New Insights into Chemical and Biological Properties of Funicone-like Compounds

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Abstract: Funicone-like compounds are a homogeneous group of polyketides that, so far, have only been reported as fungal secondary metabolites. In particular, species in the genus *Talaromyces* seem to be the most typical producers of this group of secondary metabolites. The molecular structure of funicone, the archetype of these products, is characterized by a γ-pyrene ring linked through a ketone group to a α-resorcylic acid nucleus. This review provides an update on the current knowledge on the chemistry of funicone-like compounds, with special emphasis on their classification, occurrence, and diverse biological activities. In addition, their potential relevance as mycotoxins is discussed.

Keywords: fungal metabolites; natural products; *Talaromyces; Penicillium*; secondary metabolites; mycotoxins

Key Contribution: This review describes recent progress on the occurrence, detection, chemical diversity, and bioactivities of the funicone-like compounds.

1. Introduction

Research on fungal secondary metabolites is mainly driven by remarks concerning their bioactive properties, which can either be inherent to their role in biocenotic inter-relations or their effects on human health, the latter depending on either their possible accumulation in foodstuffs as mycotoxins, or eventual pharmaceutical relevance.

Funicones and structurally related compounds represent a homogeneous group of fungal polyketides that were initially characterized as determinants of the antagonistic abilities by the producers against other microorganisms, but were later found to possess remarkable biological properties that have promoted their consideration as drug prospects. Considering that these properties are partly based on observations concerning cytostatic and antiproliferative effects on human cells, these products should be also evaluated with reference to toxicological aspects related to possible contamination of foodstuffs by the producing fungi.

In light of the novel knowledge developed in over a decade since the publication of a previous review [1], this paper offers an update on the state of the art concerning occurrence, bioactivities, structural, synthetic, and biosynthetic aspects of funicone-like compounds.

2. Structures and Chemical Properties

Funicone-like compounds include natural products characterized by a molecular structure that is built on a γ-pyrene ring linked through a ketone group to a α-resorcylic
acid nucleus. A total of 34 chemically defined compounds, which are referable to this basic structural model, have been identified and characterized so far. Among them, 13 can be considered true funicones because the typical moieties are present without alterations. The other compounds, showing modifications on the α-resorcylic acid nucleus, on the γ-pyrone ring, or on both moieties, are grouped in three subclasses, namely phthalide, furopyrone, and pyridone types, depending on peculiar substructural variations (Table 1).

Table 1. List of funicone-like compounds gathered from the literature.

