) [105].](image)

### 3.4. Atranones and Dolabellane Diterpenoids

Atranones are an uncommon type of C-alkylated dolabellanes that are featured by a 5/11-fused bicyclic carbon skeleton. They comprise three groups: C22, C23, and C24 atranones. Li et al. separated seven new atranones, 164, 175–179, and 190 in addition to formerly reported analogs 161–163, from soybean and rice culture media CHCl\textsubscript{3} fraction of S. chartarum using Sephadex LH-20 and SiO\textsubscript{2} CC and HPLC (Figure 21).
m moiety. In the HIV-inhibition luciferase assay, 156–158 demonstrated promising inhibitory potential against HIV-1 virus (IC50 9.3, 1.0, and 9.6 μM, respectively) compared to efavirenz (IC50 2.0 nM) using 293T cells. It was reported that the farnesyl chain cyclization reducing the effectiveness and the N-attached side chain, as well as sulphate moiety existence, could influence the activity [76].

Figure 20. Structures of isoindoline derivatives (156–159) reported from S. chartarum.

3.4. Atranones and Dolabellane Diterpenoids

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Their structures were established by spectral and X-ray analyses, as well as ECD (electronic circular dichroism) calculations and optical rotation. DRG (Dorsal root ganglia) neuron is commonly utilized for assessing the growth capacity of neurons and drugs' therapeutic potential in peripheral nerve regeneration [108]. For successful peripheral nerve regeneration, the first step is the axonal regrowth from injured neurons. The axonal regeneration potential of 162 was estimated using primary DRG neurons. Compound 162 boosted neurite outgrowth from adult dorsal root ganglia neurons remarkably without influencing cell survival (conc. 1 μg/mL) Besides, 161–164, 175, 176, 178, and 179 (Figure 22) had no cytotoxic potential versus MDA-MB-435 in the MTT [108].

Figure 21. Structures of atranones (160–171) reported from S. chartarum.
Their structures were established by spectral and X-ray analyses, as well as ECD (electronic circular dichroism) calculations and optical rotation. DRG (Dorsal root ganglia) neuron is commonly utilized for assessing the growth capacity of neurons and drugs’ therapeutic potential in peripheral nerve regeneration [108]. For successful peripheral nerve regeneration, the first step is the axonal regrowth from injured neurons. The axonal regeneration potential of 162 was estimated using primary DRG neurons. Compound 162 boosted neurite outgrowth from adult dorsal root ganglia neurons remarkably without influencing cell survival (conc. 1 µg/mL). Besides, 161–164, 175, 176, 178, and 179 (Figure 22) had no cytotoxic potential versus MDA-MB-435 in the MTT [108].

Figure 22. Structures of atranones (172–180) reported from S. chartarum.

In 2019, Yang et al. purified new atranones Q-S (180–182) and new dolabellane diterpenoids: stachatranone A–C (185–187) from the EtOAc extract of a marine-derived S. chartarum by SiO2 CC and RP-HPLC that were characterized by extensive spectral and X-ray analyses. Structurally, 186 and 187 possess 1,14-seco-dolabellane diterpenoid skeleton, whereas 180 featured C23 atranone having propan-2-one moiety connected via C-C bond to a dolabellane diterpenoid and 181 is C24 atranone with a 2-methyltetrahydrofuran-3-
carboxylate unit linked at C5–C6 to dolabellane diterpenoid. Compound 186 had antimicrobial potential versus *E. faecalis* and *A. baumannii* (MIC 32 and 16 µg/mL, respectively), whereas 180 possessed noticeable inhibition versus MRSA, *C. albicans*, and *E. faecalis* (MICs 32, 8, and 16 µg/mL, respectively). Treatment of *C. albicans* with 180 (8 µg/mL) induced obvious agglutination in cytoplasm and thinning, deformity, wrinkling, and irregularity of the cell wall, whereas at 16 µg/mL it resulted in the appearance of cytoplasmic vacuoles, deformation of the cell membrane and wall, and complete or partial leakage of the cell contents in TEM (transmission electron microscopy). This revealed that 180 had a destructive potential on *C. albicans* cell wall and cell membrane [61] (Figure 23).

