Review
Structures and Biological Activities of Secondary Metabolites from *Trichoderma harzianum*

Rui Guo \(^1\), Gang Li \(^1\), Zhao Zhang \(^2\) and Xiaoping Peng \(^1\,*\)

\(^1\) Department of Natural Medicinal Chemistry and Pharmacognosy, School of Pharmacy, Qingdao University, Qingdao 266071, China
\(^2\) Department of Hand and Foot Surgery, Affiliated Hospital of Qingdao University, Qingdao 266003, China
* Correspondence: pengxiaoping@qdu.edu.cn

Abstract: The biocontrol fungus *Trichoderma harzianum*, from both marine and terrestrial environments, has attracted considerable attention. *T. harzianum* has a tremendous potential to produce a variety of bioactive secondary metabolites (SMs), which are an important source of new herbicides and antibiotics. This review prioritizes the SMs of *T. harzianum* from 1988 to June 2022, and their relevant biological activities. Marine-derived SMs, especially terpenoids, polyketides, and macrolides compounds, occupy a significant proportion of natural products from *T. harzianum*, deserving more of our attention.

Keywords: natural products; *Trichoderma harzianum*; marine sources; bioactivity; secondary metabolites

1. Introduction

The unique marine environment with high pressure, high salinity, and low temperature, breeds unique marine microorganisms [1,2]. Secondary metabolites obtained from marine-derived fungi have attracted considerable attention in recent years for potential use in the discovery of unique structures and diverse biological properties [3,4].

The biocontrol fungi *Trichoderma* spp. (sordariomycetes) are widely spread in the environment [5], such as in the ocean. With the deepening of marine science and technology exploration, more and more *Trichoderma* sp. strains have been discovered from marine sources. From marine and terrestrial environments, there are no fewer than 250 *Trichoderma* species discovered so far [6]. *Trichoderma* species are famous for producing plentiful secondary metabolites [7]. Among them, *Trichoderma harzianum* probably contributed the most secondary metabolites (SMs) originating from *Trichoderma* species [8,9]. The SMs from *T. harzianum* showed antifungal activity [10]. Additionally, cytotoxicity [11] and antimicrobial activity [12], and so on, have also been found in its SMs.

The SMs of *T. harzianum* have not been summarized in detail or systematically. Up to now, nearly 200 compounds of *T. harzianum* have been reported. The secondary metabolites of *T. harzianum* include terpenoids, polyketides, peptides, alkaloids, and lactones. Herein, this review reports the isolated compounds of *T. harzianum* and their bioactivities. Furthermore, details of the source organisms were analyzed for marine and terrestrial sources. A total number of 180 compounds are presented in this review with 58 cited references. These references cover the time period from 1988 to June 2022.

2. Structural and Biological Activity Studies

2.1. Terpenoids

Seven new potent phytotoxic harziane diterpenes harzianelactones A and B (1 and 2), harzianones A–D (3–6) and harziane (9) were isolated from the soft coral-derived fungus *T. harzianum* XS-20090075 [13]. Compounds 1 and 2 belonged to a unique class of terpenes with a 6-5-7-5-fused carbocyclic core and a lactone ring. Harzianones A–D (3–6) consisted of a fused tetracyclic 6-5-7-4-fused tetra-cyclic skeleton. Chemical epigentic
manipulation was applied to activate silent genes of T. harzianum XS-20090075 by appending a histone deacetylase (HDAC) inhibitor. With this experimental technique, two new diterpenoids harzianone E (7) and harzianolic acid A (41), and one new sesquiterpenoid 3,7,11-trihydroxy-cycloneron (16) were isolated from the same strain T. harzianum XS-20090075. At the same time, 11 known sesquiterpenoids, methyl 3,7-dihydroxy-15-cycloneronate (17), catenioblinc (18), ascorbic acid (19), cycloneroniol (20), (10E)-12-acetoxy-10-cycloneron-3,7-diol (21), cyclonerodiol (22), cyclonerodiol oxide (27), epicyclonerodiol oxide (28), ent-trichoacorenol (29), trichoacorenol (30), and ophioceric acid (40) were isolated from T. harzianum XS-20090075 [14]. It was the first time for obtaining cleistanthane diterpenoid from T. harzianum XS-20090075. Trichodermanins C–H (10–15) were new diterpenes with a rare fused 6-5-6-6 ring system, and have been isolated from a fungus T. harzianum OUPS-111D-4 [15,16]. This strain was separated from a piece of sponge Halichondria okadai. Compounds 10–15 were evaluated for their cytotoxicity by using murine P388 leukemia, human HL-60 leukemia, and murine L1210 leukemia cell lines. Compound 10 with a fused 6-5-6-6 ring system exhibited potent cytotoxic activity [15], and compounds 12 and 13 exhibited modest activity [16]. Six new terpenes, including one harziane diterpene, 3R-hydroxy-9R,10R-dihydroharzianone (8), three cyclonerane sesquiterpenes, methyl 3,7-dihydroxy-15-cycloneronate (17), 11-methoxy-9-cycloneron-3,7-diol (23), 10-cycloneron-3,5,7-triol (25), and one acorane sesquiterpene, 8-acoren-3,11-diol (36), and one cyclonerane 11R-methoxy-5,9,13-proharzitrien-3-ol (42), together with four known sesquiterpenes, cyclonerodio (22), 9-cycloneron-3,7,11-triol (24), trichoacorenol (30) and trichoacorenol B (37) were isolated from T. harzianum X-5 [17]. The strain X-5 was an endophytic fungus isolated from the marine brown alga Laminaria japonica. The above six new compounds (8, 17, 23, 25, 36, and 42) were evaluated to inhibit four marine phytoplankton species and four marine-derived pathogenic bacteria [17]. Compounds 23 and 42 exhibited potent inhibition activity [17]. Harzianoic acid A (38) is a sesquiterpene, and harzianoic acid B (39) is a norsesquiterpene with a cyclobutane nucleus. They were isolated from a sponge-isolated fungus, T. harzianum LZDX-32-08 [18], and were found to have new natural scaffolds to exert anti-HCV activity for their capability to inhibit multi-targets, including those for virus replication and entry [18]. (10E)-12-Acetoxy-10-cycloneron-3,7-diol (21) and 12-acetoxycycloneran-3,7-diol (26) were two new cyclonerane sesquiterpenoids, which were isolated from the marine sediment-derived fungus T. harzianum P1-4 [9]. A new acorane-type sesquiterpene, 15-hydroxyacorenone (31), was isolated from T. harzianum [19], together with acorenene (32), acorenene-B (33), 4-epiacorenene (34), and 4-epiacorenene-B (35). Stigmastera-7,22-dien-3β,5α,6α-triol (43) was isolated from T. harzianum XS-20090075, cultivated by the Czapek’s culture [20]. Compound 43 exhibited antifouling activity with an EC50 value of 39.2 µg/mL and Topo I inhibitory activity with an MIC value of 50.0 µM [20]. Two fungal strains of T. harzianum T-4 and T. harzianum T-5 were obtained from Palampur, Himachal Pradesh (India). Stigmasterol (44) and β-sitosterol (45) were isolated from T. harzianum T-4 [21]. Ergosterol (46) was isolated from T. harzianum T-5 [21]. Trichosor- darin A (47), a unique norditerpene aglycone, was isolated from T. harzianum R5 [22]. Compound 47 was toxic to the marine zooplankton Artemia salina with an LC50 value of 233 µM [22] (Figure 1).
Figure 1. Chemical structures of terpenoids (1–47) from T. harzianum. * Means marine source compounds.
2.2. Polyketides

