toxins

MDPI

Review

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

Maria Michela Salvatore [1,2], Marina DellaGreca [1], Anna Andolfi [1,3,*] and Rosario Nicoletti [4,5]

[1] Department of Chemical Sciences, University of Naples Federico II, 80126 Naples, Italy; mariamichela.salvatore@unina.it (M.M.S.); dellagre@unina.it (M.DG.)
[2] Institute for Sustainable Plant Protection, National Research Council, 80055 Portici, Italy
[3] BAT Center—Interuniversity Center for Studies on Bioinspired Agro-Environmental Technology, University of Naples Federico II, 80055 Portici, Italy
[4] Department of Agricultural Sciences, University of Naples Federico II, 80055 Portici, Italy; rosario.nicoletti@crea.gov.it
[5] Council for Agricultural Research and Economics, Research Center for Olive, Fruit, and Citrus Crops, 81100 Caserta, Italy
* Correspondence: andolfi@unina.it; Tel.: +39-081-2539179

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-pyrone 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.

check for updates

Citation: Salvatore, M.M.; DellaGreca, M.; Andolfi, A.; Nicoletti, R. New Insights into Chemical and Biological Properties of Funicone-like Compounds. *Toxins* **2022**, *14*, 466. https://doi.org/10.3390/toxins14070466

Received: 10 June 2022
Accepted: 4 July 2022
Published: 8 July 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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 interrelations 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-pyrone 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	Nominal Mass (U)	Source
		True Funicones		
1	Funicone	$C_{19}H_{18}O_8$	374	[2–8]
2	Actofunicone	$C_{21}H_{22}O_9$	418	[9]
3	Deoxyfunicone	$C_{19}H_{18}O_7$	358	[5,7,9–14]
4	9,14-Epoxy-11-deoxyfunicone	$C_{19}H_{18}O_8$	374	[4]
5	9*R*,14*S*-Epoxy-11-deoxyfunicone	$C_{19}H_{18}O_8$	374	[14]
6	9*S*,14*R*-Epoxy-11-deoxyfunicone	$C_{19}H_{18}O_8$	374	[14]
7	3-*O*-Methyl-5,6-epoxyfunicone	$C_{20}H_{20}O_9$	404	[15]
8	6-Hydroxyl-deoxyfunicone	$C_{19}H_{18}O_8$	374	[8]
9	Isofunicone	$C_{19}H_{18}O_8$	374	[16]
10	3-*O*-Methylfunicone	$C_{20}H_{20}O_8$	388	[5,7,17–26]
11	Rapicone	$C_{17}H_{16}O_7$	332	[27]
12	Pinophilone A	$C_{19}H_{18}O_8$	374	[28]
13	Pinophilone B	$C_{19}H_{18}O_8$	374	[28]
		Furopyrone type		
14	Penifupyrone	$C_{19}H_{18}O_8$	374	[5,17,18]
		Phthalide type		
15	Vermistatin (=fijiensin)	$C_{18}H_{16}O_6$	328	[3,4,6,7,9,12,20,21,28–48]
16	Acetoxydihydrovermistatin	$C_{20}H_{20}O_8$	388	[6,33]
17	6-Demethylvermistatin	$C_{17}H_{14}O_6$	314	[8,21,28,40,49]
18	14,15-Dihydrovermistatin	$C_{18}H_{18}O_6$	330	[6,8,12,28,33,36,38,41,44–46]
19	2″-epihydroxydihydrovermistatin	$C_{18}H_{18}O_7$	346	[21,28]
20	Hydroxydihydrovermistatin	$C_{18}H_{18}O_7$	346	[6,33]
21	Hydroxyvermistatin	$C_{18}H_{16}O_7$	344	[7,21,28,34]
22	5′-*O*-methyldihydrovermistatin	$C_{19}H_{20}O_7$	360	[28]
23	Methoxyvermistatin	$C_{19}H_{18}O_7$	358	[6,7,21,28,34,40,42,50]
24	Neosarphenol A	$C_{18}H_{16}O_6$	344	[40]
25	Penisimplicissin	$C_{16}H_{14}O_6$	302	[3,6,20,21,28,33,44,45]
26	6-Demethylpenisimplicissin	$C_{15}H_{12}O_6$	288	[21,28]
27	5′-Hydroxypenisimplicissin	$C_{16}H_{14}O_7$	318	[21]
28	Pinophilone C	$C_{17}H_{16}O_6$	316	[28]
29	Pinophilone D	$C_{18}H_{18}O_7$	346	[28]
		Pyridone type		
30	Penicidone A	$C_{18}H_{17}NO_5$	327	[51]
31	Penicidone B	$C_{17}H_{15}NO_5$	313	[51]
32	Penicidone C	$C_{19}H_{19}NO_6$	357	[18,21,28,51]
33	Penicidone D	$C_{20}H_{21}NO_7$	387	[17,18,28]
34	Talarodone A	$C_{20}H_{23}NO_8$	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 γ-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 γ-pyrone ring and the double bond on the propenyl chain [28].

