

Review

Direct Antifungal Effects of Actinobacteria as Biocontrol Agents Against Pre- and Postharvest Diseases in Fruits, Vegetables, and Cereals

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Abstract

Pre- and postharvest losses caused by fungal infections represent one of the greatest constraints in agricultural production worldwide. Due to increasingly stringent regulations, as well as environmental and health concerns associated with their use, synthetic fungicides have been restricted, driving the development and application of sustainable alternatives within the framework of integrated plant disease management. Among these, *Actinobacteria* (also referred to as *Actinomycetota*) have attracted considerable attention over the past decades due to their versatile metabolites and plant growth-promoting properties, supporting their potential application as bacterial biocontrol agents. Their activity against phytopathogenic fungi is largely associated with direct antagonistic mechanisms. Currently, special attention is paid to the excreted secondary metabolites, lytic enzymes, volatile organic compounds and their *in vitro* antifungal activity. Therefore, this review summarizes current knowledge on these direct mechanisms, aiming to support the future application of actinobacteria and their metabolites as part of biological plant disease management strategies.

Keywords: actinobacteria; biocontrol; antifungal; preharvest; postharvest

1. Introduction

In light of the increasing global population and the pronounced effects of climate change, food security has become a pressing issue, especially concerning the availability of fresh produce [1]. Fruits, vegetables, and cereals are essential components of the human diet due to providing nutrients, minerals, vitamins, phytochemicals, antioxidants, and dietary fiber [2]. In 2023, the production of primary crops worldwide reached 9.9 billion metric tons, with cereals, vegetables, and fruits contributing about 3.1, 1.2, and 1.0 billion metric tons, respectively [3].

Nonetheless, these crops are highly susceptible to infections caused by a diverse range of organisms. Contamination of agricultural products can occur at any point along the cultivation–retail continuum [2], but it frequently stems from direct contact with soil. Additionally, postharvest practices, such as handling, processing, and storage, can significantly alter the microbiota of agricultural products [4].

Plant pathogenic fungi present a critical threat to agricultural biosecurity, accounting for substantial economic losses worldwide [5]. Meanwhile, many spoilage and phy-



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topathogenic species can produce mycotoxins causing potential mutagenic and carcinogenic effects in humans and animals [6]. Notably, considerable postharvest losses have been attributed to fungal infections and the associated production of mycotoxins [7]. Currently, up to 30% of all agricultural products can be destroyed by phytopathogenic fungi, underscoring the need for effective control strategies [8].

The control of these fungal diseases has traditionally relied on the application of synthetic fungicides both before and after harvest in conventional agricultural systems [8–10]. However, the widespread and intensive use of these agents, often at elevated concentrations, has contributed to the emergence of resistance in filamentous fungi. Additionally, some pathogens are insensitive to the currently available systemic fungicides, including *Cladosporium*, *Penicillium*, *Sclerotinia*, and *Verticillium* species [11–13]. This issue is further complicated by the detrimental effects on non-target organisms, including pollinators [14]. The challenges posed by the reduced availability of authorized active ingredients, the emergence of resistant fungal strains [15], environmental concerns, and health risks associated with these chemicals have highlighted the need for sustainable alternatives [10].

Promising strategies include the use of safer natural compounds, biocontrol agents, and horticultural practices [10,16]. Beyond conventional chemical and physical treatments, microbial antagonists and their metabolites represent a particularly promising class of novel crop protection solutions [16,17]. These compounds, distinguished by their versatile chemical structures and broad biological activities, can effectively inhibit fungal infections. Furthermore, their biodegradable nature enables their decomposition, typically within days to weeks under standard agricultural conditions [11].

