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Review

Chromatographic and mass spectroscopic guided discovery of *Trichoderma* peptaibiotics and their bioactivity

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ABSTRACT

Peptaibiotics are linear or cyclic peptide antibiotics characterized by the non-proteinogenic amino acid, alpha-aminoisobutyric acid. They exhibit a wide range of bioactivity against various pathogens. This report presents a comprehensive review of analytical methods for *Trichoderma* cultivation, production, isolation, screening, purification, and characterization of peptaibiotics, along with their bioactivity. Numerous techniques are currently available for each step, and we focus on describing the most commonly used and recently developed chromatographic and spectroscopic techniques. Investigating peptaibiotics requires efficient culture media, growth conditions, and isolation and purification techniques. The combination of chromatographic and spectroscopic tools offers a better opportunity for characterizing and identifying peptaibiotics. The evaluation of the chemical and biological properties of this compound has also been explored concerning its potential application in pharmaceutical and other industries. This review aims to summarize available data on the techniques and tools used to screen and purify peptaibiotics from *Trichoderma* fungi and bioactivity against various pathogens.

1. Introduction

The genus *Trichoderma* represents one of the most diversified groups of free-living filamentous fungi in the family Hypocreaceae, commonly found in all types of soil. These fungi have been developed as biocontrol agents against several fungal diseases [67]. Their diverse metabolic capabilities enable them to produce various bioactive secondary metabolites with significant applications in agriculture, health, industry, and the environment [1,106]. These bioactive compounds have demonstrated antibacterial, antifungal, and antiviral properties [91]. Peptaibiotics are among the non-ribosomal polypeptides found in *Trichoderma*, consisting of 4–20 residue peptides (500–2200 Da) with α-aminoisobutyric acid (Aib) and other noncanonical amino acids frequently occurring in the main peptide chain [121]. They possess an acylated N-terminus, while the C-terminus may include a free or methoxy-substituted 2-amino alcohol, amine, amide, free amino acid, diketopiperazine, or sugar alcohol [12,27,106,113].

Peptaibiotics consist of two main sub-classes: peptaibols and lipoaminopeptides[106]. Peptaibols are structurally distinctive peptaibiotics that typically consist of amino acid chains ranging from 5 to 20 mers [27,59,112,113,123]. They contain a high proportion of non-proteinogenic α, α-dialkylated amino acids, such as 2-aminoisobutyric acid (Aib) and isovaline (Iva), as well as an acetylated N-terminus. Additionally, they include 1, 2-amino alcohols such as Leuol, Valol, Pheol, Tyrol, Ileol, Alaol, and Prool at the C-terminus [12,29]. The peptide backbone is typically dominated by α-aminoisobutyrate (Aib) compared to other non-proteinogenic amino acid residues. This dominance imposes significant conformational constraints on the backbone, facilitating the formation of a right-handed α-helical structure [9,66]. Peptaibols are produced by most *Trichoderma* species, and alamethicin F30 was the first peptaibol reported from *T. viride* [14,27,69,113]. However, the strain was later identified as *T. arundinaceum*, a species belonging to the Brevicompactum clade [29,59]. The other subfamily of peptaibiotics containing lipoaminoacids among the general non-proteinogenic amino acids was named “lipoaminopeptides” [27,113].

Based on their chain length and sequence alignment, peptaibiotics are categorized into three subclasses and nine subfamilies (SF1 to SF9) respectively [22]; 1) long-sequence peptaibols consist of 18–20 amino acid residues with a high content of Aib, 2) short sequence peptaibols having 11–16 residues long and several Aib-Pro motifs, and 3) lipopeptaibols consist of either 7 or 11 residues, characterized by a significant amount of glycine, C-terminal amino alcohol, and an N-terminal

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acylated by an 8-10 carbon linear fatty acid [37]. The 9 subfamilies (SF1-SF9) are classified based on sequence alignment, structures, and specific amino acid compositions [22]. Among these subfamilies, SF1, SF4, SF5, and SF9 belong to *Trichoderma* fungi [106]. SF1 is the largest SF (17–20 residues) and is characterized by the prevalence of Gln, mostly at positions 6 or 7. Gln or Glu residues are commonly found at the C-terminal end, while Aib-Pro motifs frequently occur at positions 13 or 14. A Gln-Gln or Glu-Gln pair typically exists at the 18th or 19th positions. Sequences in this subfamily commonly feature Gln predominantly at the 6th or 7th positions, Aib-Pro bonds in the middle, and Gln or Glu at the 18th or 19th positions. Shorter sequences usually contain only a single Gln residue [22]. These sequences are characterized by the frequent presence of Aib, suggesting the formation of α-helical structures. SF4 members differ significantly from other subfamilies, containing either 11 or 14 amino acids. They contain a conserved Gln or Asn residue at the 2nd position. The 11-residue members have two Pro at positions 9 and 13, whereas the 14-residue members have three Pro at positions 5, 9, and 13. SF5 peptaibols are short and referred to as Gly-rich, containing either 7 or 11 residues. Their sequences never include Pro, Gln, or any charged residue. SF9 comprises the smallest peptaibol with 5 residues, namely trichopolins I, II, III, IV, and V. These sequences differ significantly, preventing their classification into any other subfamilies [22,106].

The amphipathic nature of peptaibiotics enables them to self-associate into oligomeric ion-channel assemblies that span the width of lipid bilayer membranes [22]. This bilayer membrane pore-forming and destabilizing behavior exhibited by many of these compounds contributes significantly to their potent antimicrobial and cytotoxic activities. Their action is particularly challenging for pathogens and tumor cells to develop resistance against [86,106,116,120]. The physicochemical and biological properties of peptaibiotics also render them effective as antiviral, anti-tumoral, and antimycoplasmic agents [78,106]. Furthermore, when they act synergistically with cell wall-degrading enzymes, they function as elicitors in plant defense mechanisms. They induce local or systemic resistance in plants against microbial invasion. These activities trigger a cascade of plant antifungal proteins, such as chitinases and glucanases, in response to the impending attachment of the pathogen [41].

The process of discovering and identifying peptaibiotics involves a sequence of steps. It begins with cultivating and fermenting fungi on solid media, followed by the extraction of peptaibols either from the culture medium or the mycelium using organic solvents. Purification and enrichment of peptaibiotics can be achieved through liquid chromatography (LC) employing polar or nonpolar stationary phases. Various detection techniques such as ultraviolet (UV) and mass spectrometry can be utilized [106]. This review aims to summarize available data on cultivation techniques, extraction and purification methods, chemical profiling techniques, structural diversity, and the biological activity of peptaibiotics discovered from *Trichoderma* fungi species.

1.1. Cultivation of Trichoderma for peptaibiotic production

The optimization and formulation of nutrient media and culture conditions represent critical steps in the production of novel compounds from *Trichoderma* fungi [105,109]. However, the selection and optimization of a medium can vary depending on the specific *Trichoderma* species. Efficient production and purification of surface-active compounds necessitate an optimal culture medium and growth conditions, which are crucial for characterizing the structure and function of novel compounds. The screening of peptaibiotics from *Trichoderma* spp. generally follows similar procedures, except for a few specific groups of *Trichoderma*. This process often involves growing mycelial cultures on solid-phase or broth media and subsequent extraction using various organic solvents from the ferment [7,11,20,120]. Culture conditions, such as temperature, pH of the media, fermentation cycle, and aeration, are typically controlled. In most laboratories, preparing a seed culture in appropriate nutrient media is a prerequisite for large-scale cultivation of the desired *Trichoderma* strain and the production of sufficient bioactive compounds. Fermentation is carried out by incubating the culture under consistent illumination, agitation, and aeration at temperatures ranging from 25°C to about 30°C. The pH of the medium is maintained between approximately 5.8 to 7.0 for an adequate growth cycle [114]. The production of peptaibols and lipopeptaibols using this method depends on various fermentation factors, such as nutrient composition (carbon and nitrogen sources), inoculum size, incubation and fermentation temperature, pH, initial moisture content, and culture oxygen levels [110,111,114]. Analytical cultivation of *Trichoderma* fungi and the production of peptaibols and lipopeptaibols can be achieved using diverse nutrient media, including potato dextrose agar (PDA), malt extract agar (MEA), peptone yeast glucose (PYG), dextrose casein agar (DCA), *Trichoderma*-selective agar medium (TSM), and Sabouraud medium (Difco Sabouraud agar). Additionally, the addition of small amounts of inorganic salts, such as $MgSO_4$, $FeCl_2$, $MnSO_4$, $ZnSO_4$, KCl, K_2HPO_4, KNO_3, $Ca(H_2PO_4)_2$, $CuSO_4$, and $FeSO_4$ can significantly enhance the cultivation and production of these compounds [21,28,34,50,56,57,65,114,121].

