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Review Article

Trichoderma as a Biological Elicitor of Medicinal Plant Bioactive Compounds: Mechanisms, Pharmaceutical Significance and Translational Challenges

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Abstract

Medicinal plants remain the principal industrial source of many pharmacologically indispensable molecules, yet the supply of these compounds is constrained by slow growth cycles, low and variable accumulation, and the ecological pressure exerted by wild harvesting. Interventions that raise the content of active constituents in cultivated material without reducing biomass are therefore of direct pharmaceutical interest. Species of the fungal genus *Trichoderma* occupy a distinctive position in this context: they are simultaneously rhizosphere-competent symbionts, mycoparasites deployed as registered biological control agents, and prolific producers of small-molecule and proteinaceous effectors. Root colonization is perceived by the host as a microbial encounter and triggers a transient, self-limiting immune response followed by a state of primed defence, in which jasmonate, salicylate, ethylene and oxylipin signalling are rewired and redox homeostasis is re-set. The proposed mechanistic framework links root perception and transient calcium/ROS/MAPK responses to context-dependent salicylate–jasmonate–ethylene crosstalk, systemic oxylipin signalling, redox regulation and chromatin-associated priming. These inputs converge on transcriptional regulators and precursor supply to influence phenylpropanoid and terpenoid biosynthesis and, depending on host context, other specialised metabolic pathways. However, pathway activation cannot be assumed to yield a higher concentration of a particular pharmaceutical marker. The 27 study records in Table 1 are therefore distinguished by treatment type and strength of attribution: five single-organism applications to living plants, one fermentation and one post-harvest enzymatic conversion, six combinations explicitly including *Trichoderma*, thirteen systems without *Trichoderma*, and one purified microbial metabolite applied to plant material. The most secure *Trichoderma*-specific results concern a dose-dependent cannabidiol increase in hemp, four rhizome marker compounds of *Atractylodes lancea* (three sesquiterpenoids and the polyacetylene *atractylodin*), grape anthocyanins and grain phenolics and anthocyanins in rice; for ginsenosides, artemisinin and medicinal storage polysaccharides, in planta evidence remains absent or indirect, and the single *Trichoderma* record for tanshinones reports a significant increase without a numerical effect size. Secreted elicitors, including cerato-platanin proteins, cellulases, peptaibols, polyketides such as harzianic acid and sorbicillinoids, and the volatile 6-pentyl-2H-pyran-2-one, have been associated with plant signalling or other biological activities, motivating the evaluation of defined elicitation protocols. This review synthesises the molecular dialogue between *Trichoderma* and medicinal plants, summarised as a working model in Figure 1, evaluates the evidence for metabolite-level outcomes by chemical class and by attribution (Table 1), and examines the pharmaceutical, safety and regulatory questions integrated in Figure 2 that determine whether the interaction can be converted into a quality-by-design strategy for herbal raw materials.

More Information

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Introduction

Higher plants elaborate a chemical diversity that remains the backbone of pharmacotherapy. Flavonoids, polyphenols, alkaloids, terpenoids and polysaccharides from medicinal plants underpin a substantial share of drug discovery leads and continue to supply botanical drugs, standardised extracts and nutraceutical ingredients [1,2]. Industrial demand is rising, but production is constrained biologically: many defense-related compounds accumulate only at low basal levels, often in a developmentally restricted or tissue-specific manner, and their content varies substantially with genotype, environment and agronomic practice [3].

Two strategic responses to this bottleneck dominate current research. The first is metabolic engineering of the biosynthetic pathway itself; the second is the exploitation of plant-associated microorganisms as biological elicitors that switch on existing pathways in situ. The latter requires no genetic modification of the plant, can be integrated into cultivation systems, and may simultaneously improve nutrient acquisition, stress tolerance and biomass [2,4]. Fungal endophytes are attractive in this respect because they colonise internal tissues without producing overt disease symptoms and are capable of reprogramming host metabolism at low inoculum densities [3].

Among these fungi, *Trichoderma* (Hypocreales, Hypocreaceae) is exceptional in the breadth of its interactions with plants. The genus comprises soil-borne and endophytic species that combine mycoparasitism with efficient root colonization, vigorous secretion of cell wall–degrading enzymes and the production of an extensive array of secondary metabolites, including peptaibols, polyketides, sorbicillinoids, pyrones and volatile organic compounds [5,6]. Because several species are already commercialised as plant protection products, an agronomic and regulatory infrastructure exists for their deployment at field scale, a practical advantage that few other elicitor organisms can claim [7].

The consequences of *Trichoderma* inoculation for the host metabolome were initially interpreted almost exclusively in terms of disease resistance. It has become clear, however, that the signalling events underpinning induced resistance are the same events that govern the biosynthesis of defense-associated secondary metabolites. A plant primed by a root symbiont is, in metabolic terms, a plant with a partially activated chemical defense arsenal. This realisation has stimulated studies of medicinal and aromatic hosts, although most reported outcomes for ginsenosides, artemisinin and storage polysaccharides originate from other endophytes, combined treatments or post-harvest conversion rather than from *Trichoderma*-alone elicitation; tanshinones are the exception, resting on a single *Trichoderma*-alone report that does not state a quantitative effect size.

This review pursues three objectives: to describe the molecular dialogue that converts root colonization into systemic metabolic reprogramming, with emphasis on perception, hormonal crosstalk, epigenetic priming and redox signalling; to evaluate, class by class, the experimental evidence that *Trichoderma* alters the accumulation of pharmacologically relevant metabolites; and to consider the translational questions — *in vitro* elicitation, field performance, formulation, standardisation and biosafety — that determine whether this interaction can become a reproducible pharmaceutical technology.

The review follows the causal chain rather than the taxonomy of the fungi. Section 2 traces the dialogue from adhesion and pattern perception through hormonal crosstalk, epigenetic priming and redox control to the transcriptional hubs that gate biosynthetic gene expression, and states the resulting model explicitly in Figure 1. Sections 3 and 4 examine the pathway-level and the molecule-level determinants of the output. Section 5 then evaluates the metabolite evidence class by class, and Table 1 records, for every study we could verify, the eliciting organism with its strain designation, the host species, the compounds actually quantified and, where the original report provides one, the numerical effect size. Each record is graded on two axes, attribution (*Trichoderma* alone, a *Trichoderma*-containing combination, a non-Trichoderma system, or a purified microbial metabolite applied to plant material) and system (living plant, fermentation, post-harvest conversion or *in vitro* culture). Conflating these categories is the main reason why the literature appears more consistent than it is, and the distinction is maintained in every subsequent statement. Sections 6 to 9 address the pharmaceutical, process, safety, and regulatory dimensions, which are assembled into a single translational scheme in Figure 2.

The *trichoderma*–plant interface: from root colonization to systemic signalling

Root colonization and niche establishment

The interaction begins with adhesion of conidia or hyphae to the root surface, a step now recognised as an active, genetically programmed process rather than passive attachment. In *T. virens*, homologues of yeast adhesion regulators and several adhesin candidates have been identified, and the properties of the hyphal surface, including hydrophobin coatings, determine the efficiency of subsequent tissue penetration [8]. Colonization is normally restricted to the apoplast of the root epidermis and outer cortex, with occasional deeper penetration; the fungus is contained by defense responses that are locally activated but not allowed to escalate into necrosis. This containment is an active outcome rather than a passive absence of virulence, and it is precisely the configuration required for elicitation: the root is simultaneously a site of microbial perception and of restrained host defence, so that signalling proceeds while tissue damage does not.

Colonization efficiency depends strongly on host genotype. In lentil, the abundance of individual *Trichoderma* species in

Table 1: Reported metabolite- or quality-related outcomes, graded by treatment attribution and by system; quantified effect sizes are quoted wherever the cited report provides them, and a category does not by itself establish compound-resolved elicitation.

