

Review

# Trichoderma: Advent of Versatile Biocontrol Agent, Its Secrets and Insights into Mechanism of Biocontrol Potential

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**Citation:** Manzar, N.; Kashyap, A.S.; Goutam, R.S.; Rajawat, M.V.S.; Sharma, P.K.; Sharma, S.K.; Singh, H.V. *Trichoderma: Advent of Versatile Biocontrol Agent, Its Secrets and Insights into Mechanism of Biocontrol Potential*. *Sustainability* **2022**, *14*, 12786. <https://doi.org/10.3390/su141912786>

Academic Editor: Gustavo Santoyo

Received: 30 June 2022

Accepted: 7 September 2022

Published: 7 October 2022

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**Abstract:** *Trichoderma* is an important biocontrol agent for managing plant diseases. *Trichoderma* species are members of the fungal genus hyphomycetes, which is widely distributed in soil. It can function as a biocontrol agent as well as a growth promoter. *Trichoderma* species are now frequently used as biological control agents (BCAs) to combat a wide range of plant diseases. Major plant diseases have been successfully managed due to their application. *Trichoderma* spp. is being extensively researched in order to enhance its effectiveness as a top biocontrol agent. The activation of numerous regulatory mechanisms is the major factor in *Trichoderma* ability to manage plant diseases. *Trichoderma*-based biocontrol methods include nutrient competition, mycoparasitism, the synthesis of antibiotic and hydrolytic enzymes, and induced plant resistance. *Trichoderma* species may synthesize a variety of secondary metabolites that can successfully inhibit the activity of numerous plant diseases. GPCRs (G protein-coupled receptors) are membrane-bound receptors that sense and transmit environmental inputs that affect fungal secondary metabolism. Related intracellular signalling pathways also play a role in this process. Secondary metabolites produced by *Trichoderma* can activate disease-fighting mechanisms within plants and protect against pathogens.  $\beta$ -Glucuronidase (GUS), green fluorescent protein (gfp), hygromycin B phosphotransferase (hygB), and producing genes are examples of exogenous markers that could be used to identify and track specific *Trichoderma* isolates in agro-ecosystems. More than sixty percent of the biofungicides now on the market are derived from *Trichoderma* species. These fungi protect plants from harmful plant diseases by developing resistance. Additionally, they can solubilize plant nutrients to boost plant growth and bioremediate environmental contaminants through mechanisms, including mycoparasitism and antibiosis. Enzymes produced by the genus *Trichoderma* are frequently used in industry. This review article intends to provide an overview update (from 1975 to 2022) of the *Trichoderma* biocontrol fungi, as well as information on key secondary metabolites, genes, and interactions with plant diseases.

**Keywords:** *Trichoderma*; antibiosis; exogenous marker genes; secondary metabolites; biochemical defense; induced systemic resistance

## 1. Introduction

It is anticipated that there will be 9.1 billion people living on the planet by the year 2050, according to current population projections. As a consequence of this, there needs to be a seventy percent increase in the amount of food that is produced by agriculture in order

to sustainably feed the rising population throughout the world. Challenges, such as global warming and environmental pollution, have pushed plants toward various forms of biotic and abiotic stress, which has caused significant reductions in yield. This will lead to issues of food shortages for future generations [1]. Plant diseases play a direct role in the destruction of agricultural crops. The loss was estimated in fruit crops (78%), vegetables (54%), and cereals (32%) [2]. Specifically, disease caused by soil-borne pathogens is destructive and spreads quickly, causing a huge economic loss of important crops. The application of pesticides was considered an excellent solution to manage soil-borne pathogens, but their excessive use has led to the development of pathogen resistance to fungicides. However, it was realized that applying these pesticides is harmful to the environment and unsafe for human health [3]. It also kills the non-target organisms present in the soil and also fertilizers were used extensively around the globe since the Green Revolution, due to the high subsidies. However, extensive fertilizer use exacerbates soil degradation and causes yield stagnation and, as a result, threatens food security and soil sustainability, especially in developing countries, such as India [4]. Hence, the utility of certain microorganisms that can antagonize the target pathogen has been explored. Bioagents use a host-specific pathogen, a microbial antagonist, to inhibit diseases and control weed populations [5,6]. Biocontrol agents comprise fungi, bacteria, viruses, nematodes, and protozoa [7]. Plants treated with biocontrol agents may become more vigorous, robust, healthier, and yield more than untreated plants. Bioagents are microbial agents that suppress the growth of other microorganisms associated with them. Bioagents can hinder the life process of other phytopathogens, including fungi, bacteria, viruses, and other microorganisms. Biocontrol fungi are mostly saprophytic. They improve plant growth and development, enable the plant to resist abiotic stresses, improve nutrient uptake from the soil, and reduce the effect of plant diseases. A fungus genus called *Trichoderma* can be found as saprotrophs, mycoparasites, degrading the cell wall components of harmful pathogens by producing chitinase or cellulase enzyme soil inhabitants and plant symbionts [8]. Different strains of *Trichoderma* account for approximately ninety percent of all fungal biocontrol agents used to combat deleterious microorganisms [9]. In 1794, soil and decomposing organic matter were used to isolate *Trichoderma* for the first time [10]. *Trichoderma* is currently the source of more than 60% of the world's most effective bio-fungicides [11]. *Trichoderma* has been broadly studied among biocontrol agents due to its ability to antagonize plant pathogenic species. *Trichoderma* is a widely distributed ubiquitous hypomycetous fungi occurring nearly in all soil types and root ecosystems, especially in those rich in organic matter. *Trichoderma*, considered a potent biocontrol agent, can be attributed to the following characteristics: high reproductive capacity, ability to survive even in stressed conditions, efficiency in utilization of nutritional capacity to alter the rhizosphere, aggressiveness against phytopathogenic fungi, helps in plant growth promotion, induced defense mechanism as well as providing plants several secondary metabolites [12], enzymes [13], and PR proteins [14]. Because of these characteristics, the genus *Trichoderma* can be found in a diverse environment with a significant population density. The most common species of *Trichoderma* as biocontrol agents are *Trichoderma virens*, *Trichoderma viride*, and *Trichoderma harzianum* [15]. The potential of *Trichoderma* as a biocontrol agent in plant disease management was first recognized in the early 1930s and, in subsequent years, control of many diseases has been reported [16]. Root rot disease, fruit rot, damping-off, wilt, and other common plant diseases can be managed by *Trichoderma* spp. In recent studies [17], it has been observed that *Trichoderma* spp. release secondary metabolites that inhibit the growth of plant pathogens and encourage the growth of plants [18]. In addition, in the plant *Trichoderma* spp. interaction, they efficiently modulate root architecture and enhance the length of lateral and primary roots, which results in the feasibility of nutrient uptake by the plant [19]. Numerous species of *Trichoderma* under soil microbiome can produce enzymes that degrade the target pathogenic fungi or produce several toxic compounds, which restrict the pathogens. The antagonistic properties of these are based on multiple mechanisms. *Trichoderma* strains exert biocontrol action against fungal phytopathogens, either indirectly or by competing for nutrients and

space, mycoparasitism, production of antibiotics, induction of resistance in host plants, and promoting plant growth [18,20]. Mycoparasitism is a process in which fungi primarily locate target hyphae by probing with persistently synthesized cell wall degrading enzymes (CWDEs) paired with precise detection of cell wall pieces produced from target fungi. This cell wall degrading enzyme complex produced from *Trichoderma* spp. is composed of chitinases,  $\beta$ -glucanases, cellulases, and proteases. These enzymes can decompose the cell wall of phytopathogens, making it possible for hyphae to penetrate, colonise, and activate myoparasitism in plants [21,22]. Chitinases are potent enzymes that showed the highest antagonistic potential against plant diseases [23]. In order to obtain a new formulation for its efficient biocontrol activity, these metabolites can either be overproduced or mixed with the suitable biocontrol strain [24]. Excellent results have been attained with *T. virens* and metalaxyl against *Pythium ultimum* infecting cotton [25]. This has resulted in commercial production of *Trichoderma* species for the protection of several plant diseases and growth enhancement of several crops in India, Israel, New Zealand, and Sweden. In 1997, it was shown that *Trichoderma* colonisation of roots could minimize foliar pathogen symptoms. This discovery gave rise to the term "induced systemic resistance" (ISR), which is also used to refer to all types of induced resistance, both local and systemic. [26]. *Trichoderma* research over the following two decades was dominated by IDR as a plant disease control method [27]. Though synergistic actions in these processes may occur, the degree of disease suppression caused by mycoparasitic activity is greater than that caused by IDR or antibiosis [28].

Due to a lack of reliable characteristics, morphological and cultural characteristics alone have proven difficult to use to distinguish individuals within the genus *Trichoderma*. The effectiveness of various biochemical and molecular approaches was assessed to distinguish among isolates of the genus *Trichoderma*. Information was also collected on ITS sequence data, RAPD, or RFLP to differentiate between morphologically indistinguishable isolates [29]. According to a new taxonomic approach, individuals of the genus *Trichoderma* are currently identified by combining cultural, biochemical, morphological, and molecular characteristics. The accuracy of sequence and RAPD data in determining *Trichoderma* phylogeny is also assessed. The ITS region of sequence data was the most reliable for predicting the phylogeny of morphologically distinct species, while RAPD and RFLP data were the most beneficial for predicting the overall phylogeny of morphologically similar strains [30–34].

The compilation of basic information about the biocontrol potential of *Trichoderma* strain and their capabilities to colonise, persist, and disseminate under environmental conditions is vital in the journey of bioformulation development [35]. Orr and Knudsen 2004 developed a method to monitor the variation in biomass of biocontrol agents in native soil by using GFP and GUS labeled *T. harzianum* ThzID1-M3 strain, an environment in which the presence of local bacteria and fungus impedes the use of conventional methods for determining biomass [36]. It was shown that epifluorescence microscopy tracking of GFP-labeled *Trichoderma harzianum* was a helpful tool in identifying biocontrol-active hyphal biomass from inactive conidia and chlamydospores, which were measured using plate counts. The GUS and GFP marker genes were intended to distinguish between BCA and native *Trichoderma* populations. Genes that produce a green fluorescent protein (gfp), hygromycin B phosphotransferase (hygB), and  $\beta$ -glucuronidase (GUS) are examples of exogenous markers that can be utilized to genetically change BCAs in order to track and analyze various strains of *Trichoderma* on field crops [37–39]. This review presents a compilation of studies regarding molecular characterization and the mechanism of *Trichoderma* species as biocontrol agents, along with a detailed description of genes involved in biocontrol activity, enzyme production, and secondary metabolites/bioactive compounds produced by *Trichoderma* and findings that discover the potentiality of *Trichoderma* spp. as a plant growth promoter agent are discussed in this review.