The fermentation of a sponge-associated fungus *T. harzianum* HMS-15-3 led to the isolation of four pairs of new C13 lipid enantiomers harzianumols A–H [48–55] [23]. Four polyketides, trichoharzin B (56), methyl-trichoharzin (57), trichoharzin (58), and eujavanicol A (59), were isolated from *T. harzianum* XS-20090075 [20], which was fermented in rice medium by one strain many compounds (OSMAC) strategy. New naphthalene compound 57, and known naphthalene compound 58 exhibited antifouling activity with the EC50 values of 29.8 and 35.6 µg/mL [20]. Six new tandyukisins, tandyukisins A–F (60–65), were isolated from *T. harzianum* OUPS-111D-4 [11,24,25], which were initially derived from the sponge *Halichondria okadai*. Among the tandyukisins A–F (60–65), compounds 60, 64 and 65 exhibited cytotoxicity against murine P388 leukemia, human HL-60 leukemia, and murine L1210 leukemia cell lines inferior to the control 5-fluorouracil [24]. Compounds 61–63 showed slightly selective growth inhibition against the central nervous system cancer SNB-75 cell line in the HCC panel [25]. Compounds 64 and 65 exhibited significant cytotoxicity against the cancer cell lines P388, HL-60, and L1210 [24]. The structure-activity relationship may be relevant to the terminals of the side chains. *T. harzianum* T-4 was obtained from Palampur, Himachal Pradesh in India, and a polyketide palmitic acid (66) was isolated from the T-4 [21]. Harzianum A (67), was a new trichothecene isolated from the soil-borne fungus *T. harzianum* in 1994 [26]. Harziphilone (68) was a new polyketide isolated from *T. harzianum* WC 47695 [27], which was isolated from sandy soil with plant debris collected in Fort Lauderdale. The REV/RRE binding assay and HIV assay revealed that compound 68 showed inhibitory activity against REV-protein binding to RRE RNA with IC50 values of 2.0 µM. In contrast, this compound did not show protection against HIV infection at concentration levels up to 200 µg/mL. The cytotoxicity assay on the murine tumor cell line M-109 showed that 68 exhibited cytotoxicity at 38 µM [27]. Seven polyketides, keto triol 3 (69), keto diol 7 (70), keto diol 6 (71), keto diol 8 (72), triacetate 9 (73), triol 10 (74) and acetal diol 2 (75) were isolated from *T. harzianum* [28]. One new trichoharzin (58), and two known compounds, tribenzoate (76) and triacetate (77), were isolated from *T. harzianum* Rifai in 1993 [29]. A new polyketide, T22azaphilone (78), was isolated from *T. harzianum* T22 [30]. A new compound, trichoharzialon (79), isolated from *T. harzianum* F031, exhibited antifungal activity against *Colletotrichum gloeosporioides* with a MIC of 128 µg/mL [31]. Three novel polyketides trichodenones A–C (80–82) were isolated from *T. harzianum* OUPS-N115 [32]. This strain was separated from the sponge *Halichondria okadai*. Trichodenones A–C (80–82) showed cytotoxicities against P388 cell line with the ED50 values of 0.21, 1.21, and 1.45 µg/mL, respectively. Homodimericin A (83) was isolated from *T. harzianum* WC13 [33,34]. In their model, compound 83 was the biologically inert aftermath of a fungal counter to a bacterial attack. The discovery of cryptenol (84) from *T. harzianum* WC13 [34] indicated that the interactions among microbes in a termite nest were not bipartite but a multipartite system.