Host species (family)	Eliciting organism or treatment	Grade	Compounds assessed	Reported effect (quantified where reported)	Ref.
Vitis vinifera cv. Aglianico (Vitaceae)	*T. afroharzianum* T22 (Trianum P; 1×10^7 conidia/mL drench, 5 applications) and 6PP (1 µM, foliar) as separate arms; field, 2 seasons	D	Anthocyanins; high-MW tannins; sensory profile	Anthocyanins ↑ in grapes and wine; low-MW tannins ↓; high-MW tannins ↑; astringency n.s.; wine odour complexity ↑	38
Atractylodes lancea (Asteraceae)	*T. harzianum* Th2/Th3/Th4 (ITS+TEF1+RPB2; 6×10^6 cfu/mL); growth-chamber pots, 70 d	D	Atractylon; atractylodin; hinesol; β-eudesmol	Atractylon 17.2× and atractylodin 10.6× vs mock (Th3); rhizome DW 0.27–0.58× control, but +35–44% in two Th3 dual treatments	44
Oryza sativa cv. Maled Phai (Poaceae)	*T. zelobreve* PBMP16 (single isolate, 6 replicates); two non-*Trichoderma* isolates as comparison; greenhouse pots, 120 d	D	Total phenolics; anthocyanins (grain)	TPC 92.8 → 122.3 mg GAE/100 g and TAC 33.1 → 55.8 mg Cy-3-G eq/100 g vs non-inoculated control ($p\leq0.01$); PBMP16 best of four isolates	67
Cannabis sativa (Cannabaceae)	*T. harzianum* T-22 (now *T. afroharzianum*; 2 or 4×10^{12} CFU/kg by fertigation at 10 and 30 DAS); greenhouse pots	D	CBD content; growth; yield	CBD 1.14 → 1.32% (high dose, cv. Fedora 17, $p\leq0.05$; low dose n.s.); height +12%, shoot DW +16%; CBD yield per plant 0.65–0.80 g (n.s.)	74
Salvia miltiorrhiza (Lamiaceae)	*T. atroviride* D16, living inoculum colonising roots; plantlets, with Ca^{2+}/H_2O_2 inhibitor arms	D	Tanshinones (T-I, T-IIA)	Tanshinones significantly ↑ (magnitude not reported); effect abolished by $LaCl_3$ and DMTU; DXR, HMGR, GGPPS, CPS, KSL and CYP76AH1 up	29
Zingiber officinale (Zingiberaceae)	*T. viride* (strain not stated); solid-state fermentation of ginger, 30 °C, pH 6.0, 7 d	F	Total phenolics; DPPH/ABTS; antibacterial activity	TPC increased "several times" (no absolute values); antioxidant and antimicrobial activity ↑; no individual phenolic quantified	37
Panax notoginseng (Araliaceae)	Cell-free crude enzymes of *T. reesei* BB8 (*bgl1*-overexpressing RUT-C30) on root powder; post-harvest	B	Ginsenoside extraction; conversion to CK and Rd	β-glucosidase 45.9 IU/mL (23× parent strain); Rb1 converted to Rd and CK; extraction efficiency ↑ (magnitude not reported)	46
Camellia sinensis (Theaceae)	*Trichoderma* sp. AM6 (OM915414) + *Bacillus* spp. D56/D42/DR15 + *Rhizobium* sp. DR23, with VAM-colonised root; pots, 6 months	C	Total flavonoids; mycorrhizal colonization	Total flavonoids ↑ with flavonoid-pathway transcripts up-regulated; mg/g and colonization values not reported	35
Grain legumes (*Glycine max*, *Phaseolus vulgaris*); field	*T. asperellum* H22 (Trichotech, 4×10^9 CFU/g) + *Rhizophagus intraradices* (Rhizatech)	C	Free amino acids; proline; total phenols	Amino acids+proline 10.1 → 13.4 mg/g fwt (soybean, +33%); phenols ↑ in common bean only (n.s. in soybean); foliar disease ↓	34
Codonopsis pilosula (Campanulaceae)	*T. longibrachiatum* FG + salicylic acid + methyl jasmonate; potted seedlings, 15–50 d	C	Untargeted metabolome (steroid/brassinosteroid pathway)	Steroid and brassinolide pathway metabolites shifted (6-deoxotyphasterol ↑); lobetyolin and polysaccharides not measured	40
Astragalus mongholicus (Fabaceae)	*T. afroharzianum* and *T. longibrachiatum* (no strain codes) + 2 DSE; pots, well-watered vs drought	C	Calycosin-7-O-glucoside; formononetin	Both isoflavones ↑ with single inoculation; formononetin higher under drought with co-inoculation; values figure-only; astragaloside IV not measured	66
Cannabis sativa, 5 cultivars (Cannabaceae)	Ferticann (*T. harzianum* + *B. subtilis* + *R. irregularis* + microalgae) and, as separate arms, forest-soil consortia K1/K2 without *Trichoderma*	C	12 phytocannabinoids	CBDVA, CBDV, CBG, CBD and CBGA differ among inoculants ($p\leq0.01$), cultivar-specific; mg/kg values figure-only; no *Trichoderma*-only arm	75
Ocimum basilicum (Lamiaceae)	Asir Horto tablet (*T. koningii* TK7 10^6 CFU/g + *R. irregulare* + *F. mosseae* + 2 *Bacillus*); greenhouse, 0/25/50 mM NaCl	C	Total polyphenols; phenolic acids; VOCs; yield	Total polyphenols +23/+29/+63% (0/25/50 mM NaCl); rosmarinic acid +49/+68%; fresh weight +7–27%; linalool, eugenol, eucalyptol unchanged	72
Cannabis sativa subsp. *sativa* RPF3 (Cannabaceae)	*R. aggregatus* BM-3g3 or *R. prolifer* PC2-2; *L. theobromae* WS-TS-A1 or *M. phaseolina* SS1R1; no *Trichoderma*	N	Fibre fractions; CBD; THC	NDF 70.5% and ADF 58.5% (*R. aggregatus*); CBD 0.9–1.0 and THC 0.7 mg/g, above unfertilised control; root colonization 14–26% (n.s.)	76
Cajanus cajan (isolation host) / *P. notoginseng* material (substrate)	*Fusarium proliferatum* G11-7 (KY303906), immobilized spores; post-harvest biotransformation	N	Ginsenoside Rd (from Rb1)	Rd 2.49±0.98 → 9.15±0.65 mg/g (3.67×); β-glucosidase 0.95 U/mL; spores reused for 6 cycles	45
Panax sokpayensis (Araliaceae)	*Aspergillus* sp. PSRF49 and 3 further endophytes; PDB flask culture	N	Ginsenoside compound K	CK 0.0019–0.0386 mg/g mycelial DW (max. PSRF49); mycelium-bound only, absent from culture filtrate	70
Glycyrrhiza uralensis (Fabaceae)	Endophytic bacterium *Rhizobium rhizolycopersici* GUH21 (16S rDNA) × temperature and irrigation regimes; pots	N	Isoliquiritin; glycyrrhizic acid; 4 further flavonoids	Isoliquiritin 0.434 → 0.958 mg/g at 21 °C/high water, but 0.462 → 0.105 mg/g (−77%) at 21 °C/low water	39
Salvia miltiorrhiza (Lamiaceae)	*Penicillium steckii* DF33 elicitor; hairy-root culture	N	Cryptotanshinone	Cryptotanshinone 1.6452±0.0925 mg/g (4× control); GGPPS, CPS1, KSL1 and CYP450 genes up-regulated	41
Salvia miltiorrhiza (Lamiaceae)	*Cladosporium tenuissimum* DF11; gnotobiotic seedlings, 8 weeks	N	Tanshinones	Tanshinones ↑ significantly (magnitude not reported); HMGR, DXS, DXR, GGPPS, CPS, KSL and CYP76AH1 up-regulated, peak 1–2 weeks	42
Catharanthus roseus cv. Prabal (Apocynaceae)	*Curvularia* sp. CATDLF5, *C. infundibulifera* CATDLF6, *A. japonicus* CATDRF2, *Pseudomonas* sp. CATDS5	N	Ajmalicine; serpentine	Serpentine +211.7 to +337.6%; ajmalicine +123.4 to +203.8% (absolute contents not reported)	48
Catharanthus roseus (Apocynaceae)	*F. solani* RN1, *C. funicola* RN3, *P. rugulosum* RN4, *C. homopilatum* WN1; extract or filtrate 1–2%, cell suspension	N	Total alkaloids; vinblastine	Total alkaloids 7.6–7.7 mg/g DW (1% extract, RN1/RN3); vinblastine not detected → detected; ajmalicine/serpentine not measured	49
Artemisia annua (Asteraceae)	*Serendipita* (*Piriformospora*) *indica* + *Azotobacter chroococcum*, dual inoculation	N	Artemisinin	Artemisinin "appreciably higher" (no values or statistics); biomass and N/P uptake +52.6–86.2%	77
Artemisia annua (Asteraceae)	*Penicillium oxalicum* B4 + artemisinic acid 2 mg/mL, 10-day co-culture	N	Artemisinic acid derivatives	Eight products (five new); 3α-hydroxyartemisinic acid = 33.3% of substrate	78
Dendrobium catenatum (Orchidaceae)	*Pestalotiopsis* sp. DO14 (CCTCC M 2015180); *in vitro* plantlet co-culture, non-intracellular	N	Polysaccharides; flavonoids	Polysaccharides and flavonoids ↑ with PCKA, CHS and UFGT up-regulated; magnitude not reported	73

Trigonella foenum-graecum (Fabaceae)	Abiotic elicitors ($CaCl_2$ 5/10 mM; penconazole 5/10 mg/L; SA and NO ineffective); hairy-root culture	N	Total steroidal sapogenins (diosgenin equivalents)	+19.9%/+25.7% (5/10 mM $CaCl_2$) and +17.6% (10 mg/L penconazole) vs untreated ($p<0.05$); decreased with SA and NO	47
Ficus carica cv. Siah (Moraceae)	*P. indica* filtrate or cell extract 2–6% and MeJA 100–300 µM, separate single-factor treatments; hairy roots	N	Phenolic acids	Gallic acid 48.6×, caffeic acid 9.0×, chlorogenic acid 10.5×; TPC −39% and TFC −36% at 4% extract, 96 h	36
Salvia miltiorrhiza (Lamiaceae)	Phenazine-1-carboxylic acid 2.5–10 µg/mL, purified metabolite of endophytic *Pseudomonas chlororaphis* KPUPH-SMC; callus	n.a.	Cryptotanshinone (relative)	Relative cryptotanshinone maximal at 5 µg/mL ($P<0.001$, n=6); absolute content not reported	43

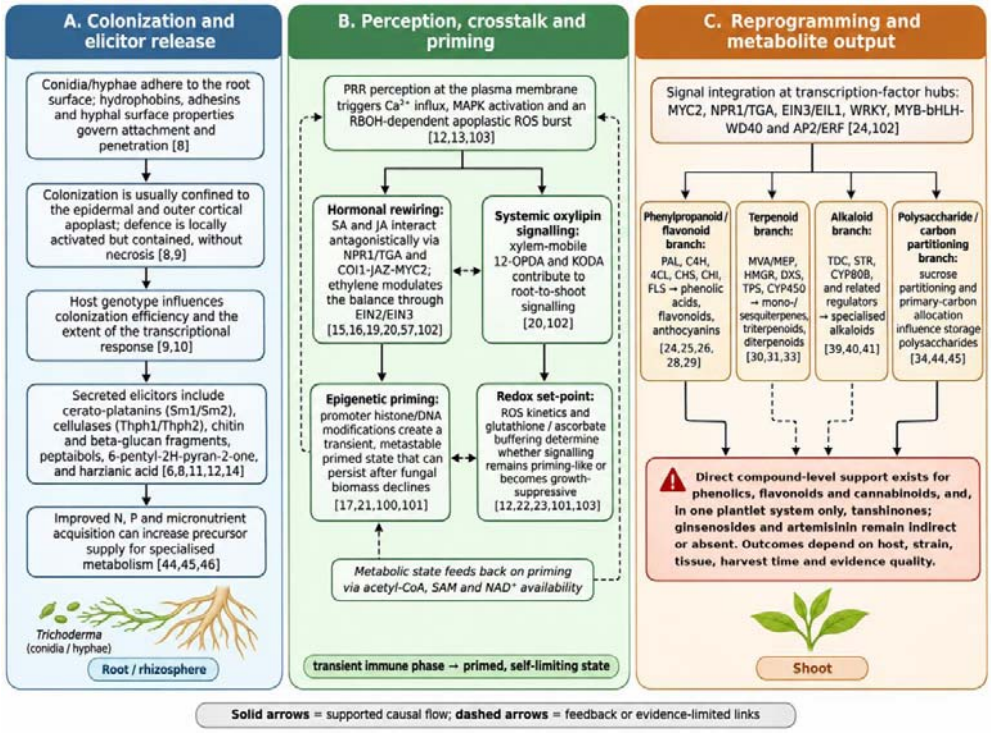


Figure 1: Molecular dialogue between *Trichoderma* and a medicinal plant, from root colonization to secondary metabolite accumulation. (A) Events at the root surface and in the apoplast, together with the repertoire of secreted elicitors. (B) Perception, hormonal crosstalk, oxylipin-mediated systemic transmission, epigenetic priming and redox control, which together establish the primed state. (C) Convergence on transcription-factor hubs and activation of the phenylpropanoid, terpenoid, alkaloid and polysaccharide branches, with the corresponding metabolite classes; the boxed statement at the foot of (C) grades the strength of the direct evidence for each class, distinguishing compound-level support for phenolics, flavonoids and cannabinoids, a single plantlet study for tanshinones, and the absence of direct evidence for ginsenosides and artemisinin. Arrows indicate the direction of information flow, and the boxed element in (B) indicates the feedback from the metabolic state of the cell to chromatin; the model is a synthesis of the studies discussed in Sections 2 and 3, most of which were performed in maize, tomato or Arabidopsis rather than in a medicinal species. Numbers in square brackets refer to the reference list.