1.2. Isolation and Purification of Peptaibiotics

Fermentation of fungi under suitable culture mediums and conditions stand as a crucial step for successfully isolating and purifying bioactive compounds. This process typically involves a series of steps, beginning with compound extraction from the culture medium or mycelium, followed by purification from matrix components, analyte enrichment, and eventual chromatographic separation. Peptaibiotics purification and separation entail the utilization of diverse chromatographic tools and solvents based on polarity. Notable methods include open column chromatography (OCC), vacuum liquid chromatography (VLC), high-performance liquid chromatography (HPLC), gel filtration chromatography (using Sephadex LH20 with MeOH as the eluent), adsorption chromatography (using SiO_2 with CH_2Cl_2/MeOH as the eluent), and semi-preparative reversed-phase HPLC (employing methanol/water as the eluent) [6,24,32,106,113]. Combining these techniques with various extraction procedures further enhances the process. For instance, Amberlite XAD-2 column chromatography using methanol (MeOH) and acetone as eluents, silica gel chromatography conditioned with chloroform ($CHCl_3$) and (MeOH), and reverse-phase (RP-C18 or RP-C8) cartridges with MeOH and water as eluents have been used for isolating trichodecenins and profiling trichorzianines [37,106]. Other methods, such as single-step offline vacuum liquid chromatography (VLC) with dichloromethane/ethanol mixtures as eluents and diol-phase gel chromatography, have also proven effective for extraction and purification of peptaibiotics [56,72]. The selection, application, and underlying principle behind the separation techniques depend on factors such as molecular size, adsorption to the stationary phase, polarity, solubility of the mobile phase or analyte, and the hydrophobic and hydrophilic interaction between the solute and resin surface [55]. Various chromatographic techniques are commonly used for both quantitative and qualitative analyses of bioactive compounds extracted from diverse biological samples, including fungal samples.

1.2.1. Thin layer chromatography (TLC)

TLC is a cost-effective and rapid technique used for separating and analyzing compound mixtures in samples, devoid of the need for sophisticated instrumentation. While crucial for identifying the chemical nature of peptides and monitoring the number, progress, quality, and purity of raw peptide extracts within mixtures, TLC has limitations in terms of resolution, sensitivity, selectivity, and sample capacity [102]. The process involves a glass plate coated with silica of varying thickness where samples are loaded and a solvent is allowed to run through for identification. These results in the creation of TLC bands, which are visualized under UV light or other non-destructive techniques based on the sample type. Subsequently, compounds separated on TLC plates can be scraped or further extracted using solvents [99]. TLC separates compounds with different properties by leveraging diverse interactions between solutes, the sorbent (silica), and the mobile phase [98]. In the context of peptaibiotics, TLC is commonly employed to detect, identify, and monitor their formation during *Trichoderma* culture fermentation, in conjunction with multiple separation techniques [49,80]. For instance, within the suzukacillins peptaibiotics (SZ-A and SZ-B) derived from *T. viride* strain 63 C-1, TLC was instrumental in distinguishing between the two microheterogeneous [95].

1.2.2. Column chromatography

Column chromatography stands as one of the most valuable methods for separating and purifying both solids and liquids, particularly in small-scale experiments. This technique facilitates liquid/solid (adsorption) or liquid/liquid (partition) separation. In this process, a vertical glass column contains the stationary phase, typically a solid adsorbent, where the mobile phase and sample are introduced from the top and allowed to flow down through the column using either gravity or external pressure. It plays a vital role in separating individual mixtures of molecules like sugars, proteins, and other substances, essential for subsequent experimentation [70]. Macroporous resin chromatography is particularly important for efficiently separating lipopeptide mixtures into distinct families by employing a straightforward stepwise solvent gradient elution under optimal conditions [51]. The properties of the resin, such as particle size, pore diameter, surface area, and polarity, dictate the separation of bioactive compound mixtures.

Various column chromatographic techniques are employed in peptide separation, including liquid chromatography (LC), high-performance liquid chromatography (HPLC), and reverse-phase high-performance liquid chromatography (RP-HPLC).

Liquid chromatography (LC) stands as the primary technique for efficiently separating and isolating similar or dissimilar compounds. The interaction between the sample mixture and the stationary phase packed in a column determines the separation of each component. Compounds with a stronger interaction with the stationary phase remain in the column longer than those with weaker interactions, thus leading to their separation. Individual chromatographic peaks represent distinct molecules at specific retention times, while the peak height and area directly relate to the concentration of the compound present in the mixture [23].

The demand for enhanced resolution and faster separation in liquid chromatography (LC) has led to the evolution of high-performance liquid chromatography (HPLC), subsequently followed by ultra-high-performance liquid chromatography (UHPLC). This specialized form of column chromatography finds utility in separation, biochemical analysis, identification, quantification, and purification of complex and clustered surface-active compounds from biological samples. These techniques are particularly valuable in identifying proteins and their peptide fragments, offering significant improvements in speed, resolution, and sensitivity. This is achieved through the utilization of stationary phases comprising very small and uniform porous particles with high ligand densities, operated at pressures of up to approximately 15,000 psi [13,46,115]. HPLC and UHPLC can be operated in either normal phase or reversed phase models [14,23]. Normal phase liquid chromatography (NPLC), encompassing both HPLC and UHPLC, involves a polar stationary phase that interacts strongly with solutes compared to the non-polar mobile phase. Initially, non-polar solutes elute first, based on the composition and ratio of polar and non-polar solvents, followed by the elution of non-polar solvents [14,68]. The commonly used stationary phase for HPLC separation is ODS (octadecylsilane), consisting of C18, C8, and C4 alkyl chains covalently bonded to silica particles [55]. The C-18 column, mainly employed for polypeptide separation, varies in length from 150 to 250 mm depending on the desired resolution and separation [118,127]. HPLC's resolving power makes it ideal for the rapid processing of multi-component samples on both analytical and preparative scales, utilizing water/acetonitrile (MeCN) or methanol/water gradient solvents. It serves to identify, quantify, and purify individual components of peptaibiotics mixtures from samples at different wavelengths using a detector [96]. For instance, the HPLC separation of 20-residue peptaibols (Longibrachins LGB II and LGB III) from *T. longibrachiatum* involved a liquid chromatograph using a semi-preparative reversed-phase C18 column with MeOH-H2O-trifluoroacetic acid (TFA) as the eluent [58]. Similarly, two peptides subfractions, namely TVA and TVB, were obtained from *T. virens* strain TV29-8 culture filtrates using exclusion chromatography and silica gel chromatography. The elution system employed MeOH-H_2O, with the separation leading to six main peaks in the TVB group. This mixture was further analyzed by semi-preparative HPLC, yielding TVB I to VI peptaibols. Subsequent spectral analysis revealed TVB I, II, and IV as homogeneous Trichorzins peptaibols, while TVB III, V, and VI remained a mixture of peptides [124].

RP-HPLC is widely recognized and preferred due to its versatility in applications and the availability of diverse mobile and stationary phases. In contrast to Normal Phase Liquid Chromatography (NPLC), RP chromatography involves using a nonpolar stationary phase in conjunction with a polar mobile phase, typically a blend of water and an organic solvent miscible with water. This technique's online coupling with sample preparation and detection units, particularly MS, renders it an ideal choice in proteomics research [3]. RP-HPLC finds extensive use in isolating, separating, structurally characterizing, quantifying, and purifying peptaibiotic components from various representative strains of *Trichoderma* fungi [6,17,18,48,49,90,94]. For instance, lipopeptaibols were purified and analyzed using reversed phase (RP)-HPLC with UV detection at 226 nm on semi-preparative C18 columns [74]. Similarly, cytotoxic lipopeptaibols (lipovelutibols A–D) from *T. velutinum* fungi were purified through semi-preparative RP-HPLC using a Reprosil Gold C18 column. Elution was performed using acetonitrile-water and methanol-water gradients at different proportions, monitored at 214 nm [106]. Moreover, an analytical Vydac Protein & Peptide, C18 platform was employed for detecting peptaibols from *T. asperellum* TR356 extract chromatogram. This method utilized gradient elution of MilliQ water with 0.1% trifluoroacetic acid (TFA) and acetonitrile with 0.1% TFA, monitored by UV detection at 216 and 280 nm [15,16].

1.3. Mass spectroscopic guided discovery and profiling of peptaibiotics

Mass spectrometry has emerged as a formidable tool for identifying and profiling polypeptide antibiotics from various biological samples [19]. In previous years, spectroscopic tools such as field desorption (FD), fast atom bombardment (FAB) MS, Ion Spray Ion Trap MS (ISI-MS), and Electrospray Ion Trap MS (ESI-MS) were employed for peptide molecule and peptaibiotics identification [26,45,49,83]. Presently, high-throughput and efficient spectroscopic tools like Matrix Assisted Laser Desorption Ionization-Time of Flight MS (MALDI-TOF-MS), liquid chromatography electrospray ionization quadrupole time of flight tandem MS (LC/ESI-QTOF MS/MS), Ultra High-Performance Liquid Chromatography (UHPLC) coupled with QTOF instrumentation, and Nuclear Magnetic Resonance (NMR) are widely utilized for investigating, detecting, evaluating, and analyzing biochemical properties, including peptaibiotics [4,13,25,51,87,111].

These tools have proven highly effective in determining molecular mass and structural information of peptides and proteins. Mass spectrometry aids in peptide identification by analyzing the mass-to-charge ratio (*m/z*) of ions, generating a mass spectrum from the plot of ion abundance versus m/*z*. Additionally, MS and tandem MS (MS/MS) techniques have significantly contributed to determining amino acid sequences and elucidating primary structures of peptides, even in complex mixtures. However, certain biomolecules cannot be ionized by the 'classical' electron ionization (EI) technique, typically used for volatile molecules, limiting its application to thermally stable compounds with low molecular weights [100]. The development of 'soft-ionization' techniques like electrospray ionization and matrix-assisted laser desorption/ionization has addressed this limitation. Nonetheless, MS cannot accurately determine peptaibols containing high numbers of isoform amino acid sequences such as leucine (Leu)/isoleucine (Ile) or valine (Val)/isovaline (Iva). Resolving such complexities often necessitates a combination of different spectroscopic tools and chemical derivatization methods. High-resolution electrospray ionization mass spectrometry (HRESIMSn) and 1D and 2D nuclear magnetic resonance (NMR) are typically used to identify amino acid compositions and sequences.

