Review

Pestalotiopsis Diversity: Species, Dispositions, Secondary Metabolites, and Bioactivities

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Abstract: Pestalotiopsis species have gained attention thanks to their structurally complex and biologically active secondary metabolites. In past decades, several new secondary metabolites were isolated and identified. Their bioactivities were tested, including anticancer, antifungal, antibacterial, and nematicidal activity. Since the previous review published in 2014, new secondary metabolites were isolated and identified from Pestalotiopsis species and unidentified strains. This review gathered published articles from 2014 to 2021 and focused on 239 new secondary metabolites and their bioactivities. To date, 384 Pestalotiopsis species have been discovered in diverse ecological habitats, with the majority of them unstudied. Some may contain secondary metabolites with unique bioactivities that might benefit pharmacology.

Keywords: Pestalotiopsis genus; secondary metabolites; biosynthesis; bioactivity

1. Introduction

As human society entered a new century, many new problems have to be faced, such as global warming, public health, and food crisis. Especially, novel coronavirus burst in 2020 spring caused a severe effect on global public health and the world economy. More effective novel medications will be investigated to respond to emerging public health challenges. Many bioactive components were already isolated and identified from plants, animals, bacteria, and fungi. Because of the great numbers of bacteria and fungi and their various habitats, they are important sources of bioactive components. Subramanian and Marudhamuthus (2020) [1] isolated and identified the endophytic bacteria, such as Bacillus flexus (DMTMMB08), Bacillus licheniforms (DMTMMB10), and Oceanobacillus picturae (DMTMMB24) from marine macroalgae Sargassum polycystum and Acanthaphora specifera in the benthic region of the Gulf of Mannar, and found that they are taxol-producing. The endophytic fungus Taxonomyes andreanae was isolated from the outer bark of Taxus brevifolia and was first found to have the ability to produce taxol in a culture medium, at approximately 24–25 ng/L [2]. Since then, a great number of taxol-producing fungi, acting as endophytic fungi, have been isolated and identified, such as the endophytic fungus Chaetomella raphigera from a medicinal plant, Terminalia arjuna [3], the endophytic fungus Epicoccum nigrum TXB502 [4], and the endophytic fungus Penicillium polonicum from Ginkgo biloba [5]. Among them, Pestalotiopsis species have been widely studied. The fungal genus Pestalotiopsis was first established by Steyaert R. L. [6]. Since then, many Pestalotiopsis species have been isolated and identified. To date, 384 Pestalotiopsis species are listed in the Index Fungorum (http://www.indexfungorum.org/Names/Names.asp, assessed on 1 August, 2022). All the described species in the Pestalotiopsis genus are differentiated primarily on morphological characteristics of conidia, conidiogenesis, teleomorph, and host associations. In addition, the presence or absence of basal and apical appendages can be used as additional taxonomic characters for identifying Pestalotiopsis species. They are widely distributed in tropical and temperate regions [7–10]. As early as 1996, taxol was first isolated and identified in Pestalotiopsis microspora, an endophytic fungus of Taxus wallachiana [11]. Besides
Pestalotiopsis microspora [12,13], some Pestalotiopsis species were also found to produce taxol, such as Pestalotiopsis mangiferae [14], Pestalotiopsis pauciseta [15], Pestalotiopsis breviseta [16,17], Pestalotiopsis terminaliae [18], and Pestalotiopsis hainanensis [19]. Pestalotiopsis microspora was found to produce between 50 and 1487 ng/L taxol, indicating that taxol production could be achieved at a higher concentration; however, the production was found unstable due to different fungal strains of P. microspora [20].

Since taxol discovery in P. microspora, several other secondary metabolites were isolated and identified from Pestalotiopsis species, and their bioactivities were tested. These secondary metabolites possess several bioactivities, such as anticancer, antifungal, antibacterial, antiviral, and insecticide. Yang XL et al. [21] and Xu J et al. [10] summarized secondary metabolites from Pestalotiopsis species. Although Helaly et al. [22] and Becker and Stadler [23] recently summarized secondary metabolites from the order Xylariales, to which the family Sporocadaceae belongs (Pestalotiopsis is a genus of ascomycete in the family Sporocadaceae), they did not focus on these secondary metabolites from the genus Pestalotiopsis. In this review, we summarize recent advances in secondary metabolites isolated and identified from Pestalotiopsis species. Our goal is to encourage the use of these secondary metabolites and the discovery of new Pestalotiopsis metabolites.

2. Habitat and Functional Diversity of Pestalotiopsis Species

Pestalotiopsis species reside in various habitats, including oceans, rivers, lakes, air, soil, and different plant tissues. For instance, Pestalotiopsis submerses, as a root endophytic fungus, were identified in the roots of plants residing in wetlands near ravine areas with elevations of 1150 and 1775 m [24]. The fungus lives in the roots of Equisetum sp., fern, and Lyonia ovalifolia, yet the occurrence frequency is low (12.5%). Pestalotiopsis species were isolated in the outside air of all four child daycare centers tested by Aydogdu and Asan [25]; however, they did not discover these fungi in the indoor air of these child daycare centers. Some Pestalotiopsis species come from the marine environment, such as Pestalotiopsis neglecta [26,27], Pestalotiopsis heterocornis [28–31], Pestalotiopsis vaccinii [32], Pestalotiopsis sydowiana [33], and other Pestalotiopsis sp. [34–37]. Pestalotiopsis papuana CBS 331.96 and Pestalotiopsis humus CBS 336.97, on the other hand, were discovered in soil [8]. Astonishingly, Pestalotiopsis hainanensis was identified from the dermatitic scurf of a giant panda (Ailuropoda melanoleuca) [19] and Pestalotiopsis sp. HC02 resides in Chondracris rosea gut [38]. Pestalotiopsis ssp. was also identified as an entomopathogenic fungus on Hemiberlesia pitysophila, an extremely harmful exotic insect in Pinus forests [39]. Thus, the isolate is promising for the biocontrol of H. pitysophila. In addition, Pestalotiopsis species might be related to human diseases. For example, Pestalotiopsis clavispora was identified from a patient’s cornea with recurrent keratitis [40].

In their respective habitats, Pestalotiopsis species show different ecological functions. Pestalotiopsis species, as plant endophytic or saprophytic fungi, reside in other plant tissues, such as bark [41], stems [42], twigs [43], roots [24], leaves [44–48], flowers [49,50], and fruits [51]. As saprophytic fungi, they cause various plant diseases, such as blight diseases in leaves and twigs [43,50,52–55], leaf necrosis [44], leaf spots [46], fruit rot [51], dry flower disease [56], dieback disease [57–59], canker [58,60,61], and even postharvest diseases [62]. Sometimes, Pestalotiopsis species cause destructive diseases. For example, Pestalotiopsis samarangensis was harmful to Syzygium samarangense in Thailand [63]. Some Pestalotiopsis species act as an endophyte or a saprobe in different plant species. For example, P. microspora causes leaf spots in blueberry (Vaccinium corymbosum L.) [46], leaf blight of loquat (Eriobotrya japonica) [64], and leaf blight of Japanese yew (Taxus cuspidate) [65]; however, the fungus more often acts as an endophyte [66–68]. Therefore, Pestalotiopsis species play a variety of ecological roles.

3. New Secondary Metabolites in Pestalotiopsis Species

In 2012, it was estimated that 196 secondary metabolites had been encountered in the Pestalotiopsis genus [21]. New secondary metabolites were isolated and identified
in the recent decade, and their bioactivities were tested (Table 1). We compared the compounds in the literature published after 2014 with those listed by Yang X-L et al. [21] and Xu J et al. [10] and came up with the following list of novel compounds listed below.
| Fungal Species | Metabolites                                                                 | Bioactivity                          | References |
|----------------|-----------------------------------------------------------------------------|--------------------------------------|------------|
| *P. adusta*    | pestalachlorides A–C, diterpenoid                                           | antifungal                           | [69]       |
| *P. besseyi*   | furanones                                                                   |                                      | [70]       |
| *P. breviseta* | a new coumarin and six known compounds                                     |                                      | [71]       |
| *P. crassiuscula* | pestalotioquinols G and H, pestalotioquinol A, phomonitroester, (R)-4,6,8-trihydroxy-3,4-dihydronaphthalen-1(2H)-one, and scylatone | antimalarial and cytotoxic activity | [72]       |
| *P. disseminata* | 6-hydroxypunctaporonin E, 6-hydroxypunctaporonin B, and 6-hydroxypunctaporonin A | anti-bacteria                        | [73]       |
|                | disseminins A–E, spiciferones D and E                                       |                                      |            |
|                | chloropuakeananin and chloropostolides                                      | antimicrobial, antitumor, and anti-HIV activities | [74]       |
|                | pestaloficiols A–E                                                          | inhibitory effects on HIV-1 replication | [75]       |
|                | isosulochrin, ficipyrone A, pestheic acid, iso-A82775C, pestaloficiol M, RES1214-1, and iso-A82775C |                                      | [76]       |
|                | pestalofenes A–E, isosulochrin, isosulochrin dehydrate, and iso-A82775C    | inhibitory effects on HIV-1 replication and antifungal activity | [77]       |
|                | chloropuakeanolides C–E                                                     | cytotoxicity                         | [78]       |
|                | pestheic acid                                                               |                                      | [79]       |
| *P. fici*      | chloropuakeananin                                                           |                                      | [80]       |
|                | melanin                                                                     |                                      | [81]       |
|                | chloropuakeanolides A and B, chloropuakeanone A                            | anti-HIV-1 and cytotoxic activity    | [82]       |
|                | isoprenylated chromone derivatives                                          |                                      | [83]       |
|                | Chloropostiolides B–G                                                       |                                      | [84]       |
|                | pestaloficiys A–E                                                           |                                      | [85]       |
|                | pestaloficiols Q–S                                                          |                                      | [86]       |
|                | DHN melanin                                                                 |                                      | [87]       |
|                | 2H-pyran-2-one and 2H-furan-2-one derivatives                              |                                      | [88]       |
| *P. flavidula* | spiroketal derivatives                                                      | cytotoxicity                         | [89]       |
| *P. foedan*   | pestalofid A, pestaphthalide A and B                                        | antifungal activity                  | [90]       |
|                | (∓)-(4S, 8S)-foedanolide and (+)-(4R, 8R)-foedanolide                       |                                      | [91]       |
|                | monoterpane derivatives                                                     |                                      | [92]       |
Table 1. Cont.

| Fungal Species | Metabolites                                                                 | Bioactivity                        | References |
|----------------|------------------------------------------------------------------------------|-----------------------------------|------------|
| *P. guepinii*  | metabolites of ciprofloxacin and norfloxacin                                |                                   | [96]       |
|                | culture broth extract                                                        | inhibit actinomycete growth       | [97]       |
|                | pestheic acid or dihidromaldoxacin                                            | genotoxicity and mutagenicity     | [98]       |
|                | alpha-pyrones                                                                |                                   | [99]       |
| *P. hainanensis* | taxol                                                                       |                                   | [19]       |
|                | caryophyllene-Type Sesquiterpenes                                            |                                   | [100]      |
| *P. heterocorni* | 7-hydroxy-5-methoxy-4,6-dimethyl-7-O-α-L-rhamnosyl-phthalide and             | cytotoxicity and antifungal       | [29]       |
|                | 7-hydroxy-5-methoxy-4,6-dimethyl-7-O-β-D-glucopyranosyl-phthalide            |                                   |            |
| *P. heterocorni* | heterocornols A–L, methyl-(2-formyl-3-hydroxyphenyl) propanoate, cladoacetals|                                   | [29]       |
|                | A, xylarinol A, agropyrenol, vaccinol G, (R)-3-hydroxy-1-[(R)-4-hydroxy-1,3-dihydroisobenzofuran-1-yl]butan-2-one, and (R)-3-hydroxy-1-[(S)-4-hydroxy-1,3-dihydroisobenzofuran-1-yl]butan-2-one | cytotoxicity and antifungal       |            |
| *P. heterocorni* | pestaloisocoumarins A and B, isopolisin B, pestalotiol A, gamahorin, pestalachloride B, pestalachloride E, pestalactone atropisomers (8a/8b), heterocornols M and N, heterocornols O and P | cytotoxicity                       | [30]       |
| *P. heterocorni* | pesticandin                                                                 | antibacterial and antifungal activity, weak cytotoxicity | [102]     |
| *P. heterocorni* | jesterone and hydroxy-jesterone                                              | antibacterial and antifungal activity | [103]     |
| *P. jesteri*    | pesticandin                                                                 | selective antimycotic activity    | [104]      |
| *P. karstenii*  | pestalrone A, pestalrone B, pestalotin, hydroxypestalotin                    | cytotoxic activity, antiprotozoal activity | [42]       |
| *P. leucothës*  | BS, GS, and YS                                                               | Immunomodulatory                   | [105]      |
| *P. mangiferæ*  | 4-(2,4,7-trioxa-bicyclo [4.1.0] heptane-3-yl) phenol                        | antibacterial and antifungal activity | [107]     |
| *P. microspora* | taxol                                                                        | antiproliferative activity         | [11,108]  |
|                | α-pyrene                                                                     |                                   | [109]      |
|                | (+)-dendocarbin L, (+)-sydonic acid, and (+)-sydowic acid                   | cytotoxicity                       | [68]       |
|                | isopestacin                                                                  | antifungal and antioxidant activities | [110]     |
|                | pesticadin                                                                   |                                   |            |
| *P. microspora* | pestalotiollide B                                                            |                                   |            |
|                | pestalotiollide B, melanin                                                   |                                   | [114]      |
|                | 7-epi-10-deacetyltaxol                                                       | induces apoptosis                  | [115]      |
| *P. microspora* | taxol, pestalotiollide B, 1, 8-dihydroxy naphthalene melanin                 | antitumor                          | [13]       |
|                | melanin                                                                       |                                   | [116]      |
Table 1. Cont.

| Fungal Species        | Metabolites                                                                                      | Bioactivity                                      | References |
|-----------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------|------------|
| **P. neglecta**       | ursoic acid                                                                                      | cytotoxic                                        | [117]      |
|                       | pestalotioprolides C, D-H, 7-O-methyl nigrosporolide, pestalotioprolide B, seiricuprolide, nigrosporolide, and 4,7-dihydroxy-13-tetradeca-2,5,8-trienolide | cytotoxic                                        | [118]      |
|                       | dibenzodioxocinons                                                                                                               | inhibitors of cholesterol ester transfer protein | [119,120]  |
|                       | pestalotioquinols A and B                                                                                                         | neuroprotective                                  | [121]      |
|                       | pithole E, pithole B, pithole D, pestalotin, PC-2, tyrosol, 4-oxo-4H-pyrain-3-acetic acid                                                                 |                                                   | [67]       |
|                       | 2H-pyranone and isocoumarin derivatives                                                                                           | antifungal                                       | [66]       |
|                       | Microsporols A–C, ambuic acid                                                                                                     | 5-lipoxygenase (5-LOX) inhibitory effects        | [122]      |
|                       | ambuic acid derivatives                                                                                                           | inhibitory activity against the NO production  | [123]      |
|                       | crude methanol and ethyl acetate extract                                                                                           | antibacterial activity                            | [124]      |
|                       | pestalotiochromenoic acids A–D, pestalotiochromones A and B                                                                       | liver X receptors modulators                     | [125]      |
|                       | ambuic acid                                                                                                                                  | anti-inflammatory action                         | [126]      |
|                       | benzophenones                                                                                                                              | inhibit pancreatic cancer cells                  | [31]       |
|                       | Ene-yne Hydroquinones                                                                                                                  |                                                   | [26]       |
|                       | pestalopyrones A–D                                                                                                                       |                                                   | [127]      |
|                       | pestallic acids F and G, pestalotiyprone N, neopestalone, sesquicaranoic acid B, monocycloalternarene B, pestalone, 2,4-dihydroxy-3,5,6-trimethyl benzoic acid, and citreorosein |                                                   | [27]       |
| **P. palmarump**      | sinopestalotillides A–D, 3′-O-methyldehydroisopenicillide, Δ1′3′-1′-dehydroxypenicillide, dehydroisopenicillide, 2′-hydroxy-3′,4′-didehydroxypenicillide, scirpyrones A, 5,6-dihydro-4-methoxy-2H-pyran-2-one, LL-P880a, (6,6′,5′,2′R)-LL-P880b, photipyrones B, PC-2, (1′S,2′R)-LL-P880γ, necpyrone C | cytotoxic                                        | [128]      |
| **P. pauciseta**      | taxol                                                                                                                                       | anticancer                                       | [15]       |
|                       | phthalide derivatives                                                                                                                  | against plant pathogens                          | [129]      |
|                       | photipyrones A, B, C                                                                                                                   | modest inhibitory effects on the growth of MDA-MB-231 | [130]      |
| **P. plotiniæ**       | 4-(3′,3′-dimethylallyloxy)-5-methyl-6-methoxyphthalide                                                                                   | induced G1 cell cycle arrest and apoptosis in a dose-dependent manner | [131]      |
|                       | 4-(3′,3’-Dimethylallyloxy)-5-methyl-6-methoxy-phthalide                                                                                  | cytoxicity                                       | [132]      |
|                       | three new phthalide derivatives and six known phthalide derivatives                                                                       | antifungal activities                             | [133]      |
|                       | photinides A–F                                                                                                                             |                                                  | [52]       |
| **Pestalotiopsis sp.**| RES-1214-1 and -2                                                                                                                          | non-peptidic endothelin type A receptor antagonists                  | [134]      |
| **Pestalotiopsis sp.**| pestalotiopamide E                                                                                                                       |                                                  | [135]      |
### Table 1. Cont.