roots differed significantly among genotypes and shifted in the presence of the root rot pathogen *Aphanomyces euteiches*, indicating that the host genotype filters the community that can establish itself in the root [9]. This has practical consequences for elicitation protocols: an inoculant that performs well in one cultivar of a medicinal species cannot be assumed to colonise a second cultivar with equal efficiency.

At the molecular level, colonization is accompanied by a spatially structured host response. In plants treated with *T. afroharzianum* T22, local root colonization produced a transcriptional signature that extended beyond the colonised tissue and was associated with altered endophytic microbiome composition and with growth promotion, implying that the fungus releases a mobile signal from the colonised zone [10]. The identity of this signal remains unresolved, but fungal cell wall–degrading enzymes are strong candidates. In *T. harzianum*, the cellobiohydrolase gene *thph2*, regulated by the C6 zinc finger transcription factor Thc6, is required both for efficient root colonization and for the induction of systemic resistance in maize [11]. The same enzyme triggers a reactive oxygen species burst and programmed cell death in a heterologous host, establishing a direct link between a single fungal protein and a plant defence output [12].

Perception of microbial patterns and local signalling

Plants perceive *Trichoderma* through pattern recognition receptors that detect conserved microbial molecules. Chitin, β-glucans and specific secreted proteins act as microbe-associated molecular patterns (MAMPs), and the resulting cascade — calcium influx, MAP kinase activation, NADPH oxidase–dependent ROS production and transcriptional

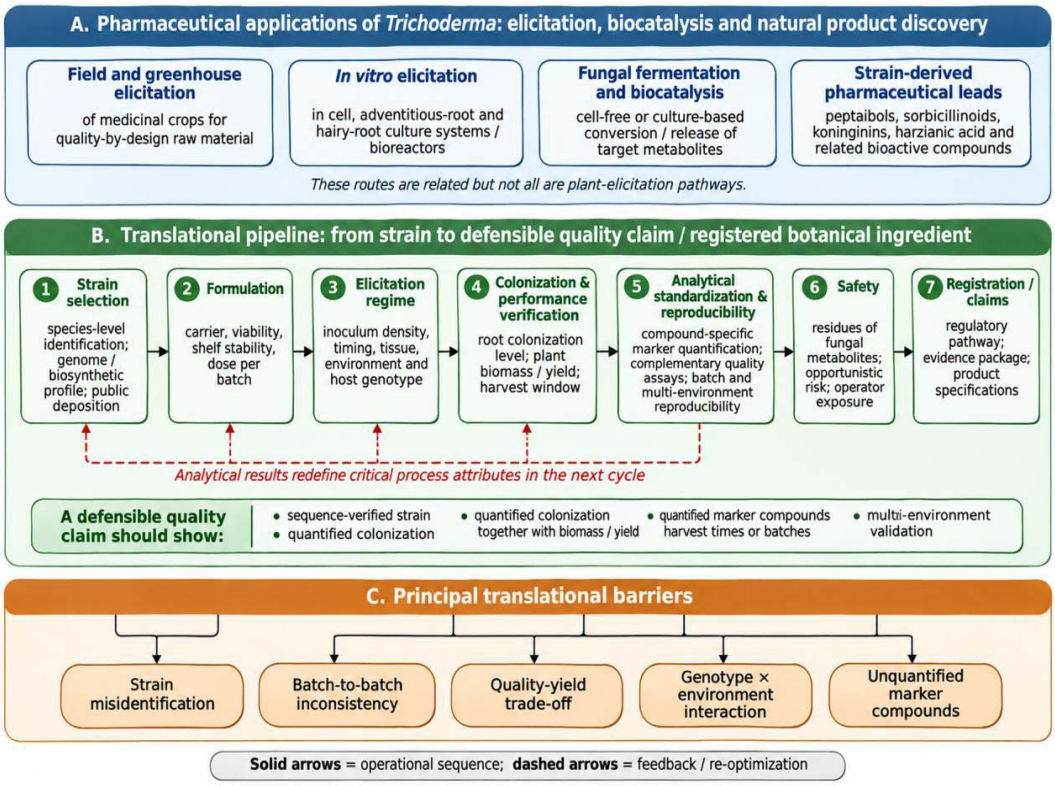


Figure 2: Pharmaceutical applications and the translational pipeline. (A) Four *Trichoderma*-related pharmaceutical development routes — field and greenhouse elicitation of medicinal crops, *in vitro* elicitation in culture systems, fungal fermentation and biocatalysis, and strain-derived bioactive leads; the first two are plant-elicitation routes, the latter two are not. (B) The operational sequence required to convert elicitation into a defensible quality claim, from strain selection to registration, with the critical parameter at each step; the dashed arrows indicate analytical feedback to earlier process-development stages for iterative optimisation, and the lower panel lists the five elements that such a claim must demonstrate. (C) Barriers that recur across the literature and that determine whether a given product can be standardised within pharmacopoeial limits. Solid arrows denote the operational sequence and dashed arrows feedback or re-optimisation. Numbers in square brackets in both figures refer to the reference list.

induction of defence genes — constitutes the first layer of the interaction. Genetic dissection in *T. atroviride* showed that root colonization triggers induced systemic resistance through a route largely independent of chitin-mediated signalling, indicating that additional patterns dominate in this system [13].

The cerato-platanin family provides the best-characterised proteinaceous example. Sm1 from *T. virens* is a small secreted cysteine-rich protein required for full biocontrol activity and for induction of systemic defence, and its paralogue Sm2 is likewise important for plant protection, the two proteins acting redundantly [14]. Cerato-platanins are amphipathic and self-assemble at hydrophobic–hydrophilic interfaces, a property that appears essential to their elicitor activity. Cellulases, swollenin-like proteins and hydrophobins complete this repertoire and generate the MAMP cocktail that the plant integrates into a quantitative assessment of the microbial encounter [8,11].

Two features of this early layer condition everything that follows. First, perception is quantitative rather than binary: the plant integrates the ratio between elicitor and suppressor molecules secreted by a given strain, together with its own receptor complement, so that the same fungal species can be read as a threat or as a symbiont depending on secretory profile and host genotype [8,13,14]. Second, the earliest outputs are ionic and redox-based rather than transcriptional: calcium influx, MAP kinase activation and phosphorylation of respiratory burst oxidase homologues occur within minutes, well before any change in secondary metabolism can be measured [12,15]. The amplitude and duration of this primary signature therefore set the gain of the whole system, which is why inoculum density and the physiological state of the root at the moment of application are process variables rather than incidental details.

Hormonal rewiring: salicylate–jasmonate crosstalk and priming

The phytohormonal outcome of colonization is not simple activation of defense but coordinated reprogramming of the salicylate (SA) and jasmonate (JA) pathways. SA and JA pathways commonly exhibit antagonistic interactions, but their balance is tissue-, time- and stimulus-dependent and may also be cooperative. Crosstalk involving NPR1–TGA and COI1–JAZ–MYC2 can change the relative emphasis on biotroph- versus necrotroph- and herbivore-associated

defence, while ethylene supplies an additional context-dependent regulatory input [16,17]. In tomato challenged with Fusarium oxysporum, *T. virens* protected plants through both JA- and SA-dependent components, with spores and cell-free culture filtrate producing distinguishable defence signatures [18]. In *Trichoderma*-induced resistance to root-knot nematodes, colonization shifted the hormonal balance from SA- to JA-regulated defence as the interaction progressed, allowing the plant to mount an appropriate response against a herbivore rather than a microbial pathogen [19]. The practical consequence is that the metabolite profile elicited by a strain is expected to change with the age of the interaction, so that sampling at different harvest times can report an increase or a decrease without any inconsistency in the underlying biology.

The temporal dimension of this rewiring has been resolved in some detail. In maize roots colonised by *T. harzianum*, JA concentrations declined while SA increased at two and six days after inoculation, and these changes were accompanied by epigenetic modification of genes in both pathways [20]. The functional significance of the SA–JA balance was demonstrated in tomato, where combined application of *T. harzianum* and arbuscular mycorrhizal fungi altered the SA–JA equilibrium and suppressed Fusarium wilt more effectively than either organism alone [21]. The SA-dependent systemic arm is also engaged: in pepper, a *Trichoderma*-enriched compost water suspension activated systemic acquired resistance and induced *CaPBR1*, *CaPO1* and *CaDEF1* expression [22]. Ethylene contributes a third and frequently overlooked input. The *Trichoderma* volatile 6-pentyl-2H-pyran-2-one requires ETHYLENE INSENSITIVE 2 to reshape root architecture, showing that a fungal volatile can act through the ethylene module rather than through auxin alone [23], and ethylene production accompanies the cellulase-triggered defence response in maize [11,12]. Because ethylene both modulates SA–JA antagonism and independently activates AP2/ERF-type regulators of terpenoid and alkaloid genes [17], a strain that emits this pyrone or a cellulase at high levels may bias the host towards a different metabolite class than a strain that does not. The prediction is testable, and to our knowledge, it has not been examined in a medicinal species.