Determining the absolute configuration of each constituent amino acid involves techniques such as Marfey's method [44]. The process begins with acid hydrolysis followed by derivatization using Na-(2, 4-dinitro-5-fluorophenyl)-L-alaninamide, commonly referred to as Marfey's reagent. Comparison of the retention times between amino acid-Marfey's derivatives and derivatized D and L standards for each amino acid is performed using LC-UV at a wavelength of 340 nm [94]. This method is pivotal in assigning absolute configurations to amino acids. To enhance accuracy and reliability, High-Resolution Mass Spectrometry (HRMS) and Nuclear Magnetic Resonance (NMR) are integrated into Marfey's analysis, providing corroborative data and mitigating uncertainties associated with UV data alone. Moreover, in scenarios where Electrospray Ionization Mass Spectrometry (ESI-MS) fails to differentiate Val/Iva, Val-OH/Iva-OH, Leu/Ile, or Leu-OH/Ile-OH, Gas Chromatography Mass Spectroscopy (GC-MS) proves to be a valuable alternative for analyzing derivatized amino acids [72]. Each spectroscopic tool used for peptide analysis holds specific advantages and limitations. Optimal selection of techniques and devices hinge upon factors such as solubility, charge, stability, and molecular size of the target compound.

1.3.1. FD-MS and FAB-MS

Fast atom bombardment (FAB), introduced as a pivotal technique for ionizing polar and non-volatile molecules normally unresponsive to electron ionization, has found extensive application in the realm of peptides and proteins [8]. The utilization of tandem mass spectrometry (MS/MS) combined with FAB has enabled the molecular identification of biochemical molecules and amino acid sequences in peptides [26]. Field desorption (FD) and fast atom bombardment (FAB) mass spectrometry (MS) have also successfully facilitated direct structural analysis of synthetic and biological polypeptides, as well as various peptide metabolite conjugates [30,38,83]. HPLC coupled with FD-MS and both positive and negative ion FAB-MS offers a highly sensitive and universal method for directly resolving and characterizing peptaibol components. Definitive structures of peptaibol antibiotics from different representative strains of *Trichoderma* fungi, exhibiting pronounced micro-heterogeneity, have been characterized using HPLC, FD-MS, and particularly FAB-MS. HPLC serves the purpose of investigating and isolating components, determining constituents, and quantifying relative amounts of polypeptides from *Trichoderma* fungi. Conversely, FD-MS and FAB-MS are used to evaluate individual molecular masses of each compound. Additionally, the combination of FAB-MS with selective acidolysis at the preferential cleavage site aids in sequencing and analyzing the isolated components [19]. For instance, FD-MS and FAB-MS have confirmed the structural identity of various peptaibols such as samarosporin, stilbellin, and emerimicini [18].

Positive ion FAB mass spectroscopy is used for sequence analysis and molecular formula determination of 11-residue Trichogin A IV (GA IV) lipopeptaibol isolated from *T. longibrachiatum*. It is characterized by two pseudo molecular ion species, $(M + Na)^+$ at m/z 1088 and $(M + K)^+$ at *m/z* 1104 with a molecular weight of 1065 and molecular formula of $C_{52}H_{95}O_{12}N_{11.}$ The amino acid sequences of this compound were also determined as X-Aib-Gly-Leu (Ile)-Aib-Gly-Gly-Leu (1le)-Aib-Gly-Leu (Ile)-Leuol, which was assigned from Acylium fragments at *m/z* 949, 836, 779, 694, 581, 524, 467, 382, 269, 212, and 127 Da [6]. Similarly, the amino acid sequence and molecular structure of several peptaibols synthesized by various species of *Trichoderma* fungi were determined using FAB-MS and FAB MS/MS [25,92].

1.3.2. MALDI-TOF Mass Spectrometry

Matrix Assisted Laser Desorption/Ionization-Time of Flight-Mass Spectrometry (MALDI-TOF-MS) has become widely adopted in proteomics due to its high mass accuracy, resolution, excellent sensitivity, and high throughput capability. Its precision in mass analysis and low detection limit are especially valuable in identifying low-abundance proteins [52]. To obtain a well-defined peptide mass fingerprint, necessary for maximum fragments derived from the original protein, a tiny amount of fungal mycelia is directly spotted on the MALDI-TOF sample plate and overlaid immediately with a matrix solution. Each sample is then ablated with laser energy, producing ions via pulsed-laser irradiation. MALDI-TOF-MS spectra, recorded in positive ion mode within an m/z range of 500-2,500, monitor the production of peptide secondary metabolites. The resulting ions are vacuum transferred for mass analysis, followed by an MS spectra-based dereplication process to identify strains with unique MALDI-TOF-MS fingerprints [39]. Various matrix compounds like trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile, α-cyano-4-hydroxycinnamic acid matrix (α-CHCA), 2,5-dihydroxybenzoic acid (DHB), sinapinic acid (SA), and a mixture of DHB-CHCA are used for MS analysis of intact peptides. These matrices absorb the laser's wavelength and indirectly vaporize the analyte, ionizing it in both positive and negative modes [15,31,75,76,104,122,125]. However, the type of matrix and the deposition technique can influence the quality of MALDI spectra. The sample and matrix are usually mixed and dried before being introduced into the vacuum system. After irradiation, the gas-phase ions formed are directed towards the mass spectrometer [39]. MALDI is particularly useful for rapidly detecting peptaibols types from mycelia/conidia, analyzing whole cells, tissues, polymers, and peptides, identifying intact peptides, and determining the full molecular mass of purified peptides. Nevertheless, its limitations in peptaibiotics discovery include the inability to generate peptide fragments and a tendency to display pseudo-molecular ions like $[M + H]^+$, $[M + Na]^+$, $[M + K]^+$, $[2M + H]^+$ and $[2M + Na]^+$.Furthermore, the presence of a matrix, aiding ionization, causes substantial chemical noise below m/z ratios of 500 Da, making analysis challenging for samples with low molecular weights [25].

Matrix-assisted laser desorption ionization time of flight mass spectrometry imaging mass spectrometry (MALDI-TOF-IMS) is an emerging approach allowing direct observation of bioactive natural products between two fungi colonies on growth media, expediting the discovery of new bioactive compounds in fungi. Using an 'intact cell matrix assisted laser desorption/ionization-time of flight mass spectrometry' (IC-MALDI-TOF-MS) approach, about 15 positively identified species of *Trichoderma*/Hypocrea are known to produce peptaibiotics, significantly enhancing peptaibiotics screening efficiency [60,74,75]. Analysis and detection of the 20 residue Atroviridins and other new peptaibols from the crude extracts *T. atroviride* 01 strain, solution conformational analysis of amphiphilic helical and synthetic analogs of the lipopeptaibol trichogin GA IV, and the peptaibols *asperelins* A and E, Trichotoxins T5D2, 1717A and A-50 E, F and G from *T. asperellum* TR356 strain, profiling of 11-residue and 14-residue peptaibol from *T. virens* and paracelsin family of peptaibols from *T. citrinoviride* were performed by MALDI-TOF mass spectrometry [15,63,73,74,121].

1.3.3. Liquid chromatography mass spectroscopy (LC-MS)

Liquid chromatography and tandem mass spectrometry (MS/MS) represent powerful techniques that offer exceptional capabilities for rapid, cost-effective, and quantitative measurements of organic molecules across various applications. This method combines the physical separation capabilities of liquid chromatography with the mass analysis provided by mass spectrometry. In MS/MS, multiple stages of mass analysis can be performed, often involving molecular fragmentation between these stages [55]. This can be achieved through either multiple mass analyzers separated in space or a single mass analyzer operated differently in time. Instruments such as QTOF, QqQ, and Orbitrap support tandem MS capabilities. The integration of LC with MS enables the determination of the elemental composition and structural elucidation of biological samples [82]. This combination is particularly useful for the efficient, sensitive, and specific detection and analysis of complex mixtures containing hundreds of proteins and peptides at various concentrations [61,64,81]. The sample first undergoes separation by LC and is then sprayed into an atmospheric pressure ion source, converting it into ions in the gas phase. The MS analyzer subsequently sorts the ions based on their molecular mass-to-charge ratio, while the detector counts the ions emerging from the mass analyzer and may amplify the signal generated by each ion. Consequently, a mass spectrum is created (a plot of the ion signal as a function of the mass-to-charge ratio), aiding in the determination of the elemental or isotopic nature of a sample, determining the masses of particles and molecules, and elucidating the chemical structures of the molecules present [53,61]. This technique is highly valuable for detecting and analyzing intricate mixtures containing numerous polypeptides at different concentration levels [60,64,81].