## 2. Insight on Trichoderma and Its Mechanism

### 2.1. Morphological Studies on Trichoderma

*Trichoderma* produces numerous spores with varied shades of color, such as white green, light green, dark green to dull green [40], and on the backside of the plate, colony color varies from yellow, buff, amber, or uncolored [41]. It proliferates; therefore, it is also characterized by the radial growth rate. Most of the *Trichoderma* spp. produces chlamydospores. Phialide lengths vary from  $3.5$  to  $10.0 \times 1.3 - 3.3 \mu\text{m}$  and the shape of phialides is flask shaped, but the length of phialides varies considerably depending on the species [42]. *T. harzianum* Rifai, *Trichoderma virens* [43] von Arx, Beih, and *T. viride* Pers.:Fr [44,45] were reported as the best effective BCAs against plant pathogenic fungi. *T. harzianum* is an assemblage of species defined by the presence of short side branches on the conidiophore, short inflated phialides, and smooth and small conidia. Based on the strains and characteristics studied, *T. harzianum* has been classified into three, four, or five subspecific groupings [46]. Gams and Meyer [47] neotypified *T. harzianum* and divided it into two main groups based on molecular analysis: *T. harzianum* sensu lato (s.l.) and *T. viride*-*T. atroviride* complex. Th1 and *T. inhamatum* are some of the most prevalent strains utilised as BCAs [48] in *T. harzianum* s.l. [49,50]. Colombian *T. harzianum* isolates were formerly categorised as *T. inhamatum* due to the lack of sterile appendages on the conidiophores and the globose shape of the conidia [51]. Th1 and *T. inhamatum* were previously thought to be two separate species due to physical distinctions and two base sequence changes in the ITS1 gene. As per molecular data, Th2 and Th4 strains are still not BCAs and are likewise distinct from *T. harzianum* s.l. *T. viride*-*T. atroviride* complex isolates, with rapidly darkening conidia identified by particular restriction fragment length polymorphism (RFLP) pattern. *T. viride* is a genus of bacteria having globose or subglobose to ellipsoidal warty conidia, most of which generate antibiotics and have a coconut-like odor. For many years, the morphology of *T. viride* was unknown until two forms of conidial ornamentation were identified [52]. Recent research has shown that *T. viride* is a paraphyletic group and a combined morphological and genomic approach has confirmed the redefinition of *T. viride* types I and II in two species. Type I includes the genuine *T. viride* species in addition to the *Hypocrea rufa* anamorph and strains of *T. atroviride* and *T. koningii* [53]. Ovoidal instead of globose conidiation, as well as darker and rapid conidiation, characterise the new species *T. asperellum* [53,54].

### 2.2. Molecular Studies on Trichoderma

The advent of molecular tools for investigations in fungal taxonomy prompted research in the mid-1990s to re-assess the morphology-based taxonomy in *Trichoderma*. For the species of bioagents that share common ecology or morphology, rDNA sequencing is a valuable tool to differentiate such species within particular groups of strains or isolates [55–57]. These can also be distinguished by randomly amplified polymorphic DNA (ISSR)—PCR, restriction fragment length polymorphisms in mitochondrial and ribosomal DNA, and sequence analysis of ribosomal DNA. Ribosomal DNA sequence analysis, RAPD, and RFLP [30,32,32–34,58–60] are effective methods to distinguish isolates from the same genera. RAPD helps decide species diversity by molecular identification and characterization of the potent biocontrol agents [61]. The laboratories of G.J. Samuels (Beltsville, MD, USA), T. Borner (Berlin, Germany), and C.P. Kubicek (Vienna, Austria) collaboratively pioneered a revision of Bissett's section *Longibrachiatum*. They combined the use of molecular markers (ITS1 and ITS2 sequence analysis, RAPD), physiological (isozyme analysis) and phenetic characters, and also, for the first time, included an analysis of potential teleomorphs of the *Trichoderma* spp. from this section [46,51,57,62–65].

The total number of phylogenetically recognised species in the *Trichoderma* and *Hypocrea* genus reached over one hundred in the year 2006 [64,65]. Many reports of new species of *Trichoderma* and *Hypocrea* are listed in Table 1. Misidentifications of particular species have happened in some cases, particularly in earlier publications, such as the name *Trichoderma harzianum*, which has been used to describe various species [66].

However, it is difficult to safely fix these inaccuracies analysing the strains that were first utilised. As a result, we will summarise the findings using the originally published names. In recent years, the safe identification of novel species has been substantially facilitated by creating an oligonucleotide barcode known as TrichoKEY and a specialised matching search engine known as TrichoBLAST. These tools are available online at [www.isth.info](http://www.isth.info) accessed on 5 June 2022 [67,68]. Detailed documentations of the genus *Trichoderma*/*Hypocrea* have been produced due to ongoing efforts to elucidate the diversity and geographical occurrence of *Trichoderma*/*Hypocrea* [69–80]. The Index Fungorum (<http://www.indexfungorum.org/Names/Names.asp> accessed on 5 April 2022) now includes 165 records for *Trichoderma* and 471 different names for *Hypocrea* species. Currently, the International Subcommittee on *Trichoderma*/*Hypocrea* compiled a list of 104 species that have been characterised at the molecular level (<http://www.isth.info/biodiversity/index.php> accessed on 20 April 2022). Even this, a huge proportion of the potential *Hypocrea* strains and an even larger portion of the *Trichoderma* strains, for which sequences have been deposited in GenBank, have not yet been identified [67] and must be investigated further. *Trichoderma* taxonomy has been greatly improved by the use of molecular phylogenetic markers and phylogenetic study of the many *Trichoderma* species is still an active research area.

### 2.2.1. Universal Marker-Based Identification

ITS is a reliable marker for the barcoding of fungal DNA. In environmental samples, ITS of the ribosomal DNA region is used to evaluate fungal diversity. The favored DNA barcoding marker is the ITS region of nuclear ribosomal DNA for molecular identification of mixed templates of single taxa [81]. The most promising method is molecular analysis of the ITS region of rDNA for identification of species [82]. Based on DNA sequence analysis and phylogenetic studies, 290 species of *Trichoderma* have been identified and characterised [83]. In eukaryotes, variable sequences with the larger subunit or smaller unit of rRNA genes are suitable for analysis of the subgeneric relationship. In many of the plant pathogenic fungal genera, the phylogenetic relationship is determined by the D2 region of the LSU [84]. Bisset concluded that *T. pseudokoningii*, *T. parceramosum*, *T. citrinoviride*, and *T. longibrachiatum* were allocated under *Longibrachiatum* section based on morphological data [85,86]. Rehner and Samuels and Samuels conducted a phylogenetic analysis of *Trichoderma* ITS region sequences and reported that *T. virens* showed similarity with *T. harzianum*, it is distinct from *Gliocladium*, and the above result supported the Vonrox and Bisset taxonomic studies [87]. The DNA oligonucleotide barcode method is a quick method through which *Trichoderma* and *Hypocrea* can be identified [88]. Oligonucleotide barcode combines many oligonucleotides (hallmarks), mainly distributed among the rDNA region of ITS1 and 2 sequences. The genus species hallmark was defined as oligonucleotide barcodes that are consistent in all *Trichoderma* and *Hypocrea* rDNA regions of ITS1 and ITS2 and differ in related fungal genera. Harmosa et al. described 16 *Trichoderma harzianum* Rifai strains and 1 *T. viride* strain previously recognised as *T. harzianum* Rifai. A certain level of polymorphism was found in hybridizations using a mitochondrial DNA probe. Three different lengths of ITS and four sequence types were confirmed by sequencing ITS1 and ITS2 [89]. Manzar et al., 2020 reported that *tef-1 $\alpha$*  gene and ITS1 and ITS4 gene sequence analysis were able to identify and differentiate 20 *Trichoderma* isolates. Based on the sequence analysis of *tef-1 $\alpha$*  and ITS1 and ITS4 gene, these isolates were divided into two species, with 19 isolates belonging to *T. asperellum* and 1 isolate belonging to *T. harzianum* [90]. Oskiera et al. identified 104 strains of *Trichoderma* based on the sequences of translation elongation factor 1 alpha (*tef-1 $\alpha$* ), internal transcribed spacers 1 and 2 regions, as *T. simmonsii*, *T. harzianum*, *T. atroviride*, *T. lentiforme*, and *T. virens*. Thus, the comparative nucleotide sequence analysis of ITS1 and ITS4 and *tef-1 $\alpha$*  gene provides better resolution to distinguish different *Trichoderma* species from the sorghum rhizosphere [91].

### 2.2.2. DNA-Fingerprinting Techniques

Many DNA-fingerprinting techniques, such as polymerase chain reaction (PCR), Southern hybridization, and restriction enzyme digestion (RED), are used by scientists to locate strain-specific DNA strands. These methods generate band patterns that can be compared. *Trichoderma* species can be identified in agro-conditions using species-specific primers. In order to distinguish between *T. harzianum* biotypes Th2 and Th4, a species-specific primer-based test was devised by Samuels et al., and then redescribed as *T. aggressivum* f. *europaeum* and *T. aggressivum* f. *aggressivum* [72]. For Schlick and colleagues, they used DNA fingerprinting to demonstrate that oligonucleotides as hybridization probes could differentiate distinct *T. harzianum* patent-protected strains. All strains could be distinguished from one another using fingerprint patterns [92]. The first approach to separate a commercially available biocontrol strain from the other *Trichoderma* strains was established by Zimand et al. and it was used to identify *T. harzianum* T-39 as a BCA against *B. cinerea*. All of the *Trichoderma* strains studied could be distinguished using a set of 10 mer primers in a random amplified polymorphic DNA (RAPD). It is clear that this idea has many benefits beyond morphological feature approaches [93]. The technique can be completed in less time and with less DNA. To follow the distribution and longevity of *T. atroviride* C65 on kiwifruit leaves, Dodd et al. (2004) used an isolate-specific RFLP marker in association with a dot-blot test [94].