| Fungal Species | Metabolites | Bioactivity | References |
|----------------|-------------|-------------|------------|
| Pestalotiopsis sp. | pestalotiopens A and B | induce G0/G1 cell cycle arrest and apoptosis in human cancer cells | [136] |
| Pestalotiopsis sp. | pestalactams A–C | | [137] |
| Pestalotiopsis sp. | pestaloficiol J, (±)-pestaloficiol X | | [138] |
| Pestalotiopsis sp. | pestaloquinols A and B | | [139] |
| Pestalotiopsis sp. | demethylincisterol Aβ, dankasterone B, (22E, 24R)-ergosta-7,9, 22-triene-3β, 5α, 6α-triol, ergosta-5,7,22-trien-3-ol, 5,8-epidioxy-5,8-ergosta-6,22-dien-3-ol, stigmaster-3-one, stigmaster-4-en-3-one, stigmaster-4-en-6-ol-3-one, flufuran, (2-cis, 4-trans)-abscisic acid, similanyprone B. | induce G0/G1 cell cycle arrest and apoptosis in human cancer cells | [140] |
| Pestalotiopsis sp. | pestaloporonins | | [141] |
| Pestalotiopsis sp. | polyketide-terpene hybrid metabolites | | [142] |
| Pestalotiopsis sp. | pestaloporinates A–G and 14-acetyllhumulane | | [143] |
| Pestalotiopsis sp. | isocoumarin derivatives | antifungal | [144] |
| Pestalotiopsis sp. | pestalotiopsolide A, taedolidol and 6-epitaedolidol | | [41] |
| Pestalotiopsis sp. | (±)-pestalachloride D | antibacterial | [415] |
| Pestalotiopsis sp. | cytosporones J-N, pestalasin A-E, pestalotiopsoid A, cyclosporine C, dothiorelone B, and 3-hydroxymethyl-6,8-dimethoxycoumarin (13). | | [146] |
| Pestalotiopsis sp. | (+)- and (−)-pestaloxazine A | antiviral | [147] |
| Pestalotiopsis sp. | pestalotiopsins A and B | immunosuppressive | [148] |
| Pestalotiopsis sp. | ambuic acid and torreyanic acid derivatives | antimicrobial activity | [149] |
| Pestalotiopsis sp. | pestalotiopsones A–F | moderate cytotoxicity | [150] |
| Pestalotiopsis sp. AcBC2 | pestals A–E, 4-hydroxyphenethyl 2-(4-hydroxyphenyl) acetate, r-hydroxyphenyl acetic acid methyl ester, transharzialactones A and F, 3-hydroxy-3-methyl-d-lactone, 3β,5α, 9α-trihydroxy-7,22-en-ergost-6-one, and 3β-hydroxy-sterol | cytotoxicity, inhibitory activities against Influenza A virus subtype (H3N2), Swine Flu (H1N1) viruses, tuberculosis | [151] |
| Pestalotiopsis sp. BC55 | exopolysaccharide | | [152] |
| Pestalotiopsis sp. cr013 | pestalpolys A–D | cytotoxic | [153] |
| Pestalotiopsis sp. cr014 | pestalotic acids A–I | antibacterial | [154] |
| Pestalotiopsis sp. PG52 | pestalpolys E–H | cytotoxic activities | [155] |
| Pestalotiopsis sp. EJC07 | (4S)-4,8-dihydroxy-1-tetralone, uracil, uridine, r-hydroxybenzoic acid, ergosterol, ergosterol peroxide, cerevisterol and ducitol | | [74] |
| Pestalotiopsis sp. FT172 | pestallic acids A–E | anti-proliferative | [156] |
| Pestalotiopsis sp. HC02 | pestalotines A and B | | [38] |
| Pestalotiopsis sp. HHL101 | pestalotiopisinor B | | [157] |
| Fungal Species | Metabolites | Bioactivity | References |
|----------------|-------------|-------------|------------|
| *Pestalotiopsis* sp. HQD-6 | pestalotiopin B and pestalotiopyrone N | very weak cytotoxic | [158] |
| *Pestalotiopsis* sp. IQ-011 | cuautepestalinor, cytosporin M, cytosporin N, oxopestalochromane, pestalone | inhibitory properties against α-glucosidase from *S. cerevisiae* | [159] |
| *Pestalotiopsis* sp. M-23 | drimane sesquiterpenoids, 2α-hydroxyisodrimenol, a new isochromane derivative | weak antibacterial | [160] |
| *Pestalotiopsis* sp. PSU-MA69 | pestalochromones A–C, pestalotethers A–D, pestaloxanthone, pestalolide | antifungal activity against *Candida albicans* and *Cryptococcus neoformans* | [161] |
| *Pestalotiopsis* sp. Z233 | 1β,5α,6α,14-tetraacetoxy-9α-benzoyloxy-7βH-eudesman-2β,11-diol and 4α,5α-diacetoxy-9α-benzoyloxy-7βH-eudesman-1β,2β,11,14-tetraol | tyrosinase inhibitory activities | [162] |
| *Pestalotiopsis* spp. | ambucic acid | antifungal | [163] |
| *Pestalotiopsis* spp. | chromones, cytosporones, polyketides, terpenoids and coumarins | | [164] |
| *P. sydowiana* | 1-O-methyldehydroisopenicillide, pestalotiollide B, pestalotiollide A, dehydroisopenicillide, 6-hydroxymethyl-4-methoxy-5,6-dihydro-2H-pyran-2-one, pestalotiopyrone D, pestalotiopyrone E, pestalotiopyrone G, LL-P880b, and photopyrone B | 20S proteasome inhibitory activities | [165] |
| *P. terminaliae* | cyclo(-Leu-Pro) and 4-hydroxyphenylacetamide | antimicrobial, | [33] |
| *P. theae* | taxol | anticancer | [18] |
| chloroisosulochrin, ficipyrone A and pestheic acid | pesthetoxin | strong activity against respiratory syncytial virus | [166] |
| pestalothedins A–D | inhibitory effect on HIV-1 LAI replication | [168] |
| pestalazines and pestalamides | inhibitory effects on HIV-1 replication and antifungal activity | [169] |
| chlorotheolides A and B, 1-undecene-2,3-dicarboxylic acid, maldoxin | | [170] |
| pestalotiones A–D | | [171] |
| chloropupukeananin and pestalofone C | regulate autophagy through AMPK and Glycolytic Pathway | [172] |
| pestathenols A and B, pestatheranone A, punctaporonins O, P, and R, ficipyrone B, and decarestrictine D | | [173] |
| pechetalphen A–C | cytotoxic and antibacterial activity | [174] |
| *P. uvicola* | pechetalphen A–C | cytotoxicity against mouse melanoma (B16-BL6) cell line | [175] |
| pechetalphen A–C | suppresses adipogenesis in 3T3-L1 adipocytes via the AMPK signaling pathway; protect BV2 microglia cells against OGD/reoxygenation injury | [176–178] |
| *P. vaccinii* | vaccinols J-S, trans-sordarial, cis-sordarial, 4-hydroxypthalide, pestalotiopin A | | [32] |
| *P. versicolor* | 4,6-dihydroxy-7-formyl-3-methyl coumarin, 6-{[7(S,8R)-8-propyloxiran-1-yl]-4-methoxy-pyran-2-one | devoid of significant antifungal activity against *F. solani*, *Ustilago maydis*, and *C. albicans* | [179] |
Table 1. Cont.

| Fungal Species | Metabolites                              | Bioactivity                              | References |
|----------------|------------------------------------------|------------------------------------------|------------|
| *P. virgatula* | pestalospiranes A and B                  |                                          | [180]      |
|               | 9-hydroxybenzo[Cl]oxepin-3[1H]-one       |                                          | [181]      |
|               | virgatolides A–C                         |                                          | [182]      |
| *P. yunnanensis* | pestalotic acids A–G                    | significant antimicrobial activity       | [183]      |
| *P. zonata*   | pestalrones A and B, pestalotin, hydroxypestalotin, pestazonatic acid, necpyrones A–B |                                          | [184]      |
3.1. Pestalotiopsis diploclisia

The marine fungus *P. diploclisia* (BCC 35283) produces two new hydroquinones bearing a 1,3-enzyme moiety, pestalotioquinos G (1) and H (2) [73]. *P. microspora* has pestalotioquinol A (3) and B (4), and the two compounds are neuroprotective [121]. Furthermore, 1–3 μM pretreatment of pestalotioquinols A (3) and B (4) rescued nerve growth factor-differentiated neuronal PC12 cells from peroxynitrite-induced cytotoxicity, and their protective activity was sustained after removing each compound from the medium; thus, the two compounds (3 and 4) exhibited relatively high neuroprotective effects. In addition, Pestalotioquinol A (3) displayed antimalarial activity against *Plasmodium falciparum* K1 with an IC50 value of 19.0 μM. In comparison, pestalotioquinol G (1) showed weak cytotoxic activity against Vero cell lines with an IC50 value of 47.9 μM [73].

*P. diploclisia* also produces the compound scylatone (5) [73]. Scylatone (5) is one of the melanin biosynthesis intermediates. *P. microspora* and *Pestalotiopsis fici* were reported to produce melanin pigment [13,84,90,114,116]. Melanin biosynthesis is complex in fungi, and some fungi have more than one biosynthesis pathway for melanins [185]. Melanization in mycelia and appressoria plays crucial roles in the protection of pathogens from antibiotic stressors and the pathogenicity or interaction with host plants [185,186], and melanin is essential not only for the protection of spores from biotic and abiotic stresses but also structural spore development [84]. Thus, scylatone and melanin are related to the infection of host plants.
3.2. Pestalotiopsis disseminate

P. disseminate produces disseminins A-E (6–10) and spiciferones D (11) and E (12) [75]. Disseminins A-E (6–10) showed no activity against Aspergillus flavus, Escherichia coli, or Candida albicans at 100 µg/disk [75]. These compounds are synthesized via the pathway shown in Figure 1 [75]:

![Synthesis pathway of disseminins and spiciferones.](image)

Spiciferone A (13) and other congeners (14–21) were also isolated and identified in Cadophora luteo-olivacea collected from Port Lockroy on the Antarctic peninsula, endophytic fungus Phoma betae collected from desert plants in West China [187,188], and Cochlioholus spicifer [12]. Spiciferone A (13) is a major phytotoxin to cotyledons of wheat (Triticum aestivum L. cv. Ushio-komugi), and spiciferone C (20) was less phytotoxic to wheat cotyledons than spiciferone A (13), while spiciferone B (19) was not phytotoxic, and dihydrosopiciferone A (21) was as active as spiciferone A (13) [12]. Hwang et al. [75] did not observe that spiciferones D (9) and E (10) showed activity against Staphylococcus aureus, Bacillus subtilis, E. coli, and C. albicans at 50 µg/disk. Spiciferone A (13), spiciferol A (14), dihydrosopiciferol A (15), spiciferone F (16), and dihydrosopiciferone A (21) showed no activity against methicillin-resistant S. aureus (MRSA), vancomycin-resistant Enterococcus faecalis (VRE), B. subtilis, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, C. neoformans, and C. albicans. These five compounds also showed no cytotoxicity against LOX IMVI (melanoma) and SF-295 (glioblastoma) human cancer cell lines [187].
3.3. Pestalotiopsis fici

*P. fici, Pestalotiopsis guepinii,* and *Pestalotiopsis theae* produce ficipyrone A (22) and pestheic acid (i.e., dihidromaldoxin) (23) [78,82,98,166]. Xu X et al. [82] proposed a biosynthesis pathway of pestheic acid. The two compounds showed moderate inhibition of respiratory syncytial virus (IC$_{50}$ values ranging from 45.00 ± 0.98 to 259.23 ± 2.36 μM) [166]. Sousa et al. [98] assessed the cytotoxic, cytostatic, and genotoxic effects of pestheic acid (23) in a gastric adenocarcinoma cell line (PG100). Their results showed a decrease in clonogenic survival. Pestheic acid (23) also significantly increased both micronucleus and nucleoplasmic bridge frequency. However, they observed no changes in cell cycle kinetics or apoptosis induction. Thus, they considered that pestheic acid (23) was not an active anticancer compound under these conditions, because the minimal inhibitory concentration was high.
Pestaloficins (24–28) were isolated and identified in *P. fici* and other *Pestalotiopsis* sp. [88,189]. In addition, Guo and Zou [190] discovered pestaloficin C (26) in the plant endophytic fungus *Monosporascus eutypoides*. However, none of the studies focused on the bioactivities of these substances, so their bioactivities need to be tested.

3.4. *Pestalotiopsis foedan*

(−)-(4S,8S)-foedanolide (29) and (+)-(4R,8R)-foedanolide (30), a pair of new spiro-γ-lactone enantiomers, were isolated from the fermentation broth of the plant endophytic fungus *P. foedan* [94]. The two compounds showed moderate activities against HeLa cells, lung adenocarcinoma cell line A-549, U-251, HepG2, and MCF-7 tumor cell lines. The IC₅₀ values of (−)-(4S,8S)-foedanolide (29) against these tumor cell lines were 15.8, 296.0, 159.0, 22.8, and 70.2 μg/mL, respectively; the IC₅₀ values of (+)-(4R,8R)-foedanolide (30) against these tumor cell lines were 5.4, 67.9, 53.0, 19.0, and 20.8 μg/mL, respectively [94].

Yang XL et al. [21] and Xu J et al. [10] introduced some sesquiterpenes, diterpenes, and triterpenes, but not monoterpenes. A new monoterpenic lactone, (1R,4R,5R,8S)-8-hydroxy-4,8-dimethyl-2-oxabicyclo[3.3.1]nonan-3-one (31), and (2R)-2-[(1R)-4-methylcyclohex-3-en-1-yl]propanoic acid (32), were isolated from the liquid culture of the plant endophytic fungus *P. foedan* [95]. Both compounds (31 and 32) exhibited strong antifungal activities against the two pathogens, *Botrytis cinerea* and *Phytophthora nicotianae*, with MIC values of 3.1 and 6.3 μg/mL, respectively, which are comparable to those of the known antifungal drug ketoconazole. The compound (32) also showed modest antifungal activity against *C. albicans* with a MIC value of 50 μg/mL [95].
3.5. Pestalotiopsis guepinii

*P. guepinii* is the fungal causal pathogen of hazelnut (*Corylus avellana*) in Turkey. *P. guepinii* produced phytotoxic α-pyrone, including 6-(1-hydroxypentyl)-4-methoxy-pyran-2-one (33), derivatives (34, 35, 37, 38) of the compound 33, and 6-pentyl-4-methoxy-pyran-2-one (36) [99]. None of these compounds (33–38) showed antibiotic activities against *B. subtilis* and Geotrichum candidum when tested up to 100 μg per diskette [99].

![Chemical structures](image-url)
3.6. Pestalotiopsis heterocornis

Heterocornols A-L (39–50), methyl-(2-formyl-3-hydroxyphenyl) propanoate (51), cladoacetal A (52), xylarinol A (53), agropyrenol (54), vaccinol G (55), (R)-3-hydroxy-1-[(R)-4-hydroxy-1,3-dihydroisobenzofuran-1-yl]butan-2-one (56), and (R)-3-hydroxy-1-[(S)-4-hydroxy-1,3-dihydroisobenzo-furan-1-yl]butan-2-one (57) were isolated and identified in the marine sponge-derived P. heterocornis [29]. Heterocornols A-C (39–41), Heterocornols F-H (44–46), methyl-(2-formyl-3-hydroxyphenyl) propanoate (51), agropyrenol (54), and vaccinol G (55) showed cytotoxic activities against four human cancer cell lines with IC₅₀ values of 15–100 µM. These also showed antibacterial activities against Gram-positive bacteria S. aureus and
B. subtilis with MIC values ranging from 25 to 100 mg/mL [30]. In addition, these compounds, heterocornol C (41), heterocornol G (45), agropyrenol (54), and vaccinol G (55), exhibited weak antifungal activities against Candida parapsilosis and C. neoformans with MIC values of 100 μg/mL [30].

Lei H et al. [28] also isolated and identified heterocornols M and N (58, 59) and a pair of epimers, heterocornols O and P (60, 61), in P. heterocornis. The four compounds (58–61) showed cytotoxic activities against four human cancer cell lines (BGC-823, Ichikawa, HepG2, 7860) with IC₅₀ values of 20.4–94.2 μM.