Among microorganisms, members of the phylum *Actinobacteria* (also referred to as *Actinomycetota*), a group of Gram-positive bacteria widely distributed in marine and terrestrial ecosystems [18], have emerged as a compelling counterpart of synthetic fungicides. As biocontrol agents, they can suppress fungal diseases through direct antagonistic mechanisms [19], including hyperparasitism and nutrient competition [20]. In addition, their ability to produce a myriad of bioactive molecules and enzymes, including antimicrobial secondary metabolites, hydrolytic enzymes, and volatile compounds, has led to their extensive application in agricultural settings to promote plant [12,21] and soil health, including compost inoculant, biowaste degradation [22], bioremediation [23], biopesticides [24], insecticides [25], and bioherbicides [26]. Genera such as *Aeromicrobium*, *Agromyces*, *Glycomyces*, *Kribella*, *Mycobacterium*, *Nocardiopsis*, *Promicromonospora*, *Pseudonocardia*, and *Streptomyces* are commonly associated with plant growth-promoting (PGP) properties [27]. Along with their antifungal activity, actinobacteria can degrade and bind mycotoxins or modulate their biosynthesis [17].

Although the use of these bacteria as biological control may represent a feasible and cost-effective alternative [28], their commercial application remains limited due to practical and environmental challenges. To address these limitations and support the development of novel antifungal bioagents, this review assesses the effectiveness of actinobacteria against phytopathogenic fungi in both preharvest protection and postharvest preservation across various crop categories, including fruits, vegetables, and cereals. Particular emphasis is placed on direct pathogen-targeted antagonistic mechanisms, including the production of secondary metabolites and hydrolytic enzymes, hyperparasitism, and the modulation, inhibition, and detoxification of mycotoxins. Furthermore, the review evaluates the efficacy of various actinobacterial compounds in open-field trials, describes advanced formulation technologies designed to enhance bacterial survival and field efficiency, and discusses critical research gaps, including strain-specific antagonistic differences, regulatory hurdles, and the characterization of mycotoxin biotransformation products. Finally, it outlines future

research priorities to facilitate the development and implementation of actinobacteria-based biocontrol strategies.

To provide a comprehensive overview of the direct antifungal effects of actinobacteria against pre- and postharvest phytopathogenic fungi, an extensive literature search was conducted. To compose Section 4 (Effect of actinobacteria on preharvest and postharvest phytopathogenic fungi), relevant peer-reviewed articles were retrieved from major scientific databases, including Google Scholar, Web of Science, Scopus, and PubMed. Grey literature was additionally screened using general web search engines (e.g., Google). Eligible records were peer-reviewed, including full-text English-language articles reporting the direct antifungal mechanisms of actinobacteria. Additional articles on related topics, including other beneficial microorganisms and antifungal compounds, were also included to provide relevant background. Search strings were built using combinations of keywords and phrases such as “actinobacteria”, “biocontrol”, “direct antifungal”, “*Streptomyces*”, “preharvest”, and “postharvest”, which were subsequently refined with the names of specific secondary metabolites and fungal targets.

The literature search primarily focused on articles published between 2010 and 2026 to ensure the inclusion of the most recent advancements in the field, although highly relevant seminal papers published prior to this period were also considered. Studies addressing exclusively indirect biocontrol mechanisms, such as plant growth promotion or the induction of systemic resistance without characterization of direct fungal antagonism, were excluded. The extracted information was subsequently categorized into the major thematic subsections, describing antibiotic compounds, volatile compounds, hydrolytic enzyme production, hyperparasitic interactions, and modulation of mycotoxin production.

2. The Spread of Preharvest and Postharvest Fungal Phytopathogens Endangering the Production of Agricultural Products

The rapid expansion of the global economy has significantly increased food demand [29], with projections suggesting that agricultural production may need to rise by up to 70% by 2050 to meet future needs [30]. This surge has driven the intensification of crop production systems [31]. However, despite these efforts, the supply of fresh produce often falls short of meeting the needs of the exponential growth of the human population, a challenge compounded by global supply chain issues and substantial pre- and postharvest losses [32].