Cross dot-blot hybridization with UP-PCR amplification products investigated *T. polysporum*, *G. roseum*, *T. hamatum*, *T. viride*, *T. virens*, and *T. koningii* isolates to find commonalities among the strains. The findings show that UP-PCR and ITS-ribotyping could be useful for identifying various species within a single species [95]. Using random, minisatellite, and microsatellite primers, Fanti et al. fingerprinted two strains of *Trichoderma*, which were potent against *Cytospora* canker of peach in the environment. The M13 minisatellite demonstrated that each strain has its own fingerprint. The antagonists were collected four months after being applied to the soil under the canopy of peach trees; however, they were not recovered from the soil itself and, after a year, they were no longer there [96]. Although there is a wide variety of PCR-based fingerprinting techniques, not all of them are strain specific. These procedures are also very easy to utilise. Both a lower annealing temperature and a shorter primer length can have an adverse effect on the precision of their results [97]. On the other hand, strain-specific fragments may be utilised as monitoring markers in accordance with SCARs (sequence-characterised-amplified regions) [98–102].

### 2.2.3. OMICS Approaches in the Service of *Trichoderma* Monitoring

Biofertilisers and biocontrol agents developed from *Trichoderma* spp. are commonly utilised in agriculture (BCAs) [103]. Information about *Trichoderma* strains' ability to colonise and stay in natural environments is critical for developing a useful *Trichoderma* strain for a BCA [104]. *Trichoderma* strains released as BCAs into the environment must be monitored for their destiny, behavior, and population dynamics. A need for the registration of new biocontrol agents based on *Trichoderma* is the capability to reliably assess and monitor the strain that has been released, as well as to monitor the changing population dynamics of that strain over time [105]. As a consequence, it is becoming increasingly important to differentiate naturally occurring *Trichoderma* populations found in agricultural areas from newly introduced *Trichoderma* strains [106]. In classic microbiological methods, colony forming units (CFU) can be estimated by diluting samples using *Trichoderma*-selective or semi-selective media [107]. A sample collected for dilution plating from the environment does not distinguish between indigenous strains of the *Trichoderma* population's existence in the environment and artificially introduced ones by the experimenter. For this, morphological or physiological characteristics are insufficient to identify the colonies [107]. The omics approach is a promising tool and is used for monitoring and differentiating the potent biocontrol agent activity, which is artificially introduced from the native biocontrol agent that is already present in the soil [108]. *T. harzianum* was monitored and quantified using a primer set and a TaqMan probe for the ITS region [109].

ITS copies were quantified using real-time PCR. The ITS copy number and the fungus biomass were found to have a 0.76 correlation. According to scientists, real-time PCR data can be used to quantify fungi in soil samples. *T. harzianum* could be detected and measured in soils and other organic materials using primers and probes designed for pure fungus cultures. Beaulieu et al. utilized this method to monitor *T. harzianum* populations in green compost and peat, which worked well [109,110]. Cultivation-dependent *Trichoderma* species identification and observation were described by Hagn, et al. using ITS-based primers. Arable soil samples were used to create a library of clones. Its results demonstrated that the primer set selected to amplify the *Trichoderma* gene encompassed a wide range of species relevant to biocontrol [111]. *Trichoderma*-specific primers targeting the ITS region were produced by Meincke et al. (2010) to study *Trichoderma* diversity. On the other hand, the reverse primer binds to an area of ITS2 that is still polymorphic, making it impossible to identify many species [112]. The ITS-based metabarcoding technique by Friedl and Druzhinina eliminated this problem by amplifying the full diagnostic ITS1 and 2 regions from all members of the genus, using six reverse primers and the forward primer ITS5. This culture-independent PCR-based method demonstrated the limited *Trichoderma* diversity in the soil of a riparian forest. Two types of *Trichoderma* populations can be incorrectly estimated using PCR methods: active and inactive hyphae and mycelia, as well as dormant conidia and spores [113]. Furthermore, the isolation of total RNA, its reverse transcription, and the subsequent detection of cDNA allow for the identification of active *Trichoderma* communities by transcriptomic techniques.

Geistlinger et al. employed Touchdown PCR to track and quantify *T. virens* using simple sequence repeats (SSRs). There were 12 distinct loci for which primers were created. According to findings, this species lives as an endophyte in the roots of tomato plants. Numerous strains of *T. virens* had their fungal biomass quantified in plant tissues and co-colonization of the roots has also been discovered [99]. Utilizing cleaved amplified polymorphic sequence (CAPS) markers, the genetic diversity of *T. atroviride* isolates was investigated [114]. Following amplification of RAPD regions, the amplicons were digested to restrict enzyme digestion with BslI, DraI, and TaqI. *T. atroviride* was distinguished from other species by three CAPS markers, which can be used to assess and monitor *T. atroviride*, particularly in environmental specimens. Meena et al. provided a strategy for detecting *T. harzianum* and *T. hamatum* species. SCAR primers were created based on the sequence of species-specific RAPD fragments [115]. Perez et al. developed a procedure to monitor the growth and colonisation of *T. harzianum* in experimental communities similar to the method described earlier [100]. Because of the pervasive and diversified nature of *T. harzianum*, scientists did not suggest using this method for detecting the species in complicated ecological samples such as soil.

Using microarray technology, it is possible to investigate *Trichoderma* populations in natural surroundings, which track gene expression changes. To monitor active *Trichoderma* populations, new field-portable microarray analysis systems are now available [101]. These systems provide data on microbial community composition, dynamics, and the physiological status of *Trichoderma* populations in soil. When conducting comparative transcriptome analyses in vitro or in soil microcosm systems, researchers can use the transcriptomic data from *Trichoderma*-fungus [102] and *Trichoderma*-plant interactions to choose target genes for microarray monitoring. After using *Trichoderma* as a biocontrol agent, a metatranscriptome investigation of agricultural habitats can reveal significant alterations in the active microbiome. On the other hand, this method is time consuming and expensive due to the need for high-throughput sequencing and computing systems.

Now, it is easy to select *Trichoderma* strains, develop BCA implementation strategies, and establish monitoring strategies for detecting specific cells, secreted proteins, or secondary metabolites; hence, volumes of information are available on the metabolome, proteome, and secretome of *Trichoderma* strains from multiple species. Because each *Trichoderma* species produces a unique peptaibome, non-ribosomally produced peptaibols could be used to build mass spectrometry-based, species-specific monitoring systems [116].