**Figure 23.** Structures of atranones (181–184) and dolabellanes (185–190) reported from *S. chartarum*. Two new atranones, T (183) and U (184), and three formerly reported analogs, 162, 180, and 187, were purified from the broth and mycelia EtOAc extract of *S. chartarum* by SiO2 CC and RP-HPLC. They were structurally verified by spectroscopic and calculated ECD analyses. Compound 183 is atranone C (165) C-13-hydroxy analog with 1S/6R/7R/13R/21S/22R configuration, however, 184 is a C22 methoxylated derivative of 183. It was proposed that these metabolites are biosynthesized starting with GGPP (geranylgeranyl pyrophosphate), as shown in Scheme 10. The cytotoxic evaluation versus MG-63 (human osteosarcoma cells) revealed that 180 (IC50 8.6 µM) possessed promising cytotoxic capacity than 5-FU (5-fluorouracil, IC 50 10.4 µM) in the MTT. Further, 180 efficiently promoted MG-63 apoptosis, accompanied with G0/G1 cell cycle arrest. Thus, this compound could be further developed to a promising antitumor agent [62].

**Figure 23.** Structures of atranones (181–184) and dolabellanes (185–190) reported from *S. chartarum*. (1S*,3R*,4R*,6S*,11S*)-3,4-Epoxy-6-hydroxydolabella-7E,12-dien-14-one (188)
Two new atranones, T (183) and U (184), and three formerly reported analogs, 162, 180, and 187, were purified from the broth and mycelia EtOAc extract of S. chartarum by SiO$_2$ CC and RP-HPLC. They were structurally verified by spectroscopic and calculated ECD analyses. Compound 183 is atranone C (165) C-13-hydroxy analog with 1S/6R/7R/13R/21S/22R configuration, however, 184 is a C22 methoxylated derivative of 183. It was proposed that these metabolites are biosynthesized starting with GGPP (geranylgeranyl pyrophosphate), as shown in Scheme 10. The cytotoxic evaluation versus MG-63 (human osteosarcoma cells) revealed that 180 (IC$_{50}$ 8.6 µM) possessed promising cytotoxic capacity than 5-FU (5-fluorouracil, IC$_{50}$ 10.4 µM) in the MTT. Further, 180 efficiently promoted MG-63 apoptosis, accompanied with G0/G1 cell cycle arrest. Thus, this compound could be further developed to a promising antitumor agent [62].

![Scheme 10. Biosynthetic pathway of atranones T and U (183 and 184) [62].](image)

### 3.5. Chromenes

Three novel meroterpenoids having a chromene moiety were joined with an isoprenoid chain; stachybotrychromenes A–C (193–195) were separated using SiO$_2$ and RP-HPLC UV. Their cytotoxic potential was assessed versus HepG2 in the Alamar Blue assay. Compound 194 (IC$_{50}$ 28.2 µM) had a more potent reduction in the cell survival than 193 (IC$_{50}$ 73.7 µM), however, 195 was inactive [64]. It is noteworthy that 195 was assumed to be generated via the intermediates 193 and 194 (Figure 24).

The new chromene metabolites, stachybonoids A–C (196–198), were purified using HPLC and SiO$_2$ and Sephadex LH-20 CC and characterized based on spectral, ECD, and X-ray analyses as well as Mosher’s method [68]. They were assessed for anti-dengue virus potential in luciferase assay using 293T cells. Compound 196 lessened the prM dengue virus protein expression. It is noteworthy that 196 inhibited the replication of dengue virus, whereas 197 increased the formation of dengue protein, when the only difference between their structures was whether 17-OH was methylated or not.
It was proposed that they are generated from the addition reaction of farnesyl diphosphate and orsellinic acid to produce an intermediate ilicicolin B (Scheme 11) [68]. After that, the ilicicolin B prenyl group terminal olefinic bond is epoxidized to produce an intermediate. Subsequently, the linkage of the aromatic OH group to C-3 of the prenyl group occurs through electrophilic addition forms 196–198 [68].