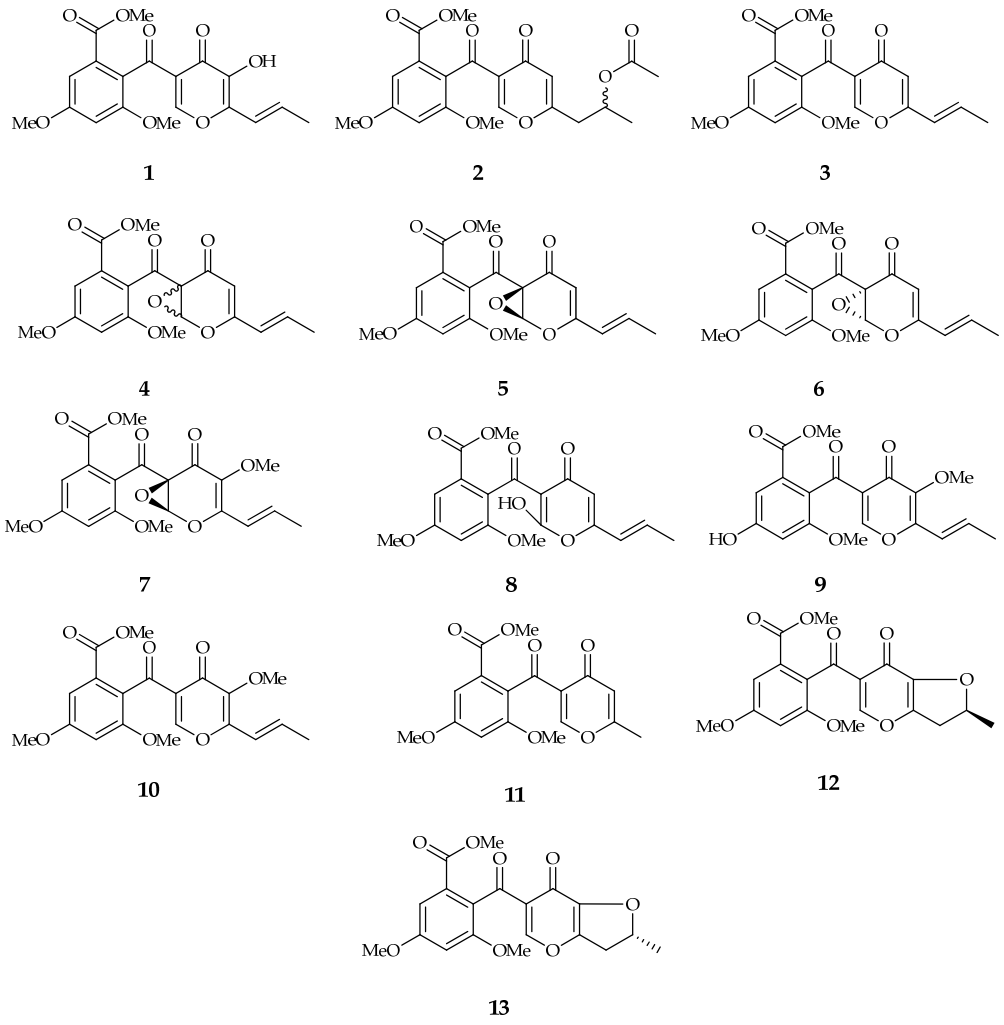


Figure 1. Structures of true funicones (**1**–**13**): funicone, actofunicone, deoxyfunicone, 9,14-epoxy-11-deoxyfunicone, 9*R*,14*S*-epoxy-11-deoxyfunicone, 9*S*,14*R*-epoxy-11-deoxyfunicone, 3-*O*-methyl-5,6-epoxyfunicone, 6-hydroxyl-deoxyfunicone, isofunicone, 3-*O*-methylfunicone, rapicone, pinophilone A, and pinophilone B.

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 γ-pyrone (Figure 2). 5-Stannane derivatives were prepared starting from commercially available kojic acid in four steps [52,53].

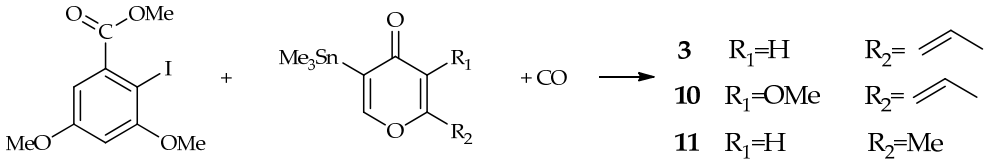
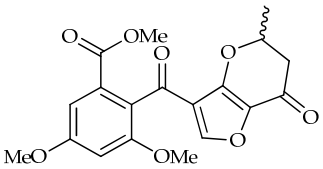


Figure 2. General procedures for synthesis of funicones.

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].



14

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 vermiculatum* [47]. This metabolite was later isolated as a product of *Pseudocercospora* (=*Mycosphaerella*) *fijiensis* and wrongly reported as a new compound with the name fijiensin [30]. 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.

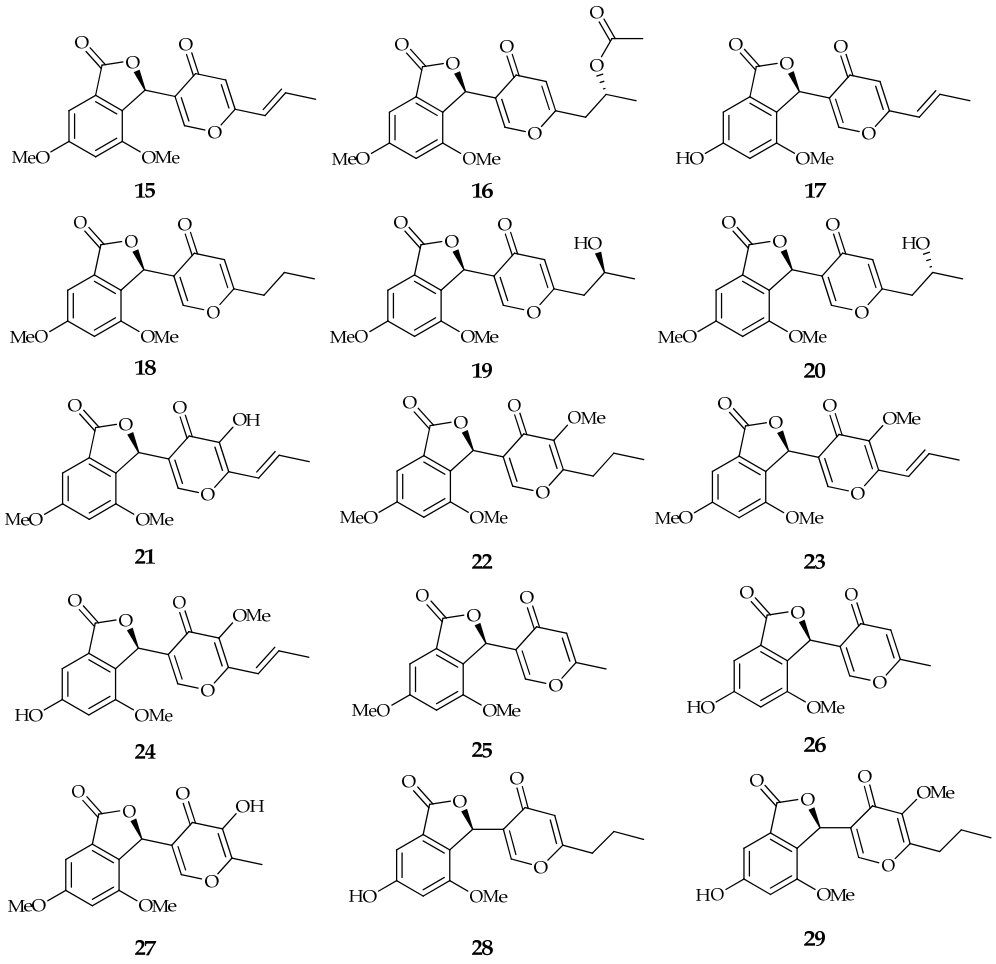


Figure 4. Structures of compounds from the phthalide type (**15**–**29**): vermistatin, acetoxydihydrovermistatin, 6-demethylvermistatin, 14,15-dihydrovermistatin, 2″-epihydroxydihydrovermistatin, hydroxydihydrovermistatin, hydroxyvermistatin, 5′-*O*-methyldihydrovermistatin, methoxyvermistatin, neosarphenol A, penisimplicissin, 6-demethylpenisimplicissin, 5′-hydroxypenisimplicissin, pinophilone C, and pinophilone D.