| Code | Name                  | Formula (C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>) | Nominal Mass (U) | Source                        |
|------|-----------------------|----------------------------------------------------|------------------|-------------------------------|
|      | True Funicones        |                                                    |                  |                               |
| 1    | Funicone              | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>         | 374              | [2–8]                         |
| 2    | Actofunicone          | C<sub>21</sub>H<sub>22</sub>O<sub>9</sub>         | 418              | [9]                           |
| 3    | Deoxyfunicone         | C<sub>19</sub>H<sub>18</sub>O<sub>7</sub>         | 358              | [5,7,9–14]                    |
| 4    | 9,14-Epoxy-11-deoxyfunicone | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>     | 374              | [4]                           |
| 5    | 9R,14S-Epoxy-11-deoxyfunicone | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>     | 374              | [14]                          |
| 6    | 9S,14R-Epoxy-11-deoxyfunicone | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>     | 374              | [14]                          |
| 7    | 3-O-Methyl-5,6-epoxyfunicone | C<sub>20</sub>H<sub>20</sub>O<sub>9</sub>   | 404              | [15]                          |
| 8    | 6-Hydroxyl-deoxyfunicone | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>     | 374              | [8]                           |
| 9    | Isofunicone           | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>       | 374              | [16]                          |
| 10   | 3-O-Methylfunicone    | C<sub>20</sub>H<sub>20</sub>O<sub>8</sub>       | 388              | [5,7,17–26]                   |
| 11   | Rapicone              | C<sub>17</sub>H<sub>16</sub>O<sub>7</sub>       | 332              | [27]                          |
| 12   | Pinophilone A         | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>       | 374              | [28]                          |
| 13   | Pinophilone B         | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>       | 374              | [28]                          |
|      | Furopyrone type       |                                                    |                  |                               |
| 14   | Penifupyrone          | C<sub>19</sub>H<sub>18</sub>O<sub>8</sub>       | 374              | [5,17,18]                     |
|      | Phthalide type        |                                                    |                  |                               |
| 15   | Vermistatin (=fijiensin) | C<sub>18</sub>H<sub>16</sub>O<sub>6</sub>   | 328              | [3,4,6,7,9,12,20,21,28–48]   |
| 16   | Acetoxydihydrovermistatin | C<sub>20</sub>H<sub>20</sub>O<sub>8</sub> | 388              | [6,33]                        |
| 17   | 6-Demethylvermistatin | C<sub>17</sub>H<sub>16</sub>O<sub>6</sub>       | 314              | [8,21,28,40,49]               |
| 18   | 14,15-Dihydrovermistatin | C<sub>18</sub>H<sub>18</sub>O<sub>6</sub>   | 330              | [6,8,12,28,33,36,38,41,44–46] |
| 19   | 2’-epihydroxydihydrovermistatin | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub> | 346              | [21,28]                      |
| 20   | Hydroxydihydrovermistatin | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>   | 346              | [6,33]                        |
| 21   | Hydroxyvermistatin    | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>       | 344              | [7,21,28,34]                  |
| 22   | 5'-O-methyldihydrovermistatin | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub> | 360              | [28]                          |
| 23   | Methoxyvermistatin    | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>       | 358              | [6,7,21,28,34,40,42,50]       |
| 24   | Neosarphenol A        | C<sub>18</sub>H<sub>18</sub>O<sub>6</sub>       | 344              | [40]                          |
| 25   | Penisimplicissin      | C<sub>18</sub>H<sub>18</sub>O<sub>6</sub>       | 302              | [3,6,20,21,28,33,44,45]       |
| 26   | 6-Demethylpenisimplicissin | C<sub>18</sub>H<sub>18</sub>O<sub>6</sub>   | 288              | [21,28]                      |
| 27   | 5'-Hydroxypenisimplicissin | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>   | 318              | [21]                          |
| 28   | Pinophilone C         | C<sub>18</sub>H<sub>18</sub>O<sub>6</sub>       | 316              | [28]                          |
| 29   | Pinophilone D         | C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>       | 346              | [28]                          |
|      | Pyridone type         |                                                    |                  |                               |
| 30   | Penicidone A          | C<sub>18</sub>H<sub>17</sub>NO<sub>5</sub>     | 327              | [51]                          |
| 31   | Penicidone B          | C<sub>17</sub>H<sub>15</sub>NO<sub>5</sub>     | 313              | [51]                          |
| 32   | Penicidone C          | C<sub>18</sub>H<sub>18</sub>NO<sub>6</sub>     | 357              | [18,21,28,51]                 |
| 33   | Penicidone D          | C<sub>20</sub>H<sub>20</sub>NO<sub>7</sub>     | 387              | [17,18,28]                    |
| 34   | Talarodone A          | C<sub>20</sub>H<sub>21</sub>NO<sub>8</sub>     | 405              | [18]                          |
2.1. True Funicones

In temporal terms, funicone [benzoic acid, 2-[5-hydroxy-4-oxo-6-(1E)-1-propenyl-4H-pyran-3-yl]carbonyl]-3,5-dimethoxy, methyl ester] (1) is the founder of this group of compounds, originally characterized from a culture of Penicillium funiculosum [2]. Subsequently, a structural isomer, namely isofunicone (9) [16], and several derivatives, which differ from the parent compound by few substitutions, were identified (Figure 1). This subclass also includes some epoxide derivatives (4–7) on the \( \gamma \)-pyrone ring, two of them (5,6) isolated from co-cultures of a strain of Penicillium sp. with the actinomycete Streptomyces fradiae [14]. Pinophilones A and B (12 and 13) are the only funicone-like compounds presenting a dihydrofuran fragment obtained from the cyclization of the hydroxyl group on the \( \gamma \)-pyrone ring and the double bond on the propenyl chain [28].

The rising interest of the scientific community in these substances has led to the development of approaches for their synthesis. In particular, deoxyfunicone (3), 3-O-methylfunicone (10) [52], and rapicone (11) [53] were efficiently prepared by carbonylative Stille cross-coupling reactions between methyl 2-iodo-3,5-dimethoxybenzoate and functionalized \( \gamma \)-pyrone (Figure 2). 5-Stannane derivatives were prepared starting from commercially available kojic acid in four steps [52,53].
Figure 2. General procedures for synthesis of funicones.

2.2. Furopyrone Type

Penifupyrone (14) is the only member of the furopyrone type carrying a 5H-furo[3,2-b]pyran-7(6H)-one moiety instead of a γ-pyrone ring (Figure 3). It was isolated for the first time from an endophytic strain of Talaromyces sp., along with funicone, deoxyfunicone, and 3-O-methylfunicone [5].