*Sinularia* sp.-associated *S. chartarum* SCSIO4-1201 EtOAc extract yielded undescribed polyketide derivatives, arthroproliferins B and C (191 and 192), that were separated using RP18 CC and HPLC. They were characterized through X-ray, spectroscopic, and ECD analyses. Compound 191 was 9R-configured and possessed structural similarity to daurichromenic acid previously reported from *Rhododendron dauricum* [123], except that the C16-C-17 double bond was dehydroxylated, whereas 192 was like 191 but it had an aldehydic group at C-2 and 9S configuration. Compounds 192 had no cytotoxic and antimicrobial potential [73].
Scheme 11. Biosynthetic pathway of stachybonoids A–C (196–198) [68].

3.6. Cochlioquinones

Cochlioquinones are a class of phytotoxic metabolites that have been firstly purified from the plant pathogenic fungi belonging to Cochliobolus genus [124]. They are meroterpenoids having quinone/or quinol moiety and displayed various bioactivities [125].

Chemokines, small signaling proteins, are secreted by various cells such as innate lymphocytes, stem, B, T, myeloid, dendritic, and stromal cells that are involved in diverse biological processes (e.g. leukocyte migration, chemotaxis, and inflammation) [126]. They are substantial for destructive or protective immune and inflammatory operations, as well as for the immune system development and homeostasis [126]. Moreover, they are linked with various illnesses such as viral infections, cancer, and autoimmune and inflammatory diseases [127]. The chemokine-induced pathway activation needs the selective chemokines binding to their target cell surface receptors. Chemokines and their receptors are found to be substantial targets by different antagonists for treating a variety of illnesses [128].

The quinoid derivatives, 11-O-methyl-epi-cochlioquinone A (200) and epi-cochlioquinone A (199), were purified from hexane fraction utilizing Rp-HPLC. Compound 200 was an 11-O-methyl derivative of 199. Their C-11 α-configuration was deduced based on $J_{\alpha\alpha}$ (9 Hz). These metabolites effectively competed with MIP-1α (macrophage inflammatory protein-1) for binding to human CCR5 (chemokine C-C motif-receptor 5) (IC$_{50}$ 7.0 and 4.0 µM, respectively) [109].

3.7. Xanthones

A new xanthone arthproliferin D (201) and formerly reported pestaxanthone (202) and prenaxanthone (203) were biosynthesized by Sinularia sp.-associated S. chartarum SCSIO4-1201.
Compound 201 was like 202 but differs in the position of CH$_3$ groups at C-4 and C-12 and its 16R-configuration was established by the CD spectrum (Figure 25). However, 202 possessed weak effectiveness (MIC 125 µg/mL) towards methicillin-resistant *S. aureus* ATCC-29213, compared to ampicillin (MIC 10.0 µg/mL). All had no cytotoxic capacity versus MDA-MB-231, C4-2B, MGC803, MDA-MB-468, and A549 cell lines in the CCK-4 assay [73].

![Diagram of compounds](image_url)

**Figure 25.** Structures of cochlioquinones (199 and 200) and xanthones (201–208) reported from *S. chartarum*.

Gan et al. reported the separation of new prenylxanthones, staprexanthones A–E (204–208) using SiO$_2$ CC and RP-HPLC from the mycelia EtOAc extract of the mangrove-harbored *S. chartarum* HDN16-358. Their structures were secured by NMR and ECD analyses. Compound 204 features a C-8-linked 4,5-dimethyl-1,3-dioxolane moiety with...
13R,14R-configuration, whereas 205–208 are rare mono-oxygenated prenylated xanthones. Compounds 204, 205, and 208 remarkably increased the number of β-cells in the zebrafish model in vivo. Further, 205 and 208 boosted the mass expansion of β-cells by increasing the existing β-cells proliferation via promoting cell-cycle progression at the G1/S phase, where 205 (Conc. 25 µM) was the most active stimulator with a 10% increased existing cell proliferation/day. This indicated the potential of these metabolites as drug leads for anti-diabetes agents through stimulating regeneration of β-cells [110].