LC/MS utilizes a mobile phase like water, acetonitrile, and methanol with or without formic acid at different concentration for isocratic and gradient eluting of peptides at different time intervals [126]. Thus, an efficient high-resolution LC-MS method is a prerequisite for the purification of microbial polypeptides, which is required for subsequent commercialization of polypeptides as a potential for several application [42,119]. It is best suited for a discovery-based approach when working on unknown peptides, as many peptides are readily amenable to LC/MS analysis. The method relies on the generation of so-called in-source fragments by collision-induced decomposition mass spectrometry (CID-MS) to the skimmer region of an electrospray ionization (ESI) mass spectrometer [44]. Online coupling of LC with MS for the analysis of peptaibols usually includes electrospray ionization and subsequent MS and MS/MS detection. MS full scan spectra can provide information such as the molecular mass of intact peptaibols (derived from $[M+H]^+$, $[M-H]^-$, molecular ions accompanied by typical adduct ions (such as $[M+Na]^+$, $[M+NH_4]^+$, $[M+K]^+$, and several charged ions), as well as the charge states of the ions formed by the ion source [101]. The major advantage of using LC/MS is for the selective detection, separation, and characterization of mixtures of peptaibiotics from diverse sources with a high degree of similarity [28,49,54]. ESI and atmospheric-pressure chemical ionization (APCI) are effective ionization techniques used for LC-MS for a wide range of compounds, including high molecular weight, nonvolatile, polar, and thermally labile compounds. In addition, it is very advantageous to determine the molecular weights of macromolecules accurately without the operational problems involved in generating a matrix [39]. It is also best suited for a discovery-based approach when working on unknown peptides. The coupling of LC with MS provides the advantages of characterizing retention time of a given peptide including peptaibiotics along with its mass spectral signature, allowing the analysis of complex mixtures of peptaibiotics. It is very sensitive for quantification of peptaibols of very low quantities (5 ng/g) in natural environmental samples. Generally, LC-MS is rapid, cost-effective, and quantitative measurements of peptaibiotics in an enormous variety of applications. However, the soft ionization techniques of electrospray ionization LC-ESI-MS will usually not induce fragments to determine the amino acid sequences of peptaibiotics. In addition, though, ESI-MS methods were improved with the different collision-induced dissociation (CID) techniques such as tandem CID-MS/MS to determine the sequence of amino acids, these methods leave certain positions with isomeric amino acids (e.g., Leu or Ile; Val or Iva) undetermined, therefore the elucidation of the complete sequence requires further examinations [106].

1.4. Diversity and biological activity of Peptaibiotics

The secondary metabolites obtained from various species of *Trichoderma* have demonstrated numerous biological activities and are commercially employed as bio-protective agents against various diseases. Peptaibiotics, among these bioactive metabolites, have attracted considerable interest due to their diverse biological effects encompassing antibacterial, antifungal, antiviral, antitumor, and neuroleptic properties. Studies have revealed that both Gram-positive and Gram-negative bacteria exhibit sensitivity to these membrane-active compounds, although Gram-positive bacteria tend to be more sensitive than Gram-negative bacteria [10,62]. Peptaibiotics have also exhibited antagonistic effects against phytopathogenic fungi [85]. For example, several disease-causing fungi strains including *Lentinula edodes, Flammulina velutipes, Pleurotus ostreatus, Saccharomyces cerevisiae, Candida albicans, C. utilis, Cryptococcus neoformans, Penicillium chrysogenum, Aspergillus niger, A. fumigatus*, and *Trichophyton mentagrophytes* were inhibited by Trichopolin I (A) and II (B) peptaibiotics [36]. On the other hand [62], explained the synergism between peptaibols and the inhibition of the membrane-bound β-1, 3-glucan synthase of the host could inhibit the re-synthesis of β-glucans of the host cell wall and sustain the disruptive action of β-glucanases, and all together resulted in an enhanced fungicidal activity. Peptaivirins A and B was the first antiviral peptaibiotics reported against the tobacco mosaic virus (TMV) infection of tobacco plant (*Nicotiana tabacum*) plant [128]. Studies also highlight the interaction of plants with *Trichoderma*, indicating that peptaibols from *Trichoderma* induce plant defense reactions through the salicylate signal pathway, potentially leading to the induction of systemic acquired resistance (SAR) against pathogens and induced systemic resistance (ISR) by the *Trichoderma* fungi. These compounds affect jasmonate and ethylene response pathways in plants, inducing ISR [20,8]. Furthermore, they induce auxin production and disrupt auxin response gradients in Arabidopsis roots. Alamethicin (ALM) has been demonstrated to induce resistance in plants [35,103]. Additionally, peptaibiotics have been evaluated for their effects on animals, including insect larvae, shrimps, mussels, and mice [19,43,56,93,97]. The amino acid sequences, structural diversity (Fig. 1), and biological activities of various peptaibols (Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12) and lipopeptaibols (Table 13) isolated from different strains of *Trichoderma* fungi are shown below.

Lxx=Leucine/Isoleucine, Vxx=Valine/Isovaline

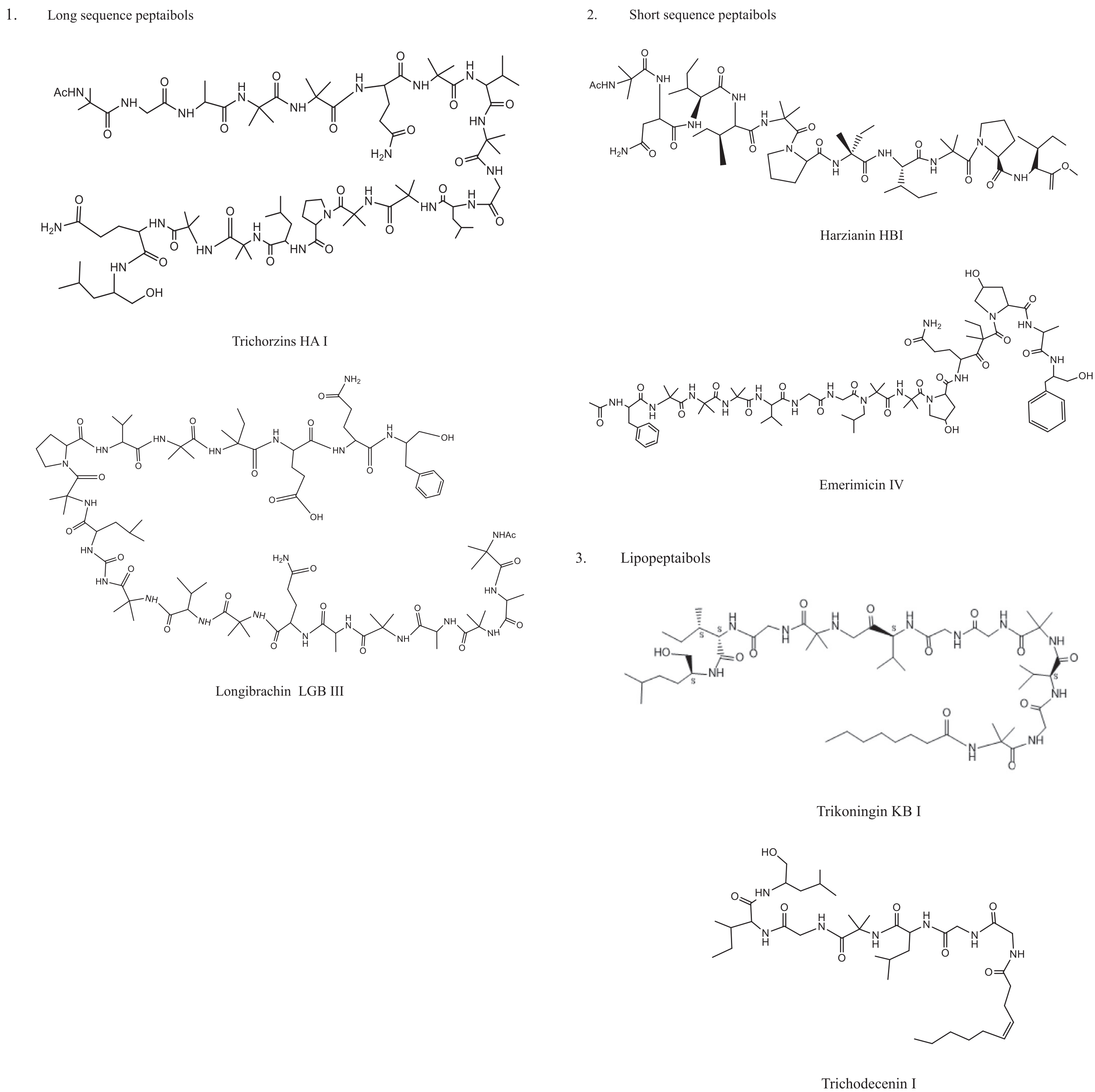

Fig. 1. Representative peptaibiotics structure and their diversity.