The structure and activity relationships of anthraquinones (AQs) in *T. harzianum* have been studied. AQs represent an important class of SMs occurring in *T. harzianum* strains, which exhibited a variety of biological functions [12]. The alkylating functionalities in the AQs maximize the anticancer activity by binding tightly with DNA to disrupt the DNA function [35]. Moreover, anthraquinone derivatives were proposed to have an anticancer function by inhibiting protein kinase CK2 [36]. Pachybasin (85) and chrysophanol (86) were isolated from *T. harzianum* ETS 323 [37]. 1,7-Dihydroxy-3-hydroxymethyl-9,10-anthaquinone (87), 1,5-dihydroxy-3-hydroxymethyl-9,10-anthaquinone (88), emodin (89), and ω-hydroxypachybasin (90) were isolated from *T. harzianum* strain Th-R16 [38]. These compounds exhibited effective antifungal activity against *Botrytis cinerea* (Ascomycota) and *Rhizoctonia solani* (Basidiomycete). At a 500 µg/mL concentration, compound 88 showed comparatively higher activity against *R. solani* and *B. cinerea* than 89 [38]. Phomarin (91), (+)-2’S-isorhodoptilometrin (92), 1,6-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione (93), harzianumnone A (94) and harzianumnone B (95) were isolated from the soft coral-derived fungus *T. harzianum* XS-20090075 [12]. Compounds 94 and 95 were identified as a
pair of epimers, the first example of hydroanthraquinones from *T. harzianum* XS-20090075. Compound 92 with Topo I inhibition activity, was further assessed for cytotoxic activity against human tumor cell lines. It exhibited cytotoxic activity against HepG2 cell line with an IC\(_{50}\) value of 2.10 \(\mu\)M, and showed cytotoxicity against Hela cell with an IC\(_{50}\) value of 8.59 \(\mu\)M [12] (Figures 2 and 3).

**Figure 2.** Chemical structures of polyketides (48–68 and 76) from *T. harzianum*. * Means marine source compounds.
Figure 3. Chemical structures of polyketides (69–75 and 77–95) from T. harzianum. * Means marine source compounds.

2.3. Peptides

Peptaibols are linear antibiotic peptides consisting of 5 to 20 amino acids [39]. It could be biosynthesized by T. harzianum. Peptaibols were characterized by the structures of alpha-aminoisobutyric acid (Aib), and C-terminal hydroxylated amino acid. Two new series peptaibols, trichokindins (TKs) and trichorozins (TZs), were isolated from T. harzianum collected at Nara in Japan. TKs and TZs comprised 18 and 11 amino acid residues, respectively, while TKs were rich in isovaline (Iva). TK-VII (106) is the most hydrophobic of TKs with 18-residue peptides. Compound 106 induced Ca\(^{2+}\)-dependent catecholamine secretion from bovine adrenal medullary chromaffin cells [40]. TKs (96–106), with a single peak on HPLC and typical IR absorptions at 3300, 1600, and 1530 cm\(^{-1}\), were confirmed as peptaibols by polarization transfer spectra [40]. With incubating 10 \(\mu\)M of TK-VII (106), 27% of the total catecholamines in bovine adrenal chromaffin cells were secreted in the presence of the Ca\(^{2+}\). In contrast, only 5% of the total catecholamines were secreted without Ca\(^{2+}\) [40]. Hydrophobicity is vital to the interaction between membranes and peptaibols [41]. HB I (107) was isolated from T. harzianum M-903603 [42]. Trichorzins HA (108–113) and MA (114–116) were isolated from T. harzianum M-903602 and T. harzianum M-922835, respectively. Compounds 108–116 are a series of 18-residue peptides [43]. Bioassays on the antifungal activity of trichorzins and harzianins on the phytopathogenic fungus Sclerotium cepivorum revealed that trichorzins were more potent (75% inhibition at 100 \(\mu\)g/mL) than harzianins (40%
inhibition at 100 μg/mL [44]. Research on the structured-activity relationships (SARs) revealed that the peptide chain length and superhydrophobicity played an essential part in the peptide/membrane interaction and the subsequent permeability by perturbing the ionic balance of the cell [44]. As new membrane-modifying peptides isolated from *T. harzianum*, trichorzians I–IV (117–120), belonged to peptaibols with 11 residues. It was reported that compounds 117–120 exhibited voltage-dependent ion channel-like activity in lipid bilayers [45]. Eleven peptides were isolated from *T. harzianum* M-903603, and named harzianins HC (121–131) [46]. The detailed study of such proline-rich 14-residue peptaibols revealed that harzianins HC increased the permeability of liposomes and improved voltage-dependent conductance [46]. An exogenous amino acid supply simplified the microheterogeneous peptide mixtures when Aib, Glu, or Arg was added to the fermentation media of *T. harzianum* M-902608. Harzianin PC$_U$4 (132), trichorizin PA$_U$4 (133), trichorizin PA II (134), trichorizin PA IV–VIII (135–139) and trichorizin PA IX (140) were isolated from this *T. harzianum* M-902608 [47]. When cultured in the Aib-enriched media, compounds 132 and 133 were isolated, while trichorzins PA was obtained from the standard culture media [47]. Trichorzianines A (TA) and B (TB) are peptaibols isolated from *T. harzianum*. TA IIc (141) induced the growth inhibition and lysis of the amoeba *Dictyostelium* [48]. With the aid of positive ion FAB mass spectrometry, COSY and NOESY experiments, seven peptides of trichorzianines B isolated from *T. harzianum* were identified, and these peptides included trichorzianine TB IIa (142), trichorzianine TB IIc (143), trichorzianine TB IVb (144), trichorzianine TB Vb (145), trichorzianine TB VIa (146), trichorzianine TB Vlb (147) and trichorzianine TB VII (148) [49]. From a mangrove-derived fungus, *T. harzianum* D13, a novel heterocyclic dipeptide trichodermamide G (149), two known biogenetically related compounds, trichodermamide A (150) and aspergillazin A (151) were isolated. A unique sulfur bridge was observed in the structures of compounds 149 and 151 [50] (Table 1 and Figure 4).