A major contributing factor to these losses is the increasing severity and frequency of plant disease outbreaks, which pose serious threats to crop productivity, food security, and biodiversity [33]. Additionally, postharvest losses, caused by improper handling, transportation, storage, processing, and microbial activity, further reduce both the quality and quantity of agricultural products [34,35].

Fungal pathogens, due to their rapid spore dispersal and high adaptability, cause significant economic losses in crop production [36]. More than 80% of crop diseases are attributed to fungal and fungal-like pathogens [37]. Estimates of crop losses caused by phytopathogenic fungi vary among studies. One study reported that approximately 25% of fruits and vegetables are lost annually during primary production along the postharvest chain [38], whereas another study estimated that fungi are responsible for 10–23% of preharvest crop losses and 10–20% of postharvest losses worldwide [36]. The most important pre- and postharvest fungal pathogens, along with their associated disease profiles and toxicological risks relevant to this review, are summarized in Table 1.

Table 1. Overview of major pre- and postharvest phytopathogenic fungi focused on in this review.

Fungal Genus	Primary Agricultural Target	Caused Disease	Associated Major Mycotoxin	References
<i>Alternaria</i>	Cereals, fruits, and vegetables	Postharvest decay	Alternariol, tentoxin, alternariol monomethyl ether, tenuazonic acid	[39,40]
<i>Aspergillus</i>	Matured/dried kernels, stored products	Postharvest decay, storage molds	Aflatoxins and ochratoxins	[41]
<i>Botrytis</i>	Fruits and vegetables	Postharvest gray mold	-	[32,40,42,43]
<i>Colletotrichum</i>	Fruits and vegetables	Anthrachnose, bitter rot	-	[32,40,42,43]
<i>Fusarium</i>	Cereals, fruits, and vegetables	Preharvest head blight, vascular wilt	Fumonisin, zearalenone, trichothecenes	[32,37,41,42,44]
<i>Penicillium</i>	Stored fruits	Postharvest blue mold, blue rot, core rot, green mold	Patulin, citrinin, chaetoglobosins	[40,43,45]
<i>Rhizopus</i>	Fruits	Postharvest rots and molds	-	[40,43,45]

Phytopathogenic fungi often exhibit a broad host range, allowing them to infect diverse plant species [46] and cause various diseases and symptoms, including rots, molds, damping-off, blast, rusts, head blight, wilt, mildew, anthracnose, and smut [40,42]. Of the estimated 100,000 known fungal species, less than 10% (approximately 8000 fungi with oomycetes) are considered phytopathogens, with just over 100 species identified as causes of postharvest decay [7,44]. Highly perishable fruits and vegetables are particularly vulnerable in the field and during storage to species of *Alternaria*, *Aspergillus*, *Botrytis*, *Colletotrichum*, *Fusarium*, *Magnaporthe*, *Penicillium*, *Phytophthora*, *Rhizopus*, and *Sclerotinia* [40,42,47]. Cereal production is heavily pressured by widespread genera, including *Fusarium*, *Magnaporthe*, and *Puccinia* spp. [37,44].

In addition to causing significant economic losses, infected agricultural products represent a potential health risk, since certain fungal genera (e.g., *Alternaria*, *Fusarium*, *Penicillium*) can produce mycotoxins [45]. Preharvest toxin formation is mainly associated with *Fusarium* spp., although in specific cases *Aspergillus* spp. may colonize mature, dried kernels. Meanwhile, storage fungi are predominantly represented by the genera *Penicillium* and *Aspergillus*. From an agricultural and clinical point of view, the most relevant mycotoxins include aflatoxins (AFB₁, AFB₂, AFG₁, AFG₂), type-A and type-B trichothecenes (e.g., T-2 toxin, HT-2 toxin, deoxynivalenol), fumonisins (FB₁, FB₂), ochratoxins, and zearalenone [41]. The causal agent of postharvest blue mold, *Penicillium expansum*, can secrete a variety of toxic secondary metabolites, such as citrinin, patulin, and chaetoglobosins [45], while *Fusarium* species are characterized by the production of fumonisins, zearalenone, and deoxynivalenol [41]. According to Pięłowski et al. [48], aflatoxin, ochratoxin, and mold contaminations were among the ten most frequently reported hazards in Rapid Alert System for Food and Feed (RASFF) border rejections between 2008 and 2023. In response, the European Union has established maximum permissible levels for the major mycotoxins [49]. Overall, mycotoxin contamination is responsible for an estimated 5–10% of global crop losses [50].