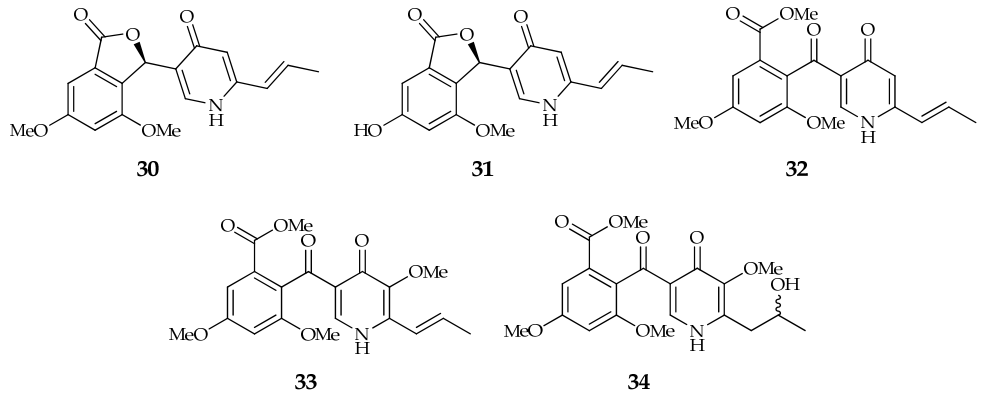


Figure 5. Structures of compounds from the pyridone type (**30**–**34**): penicidone A–D and talarodone A.

3. Fungal Sources

The data summarized in Table 2 show that the fungi reported as funicone producers 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, Trichocomaceae				
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 (identified as *Penicillium funiculosum*)	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*	Techeng 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 (identified as *Penicillium* sp.)	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. IFB-E022 (identified as *Penicillium* sp.)	Endophytic in *Quercus variabilis*	Zijin Mountain (China)	**30, 31, 32**	[51]
Talaromyces sp. XWS02F62 (identified as *Penicillium* sp.)	Sponge (*Callyspongia* sp.)	Xuwen County (China)	**15, 18**	[41]
Talaromyces thailandiasis KPFC 3399	Soil	Thailand	**15, 20, 25**	[33]
Talaromyces verruculosus CMI294548	Unknown	Pakistan	**15**	[31]

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, epoxydation, hydroxylation, methylation, and acetylation) are responsible for the ample structural variability observed in the group of funicone-like compounds.

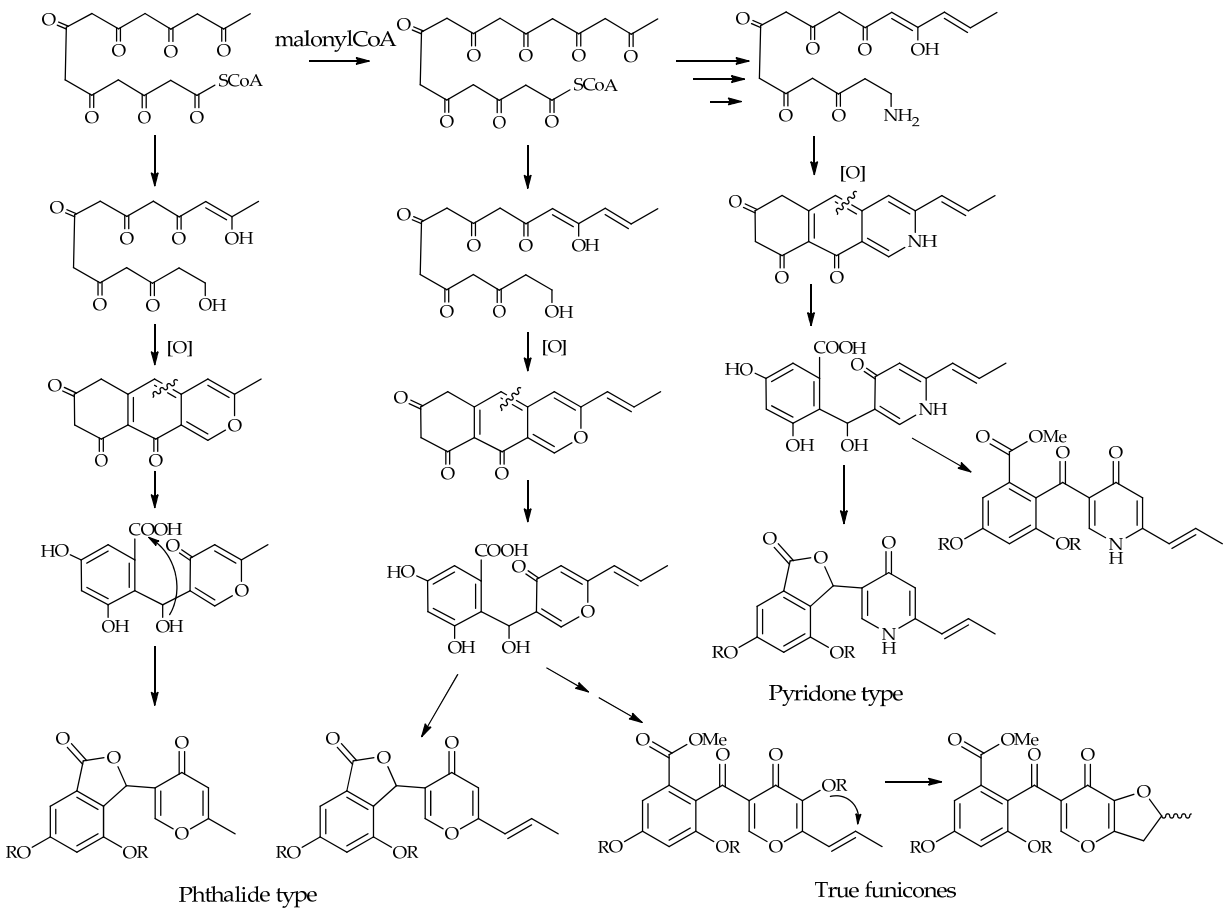


Figure 6. Proposed biosynthetic schemes of funicone-like compounds.