Table 1
Peptaibols from Trichoderma asperellum, amino acid sequences and their biological activity.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. asperellum Y19-07 (10)	Asperelin A (1)	AcAib Aib Val Aib Ile Aib Aib Ala Aib Prool		[90]
	Asperelin B (2)	AcAla Aib Val Aib Ile Aib Aib Ala Aib Prool		
	Asperelin C (3)	AcAib Aib Val Aib Ile Aib Ala Ala Aib Prool		
	Asperelin D (4)	AcAib Aib Val Aib Val Aib Aib Ala Aib Prool		
	Asperelin E (5)	AcAib Aib Val Aib Ile Aib Aib Ser Aib Prool		
	Asperelin F(6)	AcAib Val Val Aib Ile Aib Aib Ala Aib Prool		

(*continued on next page*)

Table 1 (*continued*)

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. asperellum TR356 (18)	Trichotoxin T5D2	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Aib Glu Valol	Antibacterial and antifungal activity	[2,15,84]
	Trichotoxin 1690	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Vxx Glu Valol		
	Trichotoxin 1703A	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Ala Aib Pro Lxx Aib Vxx Gln Valol		
	Trichotoxin A-40	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Aib Aib Pro Lxx Aib Vxx Gln Valol		
	Trichotoxin A-50 G	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Ala Aib Pro Lxx Aib Vxx Gln Valol		
	Trichotoxin T5D2	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Aib Gln Valol		
	Trichotoxin A-50 E (T5E)	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Ala Aib Pro Lxx Aib Aib Gln Valol		
	Trichotoxin A-50 F (T5F)	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Vxx Gln Valol		
	Trichotoxin A-50 G (T5G)	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Ala Aib Pro Lxx Aib Vxx Gln Valol		
T. asperellum IRAN 3062C	Pept-1705-a-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ser Aib Aib Pro Lxx Aib Aib Gln Vxxol	Antibacterial and antifungal activity	[2,85]
	Pept-1689-a-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Aib Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1691-a-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ser Ala Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1705-a-2	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Ala Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1719-b-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Ala Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1719-a-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Aib Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1705-a-3	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Ala Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1703-a-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Aib Ala Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1749-b-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Vxx Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin T5D2/Pept-1675-a-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1719-b-2	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Ala Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1733-b-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin A-50 F (T5F)/Pept-1689-b-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin A-50 E (T5E)/Pept-1689-a-3	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Ala Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1733-b-2	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin A-50 F (T5F)/Pept-1689-b-2	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Ala Ala Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1733-b-3	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin sequence 05/Pept-1703-a-2	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Aib Aib Pro Lxx Aib Aib Gln Vxxol		
	Pept-1703-b-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Ala Aib Ala Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1733-b-4	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1703-b-2	AcAib Gly Aib Gln Aib Gln Aib Aib Aib Gly Ala Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1747-b-1	AcAib Gly Aib Gln Aib Gln Aib Aib Aib Aib Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1703-b-3	AcAib Gly Aib Lxx Aib Gln Aib Ala Aib Ala Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1733-b-5	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ser Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin A-50 I (T5I)/Pept-1717-b-1	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Ala Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Pept-1731-b-1	AcAib Ala Aib Lxx Aib Gln Aib Aib Aib Ala Aib Aib Pro Lxx Aib Vxx Gln Vxxol		
	Trichotoxin A-50J (T5J)/Pept-1731-b-2	AcAib Gly Aib Lxx Aib Gln Aib Aib Aib Aib Aib Aib Pro Lxx Aib Vxx Gln Vxxol		

Table 2
Peptaibols from *Trichoderma atroviride*, amino acid sequences and their biological sequences

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. atroviride F80317	Atroviridin A	AcAib Pro Aib Ala Aib Ala Gln Aib Val Aia Gln Leu Aib Pro Val Aib Aib Gln Gln Phenol	Antibacterial, antifungal, and cytotoxicity activity	[77]
	Atroviridin B	AcAib Pro Aib Ala Aib Ala Gln Aib Val Aib Gln Leu Aib Pro Val Aib IVa Gln Gln Phenol		
	Atroviridin C	AcAib Pro Aib Ala Aib Aib Gln Aib Val Aib Gln Leu Aib Pro Val Aib Iva Gln Gln Phenol		
	Neoatroviridins A	AcAib Gly Ala Leu Aib Gln Aib Leu Aib Gly Iva Aib Pro Leu Aib Aib Gln Leol	Antibacterial, antifungal and cytotoxicity activity	[79]
	Neoatroviridins B	AcAib Gly Ala Leu Iva Gln Aib Leu Aib Gly Iva Aib Pro Leu Aib Aib Gln Leol		
	Neoatroviridins C	AcAib Gly Ala Leu Aib Gln Iva Leu Aib Gly Iva Aib Pro Leu Aib Aib Gln Leol		
	Neoatroviridins D	AcAib Gly Ala Leu Iva Gln Iva Leu Aib Gly Iva Aib Pro Leu Aib Aib Gln Leol		

Table 3
Peptaibols from *Trichoderma Clade Viride*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. gamsii SZMC 1656	Pept-Ia	AcAib Gly Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol	Antibacterial and antifungal	[65]
	Pept-Ib	AcAib Gly Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-IIa	AcAibGly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Pept-IIb	AcAib Gly Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-IIIa	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Pept-IIIb	AcAib Gly Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-Iva	AcAib Gly Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Pept-IVb	AcAib Gly Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-Va	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Pept-Vb	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-VIa	AcAibGly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Pept-VIb	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-VII	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-VIIIa	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Pept-VIIIb	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-IX	AcAib Gly Ala Aib Lxx Gln Aib Aib Aib Ala Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-X	AcAib Ala Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-XI	AcAib Ala Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Pept-XII	AcAib Ala Ala Aib Lxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		

(*continued on next page*)

Table 3 (*continued*)

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. koningiopsis SZMC 12500	Koningiopsin Ia	AcAib Ala Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol	Antibacterial and antifungal activity	[65]
	Koningiopsin Ib	AcAib Ala Ala Aib Vxx Gln Aib Aib Aib Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Koningiopsin IIa	AcAib Ala Ala Aib Aib Gln Aib Aib Lxx Ser Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Koningiopsin IIb	:AcAib Ala Ala Aib Aib Gln Aib Aib Aib Vxx Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Koningiopsin IIIa	AcAib Ala Ala Aib Ala Gln Aib Aib Lxx Ser Lxx Aib Pro Vxx Aib Vxx Gln Glu Lxxol		
	Koningiopsin IIIb	AcAibAla Ala Aib Aib Gln Aib Aib Aib Vxx Lxx Aib Pro Vxx Aib Vxx Gln Gln Lxxol		
	Koningiopsin IV	AcAib Ala Ala Aib Aib Gln Aib Aib Lxx Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Koningiopsin Va	AcAib Ala Ala Aib Aib Gln Aib Aib Lxx Ser Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Koningiopsin Vb	AcAib Ala Ala Aib Aib Gln Aib Aib Lxx Ser Lxx Aib Pro Vxx Aib Lxx Gln Glu Lxxol		
	Koningiopsin VIa	AcAib Ala Ala Aib Aib Gln Aib Aib Lxx Ala Lxx Aib Pro Vxx Aib Lxx Gln Gln Lxxol		
	Koningiopsin VIb	AcAib Ala Ala Aib Aib Gln Aib Aib Lxx Ala Lxx Aib Pro Vxx Aib Lxx Gln Glu Lxxol		