Figure 3. Structure of penifupyrone (14).

2.3. Phthalide Type

The molecular structure of compounds in this subclass includes a 4,6-dimethoxyphthalide moiety (Figure 4). Vermistatin (15) is the reference compound of this group, deriving its name from a strain of Talaromyces flavus identified in anamorphic-stage Penicillium verruculatum [47]. This metabolite was later isolated as a product of Pseudocercospora fijiensis [47]. This is not surprising because the attribution of different names to the same chemical structure represents a recurring nomenclatural issue in natural product research [54].

Based on the currently available data, vermistatin represents the most frequent funicone-like compound, having been extracted as a product of at least 15 species. It is frequently extracted along with some derivatives, such as hydroxy- (21) and methoxyvermistatin (22), 6-demethylvermistatin (17), 14,15-dihydrovermistatin (18), hydroxy- (20) and acetoxy-dihydrovermistatin (16), and penisimplicissin (25) [6,7,21,28,33,34,45,49].

Neosarphenol (24) is an isomer of hydroxyvermistatin, which was named on the basis of the producing fungus, Neosartorya glabra (currently reclassified as Aspergillus neoglaber), rather than with reference to its chemical structure [40].

2.4. Pyridone Type

This series includes compounds containing a γ-pyridone moiety. The molecular structures of penicidone A and B (30,31) are characterized by the presence of an α-resorcylic acid moiety linked through a ketone group to a γ-pyridone, whereas penicidone C, D and talarodone A (32–34) contain the typical 4,6-dimethoxyphthalide moiety of vermistatin replacing the α-resorcylic acid nucleus (Figure 5). Nevertheless, Murakami et al. [18] represented penicidone D (33) in γ-pyridol form, instead of γ-pyridone form.
Pseudocercospora (=Mycosphaerella) fijiensis

Ramichloridium apiculatum

Phoma

Species Source/Lifestyle

sp. No. 4382

sp. JS1-2

NHL2956

Talaromyces

Identification of strain IFM53375 as

specie and their assignment to the genus

dothideomycetes and eurotiomycetes. Members in the first class are sparse, being

have been recovered from various substrates, often in association with plants or other

organisms, and in diverse environments, both terrestrial and marine. They are also quite

heterogeneous in taxonomic terms, as they belong to two ascomycetes classes: the doth-
ideomycetes and Eurotiomycetes. Members in the first class are sparse, being ascribed to five orders, with each of them represented by a single strain. Even considering the approximate taxonomic identification of three strains, which were only identified at the genus level, it is clear that funicone biosynthetic aptitudes occur among Dothideomycetes, and might be more widespread than currently known. Conversely, the Eurotiomycetes look to be much more abiding producers and taxonomically homogeneous, with about 31 strains belonging to three genera in two families. Again, some uncertainty in identification is to be noted, deriving from the absence of adequate support by sequencing of valid DNA markers, and by the provisional ascription to *Penicillium* sp. of some strains prior to the formal separation of the biverticillate *Penicillium* species and their assignment to the genus *Talaromyces* [55]. In this respect, the identification of strain IFM53375 as *Penicillium simplicissimum* was considered unreliable by leading taxonomists of these fungi based on a secondary metabolite profile more respondent to *Talaromyces* [55]. In another case, the producing strain (AF1-2) was not identified at all [26]; however, the image provided by the authors showing its bright yellow mycelium and the overlying green sporulation in culture on agar medium unequivocally allows its ascription to *Talaromyces*. In any case, species in the genus *Talaromyces* are the most typical producers of funicone-like compounds; with reference to the recent affirmation of the horizontal gene transfer concept [56,57], it cannot be excluded that the other fungal species may have occasionally acquired their funicone-biosynthetic abilities through this intriguing biological mechanism.