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* (IC_{50})	[9]
6-Demethylpenisimplicissin (**26**)	Enzyme inhibitory	9.5 μM	α-glucosidase (IC_{50})	[21]
Deoxyfunicone (**3**)	Anticholesterol	10 μM	Efflux from RAW264.7	[7]
	Antiviral	4.6 μM	HCV (IC_{50} on Huh-7.5.1)	[61]
	Cytotoxic	22.6 μM	KB (IC_{50})	[5]
	Enzyme inhibitory	24.3 μM	Protein tyrosine phosphate 1B (IC_{50})	[13]
		1.1–4.4 μM	HIV-1-integrase (IC_{50})	[11]

Table 4. *Cont.*

Name (Code)	Bioactivity	Concentration	Bioassay	Ref.
	Lipid inhibitory	10 μM	Accumulation in HepG2	[7]
			Downregulation of FAS, ACC, HMGR	
			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]
9*R*,14*S*-Epoxy-11-deoxyfunicone (**5**)	Cytotoxic	3.97 μM	H1975 (IC_{50})	[14]
9*S*,14*R*-Epoxy-11-deoxyfunicone (**6**)	Cytotoxic	3.73 μM 5.73 μM	HL-60 (IC_{50}) 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	[7]
			Downregulation of FAS, ACC, HMGR	
Isofunicone (**9**)	Pollen growth inhibitory	8.02 mM	*Camellia sinensis* (84%)	[16]
Hydroxyvermistatin (**21**)	Anticholesterol	10 μM	Efflux from RAW264.7	[7]
			Upregulation of PPARγ, LXRα, ABCG1	
			Decrease scavenger receptors CD36, SR-1	
	Enzyme inhibitory	20.3 μM	α-glucosidase (IC_{50})	[21]
	Lipid inhibitory	10 μM	Accumulation in HepG2	[7]
			Decrease in FAS, ACC, HMGR	
			Decrease in oxLDL in RAW264.7	
Methoxyvermistatin (**23**)	Anticholesterol	10 μM	Decrease scavenger receptors CD36, SR-1	[7]
	Cytotoxic	0.056 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]
3-*O*-Methylfunicone (**10**)	Anticholesterol	10 μM	Efflux from RAW264.7	[7]
	Antifungal	0.27 mM	*Rhizoctonia solani*, *Fusarium solani*, *Cylindrocladium scoparium*, *Alternaria alternata* (IC_{100})	[19]
	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	KB (IC_{50})	[5]
		10 μM	MDBK (IC_{50})	[62]
		63.8 μM 63.3 μM	HCT116 (LD_{50}) HeLa (LD_{50})	[26]
		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.
		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]
		0.21 mM	A375M (IC_{85}, 48 h)	[66]
		0.14 mM	NCI-H2452; decreases αvβ5 integrin, MMP-2, VEGF, ERK1/2; synergism with cisplatin	[67,68]
	Enzyme Inhibitory	12.5 µM 50.1 µM 34.3 µM	DNA polymerase κ DNA polymerase η DNA polymerase ι	[26]
		5 mM	DNA polymerase κ and η	[52]
	Insecticidal	0.14 mM	*Acyrthosiphon pisum* (26.2%)	[23]
	Lipid inhibitory	10 µM	Accumulation in HepG2 Decrease in FAS, ACC, HMGR Decrease in oxLDL in RAW264.7	[7]
Penicidone A (**30**)	Cytotoxic	60.1 µM 54 µM 46.5 µM 41.5 µM	SW116 (IC_{50}) K562 (IC_{50}) KB (IC_{50}) HeLa (IC_{50})	[51]
Penicidone B (**31**)	Cytotoxic	54.2 µM 21.1 µM 29.6 µM 35.1 µM	SW116 (IC_{50}) K562 (IC_{50}) KB (IC_{50}) HeLa (IC_{50})	[51]
Penicidone C (**32**)	Cytotoxic	80.8 µM 54.3 µM 44.3 µM 54.7 µM	SW116 (IC_{50}) K562 (IC_{50}) KB (IC_{50}) HeLa (IC_{50})	[51]
	Enzyme inhibitory	51.9 µM	α-glucosidase (IC_{50})	[28]
Penifupyrone (**14**)	Cytotoxic	4.7 µM	KB (IC_{50})	[5]
Penisimplicissin (**25**)	Cytotoxic	−6.70 −5.83	CCRF-CEM ($\log_{10}$ GI_{50}) HL-60 ($\log_{10}$ GI_{50})	[45]
	Enzyme inhibitory	0.66 mM 0.33 mM	IL-1β (IC_{100}) caspase 1 (IC_{100})	[44]
Rapicone (**11**)	Enzyme inhibitory	5 mM	DNA polymerase κ	[52]
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 (IC_{50})	[34]
		33.9 µM	B16 (IC_{50})	[39]
	Enzyme inhibitory	29.2 µM	α-glucosidase (IC_{50})	[21]
		107.1 µM	α-glucosidase (IC_{50})	[42]
	Insecticidal	0.46 mM	*Helicoverpa armigera* (IC_{50})	[35]
	Lipid inhibitory	10 µM	accumulation in HepG2 Decrease in FAS, ACC, HMGR Decrease in oxLDL in RAW264.7	[7]
	NO inhibitory	52.7 µM	LPS-stimulated BV2 (IC_{50})	[46]
	Phytotoxic	3.1–6.1 mM	Banana leaves	[30]
	Reinforcement of miconazole	2.1 µM	*C. albicans* (IC_{50})	[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. minioluteus* 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

producers. 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.