Table 1. The sequences of peptides (96–148) from *T. harzianum.*

| Compounds          | Sequences of Peptides                                                                 |
|--------------------|----------------------------------------------------------------------------------------|
| 96                 | Ac Aib Ser Ala Aib Aib Gln Iva Leu Aib Ala Aib Pro Leu Aib Aib Gln Ile OH              |
| 97                 | Ac Aib Ser Ala Aib Aib Gln Aib Leu Aib Ala Aib Pro Leu Aib Aib Gln Ile OH              |
| 98                 | Ac Aib Ser Ala Aib Aib Gln Aib Leu Aib Iva Leu Aib Aib Pro Leu Aib Aib Gln Ile OH      |
| 99                 | Ac Aib Ser Ala Aib Iva Gln Aib Leu Aib Ala Aib Pro Leu Aib Aib Gln Ile OH              |
| 100                | Ac Aib Ser Ala Aib Aib Gln Aib Leu Aib Iva Leu Aib Ala Aib Pro Leu Aib Aib Gln Ile OH  |
| 101                | Ac Aib Ser Ala Aib Iva Gln Aib Leu Aib La Aib Pro Leu Aib Aib Pro Leu Aib Gln Ile OH   |
| 102                | Ac Aib Ser Ala Aib Iva Gln Iva Leu Aib Ala Aib Pro Leu Aib Aib Pro Leu Aib Gln Ile OH  |
| 103                | Ac Aib Ser Ala Aib Aib Gln Iva Leu Aib Ala Aib Pro Leu Aib Aib Pro Leu Aib Gln Ile OH  |
| 104                | Ac Aib Ser Ala Aib Iva Gln Leu Aib Ala Aib Pro Leu Aib Pro Leu Aib Gln Ile OH          |
| 105                | Ac Aib Ser Ala Aib Iva Gln Leu Aib Ala Aib Pro Leu Aib Pro Leu Aib Gln Ile OH          |
| 106                | Ac Aib Ser Ala Aib Iva Gln Iva Leu Aib Ala Aib Pro Leu Aib Pro Leu Aib Gln Ile OH      |
| 107                | Ac Aib Asn Leu Ile Aib Pro Leu Aib Pro Leu OH                                         |
| 108                | Ac Aib Gly Ala Aib Aib Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Pro Leu Aib Gln Ile OH  |
| 109                | Ac Aib Gly Ala Aib Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Gln Ile OH                  |
| 110                | Ac Aib Gly Ala Aib Iva Gln Iva Gly Leu Aib Pro Leu Aib Pro Leu Aib Gln Ile OH          |
| 111                | Ac Aib Gly Ala Aib Iva Gln Iva Gly Leu Aib Pro Leu Aib Iva Gln Ile OH                  |
| 112                | Ac Aib Gly Ala Aib Iva Gln Iva Val Aib Gly Leu Aib Pro Leu Aib Pro Leu Iva Gln Ile OH  |
| 113                | Ac Aib Gly Ala Aib Iva Gln Iva Val Aib Gly Leu Aib Pro Leu Aib Iva Gln Ile OH          |
| 114                | Ac Aib Ser Ala Aib Aib Gln Aib Leu Aib Gly Leu Aib Pro Leu Aib Pro Leu Aib Gln Val OH  |
| 115                | Ac Aib Ser Ala Aib Iva Gln Iva Leu Aib Leu Aib Pro Leu Aib Pro Leu Aib Gln Val OH      |
| 116                | Ac Aib Ser Ala Aib Iva Gln Iva Leu Aib Gly Leu Aib Pro Leu Aib Gln Ile OH              |
| 117                | Ac Aib Asn Ile Leu Aib Pro Ile Leu Aib Pro Val OH                                    |
| 118                | Ac Aib Asn Leu Aib Aib Pro Ile Leu Aib Pro Val OH                                    |
| 119                | Ac Aib Asn Ile Leu Aib Pro Ile Leu Aib Pro Val OH                                    |
| 120                | Ac Aib Asn Leu Aib Aib Pro Ile Leu Aib Pro Val OH                                    |
| 121                | Ac Aib Asn Leu Aib Aib Pro Ile Leu Aib Pro Val OH                                    |

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Table 1. Cont.

| Compounds          | Sequences of Peptides                                                                 |
|--------------------|---------------------------------------------------------------------------------------|
| 122 Harzianin HC III | Ac Aib Asn Leu Aib Pro Ser Val Aib Pro Iva Leu Aib Pro Leu OH                         |
| 123 Harzianin HC VI | Ac Aib Asn Leu Aib Pro Ala Val Aib Pro Aib Leu Pro Leu OH                             |
| 124 Harzianin HC VIII | Ac Aib Asn Leu Aib Pro Ala Val Aib Pro Iva Leu Aib Pro Leu OH                        |
| 125 Harzianin HC IX | Ac Aib Asn Leu Aib Pro Ala Ile Aib Pro Iva Leu Aib Pro Leu OH                         |
| 126 Harzianin HC X | Ac Aib Glu Leu Aib Pro Ala Val Aib Pro Iva Leu Aib Pro Leu OH                         |
| 127 Harzianin HC XI | Ac Aib Asn Leu Aib Pro Ser Ile Aib Pro Aib Leu Pro Leu OH                             |
| 128 Harzianin HC XII | Ac Aib Asn Leu Aib Pro Ser Ile Aib Pro Iva Leu Aib Pro Leu OH                         |
| 129 Harzianin HC XIII | Ac Aib Glu Leu Aib Pro Ser Ile Aib Pro Iva Leu Aib Pro Leu OH                        |
| 130 Harzianin HC XIV | Ac Aib Asn Leu Aib Pro Ala Ile Aib Pro Aib Leu Pro Leu OH                             |
| 131 Harzianin HC XV | Ac Aib Glu Leu Aib Pro Ala Ile Aib Pro Iva Leu Aib Pro Leu OH                         |
| 132 Harzianin HC XV | Ac Aib Asn Leu Aib Pro Ser Ile Aib Pro Aib Leu Pro Val OH                             |
| 133 Trichorzin PA V | Ac Aib Ser Ala Aib Aib Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Trp OH                 |
| 134 Trichorzin PA IV | Ac Aib Ser Ala Aib Iva Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Trp OH                 |
| 135 Trichorzin PA II | Ac Aib Ser Ala Aib Iva Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Trp OH                 |
| 136 Trichorzin PA VI | Ac Aib Ser Ala Aib Iva Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Trp OH                 |
| 137 Trichorzin PA VII | Ac Aib Ser Ala Aib Iva Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Phe OH                 |
| 138 Trichorzin PA VIII | Ac Aib Ser Ala Aib Iva Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Phe OH                 |
| 139 Trichorzin PA IX | Ac Aib Ser Ala Aib Iva Glu Val Aib Gly Leu Aib Pro Leu Aib Glu Phe OH                 |
| 140 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Trp OH                 |
| 141 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Trp OH                 |
| 142 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Trp OH                 |
| 143 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Trp OH                 |
| 144 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Trp OH                 |
| 145 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Trp OH                 |
| 146 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Phe OH                 |
| 147 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Phe OH                 |
| 148 Trichorzin TA IIC | Ac Aib Ala Ala Aib Aib Glu Aib Ser Leu Pro Val Aib Ile Glu Glu Phe OH                 |