**Table 2.** Fungal species/strains reported as producers of funicone-like compounds.

| Species | Source/Lifestyle/Substrate | Location | Compounds | Ref. |
|---------|----------------------------|----------|-----------|------|
| **Dothideomycetes, Pleosporales, Didymellaceae** | | | | |
| *Phoma* sp. nov. LG0217 | Endophytic in *Parkinsonia microphylla* | Tucson (Arizona, USA) | 15, 18 | [36] |
| **Dothideomycetes, Botryosphaeriales, Phyllostictaceae** | | | | |
| *Guignardia* sp. No. 4382 | Endophytic in *Kandelia candel* | Hong Kong (China) | 17 | [49] |
| **Dothideomycetes, Mycosphaerellales, Mycosphaerellaceae** | | | | |
| *Pseudocercospora* (=*Mycosphaerella*) *fijiensis* | Banana plant | Honduras | 15 | [30] |
| **Dothideomycetes, Capnodiales, Dissoconaceae** | | | | |
| *Ramichloridium apiculatum* NHL2956 | Air in bakery | Nagoya (Japan) | 11 | [27] |
| **Dothideomycetes, Cladosporiales, Cladosporiaceae** | | | | |
| *Cladosporium* sp. JS1-2 | endophytic in *Ceriops tagal* | Hainan (China) | 15 | [35] |
| **Eurotiomycetes, Eurotiales, Aspergillaceae** | | | | |
| *Aspergillus neoglaber* (identified as *Neosartorya glabra*) CGMCC 32286 | Unknown | China | 24 | [40] |
| *Aspergillus ruber* (identified as *Eurotium rubrum*) SH-823 | Soft coral (*Sarcophyton* sp.) | Xuwen (China) | 15, 23 | [42] |
| *Penicillium citreonigrum* PAI 1/1 C | Sponge (*Pseudoceratina purpurea*) | Bali (Indonesia) | 3, 15, 18 | [12] |
| *Penicillium glabrum* SF-7123 | Sediment | Ross Sea (Antarctica) | 3 | [13] |
Table 2. Cont.

| Species                     | Source/Lifestyle/Substrate          | Location               | Compounds              | Ref.  |
|-----------------------------|-------------------------------------|------------------------|------------------------|-------|
| *Penicillium simplicissimum*| IFM53375 Unknown                    | Japan                  | 1, 15, 16, 18, 20, 25 | [6]   |
| *Penicillium sp.*           | Endophytic in *Riccardia multifida*| Maoer Mountain (China) | 8, 17, 1              | [8]   |
| *Penicillium sp.*           | Unknown                             | Japan                  | 3                      | [10]  |
| *Penicillium sp.*           | Unknown                             | Japan                  | 9                      | [16]  |
| *Penicillium sp.*           | Ash                                 | Mount Pinotubo (Philippines) | 3              | [11]  |

*Eurotiomycetes, Eurotiales, Trichoconaeae*

| Species                     | Source/Lifestyle/Substrate          | Location               | Compounds              | Ref.  |
|-----------------------------|-------------------------------------|------------------------|------------------------|-------|
| *Talaromyces flavus*        |                                     |                        | 15                     | [29]  |
| *Talaromyces flavus*        | CCM-F748                            | Slovakia               | 15                     | [47]  |
| *Talaromyces flavus*        | FKI-0076 Soil                       | Hiroo (Japan)          | 2, 3, 15               | [9]   |
| *Talaromyces flavus*        | IFM52668 Unknown                    | Japan                  | 1, 4, 15               | [4]   |
| *Talaromyces pinophilus*    | F36CF Endophytic in *Arbutus unedo* | Favignana Isle (Italy) | 10                     | [58]  |
| *Talaromyces pinophilus*    | H608 Mangrove sediment              | Xiamen (China)         | 1, 3, 10, 15, 21, 23   | [7]   |
| *Talaromyces sp.* IPV2      | Apple root                          | Sondrio Province (Italy)| 1                      | [2,59]|
| *Talaromyces pinophilus*    | LT4, LT6 Soil from rhizosphere of *Nicotiana tabacum* | Lecce Province (Italy) | 7, 10                  | [15,19]|
| *Talaromyces pinophilus*    | SCAU037 Soil from rhizosphere of *Rhizophora stylosa* | Teccheng Isle (China) | 10, 12, 13, 15, 17, 18, 19, 21, 22, 23, 25, 26, 28, 29, 32, 33 | [28] |
| *Talaromyces pinophilus*    | ST2 Soil from rhizosphere of *Nicotiana tabacum* | Scafati (Italy)        | 10                     | [25]  |
| *Talaromyces purpureogenus* | MHZ 111 Soil                        | Mohe (China)           | 15, 18                 | [46]  |
| *Talaromyces ruber*         | (identified as *Penicillium rubrum*)| Water                  | Berkeley Pit lake (USA) | 15, 18, 25 | [45] |
| *Talaromyces sp.* ZHS32     | Marine sediment                     | Zhejiang (China)       | 15                     | [39]  |
| *Talaromyces sp.* AF1-2     | (unidentified in original report)   | Salt pan               | Australia              | 10     | [26]  |
| *Talaromyces sp.* HM6-1-1   | Seawater                            | Dongshan Isle (China)  | 15, 18                 | [38]  |
| *Talaromyces sp.* HN29-3B1   | Endophytic in *Cerbera manghas*     | Hainan (China)          | 15, 17, 19, 21, 23, 25, 26, 27 | [21] |
| *Talaromyces sp.* HSZ-43     | (identified as *Penicillium sp.*)   | Endophytic in *Trypterigium wilfordii* | Shanxi (China) | 1, 3, 10, 14 | [5]  |
Table 2. Cont.