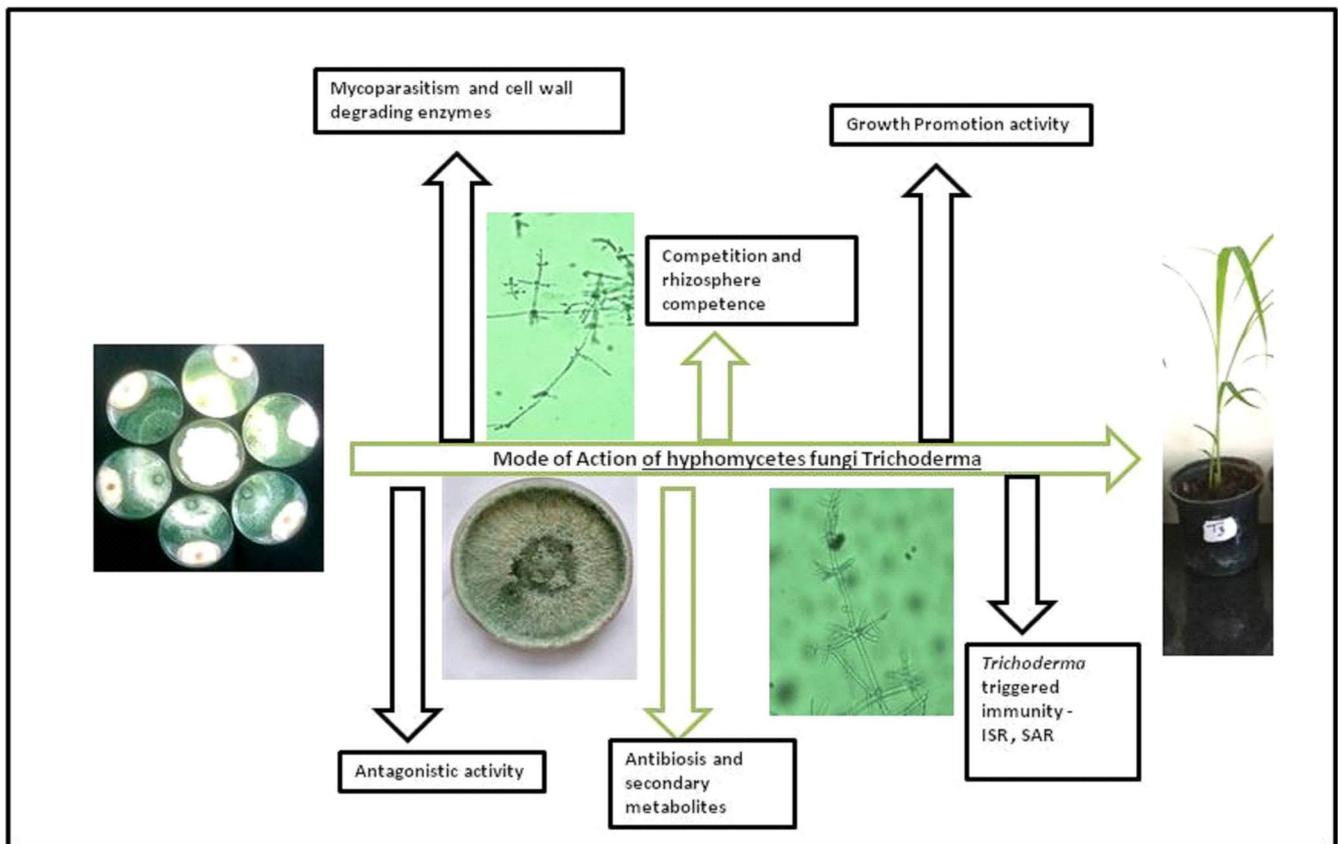
#### 2.2.4. Exogenous Marker Genes

Utilizing exogenous markers, such as glucuronidase (GUS), green fluorescent protein (gfp), hygromycin B phosphotransferase (hygB), or producing genes, certain *Trichoderma* strains in agroecosystems might be identified and tracked [117–145]. Orr and Knudsen employed the gfp-labeled and GUS, *T. harzianum* strain ThzID1-M3 to quantify the biomass changes in a fungal BCA in unsterilised soil. Indigenous bacterial and fungal populations in unsterilised soil interfere with biomass determination procedures. GUS and gfp were used to distinguish between the BCA-introduced marker genes and the indigenous *Trichoderma* populations [146,147]. It was demonstrated that epifluorescence microscopy could discriminate active hyphal biomass useful for biological control among dormant chlamydospores and conidia counted by plate counts while observing gfp-labeled *T. harzianum* [148]. Propiconazole-resistant *Trichoderma harzianum* TF3 is antagonistic to *Botrytis cinerea* and can survive at high population densities in tomato, grapevine, and phylloplane. This strain was changed to be resistant to hygromycin B using high-voltage electric pulses and the vector pHAT (an offspring of pAN7-1), which was then used to select strains with high levels of resistance [149]. When grown on tomato phylloplane, all transformants outperformed the wild-type strain, thrived for 2 weeks in the presence of hygromycin B or propiconazole, and were mitotically stable after many passages without selection pressure.

Utilising cucumber plants cultivated in sphagnum peat, Green and Jensen evaluated the population trends and durability of the transformed *T. harzianum* strain T3a. A *T. harzianum* strain inoculated into the rhizosphere was studied for the first time using the GUS marker to track its existence, population structure, and behaviors [150]. pAN7-1 and pNOM102 plasmids were used by Bowen et al. to transform the *T. harzianum* strain M1057 against *Sclerotium rolfii* [59]. Two transformants had mitotic stability and their growth rates matched wild-type ones. The co-transformant mitotic stability and ability to colonise *Sclerotinia sclerotiorum* resting sclerotia in soil were studied [129]. *T. harzianum* ThzID1-M3 strain was found to colonise about 60% of the sclerotia, suggesting that the strains can be co-transformed with GUS and gfp to assess and monitor specific strains introduced into soil [151]. ThzID1-M3 significantly reduces *S. sclerotiorum* colonisation in soil by inhibiting the growth of fungivorous and other nematode populations when applied to soil. Fungivorous nematodes seek out nutrient-rich areas in the soil. A larger hyphal net produced by a *Trichoderma* strain and fed to the soil as a pellet formulation attracts worms by providing food. To release into the environment, various countries, including those in the European Union, require authorization [152]. Therefore, it is crucial to monitor distinct, genetically unaltered biocontrol *Trichoderma* strains in agricultural contexts utilising molecular techniques based on endogenous DNA markers.

### 3. Mechanisms of *Trichoderma*

*Trichoderma* spp. uses numerous antagonistic strategies against plant diseases. These include antibiosis, mycoparasitism, competition for nutrients and space, stimulation of plant growth, and induced plant defense mechanisms (Figure 1) [113].



**Figure 1.** Biocontrol mechanism used by *Trichoderma* against plant pathogens and promoting healthy crop.

### 3.1. Mycoparasitism

Mycoparasitism is an essential antagonistic character of *Trichoderma*, which is responsible for its efficiency against the plant pathogenic fungi [153]. The complex process of mycoparasitism entails various events. In a biotrophic mycoparasitism, the hyperparasite relies on the host fungus and obtains nutrition from it via haustoria without causing the host cell to die out. Equilibrium is maintained between the host and the mycoparasitic fungus (136). For commercial biocontrol purposes, these species-specific interactions may be essential but are unlikely to be utilized due to the need for host mycelium as a substrate for synthesizing hyperparasite. This category of hyperparasites is significantly better suited for commercial use as MBCA compared to biotrophic hyperparasites since they can grow on artificial substrates in large quantities, allowing for mass production.

*Trichoderma* and *Clonostachys* are the most explored mycoparasites. Most antagonistic isolates from these genera exhibit a wide spectrum of plant pathogenic hosts among their antagonistic isolates. CWDEs (cell wall degrading enzymes) and antimicrobial secondary metabolites are typically used in tandem to kill their hosts, which develop structures for attachment and infection [121–125]. Chitinolytic enzymes produced from *T. harzianum*, such as endochitinase,  $\beta$ -1, 3 glucanase, and chitobiosidase, are more effective against plant pathogenic fungus than chitinolytic enzymes isolated from plants or bacteria. The concentration of cell wall degrading enzymes (CWDEs) viz. chitinase and  $\beta$ -1, 3-glucanase produced by *Trichoderma* isolate was high. The cellulase and protease amounts were low and the polygalacturonase produced by the pathogen was significantly reduced. The mixture of endochitinase or  $\beta$  1-3 glucanase showed antifungal activity by lysis of spore cell walls, thallus, and hyphal tips and combining chitobiosidase and endochitinases inhibited the plant pathogenic fungal spore germination and hyphal lysis more than singly [126].

After recognising the host, complicated signaling triggers the production of these lytic enzymes, which are not constitutive [124]. Recognizing the fungal host triggers transcriptional reprogramming and the development of “molecular weapons”, such as CWDEs (cell wall degrading enzymes) that are used in host attack and lysis. The host releases oligosaccharides and oligopeptides that are then recognised by *Trichoderma* receptors and function as inducers due to the early activities of cell wall degrading enzymes (CWDEs) [124]. Mycoparasites that are necrotrophic can cause more excellent permeability and disintegration of host cell walls, leading to the death of the host. Several *Trichoderma* mycoparasitism-related gene families are upregulated during mycoparasitism, including ech42 and prb1. Trichothecene, produced by *T. harzianum* gene tri5, inhibits protein and DNA synthesis, limiting pathogen growth. Trichothecene has a phytotoxic effect on *Fusarium* species [127]. *Trichoderma virens* TvBgn2 and TvBgn3 genes release a cell wall disintegrating enzyme, which aids in biocontrol activities [128]. *T. harzianum* mycoparasitic activity has been boosted by the cloning and expression of genes from five *T. harzianum* isolates encoding chitinase (chit42), N-acetyl- $\beta$ -D-glucosamidase (exc1, and exc2),  $\beta$ -glucanase (bgn 13.1), and protease (prb1) (T 30, 31, 32, 57, and 78) [154]. A gene aids mycoparasitic activity from *T. harzianum* CECT 2413 that provides adhesion to hydrophobic surfaces and shields plant cells from *R. solani* infections, according to previous research [155]. The *T. atroviride* G protein component, responsible for degrading pathogenic fungi cell walls, produces chitinase and other antifungal compounds through the Tga1 gene [156]. *B. cinerea* and *Phytophthora capsici* were found to have a synergistic effect on *Trichoderma atroviride* transcription of genes involved in cell wall breakdown [156]. The genes identified from these biocontrol agents have been discovered to have an essential role in biocontrol activity and their detailed function is discussed in Table 1.

**Table 1.** List of genes involved in biocontrol activity and enzyme production.

S.No.	Gene	Protein	Function	Reference
1	endoglucanase I (EG I)	Endoglucanase	cellulose hydrolysis	[157]
2	erg1	Squalene epoxidase	activation of plant defense system	[145]
3	tri3	Trichothecene O-acetyltransferase TRI3	trichodermin biosynthesis	[149]
4	tri4	Cytochrome P450 monooxygenase	trichodermin biosynthesis	[149]
5	tri5	Trichodiene synthase	trichothecene biosynthesis	[100]
6	tri6	Trichothecene biosynthesis transcription regulator TRI6	transcriptional activator of genes involved in <i>harzianum</i> A (HA) biosynthesis	[150,158]
7	tri11	Trichothecene C-4 hydroxylase	trichodermin biosynthesis	[149]
8	tri22	Cytochrome P450 monooxygenase	trichothecene biosynthesis	[151]
9	tri10	Transcription factor	regulation of trichothecene biosynthetic genes	[152]
10	tri11	Trichothecene C-4 hydroxylase	trichodermin biosynthesis	[149]
11	ACEI	Repressor protein	cellulase biosynthesis	[153]
12	AceII	Transcription factor	cellulase biosynthesis	[154,159]
13	CbhI	Cellobiohydrolase I	cellulase hydrolysis	[155]
14	cbhII	Cellobiohydrolase II	cellulase hydrolysis	[148]
15	bgl1	$\beta$ -glucosidase	cellulose hydrolysis	[156]
16	prb1	Basic proteinase	Mycoparasitism	[157]
17	ech42	Endochitinase	Mycoparasitism	[160]

Table 1. Cont.