Figure 4. Chemical structures of peptides (149–151) from *T. harzianum*. * Means marine source compounds.

2.4. Alkaloids

Fleephilone (152), a new HIV REV/RRE binding inhibitor, was produced by *T. harzianum* WC 47695 [27] isolated from sandy soil with plant debris collected in Fort Lauderdale, FL, USA. Compound 152 showed inhibitory activity against REV-protein binding to RRE RNA with an IC50 value of 7.6 μM, and exhibited no protection against HIV infection at concentrations up to 200 μg/mL. Harzianic acid (153) was isolated from *T. harzianum* SY-307, which exhibited antimicrobial activity against *Pasteurella piscicida* sp. 6395 [51]. Isoharzianic acid (154), a new stereoisomer of compound 153, was isolated from the *T. harzianum* strain M10, together with Harzianic acid (HA) [52]. HA was able to promote plant growth and strongly bind iron [52]. An OSMAC approach using multiple culture conditions or co-cultures has been applied to access the chemical diversity of *T. harzianum* XS-20090075 [20]. A new halogenate quinoline natural product, ethyl 2-bromo-4-chloroquinoline-3-carboxylate (155), was isolated from *T. harzianum* XS-20090075 [20]. Harzianopyridone (156) was isolated from the *T. harzianum* T-5. This strain was obtained from Palampur, Himachal Pradesh, India [21].
Compound 156 inhibited more than 90% growth of Rhizoctonia solani, Sclerotium rolfsii, and Fusarium oxysporum (EC50 35.9–50.2 μg/mL), but was less active than Bavistin [21]. A new oxazole metabolite, MR93A (159) was isolated from T. harzianum KCTC 0114BP [53], while eight metabolites MR566A (157), MR566B (158), MR93B (160), MR304A (161), 1-(1,4,5-trihydroxy-3-isocyanocyclopenten-2-enyl)-ethanol (162), 2-hydroxy-4-isocyano-α-methyl-6-oxabicyclo[3.1.0]-hex-3-ene-2-methanol (163), 4-hydroxy-8-isocyano-1-oxaspiro[4.4]cycnon-8-en-2-one (164), methyl-3-(1,5-dihydroxy-3-isocyanocyclopent-3-enyl)prop-2-enoate (165) and 3-(3′-isocyanocyclopent-2′-enylidene)propionic acid (166) were isolated from T. harzianum [54]. MR566A (157) strongly inhibited mushroom tyrosinase with an IC50 value of 1.72 μM compared with kojic acid with an IC50 value of 3.08 μM [55]. Compound 166 exhibited inhibitory activity against mushroom tyrosinase with an IC50 value of 0.0014 μM, which was more active than the kojic acid [55] (Figure 5).

![Chemical structures of alkaloids (152–166) from T. harzianum.](image)

**Figure 5.** Chemical structures of alkaloids (152–166) from T. harzianum.

### 2.5. Lactones

Two lactones, nafuredins C (169) and A (170), were isolated from the mangrove-derived fungus T. harzianum D13, and the new compound 169 exhibited antifungal activity against Magnaporthe oryzae, with an MIC value of 8.63 μM [50]. From T. harzianum XS-20090075, four known compounds, xylogibloactones A and B (167, and 168), nafuredin A (170), and dichlorodiaportin (171) [20,56,57] were isolated. Compound 170 exhibited antifouling activity with the EC50 value of 21.4 μg/mL [20]. 6-Pentyl-2H-pyran-2-one (172) and 2(5H)-furanone (173) were isolated from T. harzianum T-4 [21], while δ-decanolactone (174) was isolated from T. harzianum T-5 [21]. Compound 172, a volatile organic compound from T. harzianum [58], had the ability to inhibit primary root growth and induce lateral root formation. Penisoucomarin H (175) was isolated from the mangrove-derived fungus T. harzianum D13 [30]. Two new lactones, harzialactones A (176) and B (177), together with a known compound R-mevalonolactone (178), were isolated from T. harzianum OUPS-N115 [32]. T. harzianum OUPS-N115 was separated from the sponge Halichondria okadai, and the cytotoxicity of compounds 176–178 against the P388 cell line was tested. The results showed no significant cytotoxicity [32]. Two lactones harzianolide (179) and T39butenolide (180) were isolated from T. harzianum T39 [30] (Figure 6).
sources from the SMs distribution were exhibited, including the specific source ratio (Figure 7). The structure type proportion and the bioactivity distribution of the SMs isolated from T. harzianum were also shown (Figures 8–10).

Figure 6. Chemical structures of lactones (167–180) from T. harzianum. * Means marine source compounds.

All compounds from T. harzianum with their biological activities and habitats were summarized in Table 2. As an analysis, the percentage of marine sources and terrestrial sources from the SMs distribution were exhibited, including the specific source ratio (Figure 7). The structure type proportion and the bioactivity distribution of the SMs isolated from T. harzianum were also shown (Figures 8–10).