3. Actinobacteria-Based Biocontrol Agents for the Management of Pre- and Postharvest Fungal Diseases

Pre- and postharvest losses can be substantially reduced through the application of appropriate management techniques. Conventional systems currently rely predominantly on synthetic chemicals, including pesticides, to boost crop production [51]. Both systemic fungicides (e.g., methyl thiophanate, propiconazole, benomyl, cyproconazole, imazalil) and protective or contact fungicides (e.g., Bordeaux mixture, chlorothalonil, zinc

dimethyldithiocarbamate) have been widely used to suppress disease spread and minimize crop losses [52,53]. Nonetheless, their long-term use can lead to the emergence of resistant strains [54]. Alternative strategies, such as crop rotation and seedling grafting, can also mitigate soilborne diseases, but they are often costly and labor-intensive [55]. Meanwhile, the postharvest disease management of phytopathogenic fungi typically relies on chemical, physical, and biological approaches, including modified atmospheric packaging, low-temperature storage, heat-based sterilization, fungicide treatments, and microbial agents [19].

Nowadays, both consumers and producers are increasingly concerned about food safety and ecological sustainability [30]. The excessive usage of chemical fungicides adversely affects non-target species and ecosystems [56], prompting the European Union to commit to a substantial reduction in chemical pesticide reliance. In response, stricter regulations have been implemented to limit their application, driving interest in eco-friendly alternatives, including beneficial microbes and their bioactive metabolites [57]. These natural biocontrol agents can be used either as alternatives to or in combination with synthetic chemicals in integrated disease management strategies [58]. While they function effectively as both biopesticides and bioinoculants [59], many of these agents have shown limited success under field conditions due to diverse environmental constraints [60]. Thus, only a fraction of these agents is frequently utilized under intensive agricultural conditions, where large-scale application demands high consistency and shelf-stability. Nonetheless, they provide a vast palette of diverse agents with distinct modes of action, representing significant untapped potential [30].

Microorganisms play a vital role in the environment, maintaining a close relationship with plants and other organisms, while also interacting with other microbes through metabolite exchange [61]. The application of microbe-based biocontrol agents and/or the utilization of their active metabolites offers a sustainable alternative to conventional agrochemicals in agriculture [62]. These agents, mainly comprising fungi and bacteria, protect plants against pathogens through multiple mechanisms, such as mycoparasitism, antibiosis, induction of resistance, and growth promotion. Their biocontrol efficacy, however, largely depends on the produced active metabolites [63]. Soil-dwelling and antagonistic microbes, such as *Pseudomonas*, *Trichoderma*, *Paenibacillus*, *Bacillus*, or *Streptomyces*, along with endophytes, have demonstrated potent antifungal activity, supporting the development of eco-friendly pesticides [55,64,65].