Table 4
Peptaibols from *Trichoderma longibrachiatum*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. longibrachiatum CECT 20105	Trilongin AIV a	AcAib Asn Vxx Vxx Aib Pro Vxx Lxx Aib Pro Lxxol	Cytotoxicity activity	[71]
	Trilongin AIV b	AcAib Asn Vxx Vxx Aib Pro Lxx Lxx Aib Pro Vxxol		
	Trilongin AIV c	AcAib Asn Vxx Vxx Aib Pro Lxx Vxx Aib Pro Lxxol		
	Trilongin AIII a	AcAib Asn Lxx Vxx Aib Pro Lxx Lxx Aib Pro Vxxol		
	Trilongin AIII b	AcAib Asn Lxx Vxx Aib Pro Vxx Lxx Aib Pro Lxxol		
	Trilongin AIII c	AcAib Asn Vxx Lxx Aib Pro Lxx Lxx Aib Pro Vxxol		
	Trilongin AIII d	AcAib Asn Vxx Lxx Aib Pro Vxx Lxx Aib Pro Lxxol		
	Trilongin A II a	AcAib Asn Lxx Lxx Aib Pro Lxx Lxx Aib Pro Vxxol		
	Trilongin AII b	AcAib Asn Lxx Lxx Aib Pro Lxx Vxx Aib Pro Lxxol		
	Trilongin AII c	AcAib Asn Lxx Lxx Aib Pro Vxx Lxx Aib Pro Lxxol		
	Trilongin AII d	AcAib Asn Lxx Vxx Aib Pro Lxx Lxx Aib Pro Lxxol		
	Trilongin AII e	AcAib Asn Vxx Lxx Aib Pro Lxx Lxx Aib Pro Lxxol		
	Trilongin AI	AcAib Asn Lxx Lxx Aib Pro Lxx Lxx Aib Pro Lxxol		
	Trilongin A0	AcAib Gln Lxx Lxx Aib Pro Lxx Lxx Aib Pro Lxxol		
T. longibrachiatum Rifai	Trichobrachin A-I	Ac Aib Asn Leu Leu Aib Pro Leu Aib Aib Pro Leuol		[72]
	Trichobrachin A-II	Ac Aib Asn Leu Leu Aib Pro Val Leu Aib Pro Valol		
	Trichobrachin A-III	Ac Aib Asn Val Leu Aib Pro Leu Leu Aib Pro Valol		
	Trichobrachin A-IV*	Ac Aib Asn Leu Val Aib Pro Leu Leu Aib Pro Valol		
	Trichobrachin B-I	Ac Aib Asn Leu Leu Aib Pro Val Aib Val Pro Leuol		
	Trichobrachin B-II	Ac Aib Asn Val Leu Aib Pro Leu Aib Val Pro Leuol		
	Trichobrachin B-III	Ac Aib Asn Leu Val Aib Pro Leu Aib Val Pro Leuol		
	Trichobrachin B-IV	Ac Aib Asn Leu Leu Aib Pro Leu Aib Val Pro Valol		
	Trichorovin TV-Ib or IIa	Ac Aib Asn Val Val Aib Pro Leu Leu Aib Pro Leuol		
T. Longibrachiatum Rifai DMG-3-1-1	Longibramide A	AcAib Asn Val Val Aib Pro Leu Leu Aib Pro Leuol	Antibacterial and cytotoxicity activity	[129]
	Longibramide B	AcAib Asn Val Ile Aib Pro Leu Leu Aib Pro Leuol		
	Longibramide C	AcAib Asn Val Val Aib Pro Leu Leu Aib Hyp Leuol		
	Longibramide D	AcAib Asn Val Ile Aib Hyp Leu Leu Aib Pro Leuol		
	Longibramide E	AcAib Asn Ile Ile Aib Hyp Leu Leu Aib Pro Leuol		
	Longibramide F	AcAib Asn Val Val Aib Pro Leu Leu Aib Pro Ileol		
	Longibramide G	AcAib Asn Val Ile Aib Pro Leu Leu Aib Pro Ileol		
	Longibramide H	AcAib Asn Val Ile Aib Hyp Leu Leu Aib Pro Ileol		
	Longibramide I	AcAib Gln Val Ile Aib Pro Leu Leu Aib Pro Ileol		
	Longibramide J	AcAib Gln Ile Ile Aib Pro Leu Leu Aib Pro Ileol		
	Trichorovin-XIIa	AcAib Asn Ile Ile Aib Pro Leu Leu Aib Pro Ileol		
	Longibramide K	AcAib Asn Ile Val Aib Pro Leu Leu Aib Pro Leuol		
	Longibramide L	AcAib Asn Ile Val Aib Pro Leu Leu Aib Pro Valol		
	Longibramide M	AcAib Asn Val Val Aib Pro Leu Leu Aib Pro Valol		
	Longibramide N	AcAib Asn Val Val Aib Pro Leu Val Aib Pro Leuol		
	Longibramide O	AcAib Asn Val Ile Aib Pro Leu Val Aib Pro Valol		
	Longibramide P	AcAib Asn Val Ile Aib Pro Leu Leu Aib Pro Valol		
	Longibramide Q	AcAib Gln Val Ile Aib Pro Leu Leu Aib Pro Valol		
	Longibramide R	AcAib Gln Val Ile Aib Pro Leu Leu Aib Pro Leuol		
	Hypomurocin A-4	AcAib Gln Ile Val Aib Pro Leu Leu Aib Pro Leuol		
	Harzianin HK VI	AcAib Asn Ile Ile Aib Pro Leu Leu Aib Pro Leuol		
	Hypomurocin A-5	AcAib Gln Ile Ile Aib Pro Leu Leu Aib Pro Leuol		
	Hypomurocin A-1	AcAib Gln Val Val Aib Pro Leu Leu Aib Pro Leuol		

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Table 4 (*continued*)

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T Longibrachiatum RIFAI strain (MMS151)	A-0 A-II-a A-IV-b	AcAib Ala Aib Ala Aib Ala Glu Aib Val Aib Gly Val Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Glu Aib Val Aib Gly Leu Aib Pro Val Aib Val Gln Gln Phenol AcAib Ala Aib Ala Aib Aib Glu Aib Val Aib Gly Leu Aib Pro Val Aib Val Gln Gln Phenol	Cytotoxic, antibacterial, and antifungal activities	[73]
T Longibrachiatum LCP-853431	LGAI LGAII LGAIII LGAIV LGBII LGBIII	AcAib Ala Aib Ala Aib Ala Gln Aib Val Aib Gly Leu Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Aib Val Aib Gly Leu Aib Pro Val Aib Iva Gln Gln phenol AcAib Ala Aib Ala Aib Aib Gln Aib Val Aib Gly Leu Aib Pro Val Aib Aib Gly Gln phenol AcAib Ala Aib Ala Aib Ala Gln Aib Val Aib Gly Leu Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Aib Val Aib Gly Leu Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Aib Val Aib Gly Leu Aib Pro Val Aib Iva Gln Gln Phenol	Antibacterial activity	[58]
T. longibrachiatum IRAN 3067C	Longibrachin A II/Trilongin B II/Pept-1951-d Longibrachin A I/Trilongin B I/Pept-1936-a Longibrachin B II/Trilongin C I/Pept-1938-b Pept-1951-c Pept-1952-d Longibrachin A III/Pept-1951-a Longibrachin B III/Trilongin C III/Pept-1951-b Trilongin BIV Pept-1965-c-1 Pept-1966-d Pept-1965-c-2 Trilongin CII Trilongin CIV	AcAib Ala Aib Ala Aib Ala Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Vxx Gln Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Aib Gln Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Aib Glu Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Aib Aib Vxx Gly Lxx Aib Pro Vxx Aib Vxx Gln Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Aib Aib Vxx Gly Lxx Aib Pro Vxx Aib Vxx Glu Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Aib Gln Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Aib Glu Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Vxx Gln Gln Pheo AcAib Ala Aib Ala Aib Aib Gln Aib Ala Lxx Gly Lxx Aib Pro Vxx Aib Vxx Gln Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Ala Lxx Gly Lxx Aib Pro Vxx Aib Vxx Glu Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Ala Lxx Gly Lxx Aib Pro Vxx Aib Vxx Gln Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Vxx Glu Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Vxx Aib Gly Lxx Aib Pro Vxx Aib Vxx Glu Gln Pheol	Antibacterial activity	[85]

Table 5
Peptaibols from *Trichoderma harzianum* fungi, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. harzianum strain (M-903603)	Harzianin HB I Trichorozin I Trichorozin II Trichorozin III Trichorozin IV	AcAib Asn Leu Ile Aib Pro Iva Leu Aib Pro Leuol AcAib Asn Ile Leu Aib Pro Ile Leu Aib Pro Valol AcAib Gln Ile Leu Aib Pro Ile Leu Aib Pro Valol AcAib Asn Ile Leu Aib Pro Ile Leu Aib Pro Leuol AcAib Gln Ile Leu Aib Pro Ile Leu Aib Pro Leuol	Antibacterial activity	[5]
14-residue *T. harziunum* strains (M-903614; M-903603)	Harzianin HC XIV Harzianin HC VIII Harzianin HC I Harzianin HC III Harzianin HC VI Harzianin HC IX Harzianin HCX Harzianin HCXI Harzianin HC XII Harzianin HC XIII Harzianin HC HCXIV Harzianin HC XV	AcAib Asn Lue Aib Pro Ala Ile Aib Pro Aib Leu Aib Pro Leuol AcAib Asn Leu Aib Pro Ala Val Aib Pro Iva Leu Aib Pro Leuol AcAib Asn Leu Aib Pro Ser Val Aib Pro Aib Leu Aib Pro Leuol AcAib Asn Leu Aib Pro Ser Val Aib Pro Iva Leu Aib Pro Leuol AcAib Asn Leu Aib Pro Ser Val Aib Pro Aib Leu Aib Pro Leuol AcAib Asn Leu Aib Pro Ser Ile Aib Pro Iva Leu Aib Pro Leuol Ac Aib Gin Leu Aib Pro Ala Val Aib Pro Iva Leu Aib Pro Leuol Ac Aib Asn Leu Aib Pro Ser Ile Aib Pro Aib Leu Aib Pro Leuol AcAib Asn Leu Aib Pro Ser Ile Aib Pro Iva Leu Aib Pro Leuol Ac Aib Gln Leu Aib Pro Ser Ile Aib Pro Iva Leu Aib Pro Leuol Ac Aib Asn Leu Aib Pro Ala Ile Aib Pro Aib Leu Aib Pro Leuol AcAib Gln Leu Aib Pro Ala Ile Aib Pro Iva Leu Aib Pro Leuol	Antibacterial and antifungal Antibacterial and antifungal	[40] [89]
18-residue	Trichorzin HA I Trichorzin HA II Trichorzin HA III Trichorzin HAV Trichorzin HA VII Trichokindin Vb Trichokindin VI Trichokindin Ia	AcAib Gly Ala Aib Aib Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Leuol AcAib Gly Ala Aib Aib Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Iva Gln Leuol AcAib Gly Ala Aib Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Leuol AcAib Gly Ala Aib Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Iva Gln Leuol AcAib Gly Ala Aib Iva Gln Val Val Aib Gly Leu Aib Pro Leu Aib Iva Gln Leuol AcAib Ser Ala Aib Iva Gln Aib Leu Aib Ala Iva Aib Pro Leu Aib Aib Gln Ileol AcAib Ser Ala Aib Iva Gln Iva Leu Aib Ala Iva Aib Pro Leu Aib Aib Gln Leuol AcAib Ser Ala Aib Aib Gln Iva Leu Aib Ala Aib Aib Pro Leu Aib Aib Gln Ileol	Antibacterial and antifungal	[40]
T. harzianum strain M-902608	Trichorzin PA II Trichorzin PA IV Trichorzin PA V Trichorzin PA VI Trichorzin PA VII Trichorzin PA VIII Trichorzin PA IX Trichorzin PAU Trichorzin MA I Trichorzin MA II Trichorzin MA II	AcAib Ser Ala Aib Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Trpol AcAib Ser Ala Aib Iva Gln Iva Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Trpol AcAib Ser Ala Iva Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Trpol AcAib Ser Ala Aib Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Pheol AcAib Ser Ala Iva Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Trpol AcAib Ser Ala Aib Iva Gln Iva Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Pheol AcAib Ser Ala Iva Iva Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Pheol AcAib Ser Ala Aib Aib Gln Aib Val Aib Gly Leu Aib Pro Leu Aib Aib Gln Trpol AcAib Ser Ala Aib Aib Gln Aib Leu Aib Gly Leu Aib Pro Leu Aib Aib Gln Valol AcAib Ser Ala Aib Iva Gln Aib Leu Aib Gly Leu Aib Pro Leu Aib Aib Gln Valol AcAib Ser Ala Aib Iva Gln Iva Leu Aib Gly Leu Aib Pro Leu Aib Aib Gln Valol	Antibacterial and antifungal	[33,41]