Jasmonate is not the only oxylipin involved. Using ISR-positive and ISR-negative maize mutants, 12-oxo-phytodienoic acid (12-OPDA) and the α-ketol of octadecadienoic acid (KODA) were identified as xylem-resident systemic signals required for *T. virens*–induced systemic resistance, and a 13-lipoxygenase mutant (lox10) failed to mount the response [24]. These findings provide a plausible hypothesis for medicinal plants, but they do not establish a direct causal link between *Trichoderma*-derived oxylipin signalling and a quantified medicinal-plant metabolite. In mechanistic terms, 12-OPDA is not merely a JA precursor: it is an electrophilic species that modifies target proteins and activates a subset of jasmonate-responsive genes independently of COI1-mediated JA-Ile perception [17,24], which may help explain shoot responses without demonstrating compound-specific metabolic enhancement in medicinal species.

Epigenetic priming and redox signalling

Priming — a state in which defense genes are transcriptionally poised rather than constitutively expressed — explains how *Trichoderma* can enhance metabolite accumulation without imposing a permanent growth penalty [25]. Chromatin-level evidence supports this model. Colonization of maize roots by *T. harzianum* altered histone marks and DNA methylation in the promoter regions of JA- and SA-responsive genes, and these changes persisted after fungal biomass had declined [20]. In *T. atroviride*–inoculated plants, G-quadruplex-forming sequences were enriched in the promoters of primed defence genes and were proposed to act as epigenetic elements maintaining the primed state [26]. Three properties of this layer deserve emphasis. The marks are gene-specific rather than global, being deposited at the promoters of pathways the plant will need if challenged, which is why priming can be metabolically cheap. They are metastable, decaying over days to weeks in the absence of a second stimulus [25], so that any primed state may persist for a limited, host- and environment-dependent period. And the enzymes that write and erase them depend on acetyl-CoA, S-adenosylmethionine, and NAD+ as co-substrates, so epigenetic priming is coupled to the metabolic state of the cell: changes in acetyl-CoA or methylation potential may influence the fungal response. Whether these chromatin-level changes causally sustain higher concentrations of specific medicinal metabolites remains to be established.

Redox homeostasis constitutes the second layer of the primed state. The *T. harzianum* cellobiohydrolase Thph2 induces an apoplastic ROS burst required for resistance to southern corn leaf blight, and the response depends on ROS kinetics rather than on absolute magnitude [12]. Quantitative imaging of glutathione redox potential in a mycoparasitic *Trichoderma* species revealed robust antioxidant buffering in the fungus itself, a trait that allows it to withstand the oxidative environment of the host apoplast during colonization [27]. In the host, inoculation frequently elevates superoxide dismutase, catalase, peroxidase, and ascorbate–glutathione cycle activities, and this reinforcement is observed even under abiotic stress; in maize exposed to lead, *T. harzianum* Zag-1 improved growth, photosynthetic performance, and antioxidant defence while reducing metal accumulation [28]. The link between this layer and secondary metabolism is direct and can be stated in three steps. Apoplastic hydrogen peroxide participates in the oxidative activation of phenylpropanoid enzymes and in the cross-linking reactions that accompany cell-wall reinforcement [15]. Intracellular redox poise, read out as the glutathione redox potential, controls the monomerisation and nuclear import of NPR1 and hence the accessibility of SA-responsive promoters

[15,25]. Sustained oxidative stress may alter the balance of oxidised metabolites and suppress growth. Although *Trichoderma atroviride* D16 has been reported to increase tanshinone accumulation in *Salvia miltiorrhiza* plantlets [29], the magnitude and reproducibility of this response across strains, host genotypes and production environments remain insufficiently characterised. The distinction between a transient and a sustained ROS signal is therefore not a technicality: the first primes, whereas the second imposes a fitness cost and, beyond a threshold, triggers programmed cell death [12,15].

The pharmaceutical relevance of these redox effects is twofold. First, ROS and redox status directly regulate phenylpropanoid and terpenoid biosynthetic enzymes, so a modest, transient oxidative signal can contribute to the regulation of phenolic metabolism, although it is not established as a universal prerequisite. Second, the same network underlies the abiotic stress tolerance that determines the reliability of medicinal plant cultivation in marginal environments. A third implication follows from the two preceding sections and is developed in what follows: because redox state sets the threshold at which hormonal and epigenetic signals can act, it also determines the dose of elicitor above which the response stops being an increase in metabolite content and becomes a loss of yield.

From signal integration to pathway activation: a working model

The three layers described above converge on a small number of transcriptional hubs, and it is at this level that the specificity of the metabolic outcome is decided. Jasmonate signalling terminates in the degradation of JAZ repressors and the release of MYC2 and its partners, which activate the promoters of alkaloid and phenolic pathway genes; SA signalling acts through NPR1 and TGA factors on phenylpropanoid and pathogenesis-related genes; ethylene acts through EIN3/EIL1, which interacts physically with MYC2 and thereby biases the jasmonate output; and WRKY, MYB–bHLH–WD40 and AP2/ERF factors provide the pathway-specific tier that distinguishes, for example, a flavonol from an anthocyanin response [17,30]. A root-colonizing fungus does not address these hubs individually. It modifies upstream signalling and the activities of the regulatory complexes, and the resulting metabolite profile is a read-out of which hub predominates in that species, tissue, and developmental stage. This is the molecular explanation for a pattern that recurs in Section 5: the same strain can raise phenolics in one host and terpenoids in another, and the difference lies in the host's regulatory architecture rather than in the fungus.

Precursor supply imposes a second and equally stringent constraint. Phenylpropanoid flux is limited by phenylalanine from the shikimate pathway, terpenoid flux by cytosolic acetyl-CoA and by the dimethylallyl-diphosphate pool shared between the mevalonate and methylerythritol phosphate routes, and alkaloid flux by amino acid precursors and by S-adenosylmethionine for methylation. This is why the nutritional side of the interaction — improved nitrogen and phosphate acquisition and higher photosynthetic capacity [31-33] — is not a separate agronomic benefit but a condition for the metabolic one. It also defines the correct way to express an elicitation result: a higher concentration per unit dry weight does not necessarily imply higher compound yield per plant if plant biomass declines. Compound yield per plant equals concentration multiplied by total relevant dry biomass, and both measures should be reported.

Figure 1 assembles these elements into a single working model, running from adhesion and elicitor release in the rhizosphere, through perception and the early calcium/ROS/MAPK signature, hormonal rewiring and xylem-mediated systemic transmission, chromatin-level priming and redox buffering, to the transcription-factor hubs and the four biosynthetic branches that determine the classes of metabolites eventually quantified in the shoot. Two features of the model define the limits of present evidence and should be stated explicitly. The arrows are directional but not unidirectional: primed chromatin lowers the threshold for hub activation, and the metabolic state of the cell feeds back on chromatin through the availability of acetyl-CoA and S-adenosylmethionine. And most individual steps have been demonstrated in maize, tomato, or Arabidopsis rather than in a medicinal species, so the scheme is at present a framework to be tested rather than a description of any particular crop.

From signal to metabolite: transcriptional and metabolic reprogramming

Section 2 described how a colonization event becomes a signal; this section describes how a signal becomes flux. The distinction matters for the way the literature is read, because transcriptional induction and metabolite accumulation are frequently reported as though they were interchangeable, whereas the two diverge whenever precursor supply, enzyme turnover, or product catabolism becomes limiting. Each branch is therefore considered at both levels, with the rate-controlling step identified where the evidence permits.

The phenylpropanoid–flavonoid branch

The phenylpropanoid pathway is the most consistently responsive branch of plant secondary metabolism after *Trichoderma* inoculation. Its entry enzymes, phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase, and 4-coumarate:CoA ligase, are transcriptionally induced within hours of colonization, and flux is subsequently directed towards flavonoid end products by coordinated activation of chalcone synthase, chalcone isomerase, and flavonol synthase [30]. The regulatory architecture is reasonably well defined: MYB–bHLH–WD40 complexes control the late flavonoid

genes, WRKY factors integrate JA and SA inputs upstream of PAL, and jasmonate-responsive JAZ repressors are degraded primarily through JA-Ile-dependent COI1 signalling, whereas 12-OPDA can also engage partly COI1-independent defence responses. Flux control is not distributed evenly along the pathway. The entry and branch-point reactions are the steps most consistently induced by microbial elicitors, whereas the hydroxylation, methylation and glycosylation reactions that decide which flavonoid end product accumulates are considerably less responsive [30]. This asymmetry explains a recurring observation in the elicitation literature — total flavonoid content rising while the proportion of the pharmacologically preferred glycoside falls — and it means that a claim of improved quality requires compound-resolved analysis rather than a colorimetric total.

Empirical support for a *Trichoderma*-specific effect on this branch comes from several systems. In grain legumes, inoculation with *Trichoderma* and mycorrhizal fungi increased leaf secondary metabolite concentrations, with the response depending on the fungal combination used [34]. Co-inoculation of *Trichoderma* with tea root–associated bacteria enhanced flavonoid production and increased mycorrhizal colonization, suggesting that the flavonoid response can be amplified by designed consortia [35]. In *Ficus carica*, methyl jasmonate and fungal elicitors induced distinct but overlapping changes in gene expression and phenolic content, with the combination producing the highest accumulation of phenolic acids [36]. Comparable phenolic enrichment was obtained by solid-state fermentation with *T. viride*, in which the fermented material showed increased phenolic content together with higher antioxidant and antimicrobial activity [37]. In grape, *Trichoderma* treatments modified the phenolic and sensory quality of berries and of the resulting wine, an effect relevant to the quality of grape-derived polyphenol preparations [38]. A recent synthesis of endophyte-mediated flavonoid regulation places these observations within a coherent framework of signalling and transcriptional control [30].

Two caveats deserve emphasis. Increases in total phenolic content are frequently reported without compound-level resolution, whereas the pharmacological value of a phenolic fraction is determined by its composition rather than by its total reducing capacity. In addition, the magnitude of the response is strongly influenced by the timing of inoculation relative to the developmental window in which the target compound accumulates.