Table 2. The bioactivities and habitats of SMs (1–180) from T. harzianum.

| Compounds | Bioactivities | Habitats | Refs |
|-----------|--------------|----------|------|
| Harzianelactone A (1) * | Phytotoxicity | Soft coral | [13] |
| Harzianelactone B (2) * | Phytotoxicity | Soft coral | [13] |
| Harzianone A (3) * | Phytotoxicity | Soft coral | [13] |
| Harzianone B (4) * | Phytotoxicity | Soft coral | [13] |
| Harzianone C (5) * | Phytotoxicity | Soft coral | [13] |
| Harzianone D (6) * | Phytotoxicity | Soft coral | [13] |
| Harzianone E (7) * | Antibacterial | Soft coral | [14] |
| 3R-Hydroxy-9R,10R-dihydroharzianone (8) * | Phytotoxicity | Brown alga | [17] |
| Harziane (9) * | Phytotoxicity | Soft coral | [13] |
| Trichodermanin C (10) * | Cytotoxicity | Sponge | [15,16] |
| Trichodermanin D (11) * | — | Sponge | [15,16] |
| Trichodermanin E (12) * | Cytotoxicity | Sponge | [15,16] |
| Trichodermanin F (13) * | Cytotoxicity | Sponge | [15,16] |
| Trichodermanin G (14) * | — | Sponge | [15,16] |
| Trichodermanin H (15) * | — | Sponge | [15,16] |
| 3,7,11-Trihydroxy-cycloneran (16) * | — | Soft coral | [14] |
| Methyl 3,7-dihydroxy-15-cycloneranate (17) * | Phytotoxicity | Brown alga | [17] |
| Catemiobinc (18) * | — | Soft coral | [14] |
| Ascotrichic acid (19) * | — | Soft coral | [14] |
| Cyclonerotriol (20) * | — | Soft coral | [14] |
| (10E)-12-Acetoxy-10-cycloneran-3,7-diol (21) * | — | Sediment | [9] |
| Cyclonerodiol (22) * | Phytotoxicity | Soft coral | [14] |
| 11-Methoxy-9-cycloneran-3,7-diol (23) * | Phytotoxicity | Brown alga | [17] |
| 9-Cycloneran-3,7,11-triol (24) * | Phytotoxicity | Brown alga | [17] |
| 10-Cycloneran-3,5,7-triol (25) * | Phytotoxicity | Brown alga | [17] |
| 12-Acetoxycycloneran-3,7-diol (26) * | — | Sediment | [9] |
| Cyclonerodiol oxide (27) * | — | Soft coral | [14] |
| Epicyclonerodiol oxide (28) * | — | Soft coral | [14] |
| ent-Trichoacorenol (29) * | — | Soft coral | [14] |
| Trichoacorenol (30) * | Phytotoxicity | Brown alga | [17] |
| 15-Hydroxyacorenone (31) | — | Mushroom | [19] |
| Acorenone (32) | — | Mushroom | [19] |
| Compounds | Bioactivities | Habitats | Refs |
|-----------|--------------|----------|------|
| Acenone-B (33) | — | Mushroom | [19] |
| 4-Epiacorenone (34) | — | Mushroom | [19] |
| 4-Epiacorenone-B (35) | — | Mushroom | [19] |
| 8-Acoren-3,11-diol (36) * | phytotoxicity | Brown alga | [17] |
| Trichoacorenol B (37) * | phytotoxicity | Brown alga | [17] |
| Harzianoic acid A (38) * | Antivirus | Sponge | [18] |
| Harzianoic acid B (39) * | Antivirus | Sponge | [18] |
| Ophioceric acid (40) * | — | Soft coral | [14] |
| Harzianolic acid A (41) * | — | Soft coral | [14] |
| 11R-Methoxy-5,9,13-trihydropyroharzitren-3-ol (42) * | phytotoxicity | Brown alga | [17] |
| Stigmasta-7,22-dien-3β,5α,6α-triol (43) * | Antifouling and DNA top I inhibitory activity | Soft coral | [20] |
| Stigmasteryl (44) | — | Soil | [21] |
| β-Sitosterol (45) | — | Soil | [21] |
| Ergosterol (46) | — | Soil | [21] |
| Trichosordarin A (47) * | Toxic to zooplankton | Sediment | [22] |
| Harzianumol A (48) * | — | Sponge | [23] |
| Harzianumol B (49) * | — | Sponge | [23] |
| Harzianumol C (50) * | — | Sponge | [23] |
| Harzianumol D (51) * | — | Sponge | [23] |
| Harzianumol E (52) * | — | Sponge | [23] |
| Harzianumol F (53) * | — | Sponge | [23] |
| Harzianumol G (54) * | — | Sponge | [23] |
| Harzianumol H (55) * | — | Sponge | [23] |
| Trichoharzin B (56) * | — | Soft coral | [20] |
| Methyl-trichoharzin (57) * | Antifouling | Soft coral | [20] |
| Trichoharzin (58) * | Antifouling | Soft coral | [20] |
| Eujavanicol A (59) * | — | Sponge | [29] |
| Tandyukisin A (60) * | Cytotoxicity | Sponge | [11] |
| Tandyukisin B (61) * | Cytotoxicity | Sponge | [25] |
| Tandyukisin C (62) * | Cytotoxicity | Sponge | [25] |
| Tandyukisin D (63) * | Cytotoxicity | Sponge | [25] |
| Tandyukisin E (64) * | Cytotoxicity | Sponge | [24] |
| Tandyukisin F (65) * | Cytotoxicity | Sponge | [24] |
| Palmitic acid (66) | — | Soil | [21] |
| Harzianum A (67) | Antifungal | Soil | [26] |
| Harziphilone (68) | Cytotoxicity | Soil | [27] |
| Keto triol 3 (69) | Antifungal | Wheat roots | [28] |
| Keto diol 7 (70) | Antifungal | Wheat roots | [28] |
| Keto diol 6 (71) | Antifungal | Wheat roots | [28] |
| Keto diol 8 (72) | Antifungal | Wheat roots | [28] |
| Triacetate 9 (73) | Antifungal | Wheat roots | [28] |
| Triol 10 (74) | Antifungal | Wheat roots | [28] |
| Acetal diol 2 (75) | Antifungal | Wheat roots | [28] |
| Tribenzoate (76) * | — | Sponge | [29] |
| Triacetate (77) * | — | Sponge | [29] |
| T22azaphilone (78) | — | Commercial products | [30] |
| Trichoharzianol (79) | Antifungal | Soil | [31] |
| Trichodenone A (80) * | Cytotoxicity | Sponge | [32] |
| Trichodenone B (81) * | Cytotoxicity | Sponge | [32] |
| Trichodenone C (82) * | Cytotoxicity | Sponge | [32] |
| Homodimerin A (83) | — | Florida termite nest | [33,34] |
| Cryptenol (84) | — | Florida termite nest | [34] |
| Pachybasin (85) | — | Laboratory environment | [37] |
| Chrysophanol (86) | — | Laboratory environment | [37] |
| 1,7-Dihydroxy-3-hydroxymethyl-9,10-anthraquinone (87) | Antifungal | Plant roots | [38] |
| 1,5-Dihydroxy-3-hydroxymethyl-9,10-anthraquinone (88) | Antifungal | Plant roots | [38] |
| Emodin (89) | Antifungal | Plant roots | [38] |
| ω-Hydroxy pachybasin (90) | Antifungal | Plant roots | [38] |
| Phomarin (91) * | Cytotoxicity | Soft coral | [12] |
| (+)-2′-Isodihydroptilometrin (92) * | Cytotoxicity | Soft coral | [12] |
| 1,6-Dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione (93) * | — | Soft coral | [12] |
| Harzianumnone A (94) * | — | Soft coral | [12] |
| Harzianumnone B (95) * | — | Soft coral | [12] |
| Trichokinidin_1a (96) | — | Soil | [40] |
| Trichokinidin_1b (97) | — | Soil | [40] |
| Compounds                          | Bioactivities                   | Habitats         | Refs   |
|-----------------------------------|---------------------------------|------------------|--------|
| Trichokindin_IIa (98)             |                                 | Soil             | [40]   |
| Trichokindin_IIb (99)             |                                 | Soil             | [40]   |