S.No.	Gene	Protein	Function	Reference
18	chit33	Endochitinase 33	Mycoparasitism	[161]
19	chit42	Chitinase 42	biocontrol activity against fungus	[162]
20	cre1	Carbon catabolite repressor	Mycoparasitism	[163,164]
21	<i>xyr1</i>	Xylanase regulator 1	systemic resistance induction in plants	[165,166]
22	Rce1	Transcriptional repressor protein	regulation of cellulase biosynthesis	[167,168]
23	nag1	N-acetylglucosaminidase	essential for chitinase induction by chitin	[169,170]
24	egl1	$\beta$ -1,4-Endoglucanase	Mycoparasitism	[171]
25	tvsp1	Extracellular serine protease	Mycoparasitism	[172,173]
26	Sm1	Cerato-platanin protein	activation of plant defense mechanisms	[174]
27	Sm2	Cerato-platanin protein	activation of plant defense system	[175,176]
28	SS10	Subtilisin-like protease	Broad-spectrum antifungal activity	[177]
29	SA76	Aspartic protease	Biocontrol activity against fungus	[178]
30	SL41	Serine protease	biocontrol activity against fungus	[179]
31	<i>Tas-acdS</i>	ACC deaminase	Plant root growth-promotion	[180]
32	TgaA	G-protein $\alpha$ subunit	mycoparasitism against <i>Sclerotium rolfii</i>	[181,182]
33	TmkA	mitogen-activated protein kinase	mycoparasitism against <i>Sclerotium rolfii</i>	[183]
34	ThPG1	Endopolygalacturonase	plant defense induction by <i>T. harzianum</i>	[184,185]
35	TvPG2	Endopolygalacturonase	Induction of Plant Systemic Resistance	[186]
36	ThPTR2	Di/tri-peptide transporter	Mycoparasitic process	[187]
37	tac1	Adenylate cyclase	Growth, germination, mycoparasitism and secondary metabolism	[188]
38	Vel1	VELVET protein	Regulator of biocontrol as well as morphogenetic traits in <i>Trichoderma virens</i>	[189]
39	PPT1	4-phosphopantetheinyl transferase	Role in antibiosis and induction of SA and camalexin-dependent plant defense responses	[190]
40	Taabc2	ABC Transporter Membrane Pump	Role in antagonism and biocontrol against <i>Pythium ultimum</i> and <i>Rhizoctonia solani</i>	[191]
41	epl1	Eliciting plant response-like protein	Modulation of Systemic Disease Resistance in <i>Solanum Lycopersicum</i>	[192]
42	epl2	Eliciting plant response-like protein	<i>Trichoderma</i> mediated promotion of plant protection	[176]
43	Thctf1	Transcription factor	Production of secondary metabolites and in the antifungal activity of <i>T. harzianum</i>	[193]
44	Pgy1	Proline-glycine-tyrosine-rich protein	Role in antagonism against soil-borne pathogens of plants	[194]
45	Ecm33	GPI-anchored cell wall protein	Role in antagonism against soil-borne pathogens of plants	[194]
46	Pac1	Transcription factor	Role in antifungal activity of <i>Trichoderma harzianum</i>	[195]
47	Tvbgn3	Beta-1,6-glucanase	Mycoparasitism	[174]
48	tvhydii1	Class II hydrophobin	Mycoparasitism and plant-fungus interaction	[196]
49	Ste12	Transcription factor	Mycoparasitism	[197]
50	LaeA	Methyltransferase protein	<i>Trichoderma atroviride</i> defense and parasitism	[198]

### 3.2. Competition of Ecological Niche

For maintaining the dynamics of the microbial population, where microorganisms belong to the same community and share the exact physiological needs, the availability of nutrients is limited and, therefore, nutrient competition is essential for their survival. The *Trichoderma* is a ubiquitous fungus, which is present throughout the world in agricultural and natural soils due to its excellent competitive capability. *Trichoderma* can compete with pathogens in plants for nutritional sources, viz. nitrogen, carbon, and iron and acts as a biocontrol agent against soil-borne plant pathogens. The rhizosphere competence of *Trichoderma* strains enables them to colonise the root surface and compete with other microorganisms for nutrients secreted by roots in rhizospheric soil [199]. The term rhizosphere competence was coined by Ahmad and Baker in 1987 [200]. *Trichoderma* spp. not only controls many soil-borne pathogens but also promotes plant growth [201,202]. *Trichoderma* spp. releases siderophores that sequester iron ions, thereby making them unavailable to the pathogen. It has been established that plant pathogens produce low binding siderophore coefficients or fewer siderophores as compared to *Trichoderma*. Iron is present in the  $Fe^{3+}$  state and it is not available for the growth of microorganisms because Ferric ion is not soluble. *Trichoderma* spp. produces siderophores, which chelate  $Fe^{3+}$  and receptor protein of microbial membrane recognise the complex of siderophore-Fe. Thus, the siderophore- $Fe^{3+}$  complex makes Fe unavailable to the microorganisms, including plant pathogens present in the rhizosphere, ultimately resulting in suppressing pathogenic infection and, hence, *Trichoderma* acts as a biological control, contributing to managing the plant pathogen colonisation [203,204]. This shows the importance of competition for nutrients between *Trichoderma* and pathogenic fungi. *Trichoderma* is more competitive than other rhizospheric microorganisms because it can mobilise and take up nutrients from the soil [202]. T35 strain of *T. harzianum*, due to its rhizosphere competence, outcompetes *Fusarium oxysporum* f. sp. *melonis* for nutrients and can colonise the rhizosphere well, resulting in decreased concentration of nutrients and rhizospheric space for colonization of *F. oxysporum* f. sp. *melonis* [205].

In addition, *Trichoderma* has an advantage over many other soil microbes due to its ability to mobilise and take up soil nutrient sufficiently. Competition for nutrients is the primary mechanism utilised by *T. harzianum* against *Fusarium oxysporum* f. sp. *melonis*. Microorganisms, such as *Trichoderma* spp., mediate the solubility of nutrients in the soil and make them available at the root surface. Soil microorganisms cause changes in soil pH, a result of which being that equilibrium of many chemical and biochemical reactions is modified [206]. There is scant evidence that *Trichoderma* can enhance the bioavailability of insoluble or sparingly soluble elements viz. P, Fe, Mn, Cu, and Zn. However, results have been yielded by previous research [207–209]. Significant increases in concentrations of P, Fe, Mn, Cu, Zn, and Na in roots of cucumber inoculated with *Trichoderma* were reported by Yedidia et al. [210]. Fiorentino et al. demonstrated that *T. virens* GV41 improved the growth of lettuce and rocket and enhanced nutrient uptake by them and, hence, is the best performing microbial biostimulant. It enhanced the use efficiency of N and favored the uptake of native soil N by both the crops. The uptake of N by roots was enhanced under low-N-availability conditions. It has been revealed that *Trichoderma* acts as a nutrient solubiliser. However, the detailed effects of *Trichoderma* inoculation remain to be deciphered [211].

### 3.3. Antibiosis

*Trichoderma* strains produce low-molecular-weight volatile or nonvolatile antibiotics or diffusible compounds that interact and restrict the growth of deleterious plant pathogenic fungi. This process is called antibiosis. The metabolites viz. antibiotics, mycotoxins, and phytotoxins produced by *Trichoderma* helped in antagonism by either antibiosis or competition or through hyperparasitism. The fungus releases, viz. glucanases, chitobioses, and chitinase enzymes, or antibiotics, such as viridin, gliotoxin, or peptaibols [88]. *Trichoderma* produces a broad range of secondary metabolites, such as trichodermin, gliotoxin, viridin, and peptide antibiotics, which is described in detail in Table 2 [212]. Antibiosis plays a

vital part in managing *Pythium ultimum* and *Rhizoctonia solani*, which causes the damping of zinnias. Gliotoxin antibiotic produced by biocontrol agent *Gliocladium virens* prevents *R. solani* and *P. ultimum* growth by affecting the membrane and the leakage of metabolites from the respective pathogen [213]. Antibiotics, including gliovirin, viridin, and massilactone, and toxic nonvolatile and volatile metabolites, such as tricholin, alamethicins, and harzianic acid, are produced by *Trichoderma* strains [214]. Mendoza et al. observed that in an interaction between the *Trichoderma* spp. HTE815 strain and *M. phaseolina*, the antibiosis phenomenon is involved. There is formation of an intermediate band without growth between colonies. The culture medium changes color and growth of inhibition zone exist due to secondary metabolite excretion. Filizola et al. presented a study on antibiosis and degree of antagonism and reported that the fungi belonging to *Trichoderma* genus could potentially prevent the growth of the *Fusarium* strain [201]. This indicates the specificity between the antagonist and the potential phytopathogen determined by various genes and genetic factors that interact with the environment. Gębarowska et al. investigated the volatile secondary metabolites and biometric parameters from coriander (*Coriandrum sativum* L.) inoculated with *T. harzianum* strain T22 and *T. asperellum* strain. The treatment with liquid suspension spores of *Trichoderma* increased the yield of essential oil by about 36% without affecting the composition of essential oils, leaving it to the upper limits of pharmacopoeial standards [215]. Moreover, the treatment with *Trichoderma* spp. limited plant pathogenic fungi belonging to the genus *Fusarium*. Volatile compounds and proteins secreted by *Trichoderma* strongly inhibited the growth of bacterial isolates. This observation clarifies that *Trichoderma* significantly modifies rhizosphere bacterial communities due to the fumigant's nature of volatile compounds [216]. Gliovirin that is produced by P strains of *T. virens* is potent against *P. ultimum*. The Q strains of *T. virens* also produce gliotoxin that is effective against *Rhizoctonia solani* [217]. Antimicrobial compounds produced by *T. koningii* SMF2 have been shown to be active against Gram-positive bacterial and fungal plant pathogens. Trichokonin VI, VII, and VIII are the peptaibols that make up the metabolites. Over a broad pH range and at different temperatures, the Trichokonins remain stable and biologically active [218]. The secondary metabolites produced by the *T. harzianum* strains T22 and T39 have been investigated. They identified and analysed the chemicals T39 butenolide, harzianopyridone, and harzianopyridone. T39 butenolide and harzianopyridone demonstrated strong activity against *G. graminis* var. *tritici*, even at low doses [219]. The mutant of *T. virens*, deficient in mycoparasitism and antibiotic activity, retained its biocontrol efficacy equivalent to that of the parent strain against *Pythium ultimum* and *R. solani*, causing cotton seedling disease [220]. However, it was assumed that this was due to the synergistic effect of enzymes and antibiotic compounds [163]. Several authors have reported the involvement of lytic enzymes in biocontrol agent activity with cellulose and chitin degradation characteristics in *Trichoderma* spp. [126]. *Trichoderma* spp. produces extracellular metabolites, which are nonvolatile diffusible chemicals that have an inhibitory impact against fungal pathogens, such as *Colletotrichum graminicola*. Shorter main roots are a result of higher pyrone concentrations, as shown by Garnica-Vergara et al. [221]. Used concentrations are not always present in nature. Additionally, Lee et al. discovered no association between 6-PP generation and growth stimulation [222]. Gliovirin suppresses the *Phytophthora* and *P. ultimum* activity, but it is ineffective in managing the diseases caused by *Bacillus thuringiensis*, *Rhizopus arrhizus*, and *Rhizoctonia solani* [223].