In P. heterocornis, pestaloisocoumarins A and B (62, 63), gamahorin (64), one sesquiterpenoid degradation product, isopolisin B (65), and one furan derivative, pestalotiol A (66), were also isolated and identified [30]. Pestaloisocoumarins A and B (62, 63) and gamahorin (64) exhibited antibacterial activities against Gram-positive bacteria S. aureus and B. subtilis with MIC values ranging from 25 to 100 μg/mL. The three isocoumarins (62, 63, 64) showed weak antifungal activities against C. albicans, Candida parapsilosis, and C. neoformans with MIC values of 100 μg/mL. Natural isocoumarins were studied in terms of sources, structural styles, biosynthesis, and biological activity by Shabir et al. [191] and Noor et al. [192], who also gave some relevant information. A mixture of pestalactone atropisomer A/B (67, 68) showed moderate cytotoxic activities against four human cancer cell lines (BGC-823, H460, PC-3, SMMC-7721) with IC₅₀ values of 6.8–87.7 μM, while compounds 62–66 did not exhibit an obvious inhibition effect against the cancer lines at 100 μM [30].
3.7. Pestalotiopsis humus

Pestynol (69) and pестиocandin (70) were isolated and identified in P. humus FKI-7473 using multidrug-sensitive yeast [102,103]. Pestynol (69) was weakly cytotoxic against three floating cell lines (Jurkat, HL60, and THP-1 cells) and two adherent cell lines (HT29 and A549 cells), with IC_{50} values of 84, 19, 61, 83, and 92 μM, respectively, and the other three adherent cell lines (HeLa S3, H1299, and Panc1 cells) were not affected at 100 μM of pestynol (69) [102]. Pестиocandin (70) showed moderate or weak growth inhibition against Gram-positive bacteria (S. aureus, B. subtilis, Micrococcus luteus, and Mycobacterium smegmatis), Gram-negative bacteria (Xanthomonas oryzae pv. oryzae and Proteus vulgaris), yeasts (Saccharomyces cerevisiae BY25929 and S. cerevisiae 12geneΔ0HSR-iERG6), and a filamentous fungus (Mucor racemosa), with MIC values of 8–256 μg/mL [103]. The compound (70) did not exhibit effects on Gram-negative bacteria (B. subtilis, K. pneumoniae, and P. aeruginosa) and yeasts (C. albicans, S. cerevisiae KF237, and S. cerevisiae BY4741), with MIC values of more than 256 μg/mL.

3.8. Pestalotiopsis karstenii

Two oxysporone derivatives, pestalrone A (71) and pestalrone B (72), were isolated and characterized in the endophytic plant fungus P. karstenii isolated from stems of Camellia sasanqua and foliar endophytic fungus Pestalotiopsis zonata [42,184]. Pestalrone A (71) had no inhibitory effects on the five human tumor cell lines (HeLa, U-251, A549, HepG2, and MCF-7). At the same time, pestalrone B (72) showed significant activities against the three human tumor cell lines (HeLa, HepG2, and U-251) with IC_{50} values of 12.6, 31.7, and 5.4 μg/mL, respectively. However, this compound (72) did not show noticeable cytotoxic activities against cell lines A549 and MCF-7 [42]. In addition, pestazonomic acid (73) was isolated and identified in P. zonata [184], yet its bioactivity was not evaluated.
3.9. Pestalotiopsis mangiferae

A phenolic compound, 4-(2,4,7-trioxa-bicyclo [4.1.0]heptan-3-yl) phenol (74), was isolated and characterized from the endophytic fungus *P. mangiferae* associated with *Mangifera indica* [107]. The compound (74) showed appreciable antibacterial and antifungal activities against *B. subtilis, K. pneumoniae, C. albicans* (MIC of 0.039 mg/mL), *B. subtilis*, and *M. luteus* (MIC of 1.25 mg/mL) followed by *P. aeruginosa* (MIC of 5.0 mg/mL).

3.10. Pestalotiopsis microspora

Yang XL et al. [21] and Xu J et al. [10] introduced novel sesquiterpenes. Three new sesquiterpenes, (+)-dendocarbin L (75), (+)-sydonic acid (76), and (+)-sydowic acid (77), were isolated from the mycelium of the endophytic fungus *P. microspora* associated with the stem of *Artocarpus heterophyllus* [68]. Their cytotoxicity was evaluated on murine leukemia P-388 cells, with IC\textsubscript{50} values of 18.78, 20.30, and 2.56 µg/mL for (+)-dendocarbin L (75), (+)-sydonic acid (76), and (+)-sydowic acid (77), respectively. Thus, among the three compounds (75, 76, 77), (+)-sydowic acid (77) exhibits the most potential to inhibit murine leukemia P-388 cells.
Yang et al. [21] presented pestalotioprolides A and B. New analogs were isolated and identified as well. Pestalotioprolides C–H (78–83) and 7-O-methylnigrosporolide (84) were isolated from a mangrove-derived endophytic fungus P. microspora [118]. The four compounds, 7-O-methylnigrosporolide (84), pestalotioprolide D (79), pestalotioprolide E (80), and pestalotioprolide F (81), showed significant cytotoxicity against the murine lymphoma cell line L5178Y with IC\textsubscript{50} values of 0.7, 5.6, 3.4, and 3.9 μM, respectively, while pestalotioprolide E (80) exhibited potent activity against the human ovarian cancer cell line A2780 with an IC\textsubscript{50} value of 1.2 μM. Interestingly, co-culture of P. microspora with Streptomyces lividans caused an approximately 10-fold enhanced accumulation of pestalotioprolide E (80) and pestalotioprolide F (81), compared to axenic fungal controls [118]. The enhanced accumulation is beneficial for the formation of pestalotioprolide E (80) and pestalotioprolide F (81), and attention should be directed to associated molecular pathways.

In addition, nigrosporolide (85) and 4,7-dihydroxy-13-tetradeca-2,5,8-trienolide (86) were isolated in P. microspora and the mold Nigrospora sphaerica [118,193]. The two compounds (85 and 86) showed weak bioactivities against lymphoma cell line L5178Y with an IC\textsubscript{50} value of 21 μM, while they exhibited no biological activities against ovarian cancer cell line A2780 with an IC\textsubscript{50} value of more than 40 μM [118]. Furthermore, Harwooda et al. [193] reported that nigrosporolide (85) caused 100% inhibition in the growth of etiolated wheat coleptile sections at 10\textsuperscript{–3} M; however, it showed no effect at lower concentrations. Since auxins have a significant impact on plant development, nigrosporolide (85) could be analyzed as a new component in the auxin signaling pathway, such as the TOR kinase found via rapamycin produced by the soil bacterium Streptomyces hygroscopicus in the Easter Island [194,195].

![Chemical structures](image)

Pitholide B (87), pitholide D (88), and pitholide E (89) were isolated and identified in P. microspora and Pithomyces sp. [67,196]. However, Pitholide E (89) did not exhibit any significant antifungal activity against Cladosporium cladosporioides, while Pitholide B (87) and Pitholide D (88) were not analyzed for their bioactivity [67]. In addition, Pitholides A (90) and C (91) were isolated from Pithomyces sp. derived from the marine tunicate Oxycorynia fascicularis, and their bioactivities were also not evaluated [196].
P. microspora SC3082 was derived from the tropical tree Scaevola taccada, and a few new compounds (92–97) were isolated and characterized in the strain, including microsporaline A-D (92–95) [66]. Microsporalines B and C (93, 94) and gamahorin (96) displayed moderate antifungal activities against C. albicans (ATCC 10321) with MIC values of 25.0, 25.0, and 12.5 μg/mL, respectively, while microsporaline A and D (92, 95) and 8-acetoxy pestalopyrone (97) did not show bioactivities against C. albicans (ATCC 10321) with MIC values of > 100 μg/mL.

Yang XL et al. [21] introduced ambuic acid and several of its derivatives, and more compounds have been discovered since then. For example, three new ambuic acid derivatives (98–100) were isolated from the solid culture of P. neglecta [123]. In the nitric oxide (NO) inhibition assay, the derivative 104 exhibited weak inhibitory activity against the NO production in the lipopolysaccharide (LPS)-induced macrophage with an IC$_{50}$ value of 88.66 μM. Since NO shows a strong physiological function in plants and humans, the derivative 104 could explore the novel NO functions.

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3.11. Pestalotiopsis neglecta

Four new ambuic acid derivatives (101–104) were isolated from the solid culture of *P. neglecta* [123]. In the nitric oxide (NO) inhibition assay, the derivative 104 exhibited weak inhibitory activity against the NO production in the lipopolysaccharide (LPS)-induced macrophage with an IC$_{50}$ value of 88.66 μM. Since NO shows a strong physiological function in plants and humans, the derivative 104 could explore the novel NO functions.

Pestalotiochromenoic acids A-D (105–108), as well as two novel chromone derivatives, pestalotiochromones A (109) and B (110), were discovered for the first time in the marine algae-derived fungus *P. neglecta* SCSIO41403 [125]. All of these compounds (105–110) were inactive or showed weak cytotoxicity against seven human cancer cell lines, i.e., three renal cancer cell lines (ACHN, OS-RC-2, 786-O), three leukemia cell lines (HL-60, K-562, MOLT-4), and a liver hepatocellular carcinoma cell line (HepG2) (IC$_{50}$ > 50 μM); however, these compounds showed obvious liver X receptors (LXRs) modulatory activities in a dose-dependent manner. From the liquid cultures of *P. neglecta* SCSIO41403, three new carboxylic acid derivatives, pestalic acids F (111) and G (112), pestalotiopyrone N (113), and a new diphenylketone derivative, neopestalone (114), were obtained [27]. In addition, other known compounds were found in the strain, including sesquicaranoic acid B (115) and monocycloalternarene B (116), which were not included in the articles by Yang XL et al. [21] and Xu J et al. [10]. However, these compounds (111–116) did not exhibit biological activities against Dengue virus virulence with 10 μM, while neopestalone (114) exhibited obvious COX-2 inhibitory activities, with the IC$_{50}$ value of 5.8 μM.
3.12. Pestalotiopsis palmarum

Four diphenyl ether derivatives, sinopestalotiollides A-D (117–120), and one natural α-pyrene product (121), were newly obtained from the ethyl acetate extract of the endophytic fungus *P. palmarum* isolated from the leaves of medicinal plant *Sinomenium acutum* in China [64]. Sinopestalotiollides A-C (117–119) and 5,6-dihydro-4-methoxy-6-hydroxymethyl-2H-pyran-2-one (121) exhibited moderate cytotoxicities against two human tumor cell lines, HeLa and HCT116, and showed weak cytotoxicities against human tumor cell line A549. IC50 values of sinopestalotiollide A (117) against HeLa, HCT116, and A549 were 18.92, 15.69, and 31.29 μM, respectively; IC50 values of sinopestalotiollide B (118) against the cell lines were 12.80, 22.67, and 44.89 μM, respectively; IC50 values of sinopestalotiollide C (119) were 14.66, 18.49, and 36.13 μM, respectively. IC50 values of 5,6-dihydro-4-methoxy-6-hydroxymethyl-2H-pyran-2-one (121) were 15.60, 24.35, and 47.82 μM, respectively.

3.13. Pestalotiopsis sydowiana

Xia X et al. [165] isolated and identified our penicillide derivatives (122–125) in *P. sydowiana*. The three compounds, 3′-O-methyldehydroisopenicillide (122) and pestalotiollide A and B (123, 124), exhibited inhibitory activity against the 20S proteasome, with the IC50 values of 30.5, 12.4, and 18.5 μM, respectively.
3.14. Pestalotiopsis theae

Two new spiroketals with unique skeletons, chlorotheolides A (126) and B (127), and a new methylenesuccinic acid derivative, 1-undecene-2,3-dicarboxylic acid (128), were isolated and identified in the endophytic fungus P. theae [170]. In addition, their precursor, maldoxin (129), was also isolated. Chlorotheolides A (126) and B (127) could be biogenetically generated from the co-isolated 1-undecene-2,3-dicarboxylic acid (128) and maldoxin (129) via Diels-Alder reactions, as shown in Figure 2.

Figure 2. Conversion of 1-undecene-2,3-dicarboxylic acid and maldoxin to chlorotheolides via Diels-Alder reactions [170].

The hypothetical biosynthetic pathways for chlorotheolides A (126) and B (127) are shown in Figure 3.
Chlorotheolides A (126) and B (127) exhibited weak inhibitory effects on two human tumor cell lines, HeLa (cervical carcinoma) and MCF-7 (breast adenocarcinoma), with IC\textsubscript{50} values of 13.3–73.2 \(\mu\text{M}\), compared to the positive control cisplatin (IC\textsubscript{50} values of 4.7 and 4.9 \(\mu\text{M}\), respectively), and chlorotheolides B (127), which was found to inhibit cell viability in a time- and dose-dependent manner; however, 1-undecene-2,3-dicarboxylic acid (128) and maldoxin (129) did not display detectable activity against the tested tumor cell lines at a concentration of 20 \(\mu\text{g/mL}\) [170].

Liu G et al. [174] found two new humulane-derived sesquiterpenoids, pestalothenin A (130) and B (131), and one new caryophyllene-derived sesquiterpenoid (132) in \textit{P. theae}. However, the three compounds (130–132) did not exhibit detectable inhibitory effects on five human tumor cell lines, A549 (human lung adenocarcinoma cell line), T24 (human bladder carcinoma cell line), HeLa (human cervical carcinoma cell line), MCF-7 (human breast cancer cell line), and HepG2 (human hepatoma cell line) at 50 \(\mu\text{M}\), and neither showed antibacterial activities against \textit{S. aureus} (CGMCC 1.2465), \textit{B. subtilis} (ATCC 6633), \textit{Streptococcus pneumoniae} (CGMCC 1.1692), and \textit{B. subtilis} (CGMCC 1.2340) (MIC > 50 \(\mu\text{g/mL}\)) [174].

Two new caryophyllene-type sesquiterpenoids, pestathenols A (133) and B (134), and one new \(\alpha\)-furanone, pestatheranone A (135), were also recently isolated and characterized in \textit{P. theae} [173]. Pestathenol A (133) and pestathenol B (134) exhibited cytotoxicity against the HeLa tumor cell line, with IC\textsubscript{50} values of 78.2 and 88.4 \(\mu\text{mol/L}\), respectively. However, these sesquiterpenoids did not show cytotoxicity against tumor cell lines MCF-7, HepG2, and ACHN (human renal carcinoma cell line). In comparison, pestatheranone A (135) did not show detectable inhibitory effects on the cell lines tested at 100 \(\mu\text{mol/L}\) as well [173].
3.15. Pestalotiopsis uvicola

From the fungus *P. uvicola*, a new hybrid of dehydroergosterol and nitrogenous alternariol derivative, pestauvicomorpholine A (136), and three alternariol analogs (137–139), including a new aminated one, pestauvicolactone A (137), were found by [175]. Figure 4 depicts their possible biogenetic relationship. The two new compounds, pestauvicomorpholine A (136) and pestauvicolactone A (137), did not exhibit cytotoxicity against a mouse melanoma (B16-BL6) cell line at a concentration of 30 µM [175].

![Figure 4. Plausible biogenetic correlation of pestauvicomorpholine A and three alternariol analogues [175].](image-url)
Endophytic *P. uvicola* was further isolated and identified from the medicinal tree *Ginkgo biloba*. Both the fungus and the tree produce bilobalide (140) [177,197]. Baker et al. [197] described a concise asymmetric synthesis of (-)-bilobalide; however, the production pathway in the endophytic fungus *P. uvicola* is unknown. Bilobalide (140) from the leaves of *Ginkgo biloba* exhibits various functions [198]. For example, as an antioxidant, bilobalide (140) affects cerebral ischemia injury by activating the Akt/Nrf2 pathway [199]. Furthermore, Bilobalide (140) alleviated morphine-induced addiction in hippocampal neuron cells through the up-regulation of microRNA-101 [200]. In addition, bilobalide (140) inhibited 3T3-L1 preadipocyte differentiation and intracellular lipid accumulation [176] and protects ischemia/reperfusion-induced oxidative stress and inflammatory responses via the MAPK/NF-B pathways [201].
3.16. Pestalotiopsis vaccinii

P. vaccinii (CGMCC3.9199) was isolated from the branches of the mangrove tree *Kandelia candel*, and ten new salicyloid derivatives, namely vaccinols J–S (141–150), along with five known compounds (trans-sordarial, trans-sordariol, cis-sordariol, 4-hydroxyphthalide, pestalotiopin A), were isolated and identified [32]. All ten compounds were analyzed for their anti-enterovirus 71 (EV71) and cytotoxic activities. Vaccinol J (141) exhibited an in vitro anti-EV71 with an IC₅₀ value of 30.7 μM. However, none of these new compounds (141–150) showed cytotoxic effects on the tested cancer cell lines with IC₅₀ > 50 μM, including K562 (human erythroleukemic cell line), MCF-7 (human breast cancer cell line), and SGC7901 (human gastric cancer cell line).
3.17. Pestalotiopsis versicolor

Two new compounds, a new coumarin, 4,6-dihydroxy-7-formyl-3-methyl coumarin (151), and an α-pyrene derivative, 6-[(7S,8R)-8-propyloxiran-1-yl]-4-methoxy-pyran-2-one (152), were found from the plant endophytic fungus P. versicolor [179]. In addition, two known compounds, LL-P880g (153) and 6-pentyl-4-methoxy-pyran-2-one (154), were also found, which were not introduced by Yang XL et al. [21] and Xu J et al. [10]. Bioactivity assay showed that the four compounds (151–154) did not exhibit significant antifungal activities against the three fungal species, Fusarium solani, Ustilago maydis, and C. albicans [179].

3.18. Pestalotiopsis zonata

Two new polyketides, pestalrones A (155) and B (156), and pestazonatic acid (157), were found in the fungus P. zonata (CGMCC 3.9222). However, their bioactivities were not analyzed [184].