3.8. Cyclosporins

Cyclosporins as immune-suppressant agents were established to be efficient not only in suppressing the transplanted-organ rejection but also in treating various autoimmune disorders that do not respond to current therapy [129].

FR901459 (210), a novel immunosuppressant, had been purified along with cyclosporin A (CsA, 209) from S. chartarum No.19392 fermentation by Diaion HP-20, activated carbon, and SiO2 CC. It gave positive results with I2 ceric SO4, KMnO4, and Dragendorff’s reagents and negative ninhydrin (Figure 26). Its structure varied from other cyclosporins in having Leu at position 5 instead of Val relied on various spectral tools [111]. FR901459 possessed lymphocyte proliferation inhibitory effectiveness (IC50 26.8 ng/mL) that was one-third the effectiveness of CsA (IC50 9.9 ng/mL). It repressed IL-2 production as well as the ConA-produced mitogenic responses (IC50 50.1 ng/mL) compared to CsA (IC50 21.9 ng/mL). FR901459 (doses 100 and 320 mg/kg, oral) and CsA (doses 32 and 100 mg/kg, oral) prolonged skin allograft survival in rats. Therefore, it had one-third of the CsA potency in the in vitro and in vivo immune-suppression assays [111].

Figure 26. Structures of cyclosporins (209 and 210), nitrogenous compounds (211–213), phenolic (214), and sterol (215) reported from S. chartarum.
3.9. Other metabolites

Arthproliferin A (211) is an undescribed polyketide derivative separated from *Sinnularia* sp.-associated *S. chartarum* SCSIO4-1201. It was found to be like coleophomone B formerly reported from *Coleophoma* sp. [130], except it has C-1 oxymethylene instead of ketone group. Compounds 211 demonstrated moderate influence (MIC 78 µg/mL) versus methicillin-resistant *S. aureus* [73].

Korpi et al. reported that TSGC (thermal desorption-gas chromatography) and HPLC analyses of air samples of *S. chartarum* obtained from incubation chambers revealed the existence of 1-hexanol, 2-methy-1-propanol, formaldehyde, 3-octanone, 3-methy-1-butanol, acrolein, 1-octanol, 3-methylanisole, and geosmin [131].

In addition, trichodiene, a volatile sesquiterpene that is structurally related to trichotheceene mycotoxins, was specified by GCMS in the *S. chartarum* headspace [132]. Further, MVOCs (microbial volatile organic compounds) of three *S. chartarum* strains obtained from water damaged homes by GCMS analysis included alcohols (e.g., 2-ethyl-1-hexanol, 2-butanol, 2-methyl-3-butene-2-ol, 2-methyl-1-butanol, 3-methyl-3-buten-1-ol, 2-ethyl-1-hexanol, and 2-propanol), ketones (e.g., 2-butanone, 2,2-dimethyl-3-pentanone, cyclopentanone, 3-cycloheptene-1-one, and 2-(1-cyclopent-1-enyl-1-methylcyclopentanone, and terpenes (e.g., α-farnesene, 7-dimethyl-1,3,6-octatriene, β-himachalene, β-cedrene, β-pinene, β-myrcene, β-bisabolene, terpinolene, and limonene) [133].

4. Extract Bioactivities and Nanoparticles

*S. chartarum* spores MeOH extract had cytotoxic effectiveness, prohibited proliferation, and induced cell death towards MH-S (murine alveolar macrophage cell line) through induction of DNA damage and p53 activation [134]. FIP-sch3, a FIP (fungal immunomodulatory protein), was identified from *S. chartarum* and expressed in *E. coli*. rFIP-shc3 (recombinant FIP-sch3) exhibited a potent anti-tumor potential versus MCF-7, H520, A549, HeLa, and HepG2 but had no effect in 293 (normal human embryonic kidney) cells. It significantly inhibited cell migration and proliferation via the induced apoptosis in A549 cells [135]. Li et al. stated that the solid rice culture EtOAc extract of *S. chartarum*, harboring *Niphates recondite* sponge, displayed noticeable cytotoxic capacity (IC\text{50} < 10 mg/mL) versus a panel of tumor cell lines (e.g., BGC-823, HCT-116 NCI-H1650, A2780, and HepG2) [92].