**Table 2.** List of secondary metabolites/bioactive compounds produced by *Trichoderma*.

Serial Number	Compound (Secondary Metabolites)	Biological Activity	Produced By	References
1.	Trichorzianin TA Trichorzianin TB	Antifungal	<i>T. harzianum</i>	[224]
1.	Trichorzins TVB I, II, IV	Antifungal	<i>T. virens</i>	[224]
2.	Harzianopyridone	Antifungal, Plant growth Regulator	<i>T. harzianum</i>	[225]
3.	Harzianolide Dehydroharzianolide	Antifungal	<i>T. harzianum</i>	[224]
4.	6-pentyl- $\alpha$ -pyrone	Antifungal, Antimicrobial, Plant growth Regulator	<i>T. harzianum</i> <i>T. koningii</i> <i>T. viride</i>	[224]
5.	6-pentyl-2H-pyran-2-one	Antifungal, anti-nematode and plant growth-promoting in tomato and Arabidopsis thaliana	<i>T. atroviride</i> <i>T. harzianum</i> <i>T. koningii</i> <i>T. viride</i>	[221]
6.	6-pent-1-enyl- $\alpha$ -pyrone	Antifungal	<i>T. harzianum</i> <i>T. viride</i>	[226]
7.	Massoilactone- $\delta$ -decenolactone	Antifungal	<i>Trichoderma</i> spp.	[224]
8.	Koninginin E, B, A	Antifungal, Plant growth Regulator	<i>T. harzianum</i> <i>T. koningii</i>	[227]
9.	Koniginin D Hydroxykoninginin B Seco-koninginin	Antifungal, Plant growth Regulator	<i>T. harzianum</i>	[224]
10.	Koninginin C	Antifungal, Plant growth Regulator	<i>T. koningii</i>	[28]
11.	3,4-dihydroxycarotene	Antifungal	<i>T. virens</i>	[224]
12.	Lignoren	Antifungal Antibacterial	<i>T. lignorum</i>	[224]
13.	Trichodermin	Antifungal Antitrichomonal Mycotoxin	<i>T. polysporum</i> <i>T. sporulosum</i> <i>T. virens</i> <i>T. reesei</i>	[224]
14.	<i>Harzianum</i> A	Antifungal	<i>T. harzianum</i>	[224]
15.	Mycotoxin T2	Antifungal Mycotoxin	<i>T. lignorum</i>	[224]
16.	Ergokonin A	Antifungal	<i>T. koningii</i> <i>T. viride</i> <i>T. longibrachiatum</i>	[141]
17.	Ergokonin B	Antifungal	<i>T. koningii</i> <i>T. viride</i>	[224]
18.	Viridin	Antibiotic Inhibitor Fungal Spore germination Phytotoxic	<i>T. viride</i> <i>T. virens</i> <i>T. koningii</i>	[224]
19.	Dermadin (U21, 963)	Antimicrobial	<i>T. koningii</i> <i>T. viride</i>	[130]
20.	Cellulases	Degrade cellulose during root colonization to penetrate the plant tissue	<i>T. reesei</i>	[153]
21.	Compactin	Act as Cholesterol lowering agent	<i>T. longibrachiatum</i> <i>T. pseudokoningii</i>	[132]

Table 2. Cont.

Serial Number	Compound (Secondary Metabolites)	Biological Activity	Produced By	References
22.	5-Hydroxyvertinolide	Fungal antagonist	<i>T. longibrachiatum</i>	[133]
23.	Gliovirin	Antimicrobial	<i>T. virens</i>	[217]
24.	Bisvertinolone	Antifungal	<i>T. longibrachiatum</i>	[134]
25.	Fleephilone	Inhibitory action against Virion	<i>T. harzianum</i>	[135]
26.	Harziphilone	Cytotoxicity against murine tumor cell line M-109	<i>T. harzianum</i>	[135]
27.	Trichodimerol	Inhibit tumor necrosis factor in human monocytes.	<i>T. longibrachiatum</i>	[136]
28.	Trichocaranes A,B,D	Growth inhibitor of etiolated wheat coleoptiles	<i>T. virens</i>	[137]
29.	Viridepyronone	Fungal antagonist	<i>T. viride</i>	[138]
30.	T22azaphilone	Antifungal	<i>T. harzianum</i>	[219]
31.	T39butenolide	Antifungal	<i>T. harzianum</i>	[219]
32.	Emodin	Antimicrobial and antineoplastic agent	<i>T. viride</i>	[139]
33.	Trichosetin	Antibiotic	<i>T. harzianum</i>	[141]
34.	<i>Trichoderma mide B</i>	Displays cytotoxicity against HCT-116 human colon Carcinoma	<i>T. virens</i>	[141]
35.	Wortmannolone	Inhibitor of the phosphatidylinositol 3-kinase	<i>T. virens</i>	[141]
36.	Virone	Inhibitor of the phosphatidylinositol 3-kinase	<i>T. virens</i>	[141]
37.	Heptelidic acid	Activity against Plasmodium Falciparum	<i>T. virens</i> <i>T. viride</i>	[141]
38.	Indole-3-acetic acid (IAA)	Growth and development Regulator	<i>T. atroviride</i> <i>T. virens</i>	[140]
39.	Indole-3-acetaldehyde	Control root growth in Arabidopsis thaliana	<i>T. atroviride</i> <i>T. virens</i>	[140]
40.	Indole-3 Carboxaldehyde	Induces adventitious root formation in Arabidopsis thaliana	<i>T. atroviride</i> <i>T. virens</i>	[141]
41.	Ferricrocin	Required in the competition of iron in the rhizosphere	<i>T. atroviride</i> <i>T. virens</i> , <i>T. reesei</i>	[142]
42.	Gliotoxin	Required in the competition of iron in the rhizosphere	<i>T. hamatum</i> <i>T. viride</i> <i>T. virens</i>	[228]
43.	Cyclonerodiol	Antifungal	<i>T. harzianum</i> <i>T. koningii</i>	[153]
44.	Pachybasin	Antifungal	<i>T. harzianum</i>	[144]
45.	Trichovirin II	Induction of resistance in cucumber plants	<i>T. virens</i>	[228]
46.	Alamethicin	Induction of plant defense in lima and pathogen resistance	<i>T. viride</i>	[228]
47.	Coprogen B	Solubilize iron unavailable for the plan	<i>Trichoderma spp.</i>	[143]

Table 2. Cont.

Serial Number	Compound (Secondary Metabolites)	Biological Activity	Produced By	References
48.	Harzianic acid	Antimicrobial, plant growth Regulator	<i>T. arundinaceum</i> , <i>T. harzianum</i>	[145]
49.	cis- and trans- $\beta$ -ocimene	Induce expression of JA defense responses-related genes in Arabidopsis. Thaliana	<i>T. virens</i>	[229]
50.	$\beta$ -Myrcene	Regulates the expression of genes (abiotic and biotic stresses)	<i>T. virens</i>	[230]
51.	Abscisic acid (ABA)	Regulates stomatal aperture in Arabidopsis thaliana	<i>T. atroviride</i> , <i>T. virens</i>	[231]
52.	Ethylene (ET)	Regulates cell differentiation and defense responses	<i>T. atroviride</i>	[227]
53.	Trichokonin VI	Inhibits primary root growth in Arabidopsis thaliana	<i>T. longibrachiatum</i>	[232]
54.	Glu(OMe)18-alamethicin F50 (2)	Anti-tumor	<i>T. arundinaceum</i>	[233]
55.	trichobrevin BIII-D	Anti-tumor	<i>T. arundinaceum</i>	[233]
56.	bisabolan-1,10,11-triol	Antibacterial Growth inhibiting	<i>T. asperellum</i>	[234]
57.	12-nor-11-acetoxybisabolen-3,6,7-triol	Antibacterial Growth inhibiting	<i>T. asperellum</i>	[234]
58.	Dechlorotrichodenone-C	Antibacterial Growth inhibiting	<i>T. asperellum</i>	[234]
59.	3-hydroxytrichodenone C	Antibacterial Growth Inhibiting	<i>T. asperellum</i>	[234]
60.	3 $\beta$ , 5 $\alpha$ , 9 $\alpha$ -trihydroxyergosta-7,22-dien-6-one	Antifungal	<i>T. asperellum</i> <i>T. harzianum</i> <i>Trichoderma</i> spp.	[235]
61.	Isoechinulin A	Antimicroalgal	<i>T. koningiopsis</i>	[236]
62.	Echinuline	Antimicroalgal	<i>T. koningiopsis</i>	[236]
63.	Fructigenine A	Antimicroalgal	<i>T. koningiopsis</i>	[236]
64.	Cyclophenol	Antibacterial	<i>T. koningiopsis</i>	[236]
65.	Wickerol A	Nematicidal	<i>T. koningiopsis</i>	[236]
66.	Sorbicillin	Antibacterial	<i>T. longibrachiatum</i>	[237]
67.	10,11-dihydrocyclonerotriol	Antifungal	<i>T. longibrachiatum</i>	[238]
68.	Sohirnone A	Antifungal	<i>T. longibrachiatum</i>	[238]
69.	Trichokonin A	Antiviral Anti-tumor Antimicrobial Plant resistance	<i>T. longibrachiatum</i>	[239]
70.	Atrichodermone A,B,C	Cytotoxic Anti-inflammatory	<i>T. atroviride</i>	[240]
71.	Cerebroside A, D	Antibacteria	<i>T. saturnisporum</i> <i>Trichoderma</i> spp.	[239]
72.	Lignoren	Antibacterial	<i>T. atroviride</i> S361 <i>T. citrinoviride</i> <i>T. lignorum</i>	[235]

Table 2. Cont.