3.19. Pestalotiopsis sp.

Many Pestalotiopsis strains were isolated; however, they were not identified carefully, and some bioactive compounds were found in these strains.
From Chinese mangrove *Rhizophora mucronata*, an endophytic *Pestalotiopsis* sp. was isolated, and 11 known compounds were identified, which were not introduced by Yang XL et al. [21] and Xu J et al. [10], including demethylincisterol A\(_3\) (158), dankasterone B (159), (22\(E\), 24\(R\))-ergosta-7,9(11), 22-triene-3\(\beta\), 5\(\alpha\), 6\(\alpha\)-triol (160), ergosta-5,7,22-trien-3-ol (161), 5, 8-epidioxy-5,8-ergosta-6, 22E-dien-3-ol (162), stigmastan-3-one (163), stigmast-4-en-3-one (164), stigmast-4-en-6-ol-3-one (165), flufuran (166), and similanpyrone B (167) [140]. Demethylincisterol A\(_3\) (158), ergosta-5,7,22-trien-3-ol (161), stigmastan-3-one (163), stigmast-4-en-3-one (164), stigmast-4-en-6-ol-3-one (165), and flufuran (166) exhibited significant in vitro cytotoxicity against the human cancer cell lines HeLa, A549, and HepG [140]. Among them, demethylincisterol A\(_3\) (158) was the most potential with IC\(_{50}\) values of 0.17, 11.14, and 14.16 nM for the three cell lines, respectively. Ergosta-5,7,22-trien-3-ol (161) also showed significant cytotoxicity against HeLa and A549 cell lines with IC\(_{50}\) of 21.06 and 11.44 nM, respectively. Flow cytometric investigation also showed that demethylincisterol A\(_3\) (158) mainly inhibited cell cycle at G\(_0\)/G\(_1\) phase in a dose-dependent manner with significant induction of apoptosis on the human cancer cell lines HeLa, A549, and HepG.

Three new sesquiterpenoids, pestaloporonis A-C (168–170), related to the caryophyllene-derived punctaporonis, and the known caryophyllene-type metabolite fuscoatrol A (171) not introduced by Yang XL et al. [21] and Xu J et al. [10], were isolated from cultures of a fungiculous strain of *Pestalotiopsis* sp., and pestaloporonis A-C (168–170) did not exhibit

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**Molecules** 2022, 27, 8088

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158 demethylincisterol A\(_3\)
159 dankasterone B
160 (22\(E\), 24\(R\))-ergosta-7,9(11), 22-triene-3\(\beta\), 5\(\alpha\), 6\(\alpha\)-triol
158 ergosta-5,7,22-trien-3-ol
162 5, 8-epidioxy-5,8-ergosta-6, 22E-dien-3-ol
163 stigmastan-3-one
164 stigmast-4-en-3-one
165 stigmast-4-en-6-ol-3-one
166 flufuran
167 similanpyrone B
168 pestaloporinin A
169 pestaloporinin B
effects on \( S. \) aureus, \( B. \) subtilis, \( B. \) subtilis, and \( C. \) albicans at 50 \( \mu \)g/disk [141]. Fuscoatrol A (171) was also found in the fungus \( H. \) fuscoatra and exhibited antimicrobial activities against \( S. \) aureus and \( B. \) subtilis (MIC = 12.5 \( \mu \)g/mL) and cytotoxic activity on the developing eggs of the sea urchin \( S. \) intermedius (MIC \( 50 = 40 \) \( \mu \)g/mL) [202].

Five new ambuic acid derivatives (172–176) were found from an endolichenic fungus \( P. \) sp. [142]. The suggested biosynthetic pathways of ambuic acid and its derivatives are shown in Figure 5.

Figure 5. The suggested biosynthetic pathways of ambuic acid and its derivatives [142].
The bioactivities of these ambuic acid derivatives (172–176) were evaluated, and the results showed these compounds (172–176) did not exhibit significant cytotoxicity against several tumor cells, including A549, HepG 2, and HeLa cell lines (IC$_{50}$ > 40 μM), nor did they show antibacterial activities against S. aureus, B. subtilis, and B. subtilis (MIC > 64 μg/mL) [142]. The antifungal assay showed that compounds 172 and 176 exhibited significant biological effects against Fusarium oxysporum with a MIC value of 8 μg/mL. In contrast, compound 176 potently inhibited Fusarium gramineum at 8 μg/mL, compared with the positive control ketoconazole (MIC value of 8 μg/mL). These compounds (172–176) did not exhibit bioactivities against B. cinerea, Alternaria solani, and Rhizoctonia solani (>64 μg/mL).
From the fresh stem bark of *Melia azedarach*, an endophytic fungus, *Pestalotiopsis* sp., was isolated, and eight new caryophyllene sesquiterpenoids named pestaloporinates A-G (177–183) and 14-acetylhumulane (184) were identified from the solid cultures of the fungal strain [143]. These isolated compounds (177–184) were used to test for their inhibitory effects on nitric oxide production induced by lipopolysaccharide in the murine macrophage RAW 264.7 cell line. The results showed that pestaloporinate B (178) exhibited a potent inhibitory effect with an IC$_{50}$ value of 19.0 μM, compared to the positive control (IC$_{50}$ = 40.5 μM), while other compounds were inactive under 50 μM [143].

The endophytic fungus *Pestalotiopsis* sp. was obtained from the leaves of *Photinia frasery* in China. Five new isocoumarin derivatives, pestalactone A–C (185–187) and pestapyrone D–E (188–189), together with two known compounds (190–191), were isolated from the
solid cultures of the fungal strain [144]. Their bioactivity assay showed that only pestalactone C (187) exhibited potent antifungal activity against *Candida glabrata* (ATCC 90030) with a MIC₅₀ value of 3.49 µg/mL. They were inactive against Gram-positive bacteria (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633) and Gram-negative bacteria (*B. subtilis* ATCC 25922 and *P. aeruginosa* ATCC 9027) [144].

A *Pestalotiopsis* sp. strain was found from a soft coral, and a pair of new enantiomeric alkaloid dimers, (−)- and (+)-pestaloxazine A (192–193), were isolated from the fungal strain [147]. (±)-pestaloxazine A, (−)-pestaloxazine A (192), and (+)-pestaloxazine A (193) showed different antiviral activity against EV71 (enterovirus 71) with IC₅₀ values of 16.0, 69.1, and 14.2 µM, respectively. Their selectivity indices (SI) of anti-EV71 activity were 7.9, 2.1, and 9.2, respectively. They did not exhibit any bioactivity against the respiratory syncytial virus (RSV), coxsackie B3 virus (Cox-B 3), and H1N1 virus [147].

Five alkenyl phenol and benzaldehyde derivatives, pestalols A-E (194–198), were isolated from the endophytic fungus *Pestalotiopsis* sp. AcBC2 deriving from the Chinese mangrove plant *Aegiceras corniculatum* (Myrsinaceae family) [151]. Bioactivity assay of the five compounds showed that (1) pestalol B (195) and pestalol C (196) exhibited antiproliferative effects at a range of 23.4–42.5 µM against 10 human tumor cell lines, including MCF-7, BT474, A549, DU145, H1975, SK-BR-3, K562, MOLT-4, U937, and BGC823; (2) pestalol A-D (194–197) showed significant effects on the influenza viruses H3N2 and H1N1 with IC₅₀ values of 18.9–48.0 µM [151].
Four novel polyketides, pestal polyols A-D (199–202), were also isolated from solid fermentation products of Pestalotiopsis sp. cr013 [153]. The skeleton of 202 was almost the same as compound 201, except for one more carbon in a CH$_3$CH$_2$C = O group. These four compounds (199–202) did not exhibit any anti-fungal activities against Gaeumannomyces graminis, Fusarium moniliforme, Verticillium cinnabarium, and Phyricularia oryzae, nor any anti-bacterial activity against Pseudomonas solanacearum, S. aureus, and Salmonella typhimurium at 100 μg/disk. Neither of them (199–202) showed any nematicidal activities against Panagrellus redivivus and Caenorhabditis elegans [153]. Pestalpolyol A (199) possessed cytotoxicity against tumor cell lines HL-60, SMMC-7721, A-549, MCF-7, and SW480, with IC$_{50}$ values of 10.4, 11.3, 2.3, 13.7, and 12.4 μM, respectively. Pestalpolyol B (200) showed an IC$_{50}$ value of 10.6 μM against A-549, and Pestalpolyol D (202) exhibited IC$_{50}$ values of 15.7 μM (HL-60), 31.2 μM (SMMC-7721), 10.7 μM (A-549), 23.7 μM (MCF-7), and 21.4 μM (SW480), respectively [153].

The fungal strain Pestalotiopsis sp. cr014 is a mycoparasite of Cronartium ribicola, white pine blister rust of *Pinus armandii* in Sichuan Province, China. Nine new polyketides, pestalotic acids A-I (203–211), were isolated from solid fermentation products of Pestalotiopsis sp. cr014 [154]. In addition, pestalotic acid B (204), pestalotic acid C (205), pestalotic acid G (209), and pestalotic acid H (210) possessed antibacterial activities with MIC values of 0.78–12.5 μg/mL against Ralstonia solanacearum and Salmonella typhi [154].
Pestalotiopsis sp. PG52 is a mycoparasite isolated from aeciospore piles of *Aecidium pourthiaea*, and four novel polyketides, pestalpolyols E–H (212–215), were isolated from solid fermentations of this fungal strain [155]. Bioactivity assays showed pestalpolyol F (213) possessed cytotoxicity against lung adenocarcinoma cell line A-549 with an IC$_{50}$ value of 11.45 μM; pestalpolyol (214) exhibited weak cytotoxicity against four cell lines with IC$_{50}$ values of 14.60 μM (leukemia cell line HL-60), 27.46 μM (hepatocarcinoma cell line SMMC-7721), 11.83 μM (A-549), and 18.50 μM (breast cancer cell line MCF-7); and pestalpolyol (215) showed cytotoxicity against three cell line with IC$_{50}$ values of 22.85 μM (HL-60), 8.05 μM (A-549), and 38.89 μM (MCF-7) [155].

The endophytic fungus *Pestalotiopsis* sp. EJC07 was isolated from *Bauhinia guianensis*, a topical plant of the Amazon. Eight compounds, (4S)-4,8-dihydroxy-1-tetralone (216), uracil, uridine, p-hydroxybenzoic acid, ergosterol, ergosterol peroxide, cerevisterol, and ducitol, were isolated from the fungal strain, with (4S)-4,8-dihydroxy-1-tetralone (216), which was first reported in the *Pestalotiopsis* genus [203]. This study reported no assay on the bioactivity of (4S)-4,8-dihydroxy-1-tetralone (216).
From the cultured broth of Pestalotiopsis sp. FT172, five ambuic acid derivatives, pestallic acids A–E (217–221), and (+)-ambuic acid (222), were isolated and identified [156]. All the compounds (217–222) were tested against human cancer cell lines, cisplatin sensitive, and resistant human ovarian carcinoma (A2780S and A2780cisR). Pestallic acid E (221) showed potential cytotoxicity with IC\(_{50}\) values of 3.3 and 5.1 μM for A2780S and A2780cisR, respectively; and (+)-ambuic acid (222) also exhibited inhibition on the two cancer cell lines with IC\(_{50}\) values of 10.1 and 17.0 μM, respectively [156].

Cuautepestalorin (226) and its putative biosynthetic precursors, cytosporin M (223), cytosporin N (224), and oxopestalochromane (225), were isolated from the bioactive extract of Pestalotiopsis sp. [159]. The bioactivity assay showed that oxopestalochromane (225) and cuautepestalorin (226) showed modest inhibitory activities against \(\alpha\)-glucosidase from \(S.\) cerevisiae, with IC\(_{50}\) values of 263.0 and 42.4 μM, respectively, 2 and 14 times more potent than acarbose (604.4 μM), which was used as the positive control [159].
From the solid cultures of the endophytic fungus *Pestalotiopsis* sp. M-23, three new drimane sesquiterpenoids (227–229), the known 2α-hydroxyisodrimeninol (230), and a new isochromone derivative (231) were isolated and identified. The bioactivity assay showed that 11-dehydro-3α-hydroxyisodrimeninol (229) exhibited a weak inhibitory effect on *B. subtilis* with an IC$_{50}$ value of 280.27 μM and that none of these compounds (227–231) showed obvious biological activity against *S. aureus* and *M. luteus*. However, drimane sesquiterpenoids were found in other fungi, animals, and plants and showed extensive bioactivities, such as antioxidant, anti-inflammatory, antibacterial, and antifungal [204–211]. Thus, drimane sesquiterpenoids from *Pestalotiopsis* species should be investigated in detail for their bioactivities.

*Pestalotiopsis* sp. Z233 was isolated from the algae *Sargassum horneri*, and two new sesquiterpenes, 1β,5α,6α,14-tetraacetoxy-9α-benzoyloxy-7βH-eudesman-2β,11-diol (232) and 4α,5α-diacetoxy-9α-benzoyloxy-7βH-eudesman-1β,2β,11,14-tetraol (233), were isolated from the cultured mycelia of the fungal strain under heavy metal stress (CuCl$_2$) [162]. 1β,5α,6α,14-tetraacetoxy-9α-benzoyloxy-7βH-eudesman-2β,11-diol (232) and 4α, 5α-diacetoxy-9α-benzoyloxy-7βH-eudesman-1β,2β,11,14-tetraol (233) showed tyrosinase inhibitory activities with IC$_{50}$ values of 14.8 μM and 22.3 μM (the standard tyrosinase inhibitor kojic acid with IC$_{50}$ = 21.2 μM), respectively.
Cytosporones were not introduced by Yang XL et al. [21] and Xu J et al. [10]. The endophytic fungus Pestalotiopsis sp. was isolated from the leaves of the Chinese mangrove R. mucronata, and 11 compounds were isolated, including six cytosporones (234–239) [146,150]. When these compounds (234–239) were tested at an initial concentration of 10 μg/mL, none of the compounds showed any significant biological activity against three cancer cell lines, L5178 Y, HeLa, and PC12 [146]. Thus, their bioactivities against bacteria and fungi should be tested.

Endophytic Pestalotiopsis sp. BC55 produces exopolysaccharide (EPS), with a maximum EPS value of 4.320 g/L in a 250 ml Erlenmeyer flask containing 75 mL potato dextrose broth supplemented with 7.66 g%/L glucose, 0.29 g%/L urea, and 0.05 g%/L CaCl₂ with medium pH 6.93, after 3.76 days of incubation at 24 °C [152]. The EPS is a homopolysaccharide of (1 → 3)-linked-d-glucose. EPSs are also produced by other fungi and bacteria, such as F. solani [212], F. oxysporum [213], Stemphylium sp. [214], the mangrove endophytic fungus Aspergillus sp. Y16 [215], lactic acid bacteria [216,217], Bacillus mycoides [218], and Bacillus licheniformis [219]. EPS bioactivity greatly varied due to chain length, molecular weight, branching, etc. A bioactive EPS with Mw \(\sim 1.87 \times 10^5\) Da was isolated from endophytic fungus F. solani SD5 [212]. The isolated EPS showed in vitro anti-inflammatory and anti-allergic activity, and the EPS (1000 μg/mL) protects 55% of erythrocytes from
hypotonic solution-induced membrane lysis. EPS produced by \textit{B. mycoides} exhibited an anti-tumor effect \[218\]. EPS produced by \textit{B. mycoides} showed low cytotoxicity against normal cells of baby hamster kidney (BHK) with an IC\textsubscript{50} value of 254 \(\mu\)g/mL, while it exhibited an inhibitory effect against cancer cells of human hepatocellular carcinoma (HepG2) and colorectal adenocarcinoma cells (Caco-2) with IC\textsubscript{50} values of 138 \(\mu\)g/mL and 159 \(\mu\)g/mL, respectively. Ren Q et al. \[220\] purified EPSs with a molecular weight of \(2.7 \times 10^6\) Da to \(1.7 \times 10^7\) Da from \textit{Lactobacillus casei} and found that EPSs promote the differentiation of CD4 \(^+\) T lymphocytes into T-helper 17 cells in BALB/c mouse Peyer’s patches in vivo and in vitro. Thus, it is reasonable to speculate that EPSs produced by \textit{Pestalotiopsis} species might exhibit various similar bioactivities.

4. Accurate Biosynthesis Pathways and Enhanced Accumulation of Secondary Metabolites in \textit{Pestalotiopsis}

Nutritional and environmental factors greatly promote secondary metabolite biosynthesis in \textit{Pestalotiopsis} species \[80,83,85\]. Under the best nutritional and environmental conditions, how to maximize the yield of secondary metabolites in \textit{Pestalotiopsis} species is a key problem. Genetic modification in biosynthesis pathways of important secondary metabolites is the best choice with certainty. The aim of genetic modification is to increase or inhibit the activities of key enzymes in biosynthesis pathways of wanted secondary metabolites in order to increase their yield. Some key enzymes in the biosynthesis of secondary metabolites in \textit{Pestalotiopsis} species have been identified to date, improving our knowledge about accurate biosynthesis pathways and enhancing the accumulation of novel secondary metabolites.

4.1. Transcription Factors Involved in Secondary Metabolite Biosynthesis in \textit{Pestalotiopsis}

Given the roles of transcription factors in gene expression, transcription factors involved in the biosynthesis of secondary metabolites in \textit{Pestalotiopsis} species have been widely studied. Two transcription factors, \textit{PfmaF} and \textit{PfmaH}, cooperatively regulate 1,8-dihydroxy naphthalene (DHN) melanin biosynthesis in \textit{P. fici}. \textit{PfmaH}, as a pathway-specific regulator, mainly regulates melanin biosynthesis, and \textit{PfmaF} functions as a broader regulator to stimulate \textit{PfmaH} expression in melanin production \[90\]. In addition, \textit{PfmaH} directly regulates the expression of scytalone dehydratase, which catalyzes the transition of scytalone to 1,3,8-trihydroxynaphthalene (T3HN), which is reduced to vermelone, and vermelone is converted into DHN. Zhang P et al. \[90\] disrupted the gene \textit{PfmaF} using the CRISPR/Cas9 system. They found that the disruption affected neither DHN melanin distribution nor conidia cell wall integrity in \textit{P. fici}. Yet, the overexpression of \textit{PfmaF} leads to heavy pigment accumulation in \textit{P. fici} hyphae. Recently, two new transcription factors, Pmr1 and Pmr2, were identified in \textit{P. micropspora} \[221\]. Pmr1 and Pmr2 were located in the gene cluster for melanin biosynthesis and both of them regulated the expression of genes in the melanin biosynthesis cluster. In \(\Delta\textit{pmr1}\) and \(\Delta\textit{pmr2}\) mutant strains, most genes in the gene cluster (including 21 genes, i.e., GEM11355.g–GEM11375.g) were significantly upregulated. Their upregulation is related to increased yield of secondary metabolites in the mutant strains \(\Delta\textit{pmr1}\), compared with the wild type (WT). Meanwhile, HPLC analysis showed that the pestalotiollide B peak at 3.3 min was much greater in the \(\Delta\textit{pmr1}\) and \(\Delta\textit{pmr2}\) strains than that in WT; moreover, this increment in \(\Delta\textit{pmr1}\) was significantly greater than that in \(\Delta\textit{pmr2}\). In addition, Pmr1 played a larger regulatory role in secondary metabolism than Pmr2.