Author Contributions: Conceptualization, R.N. and A.A.; writing—original draft preparation, M.M.S. and R.N.; writing—review and editing, M.M.S., M.D.G., R.N. and A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Nicoletti, R.; Manzo, E.; Ciavatta, M.L. Occurence and bioactivities of funicone-related compounds. *Int. J. Mol. Sci.* **2009**, *10*, 1430–1444. [CrossRef] [PubMed]
2. Merlini, L.; Nasini, G.; Selva, A. The structure of funicone: A new metabolite from *Penicillium funiculosum* Thom. *Tetrahedron* **1970**, *26*, 2739–2749. [CrossRef]
3. Yilmaz, N.; Visagie, C.M.; Houbraken, J.; Frisvad, J.C.; Samson, R.A. Polyphasic taxonomy of the genus *Talaromyces*. *Stud. Mycol.* **2014**, *78*, 175–341. [CrossRef] [PubMed]
4. Komai, S.; Hosoe, T.; Itabashi, T.; Nozawa, K.; Okada, K.; de Campos Takaki, G.M.; Chikamori, M.; Yaguchi, T.; Fukushima, K.; Miyaji, M.; et al. A new funicone derivative isolated from *Talaromyces flavus* IFM52668. *Mycotoxins* **2004**, *54*, 15–19. [CrossRef]
5. Chen, M.J.; Fu, Y.W.; Zhou, Q.Y. Penifupyrone, a new cytotoxic funicone derivative from the endophytic fungus *Penicillium* sp. HSZ-43. *Nat. Prod. Res.* **2014**, *28*, 1544–1548. [CrossRef]
6. Komai, S.I.; Hosoe, T.; Itabashi, T. New vermistatin derivatives isolated from *Penicillium simplicissimum*. *Heterocycles* **2005**, *65*, 2771–2776.
7. Wu, C.; Zhao, Y.; Chen, R.; Liu, D.; Liu, M.; Proksch, P.; Guo, P.; Lin, W. Phenolic metabolites from mangrove-associated *Penicillium pinophilum* fungus with lipid-lowering effects. *RSC Adv.* **2016**, *6*, 21969–21978. [CrossRef]
8. Jiao, Y.; Zhang, X.; Wang, L.; Li, G.; Zhou, J.C.; Lou, H.X. Metabolites from *Penicillium* sp.; An endophytic fungus from the liverwort *Riccardia multifida* (L.) S. Gray. *Phytochem. Lett.* **2013**, *6*, 14–17. [CrossRef]
9. Arai, M.; Tomoda, H.; Okuda, T.; Wang, H.; Tabata, N.; Masuma, R.; Yamaguchi, Y.; Omura, S. Funicone-related compounds, potentiators of antifungal miconazole activity, produced by *Talaromyces flavus* FKI-0076. *J. Antibiot.* **2002**, *55*, 172–180. [CrossRef]
10. Sassa, T.; Nukina, M.; Suzuki, Y. Deoxyfunicone, a new γ-pyrone metabolite from a resorcylide-producing fungus (*Penicillium* sp.). *Agric. Biol. Chem.* **1991**, *55*, 2415–2416.
11. Singh, S.B.; Jayasuriya, H.; Dewey, R.; Polishook, J.D.; Dombrowski, A.W.; Zink, D.L.; Guan, Z.; Collado, J.; Platas, G.; Pelaez, F.; et al. Isolation, structure, and HIV-1-integrase inhibitory activity of structurally diverse fungal metabolites. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 721–731. [PubMed]
12. Rusman, Y. *Isolation of New Secondary Metabolites from Sponge-Associated and Plant-Derived Fungi*; Heinrich-Heine-Universität-Düsseldorf: Dusseldorf, Germany, 2006.
13. Ha, T.M.; Kim, D.C.; Sohn, J.H.; Yim, J.H.; Oh, H. Anti-inflammatory and protein tyrosine phosphatase 1b inhibitory metabolites from the antarctic marine-derived fungal strain *Penicillium glabrum* SF-7123. *Mar. Drugs* **2020**, *18*, 247. [CrossRef] [PubMed]
14. Wang, Y.; Wang, L.; Zhuang, Y.; Kong, F.; Zhang, C.; Zhu, W. Phenolic polyketides from the co-cultivation of marine-derived *Penicillium* sp. WC-29-5 and *Streptomyces fradiae* 007. *Mar. Drugs* **2014**, *12*, 2079–2088. [CrossRef] [PubMed]
15. De Stefano, S.; Nicoletti, R.; Zambardino, S.; Milone, A. Structure elucidation of a novel funicone-like compound produced by *Penicillium pinophilum*. *Nat. Prod. Lett.* **2002**, *16*, 207–211. [CrossRef]
16. Kimura, Y.; Yoshinari, T.; Shimada, A.; Hamasaki, T. Isofunicone, a pollen growth inhibitor produced by the fungus, *Penicillium* sp. *Phytochemistry* **1995**, *40*, 629–631. [CrossRef]
17. Liu, Y.; Yang, Q.; Xia, G.; Huang, H.; Li, H.; Ma, L.; Lu, Y.; He, L.; Xia, X.; She, Z. Polyketides with α-glucosidase inhibitory activity from a mangrove endophytic fungus, *Penicillium* sp. HN29-3B1. *J. Nat. Prod.* **2015**, *78*, 1816–1822. [CrossRef]
18. Murakami, S.; Hayashi, N.; Inomata, T.; Kato, H.; Hitora, Y.; Tsukamoto, S. Induction of secondary metabolite production by fungal co-culture of *Talaromyces pinophilus* and *Paraphaeosphaeria* sp. *J. Nat. Med.* **2020**, *74*, 545–549. [CrossRef]
19. De Stefano, S.; Nicoletti, R.; Milone, A.; Zambardino, S. 3-*O*-Methylfunicone, a fungitoxic metabolite produced by the fungus *Penicillium pinophilum*. *Phytochemistry* **1999**, *52*, 1399–1401. [CrossRef]