Terpenoid and steroid branches

Terpenoids derive from the mevalonate (MVA) and methylerythritol phosphate (MEP) pathways, and their accumulation is controlled by isoprenoid precursor supply as much as by terminal terpene synthases and cytochrome P450 oxidases. *Trichoderma* inoculation influences both levels. In *Glycyrrhiza uralensis*, endophytic fungi and abiotic factors jointly regulated flavone and terpenoid glycoside metabolism, with the endophyte contribution most evident under conditions limiting precursor supply [39]. In *Codonopsis pilosula*, *Trichoderma* acted synergistically with salicylic acid and methyl jasmonate to regulate growth and metabolism, and the combination produced a broader metabolic shift than any single treatment [40]. Two nodes dominate the response of this branch. Cytosolic HMG-CoA reductase controls carbon entry into the MVA route and responds to both jasmonate and redox status at the transcriptional and post-translational level, whereas DXS and the MEP route supply the plastidic pool from which monoterpenes and diterpenoids such as the tanshinones are derived. A signal that raises one route but not the other therefore shifts the spectrum of terpenoids rather than increasing all of them equally, which is one explanation for the frequent finding that total terpenoid content is unchanged while individual compounds move in opposite directions [17,40]. The tanshinones of *Salvia miltiorrhiza* are diterpenoid quinones, not alkaloids. The tanshinones and phenolic acids of *Salvia miltiorrhiza* have become a model system for endophyte-mediated elicitation. Root endophytes such as *Penicillium steckii* and *Cladosporium tenuissimum* promote tanshinone biosynthesis when inoculated into *S. miltiorrhiza*, and the effect is mediated by activation of committed pathway genes [41,42]. Importantly, root colonization by *Trichoderma*

Atroviride D16 was reported to enhance tanshinone accumulation in *Salvia miltiorrhiza* plantlets through H2O2–Ca2+ signalling [29]. This is a Trichoderma-alone plantlet result, although the numerical effect size and reproducibility under production conditions remain insufficiently reported. Separately, the purified bacterial endophyte metabolite phenazine-1-carboxylic acid promoted tanshinone biosynthesis in Salvia callus [43]; this chemical-elicitor study does not demonstrate an effect of Trichoderma.

Atractylodes lancea provides a separate, compound-resolved example. In growth-chamber pots, allochthonous *Trichoderma harzianum* isolates increased the rhizome markers atractylon (up to 17.2-fold) and *atractylodin* (up to 10.6-fold), although single-inoculation treatments reduced rhizome dry mass to 0.27–0.58 times the control [44]. Atractylon, hinesol, and β-eudesmol are sesquiterpenoids, whereas *atractylodin* is a polyacetylene, not a sesquiterpenoid. The corresponding changes in biomass underscore why compound concentration and compound yield per plant must be evaluated separately.

The triterpenoid saponins of Panax species have received particular attention because of their pharmaceutical value. Endophytes isolated from Panax tissue convert ginsenosides through glycosidase activity, and a glycosidase-producing endophytic fungus increased the reported recovery or accumulation of ginsenoside Rd in *Panax notoginseng* [45]. Cellulase-hyperproducing *T. reesei* mutants have been engineered for bioextraction and bioconversion of

ginsenosides, an approach that couples fungal hydrolytic capacity to recovery of the target glycoside from plant material [46]. The steroidal branch has been examined in *Trigonella foenum-graecum*, a legume that accumulates both steroidal sapogenins and the pyridine alkaloid trigonelline; in hairy root cultures of this species, elicitor treatment enhanced steroidal sapogenin accumulation, establishing that the sterol branch can be stimulated *in vitro* [47].

Alkaloid pathways

Alkaloid pathways are pharmacologically important but heterogeneous, and evidence from non-*Trichoderma* endophytes must not be assigned to this genus. For many alkaloid pathways, jasmonate regulation and precursor availability are important determinants because biosynthesis draws on amino acid precursors and, depending on the compound class, additional terpenoid or pyridine-derived substrates and methyl donors. That dependence is an advantage for elicitation, since the pathway is strongly inducible, and a vulnerability, since a shortfall in any one precursor caps the response however strongly the terminal genes are transcribed.

Indole alkaloids of *Catharanthus roseus* provide a second paradigm. Endophytes enhance the production of the root alkaloids ajmalicine and serpentine by modulating the terpenoid indole alkaloid pathway, and endophyte-derived elicitors have been used in cell suspension cultures to promote alkaloid and vinca alkaloid biosynthesis [48,49]. Because this pathway requires coordination of the MEP-derived secologanin branch with the tryptophan-derived indole branch, the ability of a single microbial stimulus to coordinate both branches suggests action at a nodal regulatory point rather than on individual enzymes.

Trigonelline deserves separate mention because of its expanding pharmacological profile, which now includes antifibrotic, metabolic, vascular-protective, and anticancer activities [50,51]. Its biosynthesis proceeds from nicotinate via nicotinate N-methyltransferase and therefore competes with the pyridine nucleotide pool that also feeds NAD(P)H-dependent defense metabolism. Whether *Trichoderma*-induced redox remodelling alters trigonelline accumulation is unknown, but the pathway's dependence on methyl donor supply and on NAD homeostasis makes it a plausible and experimentally tractable target.

Growth–defence trade-off, carbon allocation and photosynthesis

A recurrent concern is that activation of defense metabolism diverts resources from growth. The trade-off is real but not absolute. Modelling of the interaction between primary and secondary metabolism indicates that the apparent trade-off depends on the relative costs of precursor supply and of the defense machinery, and that plants can sustain elevated defense metabolite concentrations when photosynthetic capacity and nitrogen assimilation improve simultaneously [52]. *Trichoderma* frequently does exactly this. In wolfberry (*Lycium chinense*), *T. asperellum* increased nitrogen accumulation and photosynthetic capacity [31]; phosphate solubilisation and micronutrient mobilisation by *T. harzianum* contribute to the same outcome [32]; and nitrogen signalling in the plant is itself modulated during the interaction, blurring the distinction between nutritional and defence responses [33].

The practical implication is that elicitation should be evaluated using both compound concentration per unit dry biomass and total compound yield per plant, alongside any growth penalty. An instructive counter-example is provided by *Atractylodes lancea*, in which allochthonous *Trichoderma* isolates improved herb quality at the cost of rhizome growth, demonstrating that the balance between quality and yield is strain- and host-specific and must be quantified before any recommendation is made [44].

Chemical elicitors produced by *Trichoderma*

The chemical identity of the elicitors is treated separately from their effects because the two are not interchangeable. A molecule can be a potent elicitor in a seedling bioassay and irrelevant in the rhizosphere, where its concentration, stability and physical access to the root are governed by formulation, soil chemistry and the metabolic activity of the fungus during the first hours after application. Each class below is therefore described with two questions in mind: what is the evidence that the molecule itself elicits the response, and what prevents that activity from being exploited at field scale.

Proteinaceous elicitors

The proteinaceous fraction of the *Trichoderma* secretome contains the most potent characterised elicitors. Cerato-platanins Sm1 and Sm2 of *T. virens* are required for full biocontrol activity and for induction of systemic defence, and their redundancy indicates that the plant integrates multiple related patterns [14]. Cellulases of the glycoside hydrolase family 7, notably Thph1 and Thph2 of *T. harzianum*, act as MAMPs that trigger ROS bursts, ethylene production, and ISR; Thc6 coordinates both genes, so the elicitor output of the fungus is under defined genetic control [11,12]. Hydrophobins and adhesion-related surface proteins modulate the immunogenic properties of the hyphal surface [8]. Because these proteins are active at nanomolar concentrations and are heat-labile, they define a distinct product category: protein-based elicitor preparations that could be standardised by mass rather than by spore count.

Peptaibols

Peptaibols are non-ribosomal peptides characterised by α-aminoisobutyric acid, an acylated N-terminus and a C-terminal amino alcohol. They insert into lipid bilayers and form voltage-dependent channels, which accounts for their

antifungal activity and, at subinhibitory concentrations, for their capacity to modulate plant defence. The chemical diversity of the class continues to expand: thirteen new peptaibols with antimicrobial activity were reported from a *Trichoderma* sp. [53], new sequences were described from the endophytic *T. amazonicum* [54], and synergistic action between two peptaibols from *T. longibrachiatum* on plant responses was demonstrated, indicating that mixtures rather than single compounds determine the biological outcome [55]. Genome-guided metabolomic profiling has begun to connect peptaibol biosynthetic gene clusters to the compounds actually produced, providing a route to strain selection based on genomic rather than phenotypic criteria [56]. Since the same molecules are both antifungal and immunomodulatory in plants, they represent the clearest case of a fungal metabolite with dual agrochemical and pharmaceutical potential [6].

Polyketides, sorbicillinoids and harzianic acid

Polyketides constitute the largest and most pharmacologically diverse group of *Trichoderma* metabolites, as emphasised by a comprehensive survey covering 2018–2022 [6]. Sorbicillinoids are a structurally distinctive subgroup with potent anti-inflammatory activity: mono- and dimeric sorbicillinoids from a mangrove-derived strain inhibited IL-6 and IL-1β [57], and further sorbicillinoid derivatives were obtained from the endophytic *T. citrinoviride* [58]. Koninginins, a polyketide family first described from *Trichoderma*, have been isolated repeatedly from endophytic strains and display cytotoxic and antibacterial activity [59].

Harzianic acid occupies a special position because its plant target has been identified. Isolated from *T. afroharzianum*, it is a natural product inhibitor of acetohydroxyacid synthase, the first committed enzyme of branched-chain amino acid biosynthesis, and thus acts as a herbicidal and antimicrobial tetramic acid [60]. The same compound modulated the tomato response to *Rhizoctonia solani* when applied exogenously, demonstrating that a single fungal metabolite can act simultaneously on pathogen and host [61]. Its metal-chelating behaviour further expands its biological reach and offers a chemical explanation for its effects on metal homeostasis in the rhizosphere [60].