\textit{PfZipA}, on the other hand, is one of the bZIP transcription factors in \textit{P. fici}. Without oxidative treatment, the \(\Delta\textit{PfzipA}\) mutant strain of \textit{P. fici} produced less isosulochrin and ficipyrone A than wild type \[78\]. However, \(\textit{PfZipA}\) mediates the sensitivity of \textit{P. fici} to oxidative stress caused by the oxidative reagents butyl hydroperoxide (tBOOH), diamide, \(\text{H}_2\text{O}_2\), and menadione sodium bisulfite (MSB). tBOOH treatment decreased the production of iso-A82775C and pestaloficiol M in \(\Delta\textit{PfzipA}\) strain; MSB treatment decreased the production of RES1214-1 and iso-A82775C; however, it increased pestaloficiol M production in the mutant; and \(\text{H}_2\text{O}_2\) treatment resulted in enhanced production of isosulochrin,
RES1214-1, and pestheic acid (23), yet decreased ficipyrone A and pestaloficiol M in ΔPfzipA strain, compared to the wild type [78].

4.2. Histone Acetylation

Histone acetylation is an important modification of histone proteins, which plays an important role in condensing and relaxing DNA. Histone acetylation is also involved in the biosynthesis of secondary metabolites in Pestalotiopsis species. Zhang Q et al. [113] identified a B-type histone acetyltransferase, Hat1, in the P. microspora. Secondary metabolites dramatically decreased in a hat1 deletion mutant strain, suggesting HAT1 functions as a regulator of secondary metabolism. Therefore, it is reasonable to speculate that the overexpression of the gene hat1 improves the biosynthesis of secondary metabolites in the fungus, thus, its overexpression mutant strains might be used for specific metabolites. In P. microspora, an MYST histone acetyltransferase encoded by the gene MST2 regulates secondary metabolism and conidial development [222]. Deleting the gene (mst2) caused serious growth retardation and impaired conidial development, e.g., delayed and reduced conidiation and aberrant conidia capacity. At the same time, overexpression of mst2 triggered earlier conidiation and higher conidial production. Deletion of mst2 also reduced the production of secondary metabolites in P. microspora [222]. In P. microspora NK17, Niu X et al. [112] found that a putative histone deacetylase gene (HID1) played an important role in the biosynthesis of pestalotiollide B. In the hid1 null mutant, the yield of pestalotiollide B increased approximately 2-fold to 15.90 mg/L. In contrast, the deletion of gene hid1 resulted in a dramatic decrease in conidia production of P. microspora NK17. These results suggest that the histone deacetylase HID1 is a regulator, concerting secondary metabolism and development, such as conidiation, in P. microspora.

4.3. Polyketide Synthases

Polyketides possess diverse chemical structures and biological activities and are the most important sources of novel secondary metabolites in plants, bacteria, and fungi. Polyketide synthases (PKSs) catalyze the biosynthesis of polyketides. While type I and type II PKSs exist as large protein complexes, type III PKSs are relatively small homodimeric proteins (~45 kDa monomer). In Pestalotiopsis species, PKSs are involved in the biosynthesis of some secondary metabolites. For example, the biosynthesis of pestalotiollide B is controlled by polyketide synthase [111]. Chen L and co-workers successfully deleted 41 out of 48 putative PKSs in the genome of P. microspora NK17. Furthermore, they found that 9 of the 41 PKS deleted strains significantly increased the biosynthesis of pestalotiollide B, and the deletion of pks35 increased pestalotiollide B by 887% [111].

The fungal products dibenzodioxocinones promise a novel class of inhibitors against cholesterol ester transfer protein [112]. A gene cluster of 21 genes, including PKS8 encoding a polyketide synthase, was defined, and disruption of genes in the cluster led to the biosynthesis of loss of dibenzodioxocinones [120]. Of the 21 genes, 5 genes, i.e., GME11356, GME11357, GME11358, GME11365, and GME11367, were deduced to participate in the generation of the backbone structure, and three regulatory genes, i.e., GME11360, GME11369, and GME11370, were also identified.

After forming polyketides, they can be converted into other secondary metabolites. The pestheic acid biosynthetic gene (pta) cluster was identified through genome scanning of the fungus P. fici. The biosynthetic pathway was elucidated through gene disruption intermediate detection and enzymatic analysis [82]. The results showed that the pestheic acid biosynthesis proceeded through the formation of the polyketide backbone, cyclization of a polyketo acid to a benzophenone, chlorination, and construction of the diphenyl ether skeleton through oxidation and hydrolyzation. The gene PTAA is important in pestheic acid biosynthesis in P. fici. Pestheic acid was abolished in the ptaA disruption mutants of P. fici [82]. In the pestheic acid biosynthesis pathway, the gene PTAM encodes a flavin-dependent halogenase, catalyzing chlorination. Inactivation of flavin-dependent halogenase from the Chaetomium chiversii radicicol locus yielded dechloro-
radicicol (monocillin I) \[223\]. Thus, in \textit{P. fici}, \textit{PTAM (ptaM)} disruption might result in a change in pestheic acid biosynthesis.

4.4. Other Regulatory Proteins and Enzymes

The Snf1/AMPK is highly conserved in the eukaryotes and acts as a central regulator of carbon metabolism and energy production. In the filamentous fungus \textit{P. microspora}, \textit{SNF1} concerts carbon metabolism and filamentous growth, conidiation, cell wall integrity, stress tolerance, and the biosynthesis of secondary metabolites \[224\]. The \textit{Snf1} deletion strain of \textit{P. microspora} NK17 (Δ\textit{snf1}) displayed remarkable retardation in vegetative growth and pigmentation. Furthermore, it produced a diminished number of conidia, even in the presence of glucose, and \textit{Snf1} deletion caused damage to the cell wall of \textit{P. microspora} \[224\]. In addition, Pestalotiollide B was considerably reduced in the mutant strain Δ\textit{snf1}. These results demonstrate that \textit{SNF1} is a regulator of secondary metabolism and may be involved in either the activation or silencing of certain gene clusters in \textit{P. microspora} NK17. Therefore, the more accurate function of \textit{SNF1} should be elucidated in secondary metabolite biosynthesis research.

Evidence shows biosynthesis of secondary metabolites and development are correlated processes in fungi, and pleiotropic proteins regulate the equilibrium between the biosynthesis of secondary metabolites and development. A global regulator, \textit{RsdA (regulation of secondary metabolism and development)}, was identified through genome-wide analysis and deletion of the regulator gene in the endophytic fungus \textit{P. fici} \[225\]. Deleting \textit{rsdA} significantly reduced asexual development, resulting in low sporulation, abnormal conidia, and major secondary metabolites (such as asperpentyn, fificiolide A, and chloroisosulochrin) while remarkably increasing melanin pigment production. In addition, pestheic acid, a basic building block for a group of structurally diverse compounds, was completely abolished in the Δ\textit{rsdA} strain, implying that the biosynthesis of pestheic acid analogs was dramatically reduced.

Canonical Gcn2/Cpc1 kinase is an amino acid sensor and regulates the expression of target genes in response to amino acid starvation. When the mutant strain Δ\textit{gcn2} of \textit{P. microspora} was cultured in the presence of 3AT (5 mM) to mimic amino acid starvation conditions, biosynthesis of pestalotiollide B was almost inhibited \[114\]. Meanwhile, the loss of \textit{gcn2} led to a less-pigmented phenotype of \textit{P. microspora} \[114\]. All the results demonstrate that the protein encoded by \textit{gcn2} is a regulator of secondary metabolism and may be involved in either activation or silencing of gene clusters in \textit{P. microspora}.

G-protein-mediated signaling pathways regulate fungal morphogenesis, development, pathogenesis, and secondary metabolism \[226–231\]. In \textit{Pestalotiopsis} species, G protein-mediated signaling regulates secondary metabolites. The gene \textit{pgα1} putatively encodes the α-subunit of a group I G protein in \textit{P. microspora} NK17. The \textit{pgα1} deletion mutants showed retarded vegetative growth, mycelium aging, premature conidiation, deformed conidia, significantly increased melanin production, and a sharp decrease in the production of pestalotiollide B \[13\]. Meanwhile, the expression of \textit{pks1}, which encodes melanin polyketide synthase involved in 1,8-dihydroxy naphthalene (DHN) melanin biosynthesis, was upregulated 55-fold in \textit{pgα1} deletion mutants. All the results imply obvious changes in the biosynthesis of different secondary metabolites in \textit{pgα1} mutants. In addition, the deficiencies of pestalotiollide B production and conidiation in Δ\textit{pgα1} mutants could not be rescued by deletion or overexpression of the gene \textit{hid1} encoding histone deacetylase, suggesting that the protein PGα1 can override the effect of \textit{hid1} on pestalotiollide B production and conidiation.

In the fungus \textit{P. microspora}, two genes, \textit{choA} and \textit{choC}, encode two phospholipid methyltransferases. \textit{choC} deletion mutants (\textit{choC}Δ) resulted in defects in phosphatidylcholine production, vegetative growth, and development of asexual structure \[49\], suggesting that genetic modification might regulate secondary metabolite biosynthesis in \textit{Pestalotiopsis} species. However, \textit{choA}, but not \textit{choC}, was required to produce pestalotiollide B \[49\], suggesting distinct roles of the two genes.
The earlier examples demonstrate changes in the biosynthesis of secondary metabolites in *Pestalotiopsis* species by molecular tools, especially gene editing. Therefore, key genes encoding important enzymes in secondary metabolite biosynthesis in *Pestalotiopsis* species should be cloned, and the overexpression or deletion of these key genes is useful for enhanced biosynthesis of important secondary metabolites. More importantly, accurate biosynthesis pathways of secondary metabolites are the premise. Based on these basic studies on the effects of secondary metabolites in *Pestalotiopsis* species on human health, animals, and plants and the identification of their accurate biosynthesis pathways, it is possible to enhance biosynthesis and the accumulation of key secondary metabolites in the future. The industrial production of important secondary metabolites in this way will become possible.

5. Concluding Remarks and Future Perspectives

Given the important effects of secondary metabolites from *Pestalotiopsis* species on human health, animals, and plants, two aspects, i.e., the effects of these secondary metabolites and their accurate biosynthesis pathways, are vital. Therefore, more studies should focus on their accurate biosynthesis pathways to enhance biosynthesis and accumulation, further establishing the foundation for the industrial production of secondary metabolites from *Pestalotiopsis* species. Gene editing is a valuable method for fully comprehending secondary metabolite biosynthesis processes; however, it is very difficult to establish gene-editing systems for some *Pestalotiopsis* species, despite genome editing systems having been established for few *Pestalotiopsis* species, such as *P. fici* and *P. microspora* [90, 232–234]. Furthermore, more effective gene-editing tools are to be developed and, therefore, long-term efforts are in the pipeline.

In addition, improvements for the best growth conditions are useful for enhanced biosynthesis and accumulation of secondary metabolites. For example, the addition of some chemicals in the culture medium promotes the biosynthesis of secondary metabolites, such as salicylic acid [235]. Meanwhile, the co-cultivation of fungi and bacteria can also trigger the biosynthesis of secondary metabolites. For example, the co-cultivation of *Aspergillus flavipes* and *B. subtilis* triggers the biosynthesis machinery of taxol [236]. At present, there are no reports on the co-cultivation of *Pestalotiopsis* species with other microbes. Many gene clusters for the biosynthesis of secondary metabolites in filamentous fungi often stay silent under some culture conditions because of the absence of interaction with bacteria. For instance, Brakhage and colleagues have discovered that the silent secondary metabolite gene cluster for orsellinic acid (ors) in the filamentous fungus *Aspergillus nidulans* is activated upon physical interaction with the bacterium *Streptomyces rapamycinicus*, and the interaction of the fungus with this distinct bacterium led to increased acetylation of histone H3 lysines 9 and 14 at the ors gene cluster, thus to its activation [237–239]. Then, they identified the Myb-like transcription factor BasR, a master regulator of bacteria-triggered production of fungal secondary metabolites, by chromatin mapping [240]. However, the interaction between *Pestalotiopsis* species and bacteria and key regulator nodes for transduction of the bacterial signals in the fungi is unclear. Certainly, activating silent gene clusters in *Pestalotiopsis* species is a good strategy for enhanced biosynthesis and accumulation of fungal secondary metabolites, just as in the Brakhage and Schroeckh advocated strategies [241]. Furthermore, as mentioned above, gene editing is a good and useful approach to increase the yield of secondary metabolites. We should try our utmost to establish whole feasible systems of gene editing for important *Pestalotiopsis* species. At present, the *Pestalotiopsis* species investigated are only a small part of this genus, and more species are yet to be studied and developed for human health.

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**References**

1. Subramanian, M.; Marudhamuthu, M. Hitherto unknown terpene synthase organization in taxol-producing endophytic bacteria isolated from marine macroalgae. *Curr. Microbiol.* 2020, 77, 918–923. [CrossRef] [PubMed]

2. Stierle, A.; Strobel, G.; Stierle, D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. *Science* 1993, 260, 214–216. [CrossRef]

3. Gangadevi, V.; Muthumary, J. A Novel Endophytic taxol-producing fungus *Chaetomella raphigera* isolated from a medicinal plant, *Terminalia arjuna*. *Appl. Biochem. Biotechnol.* 2009, 158, 675–684. [CrossRef] [PubMed]

4. El-Sayed, E.-S.R.; Zaki, A.G.; Ahmed, A.S.; Ismaiel, A.A. Production of the anticancer drug taxol by the endophytic fungus *Epichoccom nigrum* TXBS02: Enhanced production by gamma irradiation mutagenesis and immobilization technique. *Appl. Microbiol. Biotechnol.* 2020, 104, 6991–7003. [CrossRef]

5. Abdel-Fatah, S.S.; El-Batal, A.I.; El-Sherbiny, G.M.; Khalaf, M.A.; El-Sayed, A.S. Production, bioprocess optimization and γ-irradiation of *Penicillium polonicum*, as a new taxol producing endophyte from *Ginkgo biloba*. *Biotechnol. Rep.* 2021, 30, e00623. [CrossRef] [PubMed]

6. Steyaert, R.L. Contributions à l’étude monographique de Pestalotia de Not. et Monochaetia Sacc. (*Truncatella* gen. nov. et *Pestalotiopsis* gen. nov.). *Bull. Jard. Bot. Brux.* 1949, 19, 285–354. [CrossRef]

7. Maharachchikumbura, S.; Guo, L.-D.; Chukeatirute, E.; Bhakali, A.; Hyde, K.D. Pestalotiopsis—Morphology, phylogeny, biochemistry and diversity. *Fungal Divers.* 2011, 50, 167–187. [CrossRef]

8. Maharachchikumbura, S.; Hyde, K.; Groenewald, J.; Xu, J.; Crous, P. *Pestalotiopsis* revisited. *Stud. Mycol.* 2014, 79, 121–186. [CrossRef]

9. Xu, J.; Ebada, S.S.; Proksch, P. Pestalotiopsis a highly creative genus: Chemistry and bioactivity of secondary metabolites. *Fungal Divers.* 2010, 44, 15–31. [CrossRef]

10. Yu, J.; Yang, X.; Lin, Q. Chemistry and biology of *Pestalotiopsis*-derived natural products. *Fungal Divers.* 2014, 66, 37–68. [CrossRef]

11. Strobel, G.; Yang, X.; Sears, J.; Kramer, R.; Sidhu, R.S.; Hess, W.M. Taxol from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus wallachiana*. *Microbiology* 1996, 142, 435–440. [CrossRef] [PubMed]

12. Nakajima, H.; Fujimoto, H.; Kimura, Y.; Hamasaki, T. Importance of the ketone function for the phytotoxicity of spiciferone A, a phytotoxin produced by the fungus *Cochlioholus spicifer*. *Biosci. Biotechnol. Biochem.* 1993, 57, 1938–1939. [CrossRef]

13. Yu, X.; Liu, H.; Niu, X.; Akhberdi, O.; Wei, D.; Wang, D.; Zhu, X. The Ga1-cAMP signaling pathway controls conidiation, development and secondary metabolism in the taxol-producing fungus *Pestalotiopsis microspora*. *Microbiol. Res.* 2017, 203, 29–39. [CrossRef] [PubMed]

14. Kathiravan, G.; Sureban, S.M. Effect of taxol from *Pestalotiopsis mangiferae* on A549 cells-in vitro study. *J. Basic Clin. Pharm.* 2010, 1, 1–9.