(*continued on next page*)

Table 5 (*continued*)

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. harzianum ATCC 20672	Trichorzianine TA IIa Trichorzianine TA IIIa Trichorzianine TA IIIb Trichorzianine TA IIIc Trichorzianine TA IVb Trichorzianine TA Vb Trichorzianine TA VIa Trichorzianine TA VIb Trichorzianine TA VII	AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Gln Trpol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Gln Trpol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Leu Gln Gln Trpol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Gln Trpol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Gln Trpol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Gln Pheol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Gln Pheol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Gln Pheol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Gln Pheol	Antifungal activity	[41]
T. harzianum ATCC 20672	Trichorzianine TB IIa Trichorzianine TB VII Trichorzianine TB Vb Trichorzianine TB VIa Trichorzianine TA IIIc Trichorzianine TB IVb Trichorzianine TB VIb KA V TA IIIc	AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Glu Trpol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Glu Pheol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Glu Pheol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Leu Aib Ile Gln Glu Pheol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Gln Trpol AcAib Ala Ala Aib Iva Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Glu Trpol AcAib Ala Ala Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Glu Pheol AcAib Gly Ala Aib Ile Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Ile Gln Gln Leuol AcAib Gly Phe Aib Aib Gln Aib Aib Aib Ser Leu Aib Pro Val Aib Iva Gln Gln Leuol	Antibacterial and antifungal	[40,88]
20-residue	Trichorzin SA II	AcAib Ala Aib Ala Aib Ala Gln Aib Leu Aib Gly Aib Aib Pro Val Aib Iva Gln Gln Phenol	Antibacterial and antifungal	[40]

Table 6
Peptaibols from *Trichoderma orientale*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. orientale LSBA1	Hyporientalin A	AcAib Ala Aib Ala Aib Ala Gln Aib Val/Iva Aib Gly Leu/Ile Aib Pro Val/Iva Aib Val/Iva Gln Gln Pheol	Antifungal, antibacterial and cytotoxicity	[117]

Table 7
Peptaibols from *Trichoderma polysporum*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. polysporum	Polysporin A Polysporin B Polysporin C Polysporin D	AcAib Pro Aib Ala Aib Aib Gln Aib Val Aib Gly Val Aib Pro Val Aib Aib Gln Gln Pheol AcAib Pro Aib Ala Aib Aib Gln Aib Val Aib Gly leu Aib Pro Val Aib Aib Gln Gln Pheol AcAib Pro Aib Ala Aib Aib Gln Aib Ile Aib Gly Leu Aib Pro Val Aib Aib Gln Gln Pheol AcAib Pro Aib Ala Aib Aib Gln Aib Ile Aib Gly Leu Aib Pro Val Aib Val Gln Gln Pheol	-	[77]

Table 8
Peptaibols from *Trichoderma pseudokoningii*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. pseudokoningii strain MVHC662	Harzianin HK VI	AcAib Asn Ile Ile Aib Pro Leu Leu Aib Pro Leuol	Antibacterial and antifungal	[88]

Table 9
Peptaibols from *Trichoderma saturnisporum* amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. saturnisporum CBS 330.70	Paracelsin A Paracelsin B (SA I) Paracelsin C Paracelsin D (SA III) Paracelsin E Saturnisporin SA I Saturnosporin SA II Saturnosporin SA IV	AcAib Ala Aib Ala Aib Ala Gln Ala Val Aib Gly Aib Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Ala Leu Aib Gly Aib Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Aib Gln Aib Val Aib Gly Aib Aib Pro Val Aib Aib Gln Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Ala Leu Aib Gly Aib Aib Pro Val Aib Aib Gln Gln Pheol AcAib Ala Aib Ala Aib Ala Gln Aib Leu Aib Gly Aib Ala Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Aib Leu Aib Gly Aib Aib Pro Val Aib Aib Gln Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Ala Leu Aib Gly Aib Aib Pro Val Aib Iva Gln Gln Pheol AcAib Ala Aib Ala Aib Aib Gln Aib Leu Aib Gly Aib Aib Pro Val Aib Iva Gln Gln Pheol	Antibacterial activity	[93]

Table 10
Peptaibols from *Trichoderma Velutinum*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. velutinum (14-residue)	Velutibol A (1) Velutibol B (2) Velutibol C (3) Velutibol D (4)	AcAib Gln Leu Aib Pro Val Leu Aib Pro Aib Aib Aib Pro Leuol AcAib Gln Leu Aib Pro Val Ile Aib Pro Aib Aib Aib Pro Leuol AcAib Gln Ile Aib Pro Val Leu Aib Pro Aib Aib Aib Pro Leuol AcVal Gln Leu/Ile Aib Pro Val Leu/Ile Aib Pro Aib Aib Aib Pro Leuol	Cytotoxic and antibacterial activity	[107]

Table 11
Peptaibols *Trichoderma viride peptaibols*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. viride NRRL 5242	Trichotoxins A-40 (TT A-40)	AcAib Gly Aib Leu Aib Gln Aib Aib Ala Ala Aib Aib Pro Leu Aib Aib Glu Valol AcAib Gly Aib Leu Aib Gln Aib Aib Aib Ala Ala Aib Pro Leu Aib Aib Glu Valol AcAib Gly Aib Leu Aib Gln Aib Aib Ala Ala Aib Aib Pro Leu Aib D-Iva Glu Valol AcAib Gly Aib Leu Aib Gln Aib Aib Aib Ala Aib Aib Pro Leu Aib Aib Glu Valol AcAib Gly Aib Leu Aib Gln Aib Aib Aib Ala Aib Aib Pro Leu Aib D-Iva Glu Valol AcAib Ala Aib Leu Aib Gln Aib Aib Aib Ala Aib Aib Pro Leu Aib Aib Glu Valol	Antibacterial	[49]
7-residue *T.virdie*	Trichodecenins I Trichodecenins II	OcGly Gly Leu Aib Gly Ile Lol OcGly Gly Leu Aib Gly Leu Lol		[37]
20-residue	Alamethicin F-30 Suzukacillin	AcAib Pro Aib Ala Aib Ala Gln Aib Val Aib Gly Leu Aib Pro Val Aib Aib Glu Gln Phenol AcAib Ala Aib Ala Aib Ala Gln Aib Aib Aib Gly Leu Aib Pro Val Aib Aib Gln Gln Phenol		[54]

Table 12
Peptaibols *Trichoderma virens*, amino acid sequences, and their biological sequences.

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. virens CMB-TN16 (11-residue)	Trichodermide A (1) Trichodermide B (2) Trichodermide C (3) Trichodermide D (4) Trichodermide E (5)	AcIva Gln Ile Val Aib Pro Ile Leu Aib Pro Leuol AcAib Gln Ile Val Aib Pro Ile Leu Aib Pro Leuol AcIva Gln Ile Val Aib Pro Ile Leu Aib Pro Valol AcAib Gln Ile Val Aib Pro Ile Leu Aib Pro Valol AcIva Gln Val Val Aib Pro Ile Leu Aib Pro Valol		[50]
T. virens Gv29-8 (11 residue)	Trichorovin (Tv29-11-Ia) Trichorovin (Tv29-11-Ib) Trichorovin (Tv29-11-Ic) Trichorovin (Tv29-11-Id) Trichorovin (Tv29-11-IIa) Trichorovin (Tv29-11-IIb) Trichorovin (Tv29-11-IIc) Trichorovin (Tv29-11-IId) Trichorovin (Tv29-11-IIe) Trichorovin (Tv29-11-IIf) Trichorovin (Tv29-11-IIg) Trichorovin (Tv29-11-IIh) Trichorovin (Tv29-11-IIIa) Trichorovin (Tv29-11-IIIb) Trichorovin (Tv29-11-IIIc) Trichorovin (Tv29-11-IIId) Trichorovin (Tv29-11-IIIe) Trichorovin (Tv29-11-IIIf) Trichorovin (Tv29-11-IIIg) Trichorovin (Tv29-11-IIIh) Trichorovin (Tv29-11-IVa) Trichorovin (Tv29-11-IVb) Trichorovin (Tv29-11-IVc) Trichorovin (Tv29-11-IVd) Trichorovin (Tv29-11-IVe) Trichorovin (Tv29-11-IVf) Trichorovin (Tv29-11-IVg) Trichorovin (Tv29-11-IVh) Trichorovin (Tv29-11-IVi) Trichorovin (Tv29-11-IVj) Trichorovin (Tv29-11-Va) Trichorovin (Tv29-11-Vb) Trichorovin (Tv29-11-Vc) Trichorovin (Tv29-11-Vd) Trichorovin (Tv29-11-VI)	AcAib Asn Leu/Ile Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol AcAib Asn Val/Iva Val/Iva Aib Pro Leul/Ile Leu/Ile Aib Pro Valol AcAib Gln Val/Iva Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol AcAib Asn Val/Iva Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol AcAib Asn Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcAib Asn Val/Iva Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcAib Gln Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcAib Gln Val/Iva Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcVal/Iva Gln Val/Iva Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol AcAib Asn Leu/Ile Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol AcAib Asn Val/Iva Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol AcAib Gln Val/Iva Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol AcAib Gln Leu/Ile Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol AcAib Gln Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcVal/Iva Gln Leu/Ile Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol AcVal/Iva Gln Val/Iva Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcAib Asn Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro leuol AcAib Gln Leu/Ile Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro leuol AcAib Gln Val/Iva Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro leuol AcVal/Iva Gln Val/Iva Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro leuol AcAib Gln Leu/Ile Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcVal/Iva Gln Leu/Ile Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol AcVal/Iva Gln Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcVal/Iva Gln Val/Iva Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Valol AcAib Gln Leu/Ile Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro leuol AcAib Gln Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro leuol AcAib Gln Val/Iva Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro leuol Ac Val/Iva Gln Val/Iva Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro leuol Ac Val/Iva Gln Leu/Ile Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro leuol Ac Val/Iva Gln Val/Iva Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro leuol Ac Val/Iva Gln Leu/Ile Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Valol Ac Aib Gln Leu/Ile Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol Ac Val/Iva Gln Leu/Ile Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol Ac Val/Iva Gln Val/Iva Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol Ac Val/Iva Gln Leu/Ile Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol	Cytotoxicity activity	[74]