| Species                          | Source/Lifestyle/Substrate                      | Location            | Compounds | Ref.  |
|----------------------------------|------------------------------------------------|---------------------|-----------|-------|
| **Talaromyces sp.**               | Endophytic in *Quercus variabilis*              | Zijin Mountain (China) | 30, 31, 32 | [51] |
| IFB-E022 (identified as Penicillium sp.) |                                                |                     |           |       |
| **Talaromyces sp.**               | Sponge (*Callyspongia* sp.)                     | Xuwen County (China) | 15, 18    | [41] |
| XWS02F62 (identified as Penicillium sp.) |                                               |                     |           |       |
| **Talaromyces thailandiatis**     | Soil                                           | Thailand            | 15, 20, 25 | [33] |
| KPFC 3399                        |                                                |                     |           |       |
| **Talaromyces verruculosus**      | Unknown                                        | Pakistan            | 15        | [31] |
| CMI294548                        |                                                |                     |           |       |

Recently, some independent studies have reported that production of funicone-like compounds may occur in co-cultures of various microbial strains (Table 3). Again, the Eurotiomycetes are more represented in these few studies, and can be thought to provide the genetic base for biosynthesis, which is eventually stimulated by the co-cultured strain in the course of an antibiotic struggle, as clearly demonstrated in the case of the pairing between *Talaromyces siamensis* and *Phomopsis* sp. (Sordariomycetes, Diaporthaceae) [43]. In two cases, the partner microbe was represented by *Streptomyces* strains (Actinomycetota), which are well-known for their capacity to modulate the metabolic potential of fungi [60].

Table 3. Microbial species/strains reported as producers of funicone-like compounds in co-cultures.

| Species 1                  | Species 2                  | Source/Substrate                  | Location                        | Compounds   | Ref.  |
|----------------------------|----------------------------|-----------------------------------|---------------------------------|-------------|-------|
| *Alternaria alternata* YX-25| *Streptomyces exfoliatus* YX-32| mangrove mud                      | Yunxiao (China)                | 15          | [37] |
| *Penicillium* sp. WC-29-5| *Streptomyces fradiae* 007| rhizosphere of *Aegiceras corniculatum* / sediment | Hainan (China) / Jiaozhou Bay (China) | 3, 5, 6, 15 | [14] |
| *Talaromyces pinophilus* 17F4103| *Paraphaeosphaeria* sp. 17F4110| soil                             | Miyazaki (Japan)               | 10, 14, 32, 33, 34 | [18] |
| *Talaromyces siamensis* FKA-61| *Phomopsis* sp. FKA-62| soil                             | Japan                           | 15          | [43] |

4. Biosynthesis

The potential biosynthetic pathways of funicone-like compounds have been investigated by two independent research groups [21,28]. Figure 6 shows a possible scheme for each type of compound proposed in the previous section. Funicone-like compounds are epta and octaketides, originating from units of acetate-mevalonate. The main structural differences can be caused by the folding of the eptaketidic and octaketidic chains, which produce structures with a methyl or a propenyl group, respectively, on the γ-pyrone ring. The presence of an amino group in compounds belonging to the pyridone type suggests a possible transamination process during the biosynthesis of γ-pyridone. The origin of the phthalide type can be attributed to the lactonization of the carboxylic group in the α-resorcylic ring, with the hydroxyl group produced through the reduction of the exocyclic ketone group.

Subsequent functional modifications (e.g., reduction, epoxidation, hydroxylation, methylation, and acetylation) are responsible for the ample structural variability observed in the group of funicone-like compounds.
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5. Bioactivities

As previously introduced, the biological activity of funicones was initially evaluated with reference to antibiotic properties, generally evidencing poor effects against bacteria and yeasts, and more relevant activities against filamentous fungi. Subsequent investigations on antiproliferative properties against human cells line have become prevalent, underlining the potential of these compounds as antitumor drugs. Additional data have been gathered on the antiviral and the insecticidal properties, and the inhibitory effects toward several enzymes; moreover, some minor bioactivities have been described. The outcomes of this wide-ranging investigational work, as assessed in quantitative terms, are summarized in Table 4.