15. Gangadevi, V.; Murugan, M.; Muthumary, J. Taxol determination from *Pestalotiopsis pauciseta*, a fungal endophyte of a medicinal plant. *Chin. J. Biotechnol.* 2008, 24, 1433–1438. [CrossRef]

16. Kathiravan, G.; Raman, V.S. In vitro TAXOL production, by *Pestalotiopsis breviseta*—A first report. *Fitoterapia* 2010, 81, 557–564. [CrossRef]

17. Kathiravan, G.; Sureban, S.M.; Sree, H.N.; Bhuvaneshwari, V.; Kramony, E. Isolation of anticancer drug TAXOL from *Pestalotiopsis breviseta* with apoptosis and B-Cell lymphoma protein docking studies. *J. Basic Clin. Pharm.* 2012, 4, 14–19. [CrossRef]

18. Gangadevi, V.; Muthumary, J. Taxol production by *Pestalotiopsis terminaliae*, an endophytic fungus of *Terminalia arjuna* (arjun tree). *Biotechnol. Appl. Biochem.* 2009, 52, 9–15. [CrossRef]

19. Gu, Y.; Wang, Y.; Ma, X.; Wang, C.; Yue, G.; Zhang, Y.; Zhang, Y.; Li, S.; Ling, S.; Liu, X.; et al. Greater taxol yield of fungus *Pestalotiopsis hainanensis* from dermatitic scurf of the giant panda (*Ailuropoda melanoleuca*). *Appl. Biochem. Biotechnol.* 2014, 175, 155–165. [CrossRef]

20. Li, J.-Y.; Strobel, G.; Sidhu, R.; Hess, W.M.; Ford, E.J. Endophytic taxol-producing fungi from bald cypress, *Taxodium distichum*. *Microbiology* 1996, 142, 2223–2226. [CrossRef]

21. Yang, X.-L.; Zhang, J.-Z.; Luo, D.-Q. The taxonomy, biology and chemistry of the fungal *Pestalotiopsis* genus. *Nat. Prod. Rep.* 2012, 29, 622–641. [CrossRef] [PubMed]
22. Helaly, S.E.; Thongbai, B.; Studler, M. Diversity of biologically active secondary metabolites from endophytic and saprotrophic fungi of the ascomycete order Xylariales. *Nat. Prod. Rep.* 2018, 35, 992–1014. [CrossRef] [PubMed]

23. Becker, K.; Studler, M. Recent progress in biodiversity research on the Xylariales and their secondary metabolism. *J. Antibiot.* 2021, 74, 1–23. [CrossRef] [PubMed]

24. Satì, S.; Belwal, M. Aquatic hyphomycetes as endophytes of riparian plant roots. *Mycolgia* 2005, 97, 45–49. [CrossRef]

25. Aydoğdu, H.; Asan, A. Airborne fungi in child day care centers in Edirne City, Turkey. *Environ. Monit. Assess.* 2008, 147, 423–444. [CrossRef]

26. Wang, J.; Liang, Z.; Li, K.; Yang, B.; Liu, Y.; Fang, W.; Tang, L.; Zhou, X. Ene-yne hydroquinones from a marine-derived strain of the fungus *Pestalotiopsis neglecta* with effects on liver X receptor alpha. *J. Nat. Prod.* 2020, 83, 1258–1264. [CrossRef]

27. Wang, J.; Peng, Q.; Yao, X.; Li, Y.; Zhou, X. New pestalic acids and diphenylketone derivatives from the marine alga-derived endophytic fungus *Pestalotiopsis neglecta* SC5101403. *J. Antibiot.* 2020, 73, 585–588. [CrossRef]

28. Lei, H.; Zhou, X.; Hu, M.; Niu, H.; Song, C.; Chen, S.; Liu, Y.; Zhang, D. Cytotoxic polyketides from the marine sponge-derived fungus *Pestalotiopsis heterocornis* XWS03F09. *Molecules* 2019, 24, 2655. [CrossRef]

29. Lei, H.; Lin, X.; Han, L.; Ma, J.; Dong, K.; Wang, X.; Zhong, J.; Mu, Y.; Liu, Y.; Huang, X. Polyketide derivatives from a marine-sponge-associated fungus *Pestalotiopsis heterocornis*. *Phytochemistry* 2017, 142, 51–59. [CrossRef]

30. Lei, H.; Lin, X.; Han, L.; Ma, J.; Ma, Q.; Zhong, J.; Wang, X.; Liu, Y.; Sun, T.; Wang, J.; Huang, X. New metabolites and bioactive chlorinated benzophenone derivatives produced by a marine-derived fungus *Pestalotiopsis heterocornis*. *Mar. Drugs* 2017, 15, 69. [CrossRef]

31. Wikee, S.; Hatton, J.; Turb

32. Magnan, R.F.; Rodrigues-Fo, E.; Daolio, C.; Ferreira, A.G.; de Souza, A.Q.L. Three highly oxygenated caryophyllene sesquiterpenes from *Pestalotiopsis clavispora*, a fungus isolated from *Perna perna* (Bivalvia:Mytilidae) cultured on marine farms in Southeastern Brazil and destined for human consumption. *Mar. Pollut. Bull.* 2020, 153, 110976. [CrossRef] [PubMed]

33. Koh, S.; Mizuno, M.; Izuoka, Y.; Fujino, N.; Hamada-Sato, N.; Amano, Y. Xylanase from marine filamentous fungus *Pestalotiopsis neglecta*. *Zeitschrift für Naturforschung C* 2021, 76, 319–324. [CrossRef] [PubMed]

34. Magnan, R.F.; Rodrigues-Fo, E.; Daolio, C.; Ferreira, A.G.; de Souza, A.Q.L. Three highly oxygenated caryophyllene sesquiterpenes from *Pestalotiopsis clavispora*, a fungus isolated from bark of *Pinus taeda*. *Zeitschrift für Naturforschung C* 2003, 58, 319–324. [CrossRef] [PubMed]

35. Luo, D.Q.; Zhang, L.; Shi, B.Z.; Song, X.M. Two new oxysporone derivatives from the fermentation broth of the endophytic plant fungus *Pestalotiopsis karsteni* isolated from stems of *Camellia sasanqua*. *Molecules* 2012, 17, 8554–8560. [CrossRef] [PubMed]

36. Chen, H.-Y.; Xue, D.-S.; Feng, X.-Y.; Yao, S.-J. Screening and production of ligninolytic enzyme by a marine-derived fungal fungus *Pestalotiopsis* sp. isolated from *Perna perna* (Bivalvia:Mytilidae) cultured on marine farms in Southeastern Brazil and destined for human consumption. *Mar. Pollut. Bull.* 2020, 153, 110976. [CrossRef] [PubMed]

37. Ren, H.; Wu, Y.; Ahmed, T.; Qi, X.; Li, B. Response of resistant and susceptible bayberry cultivars to infection of twig blight pathogen by histological observation and gibberellin related genes expression. *Pathogens* 2021, 10, 402. [CrossRef] [PubMed]

38. Chen, X.-R.; Xing, Y.P.; Zhang, T.X.; Zheng, J.T.; Xu, J.Y.; Wang, Z.R.; Tong, Y.H. First report of *Pestalotiopsis sydowiana* causing leaf necrosis of *Myrica rubra* in China. *Plant Dis.* 2012, 96, 764. [CrossRef]

39. Feng, Y.R.; Liu, B.S.; Sun, B.B. First Report of Leaf Blotch Caused by *Pestalotiopsis clavispora* on *Rosa chinensis* in China. *Plant Dis.* 2014, 98, 1009. [CrossRef]

40. Jin, Y.-L.; Jiang, S.-L.; Jiang, X.-L. Disease-resistant identification and analysis to transcriptome differences of blueberry leaf spot induced by beta-aminobutyric acid. *Arch. Microbiol.* 2021, 203, 3623–3632. [CrossRef]

41. Mahadevakumar, S.; Janardhana, G.R. First report of *Pestalotiopsis* species causing leaf spot of cowpea (*Vigna unguiculata*) in India. *Plant Dis.* 2014, 98, 686. [CrossRef]

42. Nozawa, S.; Seto, Y.; Watanabe, K. First report of leaf blight caused by *Pestalotiopsis chamaeropis* and *Neopestalotiopsis* sp. in Japanese andromeda. *J. Gen. Plant Pathol.* 2019, 85, 449–452. [CrossRef]
49. Akhberdi, O.; Zhang, Q.; Wang, H.; Li, Y.; Chen, L.; Wang, D.; Yu, X.; Wei, D.; Zhu, X. Roles of phospholipid methyltransferases in pycnidia development, stress tolerance, and secondary metabolism in the taxol-producing fungus Pestalotiopsis microspora. Microbiol. Res. 2018, 210, 33–42. [CrossRef]

50. Prasannath, K.; Galea, VJ.; Akinsanmi, O.A. Influence of climatic factors on dry flower, grey and green mould diseases of macadamia flowers in Australia. J. Appl. Microbiol. 2021, 132, 1291–1306. [CrossRef]

51. Keith, L.M. First report of Pestalotiopsis virgatula causing Pestalotiopsis Fruit Rot on rambutan in Hawaii. Plant Dis. 2008, 92, 835. [CrossRef] [PubMed]

52. Ding, G.; Zheng, Z.; Liu, S.; Zhang, H.; Guo, L.; Che, Y. Photinides A–F, cytototoxic benzofuranone-derived γ-lactones from the plant endophytic fungus Pestalotiopsis photiniae. J. Nat. Prod. 2009, 72, 942–945. [CrossRef] [PubMed]

53. Qi, M.; Xie, C.-X.; Chen, Q.-W.; Yu, Z.-D. Pestalotiopsis trachicaripcola, a novel pathogen causes twig blight of Pinus bungeana (Pinaceae: Pinoideae) in China. Antonie Van Leeuwenhoek 2021, 114, 1–9. [CrossRef] [PubMed]

54. Sowndhararajan, K.; Marimuthu, S.; Manian, S. Biocontrol potential of phylloplane bacterium Ochrobactrum anthropi BMO-111 against blister blight disease of tea. J. Appl. Microbiol. 2013, 114, 209–218. [CrossRef] [PubMed]

55. Wang, Y.; Xiong, F.; Lu, Q.; Hao, X.; Zheng, M.; Wang, L.; Li, N.; Ding, C.; Wang, X.; Yang, Y. Diversity of Pestalotiopsis microspora SC3082 derived from Pestalotiopsis microspora in China. Antonie Van Leeuwenhoek 2021, 100, 852. [CrossRef]

56. Espinoza, J.G.; Briceño, E.X.; Keith, L.M.; Latorre, B.A. Canker and twig dieback of blueberry caused by Pestalotiopsis spp. Plant Dis. 2008, 92, 1407–1414. [CrossRef] [PubMed]

57. Chen, F.; Lu, L.; Wang, D.; Wang, Y.; Ni, H.; Du, Z. Biological characterization and genetic diversity analysis of two species of Pestalotiopsis causing twig dieback of Myrica rubra. Eur. J. Plant Pathol. 2013, 136, 737–747. [CrossRef]

58. Liao, G.; Wu, P.; Liu, Z.; Xue, J.; Li, H.; Wei, D.; Zhu, X. α-Rodriguez-γ-F, cytotoxic benzofuranone-derived β-lactones from the new species Pestalotiopsis disseminata in China. J. Nat. Prod. 2013, 76, 1–9. [CrossRef] [PubMed]

59. Qi, H.; Swenson, D.C.; Gloer, J.B.; Wicklow, D.T. Disseminins and spiciferone analogues: Polyketide-derived metabolites from a fungicidal isolate of Pestalotiopsis disseminata. J. Nat. Prod. 2006, 69, 608–611. [CrossRef] [PubMed]

60. Hwang, I.H.; Swenson, D.C.; Gloer, J.B.; Wicklow, D.T. Pestalotiopsis disseminans and spiciferone analogues: Polyketide-derived metabolites from a fungicidal isolate of Pestalotiopsis disseminata. J. Nat. Prod. 2016, 79, 523–530. [CrossRef]
76. Pan, Y.; Liu, L.; Guan, F.; Li, E.; Jin, J.; Li, J.; Che, Y.; Liu, G. Characterization of a prenyltransferase for Iso-A82775C biosynthesis and generation of new congeners of chlorolepocephalos. ACS Chem. Biol. 2018, 13, 703–711. [CrossRef]

77. Liu, L.; Tian, R.; Liu, S.; Chen, X.; Guo, L.; Che, Y. Pestaloficiols A–E, bioactive cyclopropane derivatives from the plant endophytic fungus Pestalotiopsis fici. Bioorganic Med. Chem. 2008, 16, 6021–6026. [CrossRef]

78. Wang, X.; Wu, F.; Liu, L.; Che, Y.; Keller, N.P.; Guo, L.; Yin, W.-B. The bZIP transcription factor PfZipA regulates secondary metabolism and oxidative stress response in the plant endophytic fungus Pestalotiopsis fici. Fungal Genet. Biol. 2015, 81, 221–228. [CrossRef]

79. Liu, L.; Liu, S.; Chen, X.; Guo, L.; Che, Y. Pestalofones A–E, bioactive cyclohexane derivatives from the plant endophytic fungus Pestalotiopsis fici. Bioorg. Med. Chem. 2009, 17, 606–613. [CrossRef]

80. Liu, L.; Li, Y.; Liu, S.; Zheng, Z.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. Chloroprostolidate A, an antitumor metabolite with an unprecedented spiroketal skeleton from Pestalotiopsis fici. Org. Lett. 2009, 11, 2836–2839. [CrossRef]

81. Liu, L.; Bruhn, T.; Guo, L.; Götz, D.C.G.; Brun, R.; Stich, A.; Che, Y.; Bringmann, G. Chloropupukeanoides C–E: Cytoxic pupukeanane chlorides with a spiroketal skeleton from Pestalotiopsis fici. Chem. A Eur. J. 2011, 17, 2604–2613. [CrossRef][PubMed]

82. Xu, X.; Liu, L.; Zhang, F.; Wang, W.; Li, J.; Guo, L.; Che, Y.; Liu, G. Identification of the first diphényl ether gene cluster for pestheic acid biosynthesis in plant endophyte Pestalotiopsis fici. Chem Bio Chem 2014, 15, 284–292. [CrossRef][PubMed]

83. Liu, L.; Liu, S.; Jiang, L.; Chen, X.; Guo, L.; Che, Y. Chloropupukeananin, the first chlorinated pupukeanane derivative, and its precursors from Pestalotiopsis fici. Org. Lett. 2008, 10, 1397–1400. [CrossRef][PubMed]

84. Zhang, P.; Wang, X.; Fan, A.; Zheng, Y.; Liu, X.; Wang, S.; Zou, H.; Oakley, B.R.; Keller, N.P.; Yin, W.-B. A cryptic pigment biosynthetic pathway uncovered by heterologous expression is essential for conidial development in Pestalotiopsis fici. Mol. Microbiol. 2017, 105, 469–483. [CrossRef]

85. Liu, L.; Niu, S.; Lu, X.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. Unique metabolites of Pestalotiopsis fici suggest a biosynthetic hypothesis involving a Diels–Alder reaction and then mechanistic diversification. Chem. Commun. 2010, 46, 460–462. [CrossRef]

86. Liu, L.; Liu, S.; Niu, S.; Guo, L.; Chen, X.; Che, Y. Isoprenylated chromone derivatives from the plant endophytic fungus Pestalotiopsis fici. J. Nat. Prod. 2009, 72, 1482–1486. [CrossRef]

87. Liu, L.; Li, Y.; Li, L.; Cao, Y.; Guo, L.; Che, Y. Spiroketais of Pestalotiopsis fici provide evidence for a biosynthetic hypothesis involving diversified Diels–Alder reaction cascades. J. Org. Chem. 2013, 78, 2992–3000. [CrossRef]

88. Zheng, Y.; Ma, K.; Lyu, H.; Huang, Y.; Liu, H.; Liu, L.; Che, Y.; Liu, X.; Zou, H.; Yin, W.-B. Genetic manipulation of the COP9 signalosome subunit PcsnE leads to the discovery of pestaloficins in Pestalotiopsis fici. Org. Lett. 2017, 19, 4700–4703. [CrossRef]

89. Liu, S.; Guo, L.; Che, Y.; Liu, G. Pestaloficiols Q–S from the plant endophytic fungus Pestalotiopsis fici. Fitoterapia 2013, 85, 114–118. [CrossRef][PubMed]

90. Zhang, P.; Zhou, S.; Zhou, C.; Wang, W.; An, Z.; Liu, X.; Li, K.; Yin, W. Two transcription factors cooperatively regulate DHN melanin biosynthesis in Pestalotiopsis fici. Mol. Microbiol. 2019, 112, 649–666. [CrossRef]

91. Liu, S.; Liu, X.; Guo, L.; Che, Y.; Liu, L. 2H-pyran-2-one and 2H-furan-2-one derivatives from the plant endophytic fungus Pestalotiopsis fici. J. Nat. Prod. 2013, 76, 1482–1483. [CrossRef]

92. Rao, L.; You, Y.-X.; Su, Y.; Liu, Y.; He, Q.; Fan, Y.; Hu, F.; Xu, Y.-K.; Zhang, C.-R. Two spiroketal derivatives with an unprecedented amino group and their cytotoxicity evaluation from the endophytic fungus Pestalotiopsis flavidula. Fitoterapia 2019, 135, 5–8. [CrossRef][PubMed]

93. Ding, G.; Liu, S.; Guo, L.; Zhou, Y.; Che, Y. Antifungal metabolites from the plant endophytic fungus Pestalotiopsis foedana. J. Nat. Prod. 2008, 71, 615–618. [CrossRef][PubMed]