Volatile organic compounds

Volatile organic compounds emitted by *Trichoderma* diffuse through soil air spaces and the phyllosphere and therefore act at distances that proteins and peptides cannot reach. The most studied compound is 6-pentyl-2H-pyran-2-one (6-PP), which regulates root morphogenesis in *Arabidopsis thaliana* by interfering with auxin signalling and transport [23]. Volatiles from *T. atroviride* improved seedling growth by modulating sucrose metabolism, indicating integration of the volatile signal into primary carbon metabolism rather than a generic growth stimulation [62]. Volatile blends from *T. asperelloides* PSU-P1 and *T. koningiopsis* T-51 combined biocontrol activity with plant growth promotion [63,64], and 6-PP itself is fungicidal against the litchi downy blight pathogen *Peronophythora litchii*, so the same molecule that stimulates the plant can directly inhibit the pathogen [65].

Polysaccharides and other pattern molecules

Fungal extracellular polysaccharides and cell wall fragments act as additional MAMPs. Chitin oligomers and β-1,3-glucans released from the hyphal wall during colonization engage receptor complexes that converge on the same calcium and ROS machinery as proteinaceous elicitors [15], and fungal exopolysaccharides contribute to root attachment and to the water-retaining matrix in which the interaction takes place. Dark septate endophytes and *Trichoderma* strains applied in combination produced complementary effects on growth and active ingredient accumulation in medicinal plants [66]. The elicitor activity of *Trichoderma* is therefore not attributable to a single molecule but emerges from the combination of proteins, peptides, polyketides, volatiles and carbohydrate polymers presented to the root. A practical consequence is that the elicitor-active fraction of a preparation cannot be inferred from spore count or from total secreted protein: two formulations of the same strain can differ several-fold in the quantity of cerato-platanin and cellulase delivered to the root zone while carrying identical viable counts. This is one reason why dose–response relationships are so rarely reproducible between laboratories, and why the formulation step in Figure 2B is specified in terms of elicitor-active fraction rather than of colony-forming units.

Documented effects on pharmacologically relevant metabolites

The studies in this section differ both in experimental treatment and in what can be attributed to *Trichoderma*. We distinguish *Trichoderma* alone applied to living plants (D), *Trichoderma*-based fermentation (F), post-harvest *Trichoderma* bioconversion (B), explicitly *Trichoderma*-containing combinations (C), systems without *Trichoderma* (N), and treatments whose fungal identity or contribution is insufficiently specified in the information tabulated (U). D does not guarantee that an individual metabolite was quantified: the measurement column distinguishes defined chemical markers from total phenolics, quality indices, and other composite outcomes. Fermentation and bioconversion cannot demonstrate elicitation of an intact growing plant, and combinations do not isolate the fungal contribution. Table 1 reports study design and endpoints without imputing effect sizes absent from the original reports. Every record could be assigned to a category once the original reports were consulted: no entry remains in category U, and the single record in which the elicitor is a purified metabolite rather than an organism is marked n.a.

D, *Trichoderma* applied alone to living plants; F, *Trichoderma*-based fermentation of harvested plant material;

B, *Trichoderma*-mediated post-harvest bioextraction/bioconversion, including cell-free enzyme preparations; C, combination explicitly including *Trichoderma*; N, non-*Trichoderma* system (other endophytes, other microbial consortia, or abiotic elicitors); U, organism identity or *Trichoderma* membership insufficiently specified in the tabulated description, a category to which no record in the final table belongs; n.a., purified microbial metabolite applied to plant material, for which no inoculation category applies. Where one record comprises both a *Trichoderma*-containing and a non-*Trichoderma* inoculant, it is assigned to C, and the non-*Trichoderma* arms are named in the treatment column. Strain designations and sequence-based identifications are given where the cited report provides them. An increase in a composite assay or quality index is not equivalent to a quantified increase in an individual compound, and the measurement column keeps the two apart. Effect sizes are quoted only where they appear in the abstract or text of the cited report; "figure only" marks a value that exists solely in a figure or in a paywalled table and is therefore not reproduced. Arrows indicate the direction reported by the authors. These categories concern attribution and treatment type, not study quality or replication, and they combine two independent axes, namely whether *Trichoderma* is the eliciting organism and whether the system is a living plant, an *in vitro* culture, a fermentation or a post-harvest process.

Phenolic acids and flavonoids

Phenolic acids and flavonoids constitute the largest group of constituents for which a *Trichoderma* effect has been documented, and also the group in which the evidence is most uneven, because many studies report total phenolic content and radical-scavenging activity rather than quantified individual compounds. Where compound-level data exist, hydroxycinnamic acid derivatives and flavonol glycosides tend to increase preferentially, whereas anthocyanin accumulation is more variable. Three *Trichoderma*-associated examples illustrate why treatment type and analytical endpoint must be kept separate. Solid-state fermentation of ginger with *T. viride* raised total phenolic content, described by the authors only as increasing "several times", together with the antioxidant and antimicrobial activity of the preparation [37] — an effect on a processed matrix rather than on a growing plant, but a useful demonstration that the fungal secretome can mobilise bound phenolics; no individual phenolic was quantified. Treatment of Aglianico grapevines with *T. afroharzianum* T22 increased anthocyanins in both berries and wine, reduced low-molecular-weight tannins and modified the sensory profile, without changing perceived astringency [38], the only case in this group in which the response was followed into a processed product. The chemically distinct Atractylodes markers (sesquiterpenoids and the polyacetylene *atractylodin*) are discussed in Section 3.2 rather than being treated as phenolic or flavonoid products [44]. One further record isolates a *Trichoderma* effect without resolving individual compounds: in Maled Phai rice, four endophytes were each inoculated separately against a non-inoculated control with six replicates, and the best isolate, *T. zelobreve* PBMP16, raised grain total phenolics from 92.8 to 122.3 mg gallic acid equivalents per 100 g and anthocyanins from 33.1 to 55.8 mg cyanidin-3-glucoside equivalents per 100 g ($p \leq 0.01$) [67]. Three other studies frequently cited in this context do not isolate the fungal contribution. In grain legumes, *T. asperellum* H22 with *Rhizophagus intraradices* raised leaf free amino acids and proline from 10.1 to 13.4 mg per g fresh weight in soybean and increased total phenols in common bean only [34]. In *Ficus carica* hairy roots, culture filtrate and cell extract of *Piriformospora indica* and methyl jasmonate were applied separately, and each raised a different phenolic acid, gallic acid by up to 49-fold, caffeic acid by 9-fold and chlorogenic acid by 10-fold, whereas the highest concentration of cell extract lowered total phenolics and flavonoids; no combined elicitation was tested [36]. In tea, co-inoculation of *Trichoderma* sp. AM6 with root-associated bacteria and mycorrhizal root material raised total flavonoid content [35], again without compound-level quantification. Within the phenolic/flavonoid scope of this subsection, *Trichoderma*-attributable outcomes include grape anthocyanins and a quantitative but composite result for rice grain phenolics and anthocyanins; these come from one vineyard study over two seasons and one greenhouse experiment, respectively. The separate Atractylodes marker results are considered in Section 3.2.

Three questions remain unresolved. Which individual compounds respond, and by what fold-change? Is the response reproducible across seasons and sites? Does the altered profile translate into a measurable difference in a validated bioactivity assay? Only the first has been addressed systematically, and even then in a minority of studies.

Saponins, triterpenoids and steroids

The ginsenosides of Panax are the most economically significant saponin target, and also the class in which the gap between expectation and evidence is widest. *T. gamsii* YIM PH30019, isolated from *P. notoginseng*, combines hyperosmotic tolerance, mycoparasitism and antagonism against root-rot pathogens and acts as a protective agent [68]; *T. asperellum* Ta1 alleviated Fusarium root rot and promoted growth of the same host [69]. In both studies, the reported endpoints are disease suppression and biomass rather than ginsenoside content, so neither can be cited as evidence of elicitation. Beyond elicitation, *Trichoderma* enzymes are used to convert ginsenosides: a crude enzyme preparation from *T. reesei* BB8, a *bgl1*-overexpressing derivative of RUT-C30, enhanced ginsenoside extraction from root powder and converted the major saponins to Rd and compound K, with 23-fold the p-nitrophenyl-β-D-glucopyranoside activity of the parent strain [46]. That is a post-harvest route operating on dead tissue and on an extracted substrate; it is mechanistically distinct from elicitation and should not be counted as evidence

for it. The other frequently cited conversion study involves no *Trichoderma* at all: *Fusarium proliferatum* G11-7 was isolated from pigeon pea rather than from Panax, and its immobilised spores raised ginsenoside Rd in harvested *P. notoginseng* material from 2.5 to 9.2 mg per g through hydrolysis of Rb1 [45]. A compound K-producing endophyte from a related Panax species illustrates the metabolic overlap between endophytic capability and host chemistry [70], again without implicating this genus.

In *Glycyrrhiza uralensis*, endophytes and abiotic factors co-regulated flavone and terpenoid glycoside metabolism, the endophyte effect being conditional on environmental context [39], and in *Trigonella foenum-graecum*, elicitation enhanced steroidal sapogenin accumulation in hairy root cultures [47]. Neither report identifies the eliciting organism as a *Trichoderma* strain, and the second does not specify the elicitor at all. The saponin class is therefore in an unusual position: it carries the strongest commercial rationale of any group considered here, and it currently has no study in which a *Trichoderma* strain applied alone has been shown to raise the concentration of a quantified ginsenoside or astragaloside in planta. What exists is protective [68,69], enzymatic [46], or attributable to other fungi [45,70]. For the triterpenoid saponins of *Astragalus* and *Glycyrrhiza,* the position is weaker still; most available data concern endophyte diversity rather than quantified elicitation.