| Trichokindin_IIla (100)           |                                 | Soil             | [40]   |
| Trichokindin_IIlb (101)           |                                 | Soil             | [40]   |
| Trichokindin_IV (102)             |                                 | Soil             | [40]   |
| Trichokindin_Va (103)             |                                 | Soil             | [40]   |
| Trichokindin_Vb (104)             |                                 | Soil             | [40]   |
| Trichokindin_VI (105)             |                                 | Soil             | [40]   |
| Trichokindin_VII (106)            | Induced catecholamine secretion | Soil             | [40]   |
| Harzianin_HB_I (107)              | Membrane-modifying activity     | Soil             | [42]   |
| Trichorzin_HA_I (108)             | Antifungal                      | Soil             | [43,44]|
| Trichorzin_HA_II (109)            | Antifungal                      | Soil             | [43,44]|
| Trichorzin_HA_III (110)           | Antifungal                      | Soil             | [43,44]|
| Trichorzin_HA_V (111)             | Antifungal                      | Soil             | [43,44]|
| Trichorzin_HA_VI (112)            | Antifungal                      | Soil             | [43,44]|
| Trichorzin_HA_VII (113)           | Antifungal                      | Soil             | [43,44]|
| Trichorzin_MA_I (114)             | Antifungal                      | Soil             | [43,44]|
| Trichorzin_MA_II (115)            | Antifungal                      | Soil             | [43,44]|
| Trichorzon_MA_III (116)           | Antifungal                      | Soil             | [43,44]|
| Trichorzon_I (117)                | ion channel activity            | Soil             | [45]   |
| Trichorzon_II (118)               | ion channel activity            | Soil             | [45]   |
| Trichorzon_III (119)              | ion channel activity            | Soil             | [45]   |
| Trichorzon_IV (120)               | ion channel activity            | Soil             | [45]   |
| Harzianin_HC_I (121)              | Antibacterial                   | —                | [46]   |
| Harzianin_HC_II (122)             | Antibacterial                   | —                | [46]   |
| Harzianin_HC_VI (123)             | Antibacterial                   | —                | [46]   |
| Harzianin_HC_VIII (124)           | Antibacterial                   | —                | [46]   |
| Harzianin_HC_IX (125)             | Antibacterial                   | —                | [46]   |
| Harzianin_HC_X (126)              | Antibacterial                   | —                | [46]   |
| Harzianin_HC_XI (127)             | Antibacterial                   | —                | [46]   |
| Harzianin_HC_XII (128)            | Antibacterial                   | —                | [46]   |
| Harzianin_HC_XIII (129)           | Antibacterial                   | —                | [46]   |
| Harzianin_HC_XIV (130)            | Antibacterial                   | —                | [46]   |
| Harzianin_HC_XV (131)             | Antibacterial                   | —                | [46]   |
| Harzianin_PC4 (132)               | —                               | —                | [47]   |
| Trichorzin_PA4 (133)              | —                               | —                | [47]   |
| Trichorzin_PA_II (134)            | —                               | —                | [47]   |
| Trichorzin_PA_IV (135)            | —                               | —                | [47]   |
| Trichorzin_PA_V (136)             | —                               | —                | [47]   |
| Trichorzin_PA_VI (137)            | —                               | —                | [47]   |
| Trichorzin_PA_VII (138)           | —                               | —                | [47]   |
| Trichorzin_PA_VIII (139)          | —                               | —                | [47]   |
| Trichorzin_PA_IX (140)            | —                               | —                | [47]   |
| Trichorzianine_TA_IIlc (141)      | Anti-parasite                   | —                | [48]   |
| Trichorzianine_TB_Bla (142)       | —                               | —                | [49]   |
| Trichorzianine_TB_IIlc (143)      | —                               | —                | [49]   |
| Trichorzianine_TB_IVb (144)       | —                               | —                | [49]   |
| Trichorzianine_TB_Vb (145)        | —                               | —                | [49]   |
| Trichorzianine_TB_Vla (146)       | —                               | —                | [49]   |
| Trichorzianine_TB_Vlb (147)       | —                               | —                | [49]   |
| Trichorzianine_TB_VII (148)       | —                               | —                | [49]   |
| Trichodermaidamide G (149) *      | —                               | Mangrove         | [50]   |
| Trichodermaidamide A (150) *      | —                               | Mangrove         | [50]   |
| Aspergillazin A (151) *           | —                               | Mangrove         | [50]   |
| Fleephilone (152)                 | Antivirus                       | Soil             | [27]   |
| Harzianic acid (153) *            | Antibacterial                   | Water sample     | [51]   |
| Isoharzianic acid (154)           | Plant growth promotion          | Hardwood bark    | [52]   |
| Ethyl 2-bromo-4-chloroquinoline-3-carboxylate (155) | —         | Soft coral       | [20]   |
| Harzianopyridone (156)            | Antifungal                      | Soil             | [21]   |
| MR566A (157)                     | Melanin synthesis inhibition    | Soil             | [54,55]|
| MR568B (158)                     | Melanin synthesis inhibition    | Soil             | [54]   |
| MR93A (159)                      | leaf                            | —                | [53]   |
| MR93B (160)                      | Soil                            | —                | [54]   |
| MR304A (161)                     | Soil                            | —                | [54]   |
Table 2. Cont.