20. Salvatore, M.M.; DellaGreca, M.; Nicoletti, R.; Salvatore, F.; Vinale, F.; Naviglio, D.; Andolfi, A. Talarodiolide, a new 12-membered macrodiolide, and GC/MS investigation of culture filtrate and mycelial extracts of *Talaromyces pinophilus*. *Molecules* **2018**, *23*, 950. [CrossRef]
21. Liu, Y.; Xia, G.; Li, H.; Ma, L.; Ding, B.; Lu, Y.; He, L.; Xia, X.; She, Z. Vermistatin derivatives with α -glucosidase inhibitory activity from the mangrove endophytic fungus *Penicillium* sp. HN29-3B1. *Planta Med.* **2014**, *80*, 912–917. [CrossRef]
22. Lacatena, F.; Marra, R.; Mazzei, P.; Piccolo, A.; Digilio, M.C.; Giorgini, M.; Woo, S.L.; Cavallo, P.; Lorito, M.; Vinale, F. Chlamyphilone, a novel *Pochonia chlamydosporia* metabolite with insecticidal activity. *Molecules* **2019**, *24*, 750. [CrossRef] [PubMed]
23. Vinale, F.; Nicoletti, R.; Lacatena, F.; Marra, R.; Sacco, A.; Lombardi, N.; D'Errico, G.; Digilio, M.C.; Lorito, M.; Woo, S.L. Secondary metabolites from the endophytic fungus *Talaromyces pinophilus*. *Nat. Prod. Res.* **2017**, *31*, 1778–1785. [CrossRef] [PubMed]
24. Stammati, A.; Nicoletti, R.; De Stefano, S.; Zampaglioni, F.; Zucco, F. Cytostatic properties of a novel compound derived from *Penicillium pinophilum*: An in vitro study. *Altern. Lab. Anim.* **2002**, *30*, 69–75. [CrossRef] [PubMed]
25. Nicoletti, R.; De Stefano, M.; De Stefano, S.; Trincone, A.; Marziano, F. Antagonism against *Rhizoctonia solani* and fungitoxic metabolite production by some *Penicillium* isolates. *Mycopathologia* **2004**, *158*, 465–474. [CrossRef] [PubMed]
26. Mizushina, Y.; Motoshima, H.; Yamaguchi, Y.; Takeuchi, T.; Hirano, K.; Sugawara, F.; Yoshida, H. 3-*O*-methylfunicone, a selective inhibitor of mammalian Y-family DNA polymerases from an Australian sea salt fungal strain. *Mar. Drugs* **2009**, *7*, 624–639. [CrossRef]
27. Nozawa, K.; Nakajima, S.; Kawai, K.I.; Udagawa, S.I. A γ-pyrone derivative, rapicone from *Ramichloridium apiculatum*. *Phytochemistry* **1992**, *12*, 4177–4179. [CrossRef]
28. He, F.; Li, X.; Yu, J.H.; Zhang, X.; Nong, X.; Chen, G.; Zhu, K.; Wang, Y.Y.; Bao, J.; Zhang, H. Secondary metabolites from the mangrove sediment-derived fungus *Penicillium pinophilum* SCAU037. *Fitoterapia* **2019**, *136*, 104177. [CrossRef]
29. Massias, M.; Molho, L.; Rebuffat, S.; Cesario, M.; Guilhen, J.; Pascard, C.; Bodo, B. Vermiculinol and mermiculidiol, macrodiolides from the fungus *Penicillium vermiculatum*. *Phytochemistry* **1989**, *28*, 1491–1494. [CrossRef]
30. Upadhyay, R.K.; Strobel, G.A.; Coval, S.J.; Clardy, J. Fijiensin, the first phytotoxin from *Mycosphaerella fijiensis*, the causative agent of Black Sigatoka disease. *Experientia* **1990**, *46*, 982–984. [CrossRef]
31. Murtaza, N.; Husain, S.A.; Sarfaraz, T.B.; Sultana, N.; Faizi, S. Isolation and identification of vermistatin, ergosterol, stearic acid and mannitol, metabolic products of *Penicillium verruculosum*. *Planta Med.* **1997**, *63*, 191. [CrossRef]
32. Komai, S.I.; Hosoe, T.; Itabashi, T.; Nozawa, K.; Yaguchi, T.; Fukushima, K.; Kawai, K.I. New penicillide derivatives isolated from *Penicillium simplicissimum*. *J. Nat. Med.* **2006**, *60*, 185–190. [CrossRef] [PubMed]
33. Dethoup, T.; Manoch, L.; Kijjoa, A.; Pinto, M.; Gales, L.; Damas, A.M.; Silva, A.M.S.; Eaton, G.; Herz, W. Merodrimanes and other constituents from *Talaromyces thailandiasis*. *J. Nat. Prod.* **2007**, *70*, 1200–1202. [CrossRef] [PubMed]
34. Xia, X.K.; Huang, H.R.; She, Z.G.; Cai, J.W.; Lan, L.; Zhang, J.Y.; Fu, L.W.; Vrijmoed, L.L.P.; Lin, Y.C. Structural and biological properties of vermistatin and two new vermistatin derivatives isolated from the marine-mangrove endophytic *Guignardia* sp. No. 4382. *Helv. Chim. Acta* **2007**, *90*, 1925–1931. [CrossRef]
35. Bai, M.; Zheng, C.J.; Tang, D.Q.; Zhang, F.; Wang, H.Y.; Chen, G.Y. Two new secondary metabolites from a mangrove-derived fungus *Cladosporium* sp. JS1-2. *J. Antibiot.* **2019**, *72*, 779–782. [CrossRef]
36. Gubiani, J.R.; Wijeratne, E.M.K.; Shi, T.; Araujo, A.R.; Arnold, A.E.; Chapman, E.; Gunatilaka, A.A.L. An epigenetic modifier induces production of (10′*S*)-verruculide B, an inhibitor of protein tyrosine phosphatases by *Phoma* sp. nov. LG0217, a fungal endophyte of *Parkinsonia microphylla*. *Bioorganic Med. Chem.* **2017**, *25*, 1860–1866. [CrossRef]
37. He, X.P. Secondary metabolites of co-culture of *Alternaria alternate* YX-25 and *Streptomyces exfoliatus* YX-32. *Chinese Tradit. Herb. Drugs* **2018**, *24*, 5772–5779.
38. Hong, X.; Guan, X.; Lai, Q.; Yu, D.; Chen, Z.; Fu, X.; Zhang, B. Characterization of a bioactive meroterpenoid isolated from the marine—Derived fungus *Talaromyces* sp. *Appl. Microbiol. Biotechnol.* **2022**, *106*, 2927–2935. [CrossRef]
39. Liu, G.; Huo, R.; Niu, S.; Song, F.; Liu, L. Two new cytotoxic decalin derivatives from marine-derived fungus *Talaromyces* sp. *Chem. Biodivers.* **2022**, *19*, 1–8. [CrossRef]
40. Liu, W.; Zhao, H.; Li, R.; Zheng, H.; Yu, Q. Polyketides and meroterpenoids from *Neosartorya glabra*. *Helv* **2015**, *98*, 515–519. [CrossRef]
41. Luo, X.W.; Gao, C.H.; Han, F.H.; Chen, X.Q.; Lin, X.P.; Zhou, X.F.; Wang, J.J.; Liu, Y.H. A new naphthopyranone from the sponge-associated fungus *Penicillium* sp. XWS02F62. *Magn. Reson. Chem.* **2019**, *57*, 982–986. [CrossRef]
42. Liu, Z.; Xia, G.; Chen, S.; Liu, Y.; Li, H.; She, Z. Eurothiocin a and B, sulfur-containingbenzofurans from a soft coral-derived fungus *Eurotium rubrum* SH-823. *Mar. Drugs* **2014**, *12*, 3669–3680. [CrossRef] [PubMed]
43. Nonaka, K.; Iwatsuki, M.; Horiuchi, S.; Shiomi, K.; Omura, S.; Masuma, R. Induced production of BE-31405 by co-culturing of *Talaromyces siamensis* FKA-61 with a variety of fungal strains. *J. Antibiot.* **2015**, *68*, 573–578. [CrossRef] [PubMed]
44. Stierle, A.A.; Stierle, D.B. Bioactive secondary metabolites from acid mine waste extremophiles. *Nat. Prod. Commun.* **2014**, *9*, 1037–1044. [CrossRef] [PubMed]
45. Stierle, A.A.; Stierle, D.B.; Girtsman, T. Caspase-1 inhibitors from an extremophilic fungus that target specific leukemia cell lines. *J. Nat. Prod.* **2012**, *75*, 344–350. [CrossRef]
46. Sun, J.; Zhu, Z.X.; Song, Y.L.; Ren, Y.; Dong, D.; Zheng, J.; Liu, T.; Zhao, Y.F.; Tu, P.F.; Li, J. Anti-neuroinflammatory constituents from the fungus *Penicillium purpurogenum* MHZ 111. *Nat. Prod. Res.* **2017**, *31*, 562–567. [CrossRef]