94. Yang, X.-L.; Li, Z.-Z. New spiral γ-lactone enantiomers from the plant endophytic fungus Pestalotiopsis foedana. Molecules 2013, 18, 2236–2242. [CrossRef][PubMed]

95. Xu, D.; Zhang, B.-Y.; Yang, X.-L. Antifungal monoterpenoid derivatives from the plant endophytic fungus Pestalotiopsis foedana. Chem. Biodivers. 2016, 13, 1422–1425. [CrossRef][PubMed]

96. Parshikov, I.A.; Heinze, T.M.; Moody, J.D.; Freeman, J.P.; Williams, A.J.; Sutherland, J.B. The fungus Pestalotiopsis guepini as a model for biotransformation of ciprofloxacin and norfloxacin. Appl. Microbiol. Biotechnol. 2001, 56, 474–477. [CrossRef][PubMed]

97. Rodrigues, K.F.; Hesse, M.; Werner, C. Antimicrobial activities of secondary metabolites produced by endophytic fungi from Spondias mombin. J. Basic Microbiol. 2000, 40, 261–267. [CrossRef]

98. Sousa, J.; Matos, L.; Alcântara, D.; Ribeiro, H.; Santos, L.; Oliveira, M.; Brito-Junior, L.; Khayat, A.; Guimarães, A.; Cunha, L.; et al. Cellular responses induced in vitro by pestheic acid, a fungal metabolite, in a gastric adenocarcinoma cell line (PG100). Genet. Mol. Res. 2013, 12, 4106–4115. [CrossRef]

99. Evidente, A.; Zonno, M.C.; Andolfi, A.; Troise, C.; Cimmino, A.; Verro, M. Phytotoxic α-pyrones produced by Pestalotiopsis guepinii, the causal agent of hazelnut twig blight. J. Antibioto. 2012, 65, 203–206. [CrossRef]

100. Zhang, Y.; Bai, J.; Yan, D.; Liu, B.; Zhang, L.; Zhang, C.; Chen, M.; Mou, Y.; Hu, Y. Highly oxygenated caraphyllene-type Sesquiterpenes from a plant-associated fungus, Pestalotiopsis hainanensis, and their biosynthetic gene cluster. J. Nat. Prod. 2020, 83, 3262–3269. [CrossRef]

101. Xing, J.-G.; Deng, H.-Y.; Luo, D.-Q. Two new compounds from an endophytic fungus Pestalotiopsis heterocorns. J. Asian Nat. Prod. Res. 2011, 13, 1069–1073. [CrossRef][PubMed]
102. Sakai, K.; Hirose, T.; Iwatsuki, M.; Chinen, T.; Kimura, T.; Suga, T.; Nonaka, K.; Nakashima, T.; Sunazuka, T.; Usui, T.; et al. Pestynol, an antifungal compound discovered using a Saccharomyces cerevisiae 12 gene ΔOHSR-IERG6-based assay. J. Nat. Prod. 2018, 81, 1604–1609. [CrossRef] [PubMed]

103. Sakai, K.; Suga, T.; Iwatsuki, M.; Chinen, T.; Nonaka, K.; Usui, T.; Asami, Y.; Ōmura, S.; Shiomi, K. Pestiocandin, a new papulacandin class antibiotic isolated from Pestalotiopsis humus. J. Antibiot. 2018, 71, 1031–1035. [CrossRef] [PubMed]

104. Li, J.Y.; Strobel, G.A. Jesterone and hydroxy-jesterone antioomycete cyclohexenone epoxides from the endophytic fungus Pestalotiopsis jesteri. Phytochemistry 2001, 57, 261–265. [CrossRef]

105. Kumar, D.S.S.; Lau, C.S.; Wan, J.M.; Yang, D.; Hyde, K.D. Immunomodulatory compounds from Pestalotiopsis leucothiès, an endophytic fungus from Tripterygium willofordii. Life Sci. 2005, 78, 147–156. [CrossRef]

106. Kumar, S.S.D.; Lau, C.S.; Chan, W.K.; Yang, D.; Cheung, H.Y.; Chen, F.; Hyde, K.D. Immunomodulatory activity of an endophytic fungus from Tripterygium willofordii. In Proceedings of the 2nd International Conference on Medicinal Mushroom and the International Conference on Biodiversity and Bioactive Compounds, Pattaya, Thailand, 17–19 July 2003; pp. 367–373.

107. Subban, K.; Subramani, R.; Johnpaul, M. A novel antibacterial and antifungal phenolic compound from the endophytic fungus Pestalotiopsis mangiferae. Nat. Prod. Res. 2013, 27, 1445–1449. [CrossRef]

108. Metz, A.M.; Haddad, A.; Worapong, J.; Long, D.M.; Ford, E.J.; Hess, W.M.; Strobel, G.A. Induction of the sexual stage of Pestalotiopsis microsora, a taxol-producing fungus The GenBank accession numbers for the sequences determined in this work are: Pestalotiopsis microsora NE-32 18S rDNA, AF104356; Pestalosphora hansenii ATCC 48245 18S rDNA, AF242846. Microbiology 2000, 146, 2079–2089. [CrossRef]

109. Li, X.; Guo, Z.; Deng, Z.; Yang, J.; Zou, K. A new a-pyrene derivative from endophytic fungus Pestalotiopsis microsora. Ref. Nat. Prod. 2015, 9, 503–508.

110. Strobel, G.; Ford, E.; Worapong, J.; Harper, J.K.; Arif, A.M.; Grant, D.M.; Fung, P.C.; Chau, R.W.M. Isopestacin, an isobenzofuranone from Pestalotiopsis microsora, possessing antifungal and antioxidiant activities. Phytochemistry 2002, 60, 179–183. [CrossRef]

111. Chen, L.; Li, Y.; Zhang, Q.; Wang, D.; Akhberdi, O.; Wei, D.; Pan, J.; Zhu, X. Improved pestalotiollide B production by deleting competing polyketide synthase genes in Pestalotiopsis microsora. J. Ind. Microbiol. Biotechnol. 2017, 44, 237–246. [CrossRef]

112. Niu, X.; Hao, X.; Hong, Z.; Chen, L.; Yu, X.; Zhu, X. A Putative histone deacetylase modulates the biosynthesis of pestalotiollide B and conidiation in Pestalotiopsis microsora. J. Microbiol. Biotechnol. 2015, 25, 579–588. [CrossRef] [PubMed]

113. Zhang, Q.; Chen, L.; Yu, X.; Liu, H.; Akhberdi, O.; Pan, J.; Zhu, X. A B-type histone acetyltransferase HAT1 regulates secondary metabolism, conidiation, and cell wall integrity in the taxol-producing fungus Pestalotiopsis microsora. J. Basic Microbiol. 2016, 56, 1380–1391. [CrossRef] [PubMed]

114. Wang, D.; Akhberdi, O.; Hao, X.; Yu, X.; Chen, L.; Liu, Y.; Zhu, X. Amino acid Sensor kinase Gcn2 is required for conidiation, secondary metabolism, and cell wall integrity in the taxol-producer Pestalotiopsis microsora. Front. Microbiol. 2017, 8, 1879. [CrossRef] [PubMed]

115. Subban, K.; Singh, S.; Subramani, R.; Johnpaul, M.; Chelliah, J. Fungal 7-epi-10-deacetyltaxol produced by an endophytic Pestalotiopsis microsora induces apoptosis in human hepatocellular carcinoma cell line (HepG2). BMC Complement. Altern. Med. 2017, 17, 504. [CrossRef] [PubMed]

116. Yu, X.; Huo, L.; Liu, H.; Chen, L.; Wang, Y.; Zhu, X. Melanin is required for the formation of the multi-cellular conidia in the endophytic fungus Pestalotiopsis microsora. Microbiol. Res. 2015, 175, 1–11. [CrossRef]

117. Fu, S.-B.; Yang, J.-S.; Cui, J.-L.; Meng, Q.-F.; Feng, X.; Sun, D.-A. Multihydroxylation of ursolic acid by Pestalotiopsis microsora isolated from the medicinal plant Huperzia serrata. Fitoterapia 2011, 82, 1057–1061. [CrossRef]

118. Liu, S.; Dai, H.; Makhloifi, G.; Heering, C.; Janiak, C.; Hartmann, R.; Mándi, A.; Kurtán, T.; Müller, W.E.G.; Kassack, M.U.; et al. Cytotoxic 14-membered macrolides from a mangrove-derived endophytic fungus, Pestalotiopsis microsora. J. Nat. Prod. 2016, 79, 2332–2340. [CrossRef]

119. Brückner, D.; Hafner, F.-T.; Li, V.; Schmeck, C.; Telser, J.; Vakalopoulou, A.; Wirtz, G. Dibenzooxocinocines—A new class of CETP inhibitors. Bioorganic Med. Chem. Lett. 2005, 15, 3611–3614. [CrossRef]

120. Liu, Y.; Chen, L.; Xie, Q.; Yu, X.; Duan, A.; Lin, Y.; Xiang, B.; Hao, X.; Chen, W.; Zhu, X. A gene cluster for the biosynthesis of dibenzooxocinocins in the endophyte Pestalotiopsis microsora, a taxol producer. J. Microbiol. Biotechnol. 2019, 29, 1570–1579. [CrossRef]

121. Kanno, K.; Tsurukawa, Y.; Kamisuki, S.; Shibasaki, H.; Iguchi, K.; Murakami, H.; Uchiyama, J.; Kuramochi, K. Novel neuroprotective hydroquinones with a vinyl alkyne from the fungus, Pestalotiopsis microsora. J. Antibiot. 2019, 72, 793–799. [CrossRef]

122. Wu, X.; Wang, Y.; Liu, S.; Liu, X.; Guo, L. Microsorops A-C from the plant endophytic fungus Pestalotiopsis microsora. Nat. Prod. Commun. 2015, 10, 1643–1646. [CrossRef] [PubMed]

123. Qi, Q.-Y.; Li, E.-W.; Han, J.-J.; Pei, Y.-F.; Ma, K.; Bao, L.; Huang, Y.; Zhao, F.; Liu, H.-W. New ampic acid derivatives from the solid culture of Pestalotiopsis neglecta and their nitric oxide inhibitory activity. Sci. Rep. 2015, 5, srep09958. [CrossRef] [PubMed]

124. Sharma, D.; Pramanik, A.; Agrawal, P.K. Evaluation of bioactive secondary metabolites from endophytic fungus Pestalotiopsis neglecta BAB-5510 isolated from leaves of Cupressus torulosa D.Don. 3 Biotech 2016, 6, 210. [CrossRef] [PubMed]

125. Liang, Z.; Gu, T.; Wang, J.; She, J.; Ye, Y.; Cao, W.; Luo, X.; Xiao, J.; Liu, Y.; Tang, L.; et al. Chromone and chromone derivatives as liver X receptors modulators from a marine-derived Pestalotiopsis neglecta fungus. Bioorganic Chem. 2021, 112, 104927. [CrossRef]
126. Zhang, Q.; Luan, R.; Li, H.; Liu, Y.; Liu, P.; Wang, L.; Li, D.; Wang, M.; Zou, Q.; Liu, H.; et al. Anti-inflammatory action of ambuc acid, a natural product isolated from the solid culture of Pestalotiopsis neglecta, through blocking ERK/JNK mitogen-activated protein kinase signaling pathway. Exp. Ther. Med. 2018, 16, 1538–1546. [CrossRef]

127. Feng, L.; Han, J.; Wang, J.; Zhang, A.-X.; Miao, Y.-Y.; Tan, N.-H.; Wang, Z. Pestalopyrones A–D, four tricyclic pyrone derivatives from the endophytic fungus Pestalotiopsis sp. S3. Phytochemistry 2020, 179, 112505. [CrossRef]

128. Xiao, J.; Hu, J.-Y.; Sun, H.-D.; Zhao, X.; Zhong, W.-T.; Duan, D.-Z.; Wang, L.; Wang, X.-L. Sinopestalotiollides A–D, cytotoxic diphenyl ether derivatives from plant endophytic fungus Pestalotiopsis palmarum. Bioorganic Med. Chem. Lett. 2018, 28, 515–518. [CrossRef]

129. Yang, X.-L.; Zhang, S.; Hu, Q.-B.; Luo, D.-Q.; Zhang, Y. Phthalide derivatives with antifungal activities against the plant pathogens isolated from the liquid culture of Pestalotiopsis sp. J. Antibiot. 2011, 64, 723–727. [CrossRef]

130. Ding, G.; Qi, Y.; Liu, S.; Guo, L.; Chen, X. Photopyrones A and B, new pyrone derivatives from the endophytic fungus Pestalotiopsis photiniae. J. Antibiot. 2012, 65, 271–273. [CrossRef]

131. Chen, C.; Yang, R. A phthalide derivative isolated from endophytic fungi Pestalotiopsis photiniae induces G1 cell cycle arrest and apoptosis in human HeLa cells. Braz. J. Med. Biol. Res. 2013, 46, 643–649. [CrossRef]

132. Chen, C.; Hu, S.-Y.; Luo, D.-Q.; Zhu, S.-Y.; Zhou, C.-Q. Potential antitumor agent from the endophytic fungus Pestalotiopsis sp. induces apoptosis via the mitochondrial pathway in HeLa cells. Oncol. Rep. 2013, 30, 1773–1781. [CrossRef] [PubMed]

133. Yang, X.; Zhang, S.; Zhu, H.-J.; Luo, D.-Q. Dihydroberkleasmin A: A New emerphaleine sesquiterpenoid from the fermentation broth of the plant endophytic fungus Pestalotiopsis sp. Molecules 2011, 16, 1910–1916. [CrossRef] [PubMed]

134. Ogawa, T.; Ando, K.; Aotani, Y.; Shinoda, K.; Tanaka, T.; Tsukuda, E.; Yoshida, M.; Matsuda, Y. RES-1214-1 and -2, Novel non-peptidic endothelin type A receptor antagonists produced by Pestalotiopsis sp. J. Antibiot. 1995, 48, 1401–1406. [CrossRef] [PubMed]

135. Xu, J.; Lin, Q.; Wang, B.; Wray, V.; Lin, W.-H.; Proksch, P. Pestalotiopamide E, a new amide from the endophytic fungus Pestalotiopsis sp. J. Nat. Prod. Res. 2021, 8, 1–7. [CrossRef] [PubMed]

136. Ding, G.; Zhang, F.; Chen, H.; Guo, L.; Miao, Y.-Y.; Tan, N.-H.; Proksch, P. Chromones from the Endophytic Fungus Pestalothioninamide E. Phytochemistry 2015, 119–124. [CrossRef] [PubMed]

137. Davis, R.A.; Carroll, A.R.; Andrews, K.T.; Boyle, G.M.; Tran, T.L.; Healy, P.C.; Kalaitzis, J.A.; Shivas, R.G. Pestalactams A–C: Novel sesquiterpene-cyclopaldic acid hybrids from Pestalotiopsis sp. Org. Biomol. Chem. 2011, 9, 1785–1790. [CrossRef]

138. Ding, G.; Qi, Y.; Liu, S.; Guo, L.; Chen, X. Photopyrones A and B, new pyrone derivatives from the endophytic fungus Pestalotiopsis photiniae. J. Antibiot. 2012, 65, 271–273. [CrossRef] [PubMed]

139. Zhou, J.; Li, G.; Deng, Q.; Zheng, D.; Yang, X.; Xu, J. Cytotoxic constituents from the mangrove endophytic Pestalotiopsis sp. J. Asian Nat. Prod. Res. 2011, 13, 373–376. [CrossRef]

140. Hemberger, Y.; Xu, J.; Wray, V.; Proksch, P.; Wu, J.; Bringmann, G. Pestalotiopins A and B: Stereochemically challenging flexible sesquiterpene-cyclopaldic acid hybrids from Pestalotiopsis sp. Chem. A Eur. J. 2013, 19, 15556–15564. [CrossRef]

141. Davis, R.A.; Carroll, A.R.; Andrews, K.T.; Boyle, G.M.; Tran, T.L.; Healy, P.C.; Kalaitzis, J.A.; Shivas, R.G. Pestalactams A–C: Novel caprolactams from the endophytic fungus Pestalotiopsis sp. Org. Biomol. Chem. 2010, 8, 1785–1790. [CrossRef]

142. Ding, G.; Qi, Y.; Liu, S.; Guo, L.; Chen, X. Photopyrones A and B, new pyrone derivatives from the endophytic fungus Pestalotiopsis photiniae. J. Antibiot. 2012, 65, 271–273. [CrossRef] [PubMed]

143. Zhou, J.; Li, G.; Deng, Q.; Zheng, D.; Yang, X.; Xu, J. Cytotoxic constituents from the mangrove endophytic Pestalotiopsis sp. induce G0/G1 cell cycle arrest and apoptosis in human HeLa cells. Braz. J. Med. Biol. Res. 2013, 46, 643–649. [CrossRef]

144. Hwang, I.H.; Swenson, D.C.; Gloer, J.B.; Wicklow, D.T. Pestaloporonins: Caryophyllene-derived sesquiterpenoids from a fungicolous isolate of Pestalotiopsis sp. Org. Lett. 2015, 17, 4284–4287. [CrossRef]

145. Yuan, C.; Ding, G.; Wang, H.-Y.; Guo, Y.-H.; Shang, H.; Ma, X.-J.; Zou, Z.-M. Polycyctein-terpene hybrid metabolites from an endolicheic fungus Pestalotiopsis sp. BioMed Res. Int. 2017, 2017, 6961928. [CrossRef] [PubMed]