| Compounds | Bioactivities | Habitats | Refs |
|-----------|--------------|----------|------|
| 1-(1,4,5-Trihydroxy-3-isocyanocyclopent-2-enyl)-ethanol (162) | — | Soil | [54] |
| 2-Hydroxy-4-isocyano-α-methyl-6-oxabicyclo[3.1.0]hex-3-ene-2-Methanol (163) | — | Soil | [54] |
| 4-Hydroxy-8-isocyano-1-oxaspiro[4.4]cyclonon-8-en-2-one (164) | — | Soil | [54] |
| Methyl-3-(1,5-dihydroxy-3-isocyanocyclopent-3-enyl)prop-2-enoate (165) | — | Soil | [54] |
| 3-(3'-Isocyanocyclopent-2'-enylidene)propionic acid (166) | Melanin synthesis inhibition | Soil | [54,55] |
| Xylogiblactone A (167) * | — | Soft coral | [20] |
| Xylogiblactone B (168) * | — | Soft coral | [20] |
| Nafuredin C (169) * | Antifungal | Mangrove | [50] |
| Nafuredin A (170) * | — | Mangrove | [50] |
| Dichlorodiaportin (171) * | Antifouling | Soft coral | [20] |
| 6-Pentyl-2H-pyran-2-one (172) | Antifungal | Soil | [21,58] |
| 2(5H)-Furanone (173) | — | Soil | [21] |
| δ-Decanolactone (174) | — | Soil | [21] |
| Penisosoumarin H (175) * | — | Mangrove | [50] |
| Harzialactone A (176) * | — | Sponge | [32] |
| Harzialactone B (177) * | — | Sponge | [32] |
| R-Mevalonolactone (178) * | — | Sponge | [32] |
| Harzialonolide (179) | — | Commercial products | [30] |
| T39butenolide (180) | Antifungal | Commercial products | [30] |

* Means marine source fungal strains.

Figure 7. The SMs of T. harzianum from marine and terrestrial sources, and its distribution.

Figure 8. Proportion of SMs obtained from T. harzianum.
This review covers papers on metabolites isolated from *T. harzianum*. From the SMs’ distribution point of view, marine sources account for 45%, while terrestrial sources were 38%. From marine sources, 31 compounds were from sponges-derived *T. harzianum* strains, 30 compounds were isolated from soft corals-derived *T. harzianum* strains, 10 compounds were from brown alga-derived *T. harzianum* strains, 6 compounds were from mangrove samples-derived *T. harzianum* strains, and 3 compounds were from marine sediment samples. *T. harzianum* strains and their secondary metabolites were mainly derived from sponges (39%) and soft corals (38%). From the terrestrial sources, 46 compounds were purified from soil samples-derived *T. harzianum* strains, 13 compounds were from endogenous and 5 compounds were purified from mushroom-derived fungal strains. Compounds derived from terrestrial soil samples account for 67%. For the structure type proportion of the SMs isolated from *T. harzianum*, the peptides, polyketides, and terpenoids account for 31%, 27%, and 26%, respectively, followed by alkaloids (8%) and lactones (8%). Marine-derived terpenoids and polyketides have 39 and 28 natural products among the 47 and 48 total compounds, respectively. Notably, 91 of the 180 SMs exhibited bioactivities. Antifungal...
activity was exhibited by 27 natural products, and 17 compounds possessed phytotoxicity activity, while antibacterial and cytotoxicity activity SMs number were all 14. In the research on phytotoxicity and cytotoxic active products, almost all the active natural products were from marine-derived *T. harzianum* strains. Moreover, 120 of the 180 compounds were new. In summary, organic compounds are abundant in the SMs of *T. harzianum*, they may be used as a fungicide, antibacterial, antineoplastic, and weedicide, both in clinical and agricultural applications. The marine sources molecules (marked * in this paper) with their unique molecular and diverse activities, could be the basis for the development of new drug-forming lead compounds.

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