Table 4. Main bioactivities of funicone-like compounds.

| Name (Code)                  | Bioactivity                      | Concentration | Bioassay                | Ref.     |
|------------------------------|----------------------------------|---------------|-------------------------|----------|
| Actofunicone (2)             | Reinforcement of miconazole       | 3.7 µM        | Candida albicans (IC₅₀) | [9]      |
| 6-Demethylpenisimplicissin (26) | Enzyme inhibitory               | 9.5 µM        | α-glucosidase (IC₅₀)    | [21]     |
| Deoxyfunicone (3)            | Anticholesterol                  | 10 µM         | Efflux from RAW264.7    | [7]      |
|                              | Cytotoxic                        | 22.6 µM       | KB (IC₅₀)               | [5]      |
|                              | Enzyme inhibitory                | 24.3 µM       | Protein tyrosine phosphate 1B (IC₅₀) | [13]     |
|                              |                                  | 1.1–4.4 µM    | HIV-1-integrase (IC₅₀)  | [11]     |

Figure 6. Proposed biosynthetic schemes of funicone-like compounds.
Table 4. Cont.

| Name (Code) | Bioactivity          | Concentration | Bioassay                                      | Ref.     |
|-------------|----------------------|---------------|-----------------------------------------------|----------|
| Lipid inhibitory | 10 µM                | Accumulation in HepG2 | Downregulation of FAS, ACC, HMGR | [7]      |
|             |                      |               | Decrease in oxLDL in RAW264.7 |          |
| NO inhibitory | 10.6 µM, 40.1 µM | LPS-stimulated BV2 (IC_{50}) | LPS-stimulated RAW264.7 (IC_{50}) | [13]     |
| PGE_{2} inhibitory | 32.3 µM          | LPS-stimulated BV2 (IC_{50}) |   | [13]     |
| Reinforcement of miconazole | 1.6 µM          | C. albicans (IC_{50}) |   | [9]      |
| 2’-epiHydroxydihydrovermistatin (19) | Enzyme inhibitory | 8 µM | α-glucosidase (IC_{50}) | [21]     |
| 9,14-Epoxy-11-deoxyfunicone (4) | Antifungal | 0.53 µmol/disc | Aspergillus niger | [4]      |
| 9R,14S-Epoxy-11-deoxyfunicone (5) | Cytotoxic | 3.97 µM | H1975 (IC_{50}) | [14]     |
| 9S,14R-Epoxy-11-deoxyfunicone (6) | Cytotoxic | 3.73 µM, 5.73 µM | H1975 (IC_{50}) | [14]     |
| Funicone (1) |                     |               |                                               |          |
| Anticholesterol | 10 µM                | Efflux from RAW264.7 |   | [7]      |
| Antifungal | 0.27 µmol/disc | Aspergillus fumigatus | | [4]      |
| Cytotoxic | 13.2 µM            | KB (IC_{50}) |   | [5]      |
| Lipid inhibitory | 10 µM                | Accumulation in HepG2 | Downregulation of FAS, ACC, HMGR | [7]      |
| Isofunicone (9) | Pollen growth inhibitory | 8.02 mM | Camellia sinensis (84%) | [16]     |
| Hydroxyvermistatin (21) |                   |               |                                               |          |
| Anticholesterol | 10 µM                | Decrease scavenger receptors CD36, SR-1 |   | [7]      |
| Enzyme inhibitory | 20.3 µM          | α-glucosidase (IC_{50}) |   | [21]     |
| Lipid inhibitory | 10 µM                | Accumulation in HepG2 | Decrease in FAS, ACC, HMGR | [7]      |
| Methoxyvermistatin (23) |                   |               | Decrease in oxLDL in RAW264.7 | [7]      |
| Anticholesterol | 10 µM                | Decrease scavenger receptors CD36, SR-1 |   | [7]      |
| Cytotoxic | 0.036 mM, 0.042 mM | KB (IC_{50}), KBv200 (IC_{50}) |   | [34]     |
| Enzymatic inhibitory | 236 µM          | α-glucosidase (IC_{50}) |   | [42]     |
| Lipid inhibitory | 10 µM                | Decrease in oxLDL in RAW264.7 |   | [7]      |
| Anticholesterol | 10 µM                | Efflux from RAW264.7 |   | [7]      |
| 3-O-Methylfunicone (10) |                   |               |                                               |          |
| Antiviral | 5 µM                 | Decreased mortality of MDBK infected by BoHV-1 |   | [62]     |
|          | 6.2 µM              | HCV (IC_{50} on Huh-7.5.1) |   | [61]     |
| Cytotoxic/antiproliferative/ proapoptotic | 35.3 µM, 10 µM, 63.8 µM, 63.3 µM | KB (IC_{50}), MDBK (IC_{50}), HCT116 (LD_{50}), HeLa (LD_{50}) | HeLa (IC_{50}) | [24]     |
|          | 0.16 mM             | HEp-2; inhibition colony formation, decrease neutral red uptake, inhibition O_{2} consumption (IC_{50}) |   | [24]     |
|          | 0.07 mM             | HeLa (44%); promotion p21; downregulation cyclin D1/Cdk4 complex |   | [63]     |
Table 4. Cont.