146. Liu, Y.; Yang, M.-H.; Wang, X.-B.; Li, T.-X.; Kong, L.-Y. Caryophyllene sesquiterpenoids from the endophytic fungus Pestalotiopsis sp. Fitoterapia 2016, 109, 119–124. [CrossRef] [PubMed]

147. Song, R.-Y.; Wang, X.-B.; Yin, G.-P.; Liu, R.-H.; Kong, L.-Y.; Yang, M.-H. Isoxomarin derivatives from the endophytic fungus Pestalotiopsis sp. Fitoterapia 2017, 122, 115–118. [CrossRef] [PubMed]

148. Wei, M.-Y.; Li, D.; Shao, C.-L.; Deng, D.-S.; Wang, C.-Y. (+)-Pestalachloride D, an antibacterial racemate of Chlorinated benzophe none derivative from a soft coral-derived fungus Pestalotiopsis sp. Mar. Drugs 2013, 11, 1050–1060. [CrossRef] [PubMed]

149. Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H.; Edrada, R.; Müller, W.E.; Bayer, M.; Lin, W.; Wu, J.; et al. Cytosporones, coumarins, and an alkaloid from the endophytic fungus Pestalotiopsis sp. isolated from the Chinese mangrove plant Rhizophora mucronata. Bioorganic Med. Chem. 2009, 17, 7562–7567. [CrossRef] [PubMed]

150. Jia, Y.-L.; Wei, M.-Y.; Chen, H.-Y.; Guan, F.-F.; Wang, C.-Y.; Shao, C.-L. (+)- and (−)-Pestaloxazine A, a pair of antiviral enantiomeric alkaloid dimers with a symmetric spiro[oxazinane-piperazinedione] skeleton from Pestalotiopsis sp. Org. Lett. 2015, 17, 4216–4219. [CrossRef] [PubMed]

151. Pulici, M.; Sugawara, F.; Koshino, H.; Uzawa, J.; Yoshiida, S. Pestalotiopsins A and B: New carbylphenyls from an endophytic fungus of Taxus brevifolia. Phytochemistry 1996, 61, 2122–2124. [CrossRef]

152. Ding, G.; Li, Y.; Fu, S.; Liu, S.; Wei, J.; Che, Y. Ambuc acid and torreyean acid derivatives from the endophytic fungus Pestalotiopsis sp. J. Nat. Prod. 2009, 72, 182–186. [CrossRef]

153. Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H.; Edrada, R.; Lin, W.; Wu, J.; Proksch, P. Chromones from the Endophytic Fungus Pestalotiopsis sp. Isolated from the Chinese Mangrove Plant Rhizophora mucronata. J. Nat. Prod. 2009, 72, 662–665. [CrossRef] [PubMed]

154. Sun, J.-F.; Lin, X.; Zhou, X.-F.; Wan, J.; Zhang, T.; Yang, B.; Yang, X.-W.; Tu, Z.; Liu, Y. Pestalols A–E, a new alkynyl phenol and benzaldehyde derivatives from endophytic fungus Pestalotiopsis sp. AcrBC2 isolated from the Chinese mangrove plant Aegiceras corniculatum. J. Antibiot. 2014, 67, 451–457. [CrossRef] [PubMed]
180. Kesting, J.R.; Olsen, L.; Staerk, D.; Tejevis, M.V; Kini, K.R.; Prakash, H.S.; Jaroszewski, J.W. Production of unusual dispiro metabolites in Pestalotiopsis virgatula endophyte cultures: HPLC-SPE-NMR, electronic circular dichroism, and time-dependent density-functional computation study. J. Nat. Prod. 2011, 74, 2206–2215. [CrossRef]

181. Kesting, J.R.; Staerk, D.; Tejevis, M.V; Kini, K.R.; Prakash, H.S.; Jaroszewski, J.W. HPLC-SPE-NMR identification of a novel metabolite containing the benzox[e]opin skeleton from the endophytic fungus Pestalotiopsis virgatula culture. Planta Medica 2009, 75, 1104–1106. [CrossRef]

182. Perez-Cuesta, U.; Aparicio-Fernandez, L.; Guruceaga, X.; Martin-Souto, L.; Abad-Diaz-De-Cerio, A.; Antoran, A.; Buldain, I.; Hernandez, F.L.; Ramirez-Garcia, A.; Rementeria, A. Melanin and pyomelanin in Aspergillus fumigatus: From its genetics to host interaction. Int. Microbiol. 2020, 23, 55–63. [CrossRef]

183. Xu, X.; Liu, C.; Dong, Y.-J.; Liu, F.-R.; Xu, X.-M.; Li, D.-S.; Li, D.-Y.; Li, Z.-L. Polyketides from Pestalotiopsis virgatula sp. and Pestalotiopsis virgatula. Molecules 2020, 25, 4192. [CrossRef]

184. Li, J.; Kim, S.G.; Blenis, J. Rapamycin: One drug, many effects. J. Cell. Biochem. 2018, 119, 104826. [CrossRef]

185. Noor, A.O.; Almasri, D.M.; Bagalagel, A.A.; Abdallah, H.M.; Mohamed, S.G.A.; Mohamed, G.A.; Ibrahim, S.R.M. Naturally occurring bioactive metabolites production from coculture of Pestalotiopsis sp. and Penicillium bialowiezense. Biochem. Cell Mol. Res. 2021, 110, 613–617. [CrossRef]

186. Kesting, J.R.; Staerk, D.; Tejesvi, M.V.; Kini, K.R.; Prakash, H.S.; Jaroszewski, J.W. HPLC-SPE-NMR identification of a novel metabolite containing the benzox[e]opin skeleton from the endophytic fungus Pestalotiopsis virgatula culture.
206. Dai, Q.; Zhang, F.-L.; Feng, T. Sesquiterpenoids Specially Produced by Fungi: Structures, Biological Activities, Chemical and Biosynthesis (2015–2020). J. Fungi 2021, 7, 1026. [CrossRef] [PubMed]

207. Dong, W.-H.; Mei, W.-L.; Zhao, Y.-X.; Zeng, Y.-B.; Wang, H.; Dai, H.-F. A new drimane sesquiterpenoid glycoside from the seeds of Antiaris toxicaria. J. Asian Nat. Prod. Res. 2011, 13, 561–565. [CrossRef] [PubMed]

208. Edouarzin, E.; Horn, C.; Paudyal, A.; Zhang, C.; Lu, J.; Tong, Z.; Giaever, G.; Nislow, C.; Veerapandian, R.; Hua, D.H.; et al. Broad-spectrum antifungal activities and mechanism of drimane sesquiterpenoids. Microb. Cell 2020, 7, 146–159. [CrossRef] [PubMed]

209. Neuhaus, G.F.; Loesgen, S. Antibacterial drimane sesquiterpenes from Aspergillus ustus. J. Nat. Prod. 2020, 84, 37–45. [CrossRef] [PubMed]

210. Nguyen, P.-T.; Nguyen, T.-T.; Bui, D.-C.; Hong, P.-T.; Hoang, Q.-K.; Nguyen, H.-T. Exopolysaccharide production by lactic acid bacteria. Food Res. Int. 2021, 139, 1–6. [CrossRef]

211. Zhou, M.; Li, Z.; Liu, Y.; Zhang, P.; Hao, X.; Zhu, X. Transcription factors Pmr1 and Pmr2 cooperatively regulate melanin biosynthesis, conidia development and secondary metabolism in Penicillium oxalicum. J. Agric. Food Chem. 2020, 68, 2664–2672. [CrossRef]

212. Mahapatra, S.; Banerjee, D. Structural elucidation and bioactivity of a novel exopolysaccharide from endophytic Fusarium solani SD5. Carbohydr. Polym. 2012, 90, 683–689. [CrossRef] [PubMed]

213. Guo, S.; Mao, W.; Li, Y.; Tian, J.; Xu, J. Structural elucidation of the exopolysaccharide produced by fungus Fusarium oxysporum Y24-2. Carbohydr. Res. 2013, 365, 9–13. [CrossRef] [PubMed]

214. Bai, Y.; Han, M.; Li, Y.; Mao, S.; Wang, S.; Hu, J.; Zhang, L.; Zhao, H.; Meng, H.; et al. Structural characterization and antioxidant properties of an exopolysaccharide produced by the mangrove endophytic fungus Aspergillus sp. Y16. Biomater. Technol. 2011, 102, 8179–8184. [CrossRef] [PubMed]

215. Lynch, K.M.; Coffey, A.; Arendt, E.K. Exopolysaccharide producing lactic acid bacteria: Their techno-functional role and potential application in gluten-free bread products. Food Res. Int. 2018, 110, 52–61. [CrossRef]

216. Nguyen, P.-T.; Nguyen, T.-T.; Bui, D.-C.; Hong, P.-T.; Hoang, Q.-K.; Nguyen, H.-T. Exopolysaccharide production by lactic acid bacteria: The manipulation of environmental stresses for industrial applications. AIMS Microbiol. 2020, 6, 451–469. [CrossRef]

217. Farag, M.M.; Moghannem, S.A.; Shehabeldine, A.; Azab, M.S. Antitumor effect of exopolysaccharide produced by Bacillus mycoides. Microb. Pathog. 2020, 140, 103947. [CrossRef] [PubMed]

218. Asgher, M.; Urooj, Y.; Qamar, S.A.; Khalid, N. Improved exopolysaccharide production from Bacillus licheniformis MS3: Optimization and structural/functionual characterization. Int. J. Biol. Macromol. 2019, 151, 984–992. [CrossRef]

219. Ren, Q.; Tang, Y.; Zhang, L.; Xu, Y.; Liu, N.; Ren, H. Exopolysaccharide produced by Lactobacillus casei promotes the differentiation of CD4+ T cells into Th17 cells in BALB/c mouse Peyer’s patches in vivo and in vitro. J. Agric. Food Chem. 2020, 68, 2664–2672. [CrossRef]

220. Zhou, M.; Li, Z.; Liu, Y.; Zhang, P.; Hao, X.; Zhu, X. Transcription factors Pmr1 and Pmr2 cooperatively regulate melanin biosynthesis, conidia development and secondary metabolism in Penicillium micropora. J. Fungi 2021, 7, 38. [CrossRef]

221. Zhang, Q.; Akhberdi, O.; Wei, D.; Chen, L.; Liu, H.; Wang, D.; Hao, X.; Zhu, X. A MYST Histone Acetyltransferase modulates Conidia development and secondary metabolism in Penicillium micropora, a taxol producer. Sci. Rep. 2018, 8, 8199. [CrossRef]

222. Wang, S.; Xu, Y.; Maine, E.A.; Wijeratne, E.K.; Espinosa-Artiles, P.; Gunati, A.L.; Molnár, I. Functional characterization of the biosynthesis of radicicol, an Hsp90 inhibitor resorcylic acid lactone from Chaetomium chiversii. J. Fungi 2021, 7, 1026. [CrossRef] [PubMed]

223. Guo, S.; Mao, W.; Li, Y.; Tian, J.; Xu, J. Structural elucidation of the exopolysaccharide produced by fungus Fusarium oxysporum Y24-2. Carbohydr. Res. 2013, 365, 9–13. [CrossRef] [PubMed]

224. Wang, D.; Li, Y.; Wang, H.; Wei, D.; Akhberdi, O.; Liu, Y.; Xiang, B.; Hao, X.; Zhu, X. The AMP-activated protein kinase homolog Snf1 concert carbon utilization, conidia production and the biosynthesis of secondary metabolites in the taxol-producer Penicillium micropora. Genes 2018, 9, 59. [CrossRef] [PubMed]

225. Zhou, S.; Zhang, P.; Zhou, H.; Liu, X.; Li, S.; Guo, L.; Li, K.; Yin, W. A new regulator RsdA mediating fungal secondary metabolism has a detrimental impact on asexual development in Pestalotiopsis fici. Environ. Microbiol. 2019, 21, 416–426. [CrossRef] [PubMed]

226. de Souza, W.R.; Morais, E.R.; Krohn, N.G.; Savoldi, M.; Goldman, M.H.S.; Rodrigues, F.; Caldana, C.; Semelka, C.T.; Tikanov, A.P.; Macdonald, J.M.; et al. Identification of metabolic pathways influenced by the G-protein coupled receptors GprB and GprD in Aspergillus nidulans. PLoS ONE 2013, 8, e62088. [CrossRef]

227. Li, X.; Zhong, K.; Yin, Z.; Hu, J.; Wang, J.; Wang, W.; Li, L.; Zhang, H.; Zheng, X.; Wang, P.; Zhang, Z. The seven transmembrane domain protein M0rgs7 functions in surface perception and undergoes coronin MoCrm1-dependent endocytosis in complex with Go subunit MoMagA to promote cAMP signaling and appressorium formation in Magnaportha oryzae. PLOS Pathog. 2019, 15, e1007382. [CrossRef]

228. Pang, X.-M.; Tian, D.; Zhang, T.; Liao, L.-S.; Li, C.-X.; Luo, X.-M.; Feng, J.-X.; Zhao, S. G protein β subunit modulates expression of plant-biomass-degrading enzyme genes and mycelial-development-related genes in Penicillium oxalicum. Appl. Microbiol. Biotechnol. 2021, 105, 4675–4691. [CrossRef]

229. Ramanujam, R.; Calvert, M.E.; Selvaraj, P.; Naqvi, N.I. The late endosomal HOPS complex anchors active G-protein signaling essential for pathogenesis in Magnaportha oryzae. PLOS Pathog. 2013, 9, e1003527. [CrossRef]

230. Tzima, A.K.; Paplomatas, E.J.; Tsitsigiannis, D.I.; Kang, S. The G protein β subunit controls virulence and multiple growth- and development-related traits in Verticillium dahliae. Fungal Genet. Biol. 2012, 49, 271–283. [CrossRef]
231. Yan, H.; Zhou, Z.; Shim, W.B. Two regulators of G-protein signaling (RGS) proteins FlbA1 and FlbA2 differentially regulate fumonisin B1 biosynthesis in *Fusarium verticillioides*. *Curr. Genet.* 2021, 67, 305–315. [CrossRef]

232. Chen, L.; Li, Y.; Zhang, Q.; Akhberdi, O.; Wei, D.; Pan, J.; Zhu, X. Seamless deletion of a large DNA fragment in the taxol-producing fungus *Pestalotiopsis microspora*. *Mycoscience* 2017, 58, 35–39. [CrossRef]

233. Chen, L.; Wei, D.; Zhang, Q.; Yu, X.; Wang, Y.; Zhu, X. Orotidine 5′-phosphate decarboxylase-based reusable in situ genetic editing system: Development and application in taxol-producing *Pestalotiopsis microspora*. *Eng. Life Sci.* 2015, 15, 542–549. [CrossRef]

234. Xu, X.; Huang, R.; Yin, W.-B. An optimized and efficient CRISPR/Cas9 system for the endophytic fungus *Pestalotiopsis fici*. *J. Fungi* 2021, 7, 809. [CrossRef] [PubMed]

235. Subban, K.; Subramani, R.; Srinivasan, V.P.; Johnpaul, M.; Chelliah, J. Salicylic acid as an effective elicitor for improved taxol production in endophytic fungus *Pestalotiopsis microspora*. *PLoS ONE* 2019, 14, e0212736. [CrossRef]

236. El-Sayed, A.S.; Shindia, A.A.; AbouZeid, A.; Koura, A.; Hassanein, S.E.; Ahmed, R.M. Triggering the biosynthetic machinery of taxol by *Aspergillus flavipes* via cocultivation with *Bacillus subtilis*: Proteomic analyses emphasize the chromatin remodeling upon fungal-bacterial interaction. *Environ. Sci. Pollut. Res.* 2021, 28, 39866–39881. [CrossRef]

237. Nützmann, H.-W.; Fischer, J.; Scherlach, K.; Hertweck, C.; Brakhage, A.A. Distinct amino acids of histone H3 control secondary metabolism in *Aspergillus nidulans*. *Appl. Environ. Microbiol.* 2013, 79, 6102–6109. [CrossRef]

238. Nützmann, H.-W.; Reyes-Dominguez, Y.; Scherlach, K.; Schroechk, V.; Horn, F.; Gacek, A.; Schümann, J.; Hertweck, C.; Strauss, J.; Brakhage, A.A. Bacteria-induced natural product formation in the fungus *Aspergillus nidulans* requires Saga/Ada-mediated histone acetylation. *Proc. Natl. Acad. Sci. USA* 2011, 108, 14282–14287. [CrossRef]

239. Schroechk, V.; Scherlach, K.; Nützmann, H.-W.; Shelest, E.; Schmidt-Heck, W.; Schuemann, J.; Martin, K.; Hertweck, C.; Brakhage, A.A. Intimate bacterial–fungal interaction triggers biosynthesis of archetypal polyketides in *Aspergillus nidulans*. *Proc. Natl. Acad. Sci. USA* 2009, 106, 14558–14563. [CrossRef] [PubMed]

240. Fischer, J.; Müller, S.Y.; Netzker, T.; Jäger, N.; Gacek-Matthews, A.; Scherlach, K.; Stroe, M.C.; Garcia-Altares, M.; Pezzini, F.; Schoeler, H.; et al. Chromatin mapping identifies BasR, a key regulator of bacteria-triggered production of fungal secondary metabolites. *Elife* 2018, 7, e04969. [CrossRef]

241. Brakhage, A.A.; Schroechk, V. Fungal secondary metabolites—Strategies to activate silent gene clusters. *Fungal Genet. Biol.* 2011, 48, 15–22. [CrossRef]