Alkaloids

Evidence for *Trichoderma*-specific alkaloid elicitation remains limited, and studies of diterpenoid tanshinones must not be classified as alkaloid results. The *Salvia miltiorrhiza* tanshinone literature belongs instead to the diterpenoid discussion in Section 3.2, and it is not uniformly non-*Trichoderma*: *Penicillium steckii* DF33 [41] and *Cladosporium tenuissimum* DF11 [42] are non-*Trichoderma* endophytes acting on hairy roots and on gnotobiotic seedlings respectively, a purified phenazine from an endophytic *Pseudomonas* acts on callus [43], but root colonization by *Trichoderma atroviride* D16 raises tanshinone content in plantlets and is attributable to *Trichoderma* alone [29]. The distinction matters, because the *Trichoderma* records in this literature differ in exactly the way Section 5.7 describes: one reports compound-level content without a numerical effect size [29], while the field study reports crop and soil-community outcomes rather than tanshinone content [71]. In *Catharanthus roseus*, endophytes enhanced ajmalicine and serpentine production by modulating the terpenoid indole alkaloid pathway [48], and endophyte-derived elicitors promoted alkaloid and vinca alkaloid biosynthesis in cell suspension cultures [49]; in neither case is the eliciting organism reported as a *Trichoderma* strain. The pharmacological significance of trigonelline, whose activities now include antifibrotic, metabolic, vascular-protective, and anticancer effects [50,51], makes the pyridine alkaloid branch an obvious target for the same logic, although direct evidence of *Trichoderma*-mediated trigonelline enhancement is not yet available. Since the branch is methyl-donor dependent and jasmonate responsive, and since both properties are modulated by root symbionts, it is among the most tractable targets identified in this review.

Essential oils and aromatic constituents

Evidence for effects on essential oil yield and composition is thinner than for phenolics and alkaloids, and the one greenhouse study that included *Trichoderma* delivered its gains in non-volatile phenolics rather than in the volatile fraction. A commercial microbial biostimulant containing *Trichoderma koningii* TK7 together with two arbuscular mycorrhizal species and two *Bacillus* strains raised total polyphenols by 23, 29 and 63% at 0, 25 and 50 mM NaCl, raised rosmarinic acid by 49 and 68%, and increased fresh weight by 7–27%, yet left linalool, eugenol and eucalyptol unchanged; only minor volatiles, which together accounted for 7.5–9.1% of the blend, responded [72]. Because the inoculant combined four microbial groups, including two mycorrhizal fungi and two bacteria, the *Trichoderma* contribution cannot be isolated, and no comparable dataset exists for an aromatic crop treated with a *Trichoderma* strain alone. The mechanistic case nevertheless remains open, since 6-pentyl-2H-pyran-2-one and the volatile blends of *T. atroviride* and *T. asperelloides* regulate root architecture and sucrose partitioning through ethylene and auxin signalling [23,62] and could in principle reach the secretory structures of the shoot through the same air spaces. Whether this alters essential oil yield or composition has not been tested, and it is one of the clearest experimental opportunities in the field.

Polysaccharides

Polysaccharides are the principal active constituents of several medicinal orchids, and the class least well served by the *Trichoderma* literature. In *Dendrobium catenatum*, the endophytic fungus *Pestalotiopsis* sp. DO14 interacted with the host in a way that altered plant polysaccharide metabolism, and the interaction was dissected at the level of both host and fungal gene expression [73]. That study is a methodological template — it pairs transcriptome and metabolome and quantifies the polysaccharide fraction rather than a composite index — but the organism is not a *Trichoderma*, and no equivalent analysis exists for a *Trichoderma*-colonized medicinal orchid or for *Astragalus* polysaccharides. Because storage polysaccharides are products of primary carbon allocation rather than of defence metabolism, they are expected to respond to the nutritional side of the interaction [31,32] more strongly than to its signalling side; the hypothesis is testable by comparing carbon partitioning in colonized and uncolonized plants.

Cannabinoids and artemisinin

Cannabis sativa is an informative model because its target compounds are well defined and quantifiable, and a single Trichoderma strain has been shown to alter a clearly quantified

pharmaceutical metabolite in this host. Fertigation with *T. harzianum* T-22 raised cannabidiol content from 1.14 to 1.32% at the high dose but not at the low dose, and left cannabidiol yield per plant unchanged between 0.65 and 0.80 g [74]; the effect is therefore real, dose-dependent, and small. A consortium containing *T. harzianum* with *Bacillus subtilis* and *Rhizophagus irregularis* altered the concentrations of CBDVA, CBDV, CBG, CBD and CBGA in a cultivar-specific manner, whereas two forest-soil consortia lacking *Trichoderma* produced different, partly overlapping changes, so the fungal contribution cannot be isolated, and no *Trichoderma*-only arm was included [75]. In hemp, two arbuscular mycorrhizal and two endophytic fungi, none of them a *Trichoderma*, increased cellulose, acid-detergent and neutral-detergent fibre fractions and raised cannabidiol to 0.9–1.0 mg per g and THC to 0.7 mg per g [76]. These studies are notable because they quantify individual compounds, and because the pharmacological value of the crop depends on the ratio between cannabinoids rather than on total content.

For *Artemisia annua*, the evidence is dominated by other root symbionts. Dual symbiosis between *Piriformospora indica* and *Azotobacter chroococcum* enhanced artemisinin content [77], and endophytic *Penicillium oxalicum* B4 biotransformed artemisinic acid into bioactive derivatives, an alternative route to semisynthetic artemisinin analogues [78]. Neither organism is a *Trichoderma*, and the second acts by biotransformation of an isolated precursor rather than by elicitation in planta. Direct evidence for *Trichoderma*-mediated artemisinin enhancement remains limited, a notable gap given the pharmaceutical importance of the molecule. It is also an avoidable gap: the pathway is transcriptionally well characterised, jasmonate responsive and its rate-limiting steps are known, so a single dose–response experiment with a sequence-verified strain and validated quantification of artemisinin and artemisinic acid would provide an important initial test of the hypothesis; reproducibility would still require additional strains and environments.

Synthesis: how strong is the *Trichoderma*-specific evidence?

Five conclusions follow from the tabulation. First, the *Trichoderma*-specific evidence base is much smaller than the literature implies: the 27 records in Table 1 comprise five single-organism applications to living plants, one fermentation, and one post-harvest enzymatic application

Conversion study: six combinations explicitly including *Trichoderma*, thirteen systems without *Trichoderma*, and one purified microbial metabolite applied to plant material. These are descriptive classifications based on the reported treatment and must not be treated as counts of compound-resolved positive elicitation experiments. Second, the reported *Trichoderma*-associated outcomes — total phenolics in a fermented matrix, grape anthocyanins, grain phenolics and anthocyanins in rice, four rhizome markers in Atractylodes (three sesquiterpenoids and the polyacetylene *atractylodin*) and a dose-dependent cannabidiol increase in hemp — are not the classes for which the pharmacological rationale is strongest; among the three compounds most often proposed as targets, tanshinones have a single compound-level *Trichoderma* record whose magnitude is not reported [29], while ginsenosides and artemisinin rest entirely on non-*Trichoderma* endophytes, on post-harvest enzymatic conversion, or on field correlations without metabolite data. Third, the designs are dominated by single strains, single environments, and single harvests, so that the genotype × environment interaction which the field literature identifies as decisive [9,39] is almost never measured. Fourth, quantification is usually composite — total phenolics, antioxidant capacity, or a quality score aggregated from a few markers — rather than compound-resolved in pharmacopoeial terms, and fewer than half of the records pair a defined compound with a numerical effect size. Fifth, almost no study reports the dose applied or the colonization level achieved, although both determine the magnitude of the response [9,13].

These observations are not an argument against the technology; they define the minimal design of the studies that would establish it. A report able to support a quality claim would identify the strain to species level with a sequence and a culture-collection accession, quantify root colonization, measure at least one pharmacopoeial marker compound by a validated method alongside biomass, sample at two or more harvest times, and be replicated in two environments. None of the studies reviewed here satisfies all five criteria, and the absence of such studies, rather than any conflicting result, is the principal limitation of the field. The same criteria define the acceptance tests for the pipeline in Figure 2.

Trichoderma as a source of new pharmaceutical leads

The pharmaceutical value of *Trichoderma* is not confined to its effects on the host. The genus is a prolific producer of novel structures, many obtained from endophytic strains isolated from medicinal plants, so that fungus and host occupy overlapping chemical space; a comprehensive survey of metabolites reported between 2018 and 2022 documented this diversity and the dominance of polyketides and peptaibols among newly described compounds [6].

Representative findings illustrate the point. An endophytic *T. asperellum* strain produced novel bioactives with anticancer, anti-inflammatory, and haemoprotective activities [79]; cytotoxic peptaibols were isolated from *T. guizhouense* [80]; and sorbicillinoids with anti-inflammatory activity were obtained from mangrove-derived strains [57,58]. New polyketides were described from a hydrothermal vent sediment isolate [81]. Endophytic strains from medicinal plants are particularly productive: *T. koningiopsis* QA-3 from the roots of *Artemisia argyi* produced highly oxygenated polyketides [82]; *T. atroviride* yielded atrichodermones A–C

from solid culture [83]; an endophytic *Trichoderma* from *Ampelopsis japonica* showed activity against methicillin-resistant *Staphylococcus aureus*, and the active compound was isolated by bioassay-guided fractionation [84]; and two *T. afroharzianum* strains yielded a broad range of bioactive metabolites [85].

Two implications follow. The medicinal plant rhizosphere and root endosphere constitute an underexplored reservoir of *Trichoderma* diversity with pharmaceutical potential independent of the plant's own metabolites. Moreover, because the same strains can both elicit host pathways and produce their own bioactives, a single inoculant may deliver two distinct classes of pharmaceutical benefit, although this duality complicates regulatory classification. It is represented in Figure 2 as a separate application stream for exactly this reason: a strain-derived lead is assessed as a chemical entity, whereas an elicitation treatment is assessed as an agronomic input acting on a living plant, and the two dossiers share almost no requirements.

From interaction to product: *in vitro* systems, field application and quality control

Converting the interaction into a product requires a sequence of linked operations — strain selection, formulation, control of the elicitation regime, verification of colonization and crop performance, analytical standardisation, safety assessment and registration. Figure 2B arranges these operations as a pipeline and identifies, at each step, the parameter that most often fails in practice. The literature is very uneven across the steps: formulation and field agronomy are well developed for biocontrol purposes and largely transferable, whereas standardisation and the definition of critical process attributes are almost absent for medicinal plants.

In vitro elicitation systems

Cell and organ cultures offer the most controllable route to elicitor application. Biotic elicitors in adventitious and hairy root cultures have been reviewed systematically for 2010–2022, and the accumulated evidence shows that fungal-derived preparations can raise alkaloid, phenolic and terpenoid yields by one to two orders of magnitude in optimised systems [86]. Endophyte-based fungal elicitors enhanced the production of valepotriates and sesquiterpenoids in leaf cell suspension cultures [87], and in *Trigonella foenum-graecum* hairy roots, elicitation enhanced steroidal sapogenin accumulation [47]. The advantages of these systems — defined conditions, short cycle times, no environmental variability and compatibility with good manufacturing practice — are offset by their cost and by the frequent discrepancy between the metabolite profile of cultured tissues and that of the intact plant.