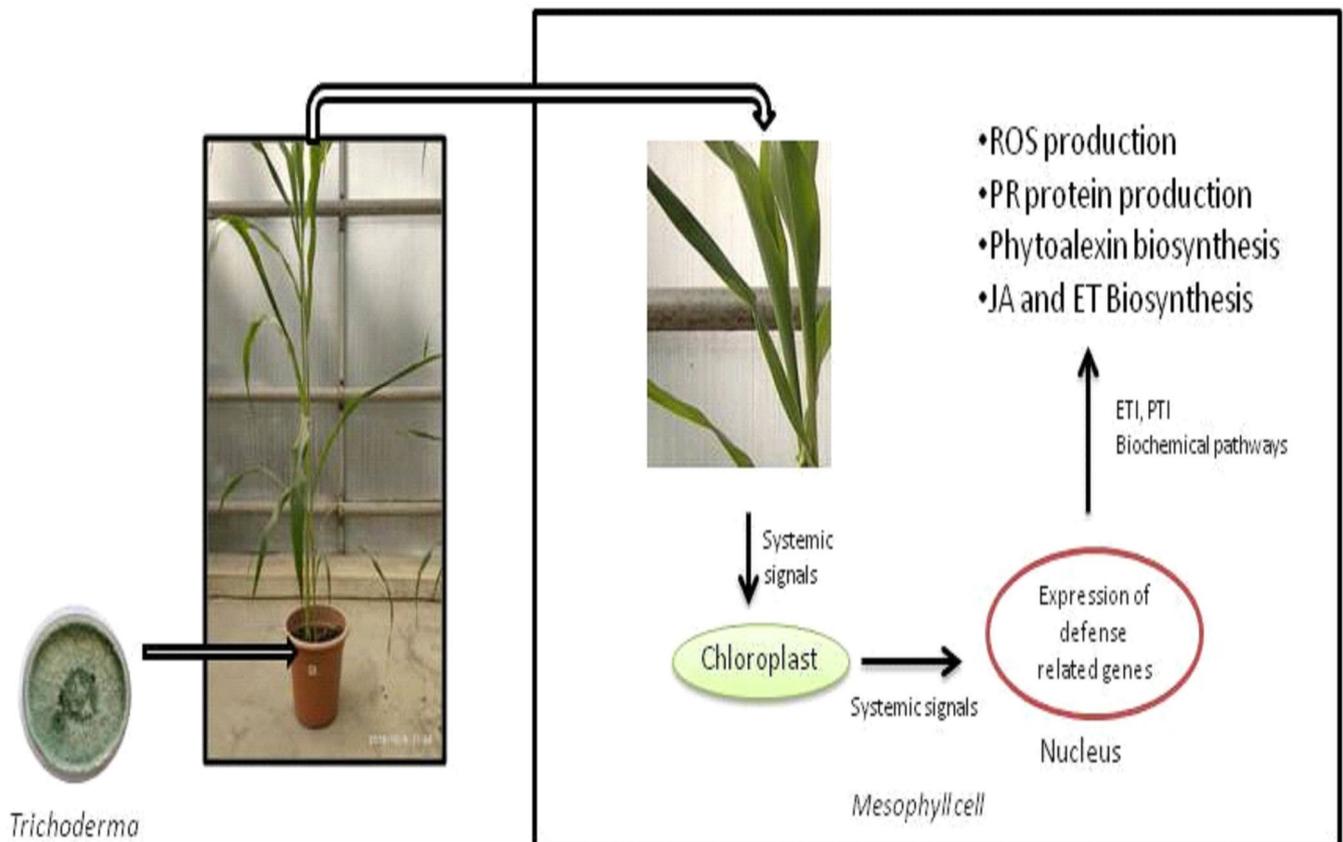
Serial Number	Compound (Secondary Metabolites)	Biological Activity	Produced By	References
73.	Catenioblin C	Antifungal	<i>T. atroviride</i> <i>T. longibrachiatum</i>	[241]
74.	Trichocarotin E,H	Antimicroalgal	<i>T. virens</i>	[237]
75.	Trichocitrin	Antimicroalgal	<i>T. citrinoviride</i>	[242]
76.	Nafuredin	Antimicroalgal Antibacterial	<i>T. citrinoviride</i> <i>Trichoderma</i> sp.	[235]
77.	Chromone	Antifungal	<i>T. virens</i>	[237]
78.	Aspochalasin D, J, I	Cytotoxic	<i>T. gamsii</i>	[241]
79.	Epicycloneodiol oxide	Antibacterial	<i>T. harzianum</i> <i>T. koningiopsis</i>	[235]
80.	cycloneodiol oxide	Antibacterial	<i>T. harzianum</i> <i>T. koningiopsis</i>	[235]
81.	ZSU-H85 A	Antiviral	<i>Trichoderma</i> spp.	[243]
82.	Trichokindin I, II, III, IV, V,VI, VII	Bioinducer	<i>T. harzianum</i>	[244]
83.	2,5-cyclohexadiene-1,4-dione- 2,6-bis(1,1-dimethylethyl)	Antifungal	<i>Trichoderma</i> spp. T-33	[245]
84.	N-2'-hydroxy-3'E-octadecenoyl- 1-o-β-D-glucopyranosyl-9- methyl-4E,8E-sphingadiene	Antifungal	<i>Trichoderma</i> spp. 09	[246]
85.	Tyrosol	Anti-tumor Hyperplasia-inhibitory	<i>T. harzianum</i> <i>T. spirale</i>	[235]
86.	<i>Trichoderma</i> ketone A	Antifungal	<i>T. koningi</i>	[235]
87.	Pyridoxatin	Antibiotic	<i>Trichoderma</i> spp. MF106	[247]
88.	3-(3-oxocyclopent-1- enyl)propanoic acid	Antibacterial	<i>Trichoderma</i> spp. YLF-3	[248]
89.	Oxosorbicillinol	DPPH-radical-scavenging	<i>Trichoderma</i> spp. USF-2690	[56]
90.	α-acetylorsinol	Growth inhibiting	<i>Trichoderma</i> spp. Jing-8	[249]
91.	Daidzein	Antibacterial	<i>Trichoderma</i> spp. YM311505	[238]

### 3.4. Biochemical and Molecular Defense Response Induced by *Trichoderma*

A type of active resistance, known as induced systemic resistance, depends on plant anatomy, such as structural and biochemical barriers. Different physical and biochemical alterations that are indicative of the development of plant-induced systemic resistance occur in plants that are co-cultivated with diverse *Trichoderma* strains. Callose deposition, cell wall thickening, and tylose development in xylem vessels or cork layers are examples of structural alterations [250]. The accumulation of local and systemic reactive oxygen species (ROS), as well as an increase in the production of signaling molecules and secondary metabolites, such as phytoalexins and PR proteins, was among the biochemical reactions seen in plants. In analyses of experimental *Trichoderma* strain–plant–pathogen systems, these substances are regarded as indicators of the defense response in plants [251–255]. Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), an ROS implicated in numerous defensive mechanisms, such as cell wall expansion and lignification, is given a lot of attention. The chemical transmits

signals and has the potential to activate calcium channels and peroxidases in cell walls [250]. Oxidative burst enzymes, such as NADPH oxidases attached to the plasma membrane, peroxidases bound to the cell wall, and apoplastic amine oxidases, can either directly or indirectly generate  $H_2O_2$ . It is crucial to note that the accumulation of ROS was not accompanied by cell damage processes, as indicated by the concentration of lipid peroxides. This suggests the activation of mechanisms that suppress the production of hydroxyl radicals (OH) as well as the use of ROS by enzymes, such as peroxidase or catalases, to initiate a biochemical defense response [253,256]. Application with *Trichoderma* induces the synthesis and accumulation of enzymes, as well as a range of secondary metabolites and signaling molecules, such as salicylic acid (SA), ethylene (ET), and jasmonic acid (JA) (SA) [250,251]. Ethylene and Jasmonic acid are the signaling molecules of ISR, which ultimately are responsible for producing different defense enzymes, such as polyphenol oxidase, peroxidase, catalase,  $\beta$ 1-3glucanase,  $\beta$ 1-4-glucanase, N-acetylglucosaminidases, and chitinases [106,107]. *Trichoderma* strains, after colonization, penetration, and establishment inside the root tissue or attachment with the root tissue, lead to an array of enzymatic and morphological changes inside the host plant that finally help in the production of defensive enzymes and, lastly, end with the induction of induced systemic resistance in the plant [108]. Elicitation of ISR response in plants begins with recognising specific components from microbial cell surfaces, known as microbe-associated molecular patterns (MAMPs) by plant receptors [257]. MAMPs from various biocontrol agents have been linked with ISR (Baker et al., 2007; Van Wees et al., 2008). MAMP responses start with generation ion fluxes, reactive oxygen species (ROS), nitric oxide, and ethylene (ET) and later involve the accumulation of callose and the biosynthesis of antimicrobial substances. The first MAMP identified from *Trichoderma* was ET-inducing xylanase (Xyn2/Eix consisting of five surface-exposed amino acids), eliciting plant defense responses in tomato and tobacco (Rotblat et al., 2002). *Trichoderma*-activated cellulases also trigger defence response by activating ET and SA pathways (Matinez et al., 2001). *Trichoderma* proteins involved in root colonization, such as swollen in TasSwo, also trigger defense response in cucumbers (Brotman et al., 2008). Another protein, endopolygalacturonase ThPG1, stimulates the resistance response in Arabidopsis (Moran-Diez et al., 2009). During the colonisation of maize and cotton roots by *Trichoderma atroviride* and *Trichoderma virens*, protein Ep11 and Sm1 accumulated in hyphae and act as MAMPs, respectively. Root colonisation by *Trichoderma* leads to the systemic alteration in the proteome, transcriptome, and MAMP interaction in leaves. *Trichoderma* interaction with plants leads to elicitor's production. These elicitors induce the production of signaling molecules, such as jasmonic acid (JA) and ethylene (ET), bind the receptors, and after a series of enzymatic reactions, lead to the induction of defensive genes inside the host plant. These defensive genes are directly responsible for plant pathogen suppression and strengthen the morphological and biochemical barrier of the plants [109]. In vitro inoculation of *Trichoderma* isolates against *Sclerotium rolfsii*, *Colletotrichum gloeosporioides*, and *C. capsica* inhibits mycelial growth and significantly increases the chitinase and  $\beta$ -1, 3-glucanase activities [39]. This enabled them to promote the plant growth and stimulate defense system against plant pathogens. JA/ET-dependent pathways elicit ISR by *Trichoderma* and trigger priming responses in plants, such as other beneficial microbes. The interaction of *Trichoderma* with the plant is dynamic. During this interaction, overlapping the expression of defense-related genes of the JA/ET and SA pathways may occur [102]. It depends on the strains of *Trichoderma*, the concentrations used, the plant material, the developmental stage of the plant, and the time of interaction. The *Trichoderma* produces plant hormones ET and IAA. These hormones play a vital part in interconnecting development of plants and their defense responses [103]. The *Trichoderma* is endowed with genes whose expression in plants helps them manage diseases and imparts resistance to stressed environmental conditions. The experimental evidence shows that interactions of *Trichoderma* with plants have traits in common with other beneficial microbial associations and they also show their particular lifestyle characteristics of *Trichoderma* spp. However, more investigations are required to decipher the signaling transduction pathways of defense and development.