| Name (Code)     | Bioactivity | Concentration | Bioassay                                                                 | Ref.                  |
|-----------------|-------------|---------------|--------------------------------------------------------------------------|-----------------------|
| Penicidone A (30) | Cytotoxic    | 60.1 µM       | SW116 (IC₅₀)                                                             | [51]                  |
|                 |             | 54.0 µM       | K562 (IC₅₀)                                                              |                       |
| Penicidone B (31) | Cytotoxic    | 54.2 µM       | SW116 (IC₅₀)                                                             | [51]                  |
|                 |             | 21.1 µM       | K562 (IC₅₀)                                                              |                       |
| Penicidone C (32) | Cytotoxic    | 80.8 µM       | SW116 (IC₅₀)                                                             | [51]                  |
|                 |             | 54.3 µM       | K562 (IC₅₀)                                                              |                       |
|                 |             | 44.3 µM       | KB (IC₅₀)                                                                |                       |
| Penifupyrone (14)       | Cytotoxic    | 4.7 µM        | KB (IC₅₀)                                                                | [5]                   |
| Penisimplicissin (25)     | Cytotoxic    | −6.70         | CCRF-CEM (log₁₀ GI₅₀)                                                    | [45]                  |
|                 |             | −5.83         | HL-60 (log₁₀ GI₅₀)                                                       |                       |
| Rapicone (11)       | Enzyme inhibitory | 0.66 mM       | IL-1β (IC₁₀₀)                                                            | [44]                  |
|                 |             | 0.33 mM       | caspase 1 (IC₁₀₀)                                                        |                       |
| Vermistatin (15)     | Antibacterial | 0.076 mM      | Staphylococcus aureus, Bacillus cereus (MIC)                             | [35]                  |
| Anticholesterol     | 10 µM       | Efflux from RAW264.7 | Decrease scavenger receptors CD36, SR-1                                   | [7]                   |
|                 | Cytotoxic    | 0.28 mM       | KB (IC₅₀)                                                                | [34]                  |
|                 |             | 33.9 µM       | B16 (IC₅₀)                                                               | [39]                  |
|                 | Enzyme inhibitory | 29.2 µM | α-glucosidase (IC₅₀)                                                      | [21]                  |
|                 |             | 107.1 µM      | α-glucosidase (IC₅₀)                                                     | [42]                  |
|                 | Insecticidal | 0.46 mM       | Helicoverpa armigera (IC₅₀)                                              | [35]                  |
|                 | Lipid inhibitory | 10 µM | Decrease in oxLDL in RAW264.7                                             | [7]                   |
|                 |             | 0.21 mM       | A375M (IC₅₀, 48 h)                                                       | [66]                  |
|                 | Enzyme Inhibitory | 12.5 µM | DNA polymerase α                                                         | [26]                  |
|                 |             | 50.1 µM       | DNA polymerase η                                                         |                       |
|                 |             | 34.3 µM       | DNA polymerase ι                                                         |                       |
|                 | Insecticidal | 0.14 mM       | Acyrthosiphon pisum (26.2%)                                              | [23]                  |
|                 | Lipid inhibitory | 10 µM | Decrease in FAS, ACC, HMGR                                                |                       |
|                 |             | 0.21 mM       | MCF-7; downregulates αvβ5 integrin, MMP-9 inhibitor, impairs microtubule assemblage, inhibitor of survivin, hTERT and Nanog-1 expression, reduces mammospheres | [64,65] |
|                 |             | 0.14 mM       | NCI-H2452; decreases αvβ5 integrin, MMP-2, VEGF, ERK1/2; synergism with cisplatin | [67,68] |
|                 | Enzyme inhibitory | 5 mM | DNA polymerase α and η                                                   | [52]                  |
|                 | Lipid inhibitory | 10 µM | Decrease in FAS, ACC, HMGR                                                |                       |
|                 |             | 33.9 µM       | B16 (IC₅₀)                                                               |                       |
|                 | Lipid inhibitory | 0.46 mM       | Helicoverpa armigera (IC₅₀)                                              | [35]                  |
|                 | Lipid inhibitory | 10 µM | Decrease in oxLDL in RAW264.7                                             | [7]                   |
|                 | Lipid inhibitory | 52.7 µM       | LPS-stimulated BV2 (IC₅₀)                                                | [46]                  |
|                 | Lipid inhibitory | 3.1-6.1 mM | Banana leaves                                                             | [30]                  |
| Reinforcement of miconazole | 2.1 µM | C. albicans (IC₅₀)                                                      | [9]                   |
6. Potential Role of Funicone-like Compounds as Mycotoxins