Field and greenhouse performance

Evidence from production settings is more limited but more directly relevant to raw material supply. In *Atractylodes lancea*, three allochthonous *T. harzianum* isolates improved rhizome quality at the cost of rhizome growth in growth-chamber pots, quantifying the quality–yield trade-off under controlled conditions but not, so far, in the field [44]. In continuously cropped *Salvia miltiorrhiza*, addition of *Trichoderma* spp. affected growth and soil microbial communities [71]. Integrated organic fertilisation with *Trichoderma* enhanced productivity and soil nutrient availability in wheat [88], and inoculation improved yield and bread-making quality of wheat in high-altitude drylands [89]. These results establish that the agronomic effect is real, but they also expose the central weakness of the field literature: quality is usually reported as a composite index, or as one marker compound in a single environment, rather than as the concentration of defined active constituents across replicated sites, and trials are rarely designed to detect interaction with genotype or environment.

Formulation, delivery and stability

A biological elicitor is useful only if it can be delivered reproducibly. Formulation science has addressed this problem extensively for biocontrol, and the solutions are largely transferable. Microencapsulation of *T. longibrachiatum* conidia prolonged viability and shelf life [90]; a bioreactor-in-a-granule formulation of *T. asperelloides* combined production and delivery in a single carrier [91]; and the biotechnological development of *Trichoderma*-based formulations has been reviewed with respect to carrier selection, drying, stabilisation and field performance [7]. Peptaibol production and characterisation from *T. asperellum* has been developed with a view to biofungicide application, indicating that the elicitor-active peptide fraction can be manufactured as a defined product [92]. For elicitation purposes, the performance criteria differ from those of biocontrol: what matters is not only spore viability but the quantity and quality of elicitor molecules delivered to the root zone, which depends on metabolic activity during the first hours after application.

Standardisation of herbal raw material

The pharmaceutical significance of elicitation lies in its potential contribution to quality-by-design of botanical raw materials. Predictable increases in validated marker compounds may improve batch consistency and potentially reduce the cost of meeting pharmacopoeial specifications; these economic benefits remain to be demonstrated in production settings. Realising this potential requires treating elicitation as a process with defined critical attributes: strain identity at sequence level, inoculum density and viability, timing relative to the developmental window of accumulation, and the environmental conditions that modulate the response. Figure 2B orders these attributes so that each step generates the specification for the next: strain selection fixes the elicitor repertoire, formulation fixes the delivered dose, the elicitation regime fixes the exposure, and analytical standardisation

fixes the acceptance criterion against which the preceding three are validated. The observation that host genotype filters colonization efficiency [9] and that endophytes and abiotic factors jointly regulate secondary metabolism [39] implies that these attributes must be specified jointly rather than independently. A *Trichoderma*-treated medicinal plant is not a genetically modified organism, but neither is it equivalent to an untreated plant from the perspective of a regulator assessing batch-to-batch consistency; compound-specific, replicated, multi-environment data are therefore a prerequisite for any quality claim.

Safety, biosafety and regulatory considerations

Trichoderma species are ubiquitous in soil and indoor environments, and field-scale use raises questions distinct from those associated with chemical elicitors. The genus is not regarded as a primary pathogen, but it is an emerging opportunistic agent in immunocompromised hosts. A review of infections in human populations documented invasive disease and emphasised that species-level identification is often required to distinguish clinical isolates from biocontrol strains [93]. An analysis combining literature cases with registry data characterised the clinical presentation and outcome of invasive *Trichoderma* infections and reported high mortality in profoundly immunosuppressed patients [94], and individual reports continue to appear, including a severe eye infection caused by *T. harzianum* [95]. A balanced assessment of the interface between agricultural use and human health concluded that population-level risk is low but that strain-level surveillance is warranted [96].

Industrial use of *Trichoderma* as a cell factory follows a separate and more developed pathway: safety evaluations of food enzymes produced in genetically modified *T. reesei* strains provide a template for the dossiers that enzyme products derived from this genus must satisfy [97]. For plant elicitation, the relevant framework is that of plant protection products and fertilisers, under which several *Trichoderma*-based products are already registered. A strain that both elicits host metabolism and produces pharmacologically active metabolites of its own falls between the two frameworks, and integrating both properties into a single regulatory dossier may be challenging and will depend on the jurisdiction and the claims made; this is the regulatory expression of the duality described in Section 6, and it is the step in Figure 2B where the least guidance is available.

Three recommendations follow. Strains intended for elicitation of medicinal plants should be identified to species level by sequence-based methods and deposited in a public culture collection. Applications should minimise aerosol generation and occupational exposure, particularly in enclosed greenhouse systems where spore concentrations can reach high values. Finally, the possibility that the fungus produces metabolites with pharmacological activity of their own should be considered in the safety assessment of the treated raw material, because residues of fungal origin may persist on harvested tissue.

Challenges and perspectives

Mechanistic understanding of *Trichoderma*–plant signalling has advanced faster than the ability to predict metabolic outcomes. Three gaps are particularly consequential.

First, the causal chain from a specific elicitor molecule to a specific metabolite is established in only a few cases. Harzianic acid illustrates what is achievable when a molecular target is identified [60], and the cellulase–Thc6–ISR axis shows how fungal genetics can define the elicitor output [11,12]. For most metabolites, however, the evidence remains correlative: an increase in tanshinone or ginsenoside is reported alongside an increase in defence gene expression, without demonstration that the latter causes the former.

Second, genotype and environment dependence limits extrapolation. Comparative transcriptomics has shown that the programme induced by a single strain differs between hosts [98,99], and dual RNA-seq of fungus–host interactions has revealed that both partners remodel their transcriptomes simultaneously, so that the outcome reflects a dialogue rather than a unilateral stimulus [100]. Genome sequences of biocontrol strains provide the framework for linking genomic variation to elicitor potential [101,102], and genome-guided metabolomics has begun to connect biosynthetic gene clusters to the compounds produced [56]. The logical next step is predictive strain selection: matching a strain's elicitor repertoire to the biosynthetic capacity of a target species.

Third, the temporal dynamics of the response are poorly characterised. Priming implies a conditional and transient response, and the succession of SA- and JA-dependent defences during colonization [19,20] means that harvest timing relative to inoculation is a critical but rarely optimised variable; xylem-mobile oxylipins offer a way to monitor the primed window in real time [24].

Three experimental strategies would move the field from correlation to causation within a few years, and none requires new technology. The first is the use of defined fungal mutants: strains carrying deletions in *thc6*, sm1, or the peptaibol synthetases have been described in the literature, and comparing their elicited metabolite profiles with those of the corresponding wild types would assign individual elicitor molecules to individual metabolite classes for the first time [11,12,14]. The second is reconstitution with purified elicitors, in which a candidate protein or peptide is applied at a known concentration to a characterised cell or hairy root system [86], so that the plant response is measured against a defined dose instead of an undefined inoculum. The third is the systematic application of untargeted metabolomics to colonized medicinal plants, which would detect responses

outside the compounds the experiment was designed to find and would therefore establish whether an effect is pathway-specific or a general displacement of phenolic flux.

Several developments are likely to change the field. Designed consortia combining *Trichoderma* with mycorrhizal fungi, dark septate endophytes, or plant growth–promoting rhizobacteria have produced additive or synergistic effects on metabolite accumulation [21,35,66], and community-assembly principles are beginning to be applied to medicinal plant production. Fungal biotransformation offers a complementary route to structural diversification of plant scaffolds, including glycosylation that alters solubility and bioactivity [103]. Finally, the recognition that trigonelline and related pyridine alkaloids possess substantial pharmacological activity [50] creates an incentive to test whether their accumulation can be manipulated through redox-active root symbionts, connecting the mechanistic framework developed here to a specific and pharmaceutically relevant target.

Conclusion

Trichoderma is best understood not as a fertiliser substitute or a stand-alone biocontrol agent, but as a biological elicitor that exploits the plant's own immune signalling to reprogram secondary metabolism. Root colonization generates a spatially confined MAMP signal transmitted systemically through oxylipin and hormonal pathways, reinforced by epigenetic priming and redox remodelling, and translated into transcriptional activation of phenylpropanoid, terpenoid, and alkaloid pathways. The available *Trichoderma*-specific evidence indicates that some treatments change crop quality measures, phenolic profiles, or cannabidiol content in particular hosts. However, direct compound-resolved evidence of enhanced medicinal-plant phenolics, flavonoids and storage polysaccharides after single-strain in-planta treatment is not yet sufficiently consistent to support a general claim. A *Trichoderma*-specific increase in tanshinone content has been reported in a plantlet system colonised by *T. atroviride* D16, but its quantitative magnitude and its reproducibility across production environments remain insufficiently established. Comparable direct evidence for ginsenosides and artemisinin is still lacking, and attributing those two classes to *Trichoderma* remains an extrapolation from work with other endophytes — the single most important qualification to the promise of the approach.

The pharmaceutical significance of this interaction is that it addresses the principal weakness of botanical raw materials, namely variability in active constituent content, without genetic modification of the plant. Realising that potential requires a shift in research practice: from total phenolic content to quantified defined compounds; from single-strain, single-environment trials to replicated designs capturing genotype × environment interaction; from correlation to causal demonstration using fungal mutants and purified elicitors; and from laboratory observation to formulated, standardised products with defined critical process attributes. The chemistry of the genus — peptaibols, sorbicillinoids, harzianic acid and volatile pyrones — supplies both the mechanistic tools and an independent source of pharmaceutical leads. The unresolved questions concern specificity, reproducibility and safety at scale, and they are tractable with the genomic, metabolomic and formulation technologies now available. The audit in Section 5 sets the immediate agenda and also the standard by which progress should be judged: the mechanism is increasingly well described, and the technology is plausible, yet the decisive experiment — a sequence-verified strain applied alone, a quantified pharmacopoeial marker and replication across environments — has in most systems not yet been performed. Until it has, *Trichoderma* should be described as a promising biological elicitor rather than as an established one.

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