(*continued on next page*)

Table 12 (*continued*)

Species/strain	Name of peptaibol	Sequence	Biological activity	Reference
T. virens Gv29-8 (14-residue)	Trichorovin (Tv29-14S-Ia)	AcAib Asn Val/Iva Aib Pro Ser Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol	Antibacterial, antiviral, cytotoxicity and plant defense inducer	[74]
	Trichorovin (Tv29-14S-Ib)	AcAib Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-Ic)	AcAib Asn Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-IIa)	AcAib Gln Leu/Ile Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IIb)	AcAib Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IIc)	AcVal/Iva Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IId)	AcAib Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-IIIa)	AcAib Gln Leu/Ile Aib Pro Ser Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IIIb)	AcAib Gln Val/Iva Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IIIc)	AcVal/Iva Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IIId)	AcAib Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-IVa)	AcAib Gln Leu/Ile Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IVb)	AcVal/Iva Gln Leu/Ile Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IVc)	AcVal/Iva Gln Val/Iva Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-IVd)	AcAib Gln Leu/Ile Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-IVe)	AcAib Gln Val/Iva Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-IVf)	AcVal/Iva Gln Val/Iva Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-Va)	AcVal/Iva Gln Leu/Ile Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14S-Vb)	AcAib Gln Leu/Ile Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-Vc)	AcVal/Iva Gln Leu/Ile Aib Pro Ser Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-Vd)	AcVal/Iva Gln Val/Iva Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14S-VI)	AcVal/Iva Gln Leu/Ile Aib Pro Ser Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-I a)	AcAib Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-I b)	AcAib Aln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-II a)	AcAib Gln Val/Iva Aib Pro Ala Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-II b)	AcAib Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-II c)	AcAib Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-II d)	AcVal/Iva Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-II e)	AcAib Asn Val/Iva Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-II f)	AcAib Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-III a)	AcAib Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-III b)	AcVal/Iva Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-III c)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-III d)	AcAib Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-III e)	AcAib Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-IV a)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-IV b)	AcAib Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-IV c)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-IV d)	AcVal/Iva Gln Val/Iva Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro Leuol		
	Trichorovin (Tv29-14A-V a)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro Valol		
	Trichorovin (Tv29-14A-V b)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro leuol		
	Trichorovin (Tv29-14A-V c)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Val/Iva Aib Pro Leu/Ile Leu/Ile Aib Pro leuol		
	Trichorovin (Tv29-14A-V d)	AcVal/Iva Gln Val/Iva Aib Pro Ala Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro leuol		
	Trichorovin (Tv29-14A-VI)	AcVal/Iva Gln Leu/Ile Aib Pro Ala Leu/Ile Aib Pro Leu/Ile Leu/Ile Aib Pro leuol		
	Trichorovin (Tv29-14U-I a)	AcAib Gln Val/Iva Aib Pro Leu/Ile Val/Iva Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-I b)	AcAib Gln Leu/Ile Aib Pro Val/Iva Val/Iva Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-I c)	AcVal/Iva Gln Val/Iva Aib Pro Val/Iva Val/Iva Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-II a)	AcAib Gln Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-II b)	AcVal/Iva Gln Leu/Ile Aib Pro Val/Iva Val/Iva Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-II c)	AcVal/Iva Gln Val/Iva Aib Pro Val/Iva Leu/Ile Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-III a)	AcVal/Iva Gln Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Aib Val/Iva Aib Pro Valol		
	Trichorovin (Tv29-14U-IV a)	AcVal/Iva Gln Leu/Ile Aib Pro Val/Iva Leu/Ile Aib Pro Aib Val/Iva Aib Pro Leuol		
	Trichorovin (Tv29-14U-IV b)	AcVal/Iva Gln Leu/Ile Aib Pro Val/Iva Val/Iva Aib Pro Aib Leu/Ile Aib Pro Leuol		
T. virens Gv29-8 (18-residue)	Trichorzins (TVB I)	AcAib Gly Ala Val Aib Gln Aib Ala Aib Ser Leu Aib Pro Leu Aib Aib Gln Valol	Antibacterial and plant defense inducer	[124]
	Trichorzins(TVB II)	AcAib Gly Ala Leu Aib Gln Aib Ala Aib Ser Leu Aib Pro Leu Aib Aib Gln Vallol		
	Trichorzins (TVB IV)	AcAib Gly Ala Leu Aib Gln Iva Ala Aib Ser Leu Aib Pro Leu Aib Aib Gln Valol		

Table 13
Lipopeptaibols from different species of *Trichoderma* species, amino acid sequences and their biological activity.

Species/strain	Name of lipopeptaibol	Sequence	Biological activity	Reference
Trichoderma velutinum	Lipovelutibol A (1)	OcGly Ala Leu Aib Ser Ile Leucinol	Cytotoxicity	[108]
	Lipovelutibol B (2)	OcGly Ala Leu Iva Ser Ile Leucinol		
	Lipovelutibol C (3)	OcGly Ala Leu Aib Ala Ile Leucinol		
	Lipovelutibol D (4)	OcGly Ala Leu Iva Ala Ile Leucinol		
Trichoderma longibrachiatum	Trichogin (A IV/GA IV)	OcAib Gly Leu Aib Gly Leu Aib Gly Ile Leuol	Antibacterial activity	[6]
Trichoderma koningii	Trikoningins (KBI)	OcAib Gly Val Aib Gly Gly Val Aib Gly Ileol	Antibacterial activity	[7]
	Trikoningins (KBII)	OcIva Gly Val Aib Gly Gly Val Aib Gly Ileol		
Trichoderma polysporum	Trichopolyns I	OcPro AHMO Ala Aib Aib Ile Ala Aib Aib AMAE	Cytotoxicity	[47]
	Trichopolyns II	OcPro AHMO Ala Aib Aib Val Ala Aib Aib AMAE		
	Trichopolyns III	OcPro AHMO Ala Aib Aib Ile Ala Aib Ala AMAE		
	Trichopolyns IV	OcPro AHMO Ala Aib Aib Val Ala Aib Ala AMAE		
	Trichopolyns V	OcPro AHMO Ala Aib Aib Ile Ala Aib Aib AMAE		
Trichoderma viride	Trichodecenins I	OcGly Gly Leu Aib Gly Ile Lol		[38]
	Trichodecenins II	OcGly Gly Leu Aib Gly Leu Lol		

2. Conclusion

The *Trichoderma* genus is recognized for its potential in peptaibiotic production, with a considerable number of these compounds described to date from these fungi. This review primarily focuses on the tools and techniques utilized in screening, purifying, identifying, and assessing the bioactivity of peptaibiotics (peptaibols and lipopeptaibols) derived from various species and strains of *Trichoderma* fungi. Numerous studies have indicated intensive investigations conducted to explore different peptaibiotics from various *Trichoderma* fungal strains. The interest in this class of compounds has surged annually due to the advancements in tools and techniques used for their screening and purification, meeting the high demand for these bioactive molecules. Diverse arrays of chromatographic and spectroscopic tools have been employed to study peptaibiotics from *Trichoderma* fungi. This paper extensively reviews a variety of peptaibiotics (peptaibols and lipopeptaibols), providing details regarding their amino acid sequences and bioactivity characteristics across more than twelve *Trichoderma* fungi. All these peptaibiotic groups exhibit a wide spectrum of biological activities encompassing antibacterial, antifungal, antiviral effects, as well as cytotoxicity activities like immunosuppressive and neuroleptic properties. Moreover, they have displayed the ability to elicit systemic plant resistance characteristics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT Authorship Contribution Statement

Adigo Setargie: Writing – original draft. **Chen Wang:** Writing – review & editing. **Liwen Zhang:** Supervision. **Yuquan Xu:** Supervision.

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