The applicative aspects of studies concerning fungal bioactive secondary metabolites involve their accumulation in food products and ensuing possible impact on consumers’ health. Within the multitude of such compounds described so far, a very small number have been considered mycotoxins, based on the results of toxicological studies that noted their noxious effects on humans and animals [69]. This implies that a high number of compounds yet to be examined for these aspects may represent a potentially underestimated concern [70,71].

Funicones are one of the classes of fungal secondary metabolites for which very limited assessments have been carried out in this regard so far. Most of the producing species are not established pathogens of crops, with the exception of Pseudocercospora (=Mycosphaerella) fijiensis, a vermistatin producer that is known as the agent of black sigatoka disease of banana [72]. However, this is a leaf pathogen that is not known to spread to fruit, implying that it is unlikely that bananas can be contaminated with vermistatin. Nevertheless, a search for this compound in some fruit products carried out in Nigeria evidenced its presence at low levels (0.30 µg kg⁻¹) in pineapple and mixed juices [73]. This is not at all surprising, as several Talaromyces spp. are commonly found in association with both healthy and diseased pineapples, including T. purpureogenus, T. funiculosus, and T. flavus, which may even survive pasteurization [74–77]. Conversely, a preliminary search carried out in Italy on marketed pineapple juices yielded negative results with reference to the eventual presence of 3-O-methylfunicone [78]. Recently, vermistatin was also detected in the analysis of grains used as cattle and poultry feed in Kenya [79], indicating that it may also occur as a cereal contaminant. Moreover, the finding of vermistatin as a product in co-cultures of strains of Alternaria alternata and Streptomyces exfoliatus [37] deserves to be further investigated, particularly in view of verifying the biosynthetic capacities by the first species. It is known as a pathogen of many crops and a saprophyte able to proliferate in several kinds of foodstuffs, with very important implications as a mycotoxin producer [80].

Considering the widespread endophytic occurrence of Talaromyces spp. [23,81], which are the dominant producers of funicones, the possible release of these compounds in plant products may arise during the postharvest phase, where the biosynthetic aptitudes can be boosted along with the saprophytic development. Recent reports of these fungi as postharvest pathogens concern T. albobiverticillius on pomegranate [82], T. rugulosus on grapes [83], T. minilotus on onion bulbs and quince, orange, and tomato fruit [84], and both of the latter two species on pears [85]. Although none of these species are known to produce funicones, it is quite possible that other Talaromyces spp. producers of these compounds may affect fruit and other crop products, likewise documented for pineapple. This conclusion is supported by the finding of T. funiculosus as an agent of fruit core rot of peach [86].

Among the other funicone sources, Ramichloridium apiculatum, generally recorded as a soil saprophyte and only known as a producer of rapicone [27], was reported as an agent of sooty blotch and flyspeck of apples and pears in China [87], which may represent an indication for possible contamination of these fruits and their derived transformation products.

7. Conclusions

The present review provides an update on the recent developments concerning the distribution, chemical diversity, bioactivity and implications of occurrence of funicone-like compounds. The structures and properties of 34 funicone-like compounds extracted from different fungal species were reviewed. In particular, species in the genus Talaromyces seem to be the most typical producers of this group of secondary metabolites, soliciting consideration in view of possible chemotaxonomic implications.

In addition to outlining the general anti-inflammatory, antifungal, antiviral, and cytotoxic activities of these compounds, the available data indicate vermistatin as the most credited candidate to be added to the list of mycotoxins currently considered as food contaminants, with reference to its more common occurrence amongst the known funicone
produces. The majority of these taxonomically heterogeneous fungi can perform its biosynthesis, implying that its presence in crop products may be more than just occasional. Whether this represents a threat or, conversely, can eventually be beneficial to consumers’ health based on the described bioactivities, deserves thorough further assessments.

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