The fermentation broth EtOAc extract of the fungal species isolated from *Himerometra magnipinna* revealed moderate anti-inflammation capacity (IC\text{50} 36 µM) by suppressing LPS-produced NO production in RAW264.7 cells [108].

Recently, nanotechnology has become one of the emerging research areas for developing a variety of nanomaterials [1,3]. It is considered an economical alternative for physical and chemical methods for nanoparticles’ (NPs) synthesis. The ordinary methods for NPs’ synthesis are non-eco-friendly, costly, and toxic, which necessitates the need for clean, reliable, safe, and eco-friendly methods [136]. The microorganism’s utilization in the NPs’ synthesis emerges as an exciting and eco-friendly approach. Different kinds of NPs have been synthesized using various fungal species [2,3,5,39]. Fungi are advantageous over bacteria in NPs’ preparation because of easy handling, simple nutrient requirement, great wall-binding potential, and metal intracellular uptake capacities [137]. Mohamed synthesized *S. chartarum* silver NPs (AgNPs) using AgNO\text{3} that possessed more potent potential versus bacteria than fungi [138].

5. Conclusions

Fungi represent huge reservoirs of structural varied secondary metabolites and biotechnologically useful enzymes. *S. chartarum* is a toxigenic fungus species that is separated from water-damaged buildings as well as plants, soil, and marine sponges and is known to have life-threatening health impacts on humans and animals. From this fungus, 215 metabolites with diverse and unique structural features have been separated from the period 1973 through 2022 (Figure 27), including phenylspirodrimanes (112 compounds), trichotheecenes...
(32 compounds), atranones (28 compounds), and isoindoline derivatives (13 compounds) as major metabolites (Figure 28).

![Figure 27. Number of metabolites per year reported from S. chartarum.](image)

**Figure 27.** Number of metabolites per year reported from *S. chartarum*.

![Figure 28. Different classes of metabolites reported from S. chartarum. PSD: Phenylspirodrimanes; TCT: Trichothecenes; IIDs: Isoindoline derivatives; ATs: Atranones; DLDs: Dolabellane diterpenoids; XTs: Xanthones; CHs: Chromenes; CCQ: Cochlioquinones; CS: Cyclosporins; OT: Others.](image)

**Figure 28.** Different classes of metabolites reported from *S. chartarum*. PSD: Phenylspirodrimanes; TCT: Trichothecenes; IIDs: Isoindoline derivatives; ATs: Atranones; DLDs: Dolabellane diterpenoids; XTs: Xanthones; CHs: Chromenes; CCQ: Cochlioquinones; CS: Cyclosporins; OT: Others.

These metabolites have been evaluated for various bioactivities such as cytotoxicity, anti-HIV virus, anti-inflammatory, antimicrobial, potassium channel inhibition, tyrosine kinase, and tumor-related kinase inhibitory, neuroprotective, anti-influenza A virus, human chemokine antagonist, and immunosuppressant characteristics (Figure 29). The unique scaffold of trichothecenes sesquiterpenoids may be considered one of the characteristics of
this fungus. Additionally, some trichothecenes and atranones could be promising leads for the development of antitumor agents.

![Figure 29. Biological activities of reported metabolites and the number of articles.](image)

Stachybonoid A (196) exhibited anti-dengue potential; therefore, it could be a promising metabolite for developing dengue virus inhibitory agents. Staprexanthones B (205) and E (205) markedly stimulated the regeneration of β-cells; hence, they have the potential as drug leads for anti-diabetes agents. It is noteworthy that the structural variation among these metabolites directly influences their bioactivities. It is noteworthy that this fungus possesses potential and multiple enzymatic systems that might contribute to the diversity of its metabolites. Nevertheless, the enzymes and genes accountable for these unique metabolites’ biosynthesis are a fruitful area of future research.