47. Fuska, J.; Fuskova, A.; Nemec, P. Vermistatin, an antibiotic with cytotoxic effects, produced from *Penicillium vermiculatum*. *Biologia* **1979**, *34*, 735–739.
48. Fuska, J.; Uhrín, D.; Proksa, B.; Votický, Z.; Ruppeldt, J. The structure of vermistatin, a new metabolite from *Penicillium vermiculatum*. *J. Antibiot.* **1986**, *39*, 1605–1608. [CrossRef]
49. Xia, X.K.; Liu, F.; She, Z.G.; Yang, L.G.; Li, M.F.; Vrijmoed, L.L.P.; Lin, Y.C. ^{1}H and ^{13}C NMR assignments for 6-demethylvermistatin and two penicillide derivatives from the mangrove fungus *Guignardia* sp. (No. 4382) from the South China Sea. *Magn. Reson. Chem.* **2008**, *46*, 693–696. [CrossRef]
50. Ciavatta, M.L.; Manzo, E.; Contillo, R.; Nicoletti, R. Methoxyvermistatin production by *Penicillium pinophilum* isolate LT4. In Proceedings of the 4th FEMS Congress of European Microbiologists, Geneva, Switzerland, 26–30 June 2011; pp. 26–30.
51. Ge, H.M.; Shen, Y.; Zhu, C.H.; Tan, S.H.; Ding, H.; Song, Y.C.; Tan, R.X. Penicidones A-C, three cytotoxic alkaloidal metabolites of an endophytic *Penicillium* sp. *Phytochemistry* **2008**, *69*, 571–576. [CrossRef]
52. Ehrlich, M.; Carell, T. Total syntheses and biological evaluation of 3-*O*-methylfunicone and its derivatives prepared by TMPZnCl·LiCl-mediated halogenation and carbonylative stille cross-coupling. *European J. Org. Chem.* **2013**, *2013*, 77–83. [CrossRef]
53. Manzo, E.; Ciavatta, M.L.; Nicoletti, R. Process for the Synthesis of Funicone Analogues. WO2012042482A1, 28 September 2012.
54. Salvatore, M.M.; Andolfi, A.; Nicoletti, R. The genus *Cladosporium*: A rich source of diverse and bioactive natural compounds. *Molecules* **2021**, *26*, 3959. [CrossRef] [PubMed]
55. Samson, R.A.; Yilmaz, N.; Houbraken, J.; Spierenburg, H.; Seifert, K.A.; Peterson, S.W.; Varga, J.; Frisvad, J.C. Phylogeny and nomenclature of the genus *Talaromyces* and taxa accommodatedin *Penicillium* subgenus *Biverticillium*. *Stud. Mycol.* **2011**, *70*, 159–183. [CrossRef] [PubMed]
56. Fitzpatrick, D.A. Horizontal gene transfer in fungi. *FEMS Microbiol. Lett.* **2012**, *329*, 1–8. [CrossRef]
57. Tiwari, P.; Bae, H. Horizontal gene transfer and endophytes: An implication for the acquisition of novel traits. *Plants* **2020**, *9*, 305. [CrossRef] [PubMed]
58. Vinale, F.; Nicoletti, R.; Borrelli, F.; Mangoni, A.; Parisi, O.A.; Marra, R.; Lombardi, N.; Lacatena, F.; Grauso, L.; Finizio, S.; et al. Co-culture of plant beneficial microbes as source of bioactive metabolites. *Sci. Rep.* **2017**, *7*, 1–12. [CrossRef]
59. Locci, R.; Merlini, L.; Nasini, G.; Locci, J.R. Mitorubrinic acid and related compounds from a strain of *Penicillium funiculosum* Thom. *G. Microbiol.* **1967**, *15*, 93.
60. Peng, X.Y.; Wu, J.T.; Shao, C.L.; Li, Z.Y.; Chen, M.; Wang, C.Y. Co-culture: Stimulate the metabolic potential and explore the molecular diversity of natural products from microorganisms. *Mar. Life Sci. Technol.* **2021**, *3*, 363–374. [CrossRef]
61. Nakajima, S.; Watashi, K.; Kamisuki, S.; Tsukuda, S.; Takemoto, K.; Matsuda, M.; Suzuki, R.; Aizaki, H.; Sugawara, F.; Wakita, T. Specific inhibition of hepatitis C virus entry into host hepatocytes by fungi-derived sulochrin and its derivatives. *Biochem. Biophys. Res. Commun.* **2013**, *440*, 515–520. [CrossRef]
62. Fiorito, F.; Cerracchio, C.; Salvatore, M.M.; Serra, F.; Pucciarelli, A.; Amoroso, M.G.; Nicoletti, R.; Andolfi, A. Antiviral property of the fungal metabolite 3-*O*-methylfunicone in bovine Herpesvirus 1 infection. *Microorganisms* **2022**, *10*, 188. [CrossRef]
63. Buommino, E.; Nicoletti, R.; Gaeta, G.M.; Orlando, M.; Ciavatta, M.L.; Baroni, A.; Tufano, M.A. 3-O-methylfunicone, a secondary metabolite produced by *Penicillium pinophilum*, induces growth arrest and apoptosis in HeLa cells. *Cell Prolif.* **2004**, *37*, 413–426. [CrossRef]
64. Buommino, E.; Boccellino, M.; De Filippis, A.; Petrazzuolo, M.; Cozza, V.; Nicoletti, R.; Ciavatta, M.L.; Quagliuolo, L.; Tufano, M.A. 3-*O*-methylfunicone produced by *Penicillium pinophilum* affects cell motility of breast cancer cells, downregulating αvβ5 integrin and inhibiting metalloproteinase-9 secretion. *Mol. Carcinog.* **2007**, *46*, 930–940. [CrossRef] [PubMed]
65. Buommino, E.; Tirino, V.; de Filippis, A.; Silvestri, F.; Nicoletti, R.; Ciavatta, M.L.; Pirozzi, G.; Tufano, M.A. 3-*O*-methylfunicone, from *Penicillium pinophilum*, is a selective inhibitor of breast cancer stem cells. *Cell Prolif.* **2011**, *44*, 401–409. [CrossRef] [PubMed]
66. Baroni, A.; De Luca, A.; De Filippis, A.; Petrazzuolo, M.; Manente, L.; Nicoletti, R.; Tufano, M.A.; Buommino, E. 3-*O*-methylfunicone, a metabolite of Penicillium pinophilum, inhibits proliferation of human melanoma cells by causing G2 + M arrest and inducing apoptosis. *Cell Prolif.* **2009**, *42*, 541–553. [CrossRef] [PubMed]
67. Buommino, E.; Paoletti, I.; De Filippis, A.; Nicoletti, R.; Ciavatta, M.L.; Menegozzo, S.; Menegozzo, M.; Tufano, M.A. 3-*O*-Methylfunicone, a metabolite produced by *Penicillium pinophilum*, modulates ERK1/2 activity, affecting cell motility of human mesothelioma cells. *Cell Prolif.* **2010**, *43*, 114–123. [CrossRef]
68. Buommino, E.; De Filippis, A.; Nicoletti, R.; Menegozzo, M.; Menegozzo, S.; Ciavatta, M.L.; Rizzo, A.; Brancato, V.; Tufano, M.A.; Donnarumma, G. Cell-growth and migration inhibition of human mesothelioma cells induced by 3-*O*-methylfunicone from *Penicillium pinophilum* and cisplatin. *Invest. New Drugs* **2012**, *30*, 1343–1351. [CrossRef]
69. Pleadin, J.; Frece, J.; Markov, K. Mycotoxins in food and feed. *Adv. Food Nutr. Res.* **2019**, *89*, 297–345.
70. Madariaga-Mazón, A.; Hernández-Alvarado, R.B.; Noriega-Colima, K.O.; Osnaya-Hernández, A.; Martinez-Mayorga, K. Toxicity of secondary metabolites. *Phys. Sci. Rev.* **2019**, *4*, 1–11. [CrossRef]
71. Drakopoulos, D.; Sulyok, M.; Krska, R.; Logrieco, A.F.; Vogelgsang, S. Raised concerns about the safety of barley grains and straw: A Swiss survey reveals a high diversity of mycotoxins and other fungal metabolites. *Food Control* **2021**, *125*, 107919. [CrossRef]
72. Noar, R.D.; Thomas, E.; Daub, M.E. Genetic characteristics and metabolic interactions between *Pseudocercospora fijiensis* and banana: Progress toward controlling black Sigatoka. *Plants* **2022**, *11*, 948. [CrossRef]