These pathways result from *Trichoderma*–plant interactions in the presence of biotic and abiotic stresses [102]. Biotrophs trigger the SA route, whereas necrotrophic pathogens stimulate both the ET and JA pathways [177]. In this defense, PDF1.2 (Plant defensin 1.2), Thi2.1 (Thionin), or Chib (Chitinase B) are commonly used as marker genes [235]. The systemic acquired resistance (SAR) mediated by salicylic acid (SA) results in the expression of pathogenesis-related genes (PR) [236]. These signaling pathways are tightly connected, allowing for fine control of resource allocation between plant development and response to environmental stress agents. To avoid or actively decrease defense barriers, plant enemies frequently modify the underlying network of cross-modulating channels. The necessity to prioritise the response against a specific type of biotic stress has been demonstrated. Then, to comprehend plant defense responses against pests and in the context of a beneficial microbes, molecular pathways must be studied at the metaorganism level. Such research will shed light on the co-evolutionary mechanisms that shape pest and disease communities on plants and provide useful information for creating new pest and pathogen control tactics that mimic and alter plant defensive responses (Figure 2).



**Figure 2.** *Trichoderma*-induced resistance in host plant.

### 3.5. Regulatory Mechanisms Triggering the Defense of *Trichoderma*

Much research has been conducted on the signal transduction pathways that trigger the genes involved in biocontrol and mycoparasitism. These signal transduction pathways include heterotrimeric G-protein signaling, mitogen-activated protein kinase (MAPK) cascades, and the cAMP pathway. These pathways are all interconnected with one another [258]. The MAP-kinase TVK1, which has been identified in *T. virens*, including its orthologs in *T. asperellum* (Tmka) and *T. atroviride* (TMK1), is particularly important in the regulation of signaling processes that target output pathways important for successful biocontrol [259,260]. *T. atroviride* tmk1 deletion results in increased antifungal activity and resistance against *Rhizoctonia solani* but decreased mycoparasitic activity [261]. According to

this study, *T. virens* TVK1 deficiency significantly boosts the fungus biocontrol efficacy [259]. As a result, even though deletion of the corresponding genes reduces mycoparasitic efficacy, the mutant strain biocontrol skills are improved [259].

In terms of the action of the heterotrimeric G-protein signaling pathway in *Trichoderma* spp., two genes have been studied so far in terms of biocontrol-related mechanisms: the class I (adenylate cyclase inhibiting) G-alpha subunits TGA1 of *T. atroviride* and TgaA of *T. virens*, as well as the class III (adenylate cyclase activating) G-alpha subunits TGA3 of *T. atroviride* and GNA3 of *T. reesei*. TGA1 is known to regulate coiling around host hyphae as well as the synthesis of antifungal metabolites. The absence of TGA1 causes host fungus to develop more slowly [262,263]. TgaA has been linked to a host-specific role, similar to that seen with MAP-kinases [264]. On the other hand, TGA3 is essential for biocontrol, as the absence of the corresponding gene led to the development of non-pathogenic strains [265]. Because it has been hypothesised that mycoparasitism can be favorably affected by the constitutive activation of GNA3 in *T. reesei*, a similar mechanism is at work on this fungus [266]. These findings are consistent with the analysis of cAMP signaling components, which show that cAMP has a beneficial function in biocontrol [267].

Efforts were made to identify characteristics among each of these genes and enzymes that were regulated upon the interaction of *Trichoderma* with a pathogen. These characteristics could be used to differentiate efficient biocontrol strains isolated from nature that were less effective [268,269]. However, the effectiveness of standardised marker gene assays for the assessment of the potential biocontrol strains will not be known until after additional and more in-depth research has been conducted.

### 3.6. Plant Growth Promotion

A plant's root system is colonised by microbial organisms, which simultaneously protect the plant from soil-borne diseases and stimulate growth [270]. These positive plant–microbe interactions frequently occur in the rhizosphere, enhancing plant growth or aiding the plant in resisting abiotic or biotic stresses [271]. *Trichoderma* spp. multiplies in the rhizosphere, forming a mutual association that naturally enhances plant nutrition and growth. It can colonise roots, boosting plant nutrition, growth, and development, as well as abiotic stress resistance. Plant growth is typically attributed to an indirect effect of plant disease management when biological control agents are used. *T. harzianum* was also found to enhance the concentration of trace and essential elements, such as Zn, Fe, Cu, Mn, Cu, Ca, Mg, P, N, K, and Na, in the shoots and roots of cucumber and tomato seedlings [272]. It has the ability to produce a number of phytohormones, siderophores, and phosphate-solubilizing enzymes [273]. Phytohormones enhance the absorptive surface of plant roots by stimulating root development. It has been established that plant antimicrobial chemicals produced by *Trichoderma* can stimulate plant growth. Isolated compounds, such as Trichocereus A-D, Harzianopyridone, koninginins, 6PP, cyclonerodiol, harzianic acid (HA), and harzianolide, that helped plant growth promotion are dependent on the concentration of compounds. Cerinolactone, a novel secondary metabolite identified from *Trichoderma cerinum*s, was found to have a beneficial impact on tomato seedling growth 3 days after treatment. Similarly, the iron-binding properties of HA and iso-harzianic acid reported in *T. harzianum* metabolites are known to enhance plant growth [274]. *T. virens* and *T. atroviride* have also produced indole-3-acetic acid-related indoles (IAA-related indoles). The incorporation of L-tryptophan into *Trichoderma* liquid cultures increased the IAA-related indoles production. This finding suggested that *Trichoderma* production of IAA-related indoles may be one of the processes used by the fungus to enhance plant development and secondary root number, resulting in increased biomass in Arabidopsis [275]. *Trichoderma* plant-growth-promoting action could be due to these pathways [16]. *Trichoderma* spp. application results in enhanced vegetative growth on various crop plants. *Trichoderma* spp. interactions with plants resulted in increased resistance against plant diseases [276]. Increased productivity, biomass, nutrient uptake, and stress tolerance are signs of improved plant growth [277]. *Trichoderma* isolates from the rhizosphere of the

mangrove *Avicennia marina* solubilize P from insoluble  $\text{Ca}_3(\text{PO}_4)_2$ —an extracellular phytase activity and acidic phosphatase had been exclusively enhanced in the presence of  $\text{Ca}_3(\text{PO}_4)_2$  [278]. Furthermore, it has been found that using *Trichoderma* spp. in a consortium improves the physical strength and durability of the plant's cell wall in the presence of cell wall degrading plant pathogenic fungi [279,280]. The improvement in root growth is likely the result of one or more mechanisms, including an increase in the rate of carbohydrate photosynthetic activities, a higher rate of plant growth regulation, an increase in rooting depth, and, thus, greater tolerance to drought environments [281]. When there are rich inorganic soil substrates, such as bioorganic fertilisers, *Trichoderma* spp. is more successful in colonising and boosting plant growth [282].

#### 4. Conclusions and Future Prospects

The *Trichoderma*—plant—pathogen interaction is a multi-dependent and dynamic system. A thorough understanding of *Trichoderma* mechanisms with plants and pathogens can significantly improve the efficacy of their actions. *Trichoderma* employs a wide range of complex direct and indirect biocontrol mechanisms to protect itself from biotic stresses, such as pathogenic microbes (bacteria, fungi, and nematodes). This review explains why *Trichoderma* spp. has earned its well-deserved track record as a powerful plant growth promoter, with the added benefit of enhancing localised and systemic resistance in plants. This is because *Trichoderma* spp. is capable of producing a broad range of antibiotic substances and synthesising so many secondary metabolites, each of which has the possibility to parasitise a broad range of pathogenic fungi inside the rhizosphere. *Trichoderma* elicitors and effectors are recognised by plant receptors, which begin the signaling process and govern the genetic composition of the host. This provides the foundation for these symbionts to trigger the defensive metabolism in their host. To verify a database for the responsible and long-term usage of *Trichoderma*, it is necessary to examine the ecological impact of extensive applications of biocontrol agents and their secondary metabolites. Because of this, *Trichoderma* genomes are a valuable source of gene candidates for creating transgenic plants resistant to both biotic and abiotic stresses. Finally, in the age of a green economy focused on protecting both human health and the environment, the use of *Trichoderma* species should be encouraged as a viable alternative to pesticides in light of the information presented in this research. Additionally, the current, thorough, developed, and yet affordable, quick, and successful ways of detecting and evaluating antagonists, integrating multiple mechanisms of action with cascade reactions, must be developed and used in *Trichoderma* research. The research will also focus on determining the risk of using BCAs based on *Trichoderma*, as well as their toxicity and ecotoxicity, not only in vitro but also in natural farming practices in vitro and in situ, before they are commercialised as biostimulations, biocontrols, or bioremediation preparations. In conclusion, it can be said that more research must be conducted to know the mechanism of *Trichoderma* spp. in detail so that potent *Trichoderma* biofungicides can flourish in any type of environment. The social anxiety of implementing new antifungal and antibacterial microbes into the environment must be overcome.

**Author Contributions:** Conceptualization, writing—original draft preparation, N.M.; Writing—review and editing, A.S.K. and N.M.; writing—original draft preparation, investigation, A.S.K., N.M., M.V.S.R. and R.S.G.; supervision, funding acquisition, H.V.S., S.K.S. and P.K.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by ICAR-NBAIM, Maunath Bhanjan, Uttar Pradesh.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Acknowledgments:** The authors extend their gratitude to the Indian Council of Agricultural Research, New Delhi, ICAR-National Bureau of Agriculturally Important Microorganisms, Maunath Bhanjan, U.P India, for providing financial assistance during the study. The authors wish to express their sincere thanks to Faheem Ahmad and Pusparaj for assistance during the time period of these studies.

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

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