Further, this fungus has an amazing capacity to produce diverse enzymes that could be beneficial for biotechnological and industrial applications. In addition, they could represent an eco-friendly biodegradation tool that can exchange dangerous wastes into advantageous products. It was found that certain enzymes modification could boost their activity, revealing a new area of future research in this fungus’ enzymes.

There is an only one report on the synthesis of NPs using this fungus. Thus, further studies to synthesize various types of NPs from *S. chartarum* and possible applications of these synthesized NPs can be carried out.

An obvious theme that could be garnered from this work is that, although there is remarkable progress towards the characterization of *S. chartarum* metabolites, we think that there remain many hidden metabolites that need to be discovered. Moreover, further biological evaluations of the reported metabolites and their biosynthetic pathway studies are required. Additionally, the limited in vivo and mechanistic studies of these metabolites necessitate the research focus in this direction. Many of the reported metabolites either are not tested or possessed no observed effectiveness in some of the evaluated activities, therefore, an in silico screening for the potential bioactivities, as well as their derivatization, should clearly be the goal of future research.

Finally, we believe that the therapeutic potential and chemical diversity of this fungus’ metabolites, with more in-depth research, will provide medicinal chemists and biologists with a more promising sustainable treasure-trove for drug discovery.
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Abbreviations

A-549 Human lung cancer cell line
A2780 Human ovarian cancer cell line
BGC823 Human gastric carcinoma cell line
BV2 Microglia cell line
C4-2B Human prostatic carcinoma cell line
CCR5 Chemokine (C-C motif) receptor 5
CCK-8 Cell counting Kit 8
CD Circular dichroism
ConA Concanavalin A
CH_{2}Cl_{2} Dichloromethane
CHO Chinese hamster ovary cell line
CsA Cyclosporin A
DRG Dorsal root ganglia
EC_{50} The concentration (or dose) effective in producing 50% of the maximal response
ECD Electronic circular dichroism
EtOAc Ethyl acetate
FGFR3 Fibroblast growth factor receptor 3
GC-MS Gas chromatography–mass spectrometry
HCT-116 Human colorectal carcinoma cell line
HepG2 Human hepatic cancer cell line
HIV human immunodeficiency virus
HL-60 Human myeloid leukemia cell line:
HPLC High performance liquid chromatography
IFN-γ Interferon γ
IGF1R Insulin-like growth factor 1 receptor
IL-2 Interleukin 2
MCF-7 Human breast cancer cell line
MDAMB-231 Human triple-negative breast cancer
MDA-MB-468 Epithelial, human breast cancer cell line
MG-63 Human osteosarcoma cell line
MGC803 Human gastric cancer cell line
MIC minimum inhibitory concentrations
MIP-1α Macrophage inflammatory protein-1 Alpha
MLR One-way mixed lymphocyte reaction
mRNA Messenger ribonucleic acid
MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)
MVOCs Microbial volatile organic compounds
NCI-H460 Human lung carcinoma cell line
NCI-H1655/1650 Non-small-cell lung adenocarcinoma
NRTIs Nucleoside reverse transcriptase inhibitors
RP-18 Rephased phase-18
PAP-1 (5-(4-Phenoxybutoxy)psoralen)
PC-12 Human pheochromocytoma neuronal cell line
PDGFRβ β-Type platelet-derived growth factor receptor
SK-N-SH  Human neuroblastoma cell line
SiO₂CC  Silica gel column chromatography
SMCC-7721  Human hepatocellular carcinoma cell line
SW480  Human colon cancer cell line
U-2OS  Human osteosarcoma cell line
TC  Total cholesterol
TG  Total glyceride
Tie2  Tyrosine-protein kinase receptor
TRKB  Tropomyosin receptor kinase B
VSV-G  Vesicular stomatitis virus G protein
WT  Cell Division Cycle 37

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