73. Ayeni, K.I.; Sulyok, M.; Krska, R.; Ezekiel, C.N. Fungal and plant metabolites in industrially-processed fruit juices in Nigeria. *Food Addit. Contam. Part B Surveill.* **2020**, *13*, 155–161. [CrossRef]
74. Barral, B.; Chillet, M.; Doizy, A.; Grassi, M.; Ragot, L.; Léchaudel, M.; Durand, N.; Rose, L.J.; Viljoen, A.; Schorr-Galindo, S. Diversity and toxigenicity of fungi that cause pineapple fruitlet core rot. *Toxins* **2020**, *12*, 339. [CrossRef] [PubMed]
75. Vignassa, M.; Meile, J.C.; Chiroleu, F.; Soria, C.; Leneveu-Jenvrin, C.; Schorr-Galindo, S.; Chillet, M. Pineapple mycobiome related to fruitlet core rot occurrence and the influence of fungal species dispersion patterns. *J. Fungi* **2021**, *7*, 175. [CrossRef] [PubMed]
76. Müller, W.A.; Silva, P.R.S. Da Modelagem e simulação do crescimento de *Talaromyces flavus* em abacaxi: Uma integração entre modelos cinéticos e de fenômenos de transporte. *Brazilian J. Food Technol.* **2019**, *22*, 1–15. [CrossRef]
77. Evelyn, E.; Muria, S.R.; Chairul, C.; Fozla, D.; Khoirunnisa, F.K. Thermal inactivation of *Talaromyces flavus* ascospores in pineapple juice as influenced by temperature, soluble solids, and spore age. *J. Adv. Res. Fluid Mech. Therm. Sci.* **2020**, *69*, 111–119. [CrossRef]
78. Nicoletti, R.; Carella, A. Composti a scheletro funiconico prodotti da specie di *Penicillium*. *Petria* **2004**, *14*, 1–11.
79. Kemboi, D.C.; Ochieng, P.E.; Antonissen, G.; Croubels, S.; Scippo, M.L.; Okoth, S.; Kangethe, E.K.; Faas, J.; Doupovec, B.; Lindahl, J.F.; et al. Multi-mycotoxin occurrence in dairy cattle and poultry feeds and feed ingredients from Machakos Town, Kenya. *Toxins* **2020**, *12*, 762. [CrossRef]
80. Chen, A.; Mao, X.; Sun, Q.; Wei, Z.; Li, J.; You, Y.; Zhao, J.; Jiang, G.; Wu, Y.; Wang, L.; et al. *Alternaria* mycotoxins: An overview of toxicity, metabolism, and analysis in food. *J. Agric. Food Chem.* **2021**, *69*, 7817–7830. [CrossRef]
81. Nicoletti, R.; Salvatore, M.M.; Andolfi, A. Secondary metabolites of mangrove-associated strains of *Talaromyces*. *Mar. Drugs* **2018**, *16*, 12. [CrossRef]
82. Mincuzzi, A.; Sanzani, S.M.; Garganese, F.; Ligorio, A.; Ippolito, A. First report of *Talaromyces albobiverticillius* causing postharvest fruit rot on pomegranate in Italy. *J. Plant Pathol.* **2017**, *99*, 303.
83. Yang, Q.; Wang, H.; Zhang, H.; Zhang, X.; Apaliya, M.T.; Zheng, X.; Mahunu, G.K. Effect of Yarrowia lipolytica on postharvest decay of grapes caused by *Talaromyces rugulosus* and the protein expression profile of *T. rugulosus*. *Postharvest Biol. Technol.* **2017**, *126*, 15–22. [CrossRef]
84. Stošić, S.; Ristić, D.; Gašić, K.; Starović, M.; Grbić, M.L.; Vukojević, J.; Živković, S. *Talaromyces minioluteus*: New postharvest fungal pathogen in Serbia. *Plant Dis.* **2020**, *104*, 656–667. [CrossRef] [PubMed]
85. Stošić, S.; Ristić, D.; Savković, Ž.; Grbić, M.L.; Vukojević, J.; Živković, S. *Penicillium* and *Talaromyces* species as postharvest pathogens of pear fruit (*Pyrus communis*) in Serbia. *Plant Dis.* **2021**, *105*, 3510–3521. [CrossRef] [PubMed]
86. Mukhtar, I.; Quan, X.; Chou, T.; Huang, Q.; Yan, J.; Chen, B.; Jiang, S.; Liu, F.; Wen, Z.; Xie, B. First report of *Talaromyces funiculosus* causing fruit core rot of peach (*Prunus persica*) in China. *Plant Dis.* **2019**, *103*, 2124. [CrossRef]
87. Wang, L.; Du, Y.; Ju, L.; Zhao, Y.; Zhang, R.; Sun, G.; Gleason, M.L. *Ramichloridium apiculatum*, a new record for China, causing sooty blotch and flyspeck. *Mycotaxon* **2014**, *127*, 121–127. [CrossRef]