Although numerous microorganisms have been investigated for disease management, actinobacteria have emerged as particularly promising candidates against a wide spectrum of pathogens [66]. These Gram-positive bacteria with guanine-plus-cytosine-rich DNA account for approximately 13% of the total soil microbiome on average, based on 21 16S rRNA gene libraries evaluated across a variety of soils [5,67,68]. However, in desert environments, actinobacteria are among the most prevalent bacterial groups, frequently dominating prokaryotic communities at relative abundances ranging from 75% to 98% [69]. The phylum *Actinomycetota* comprises several classes, including *Acidimicrobiia*, *Actinomycetia*, *Coriobacteriia*, *Nitriliruptoria*, *Rubrobacteria*, and *Thermoleophilia*—encompassing numerous families and genera [59,70,71]. Many actinobacterial species demonstrate resilience to nutrient limitation, desiccation, and other stress factors through the formation of resistant spores [59,62], enabling them to remain dormant in soil for extended periods [72]. They display both unicellular and mycelial growth forms [70], with certain filamentous actinomycetes reproducing via sporulation [73]. While most species are mesophilic, some are adapted to thermophilic environments. Beyond being isolated from bulk or rhizospheric soils, epiphytic and endophytic actinobacteria have also been investigated [72]. The genus *Streptomyces* is the most prevalent and extensively studied, although several

other genera (e.g., *Actinopolyspora*, *Micromonospora*, *Nocardia*, *Nonomuraea*, *Oerskovia*, and *Saccharopolyspora*) have also been frequently reported [70].

Actinobacteria employ various mechanisms (e.g., competition for nutrients, lysis of fungal cell walls, enhancement of systemic plant resistance, degradation of phytotoxins, etc.) to protect host plants from fungal pathogens [66]. Depending on the interaction, they may suppress fungal growth (fungistatic activity) or directly eliminate pathogens (fungicidal activity) [74]. Their effectiveness has been extensively studied to improve preharvest conditions and inhibit the spread of phytopathogenic fungi, including *Alternaria* spp., *Aspergillus* spp., *Botrytis* spp., *Colletotrichum* spp., *Fusarium* spp., *Penicillium* spp., *Phytophthora* spp., *Rhizoctonia* spp., and *Sclerotinia* spp. [18,27,75,76]. Furthermore, previous studies have demonstrated that actinobacteria can effectively control postharvest infections and prolong the shelf life of agricultural products [66].

4. Effect of Actinobacteria on Preharvest and Postharvest Phytopathogenic Fungi

Driven by the search for novel bioactive agents, numerous actinobacteria have been investigated for their ability to mitigate the growth of preharvest and postharvest phytopathogenic fungi, with extensive *in vitro* studies confirming their bioactivity. Although their efficacy is often species-specific, actinobacteria possess a remarkably broad antifungal spectrum. They have demonstrated activity against pathogens causing anthracnose, grapevine trunk diseases, and vascular wilts, as well as other economically important plant diseases. For instance, *Glomerella cingulata* (Stonem.) Spauld. and Schrenk (anamorph: *Colletotrichum gloeosporioides* (Penz.) Sacc.) was inhibited by six antagonistic actinomycetes which maintained their antifungal properties after treatment with chloroform [28]. Likewise, *Kitasatospora* sp. MMS16-BH015 was utilized by Yun et al. [77] to control the growth of *Colletotrichum acutatum*, alongside *Penicillium albocoremium* and *Rhizoctonia solani*. Rhizospheric and endophytic actinobacteria demonstrated antifungal activity against *Diplodia seriata*, *Dactylonectria macrodidyma*, *Phaeomoniella chlamydospora*, and *Phaeoacremonium minimum* [67]. Similarly, Iranian actinomycetes showed biocontrol potential against *Alternaria alternata*, *Alternaria solani*, *Fusarium solani*, *Phytophthora megasperma*, and *Verticillium dahliae* [78]. Together, these studies underscore the broad antifungal spectrum of actinobacteria. However, because the vast majority of current evidence is derived from *in vitro* assays, further validations under greenhouse and field conditions is needed to confirm their practical biocontrol potential.

Among actinobacterial species, members of the *Streptomyces* genus are of particular interest due to their ability to produce diverse secondary metabolites [79]. Although some *Streptomyces* species are plant pathogens, the majority are non-pathogenic saprophytes and/or endophytes [80]. Importantly, many species within this genus have been investigated for their antifungal activity. For instance, *Streptomyces rapamycinicus* HCD1–10 inhibited the growth of *Monilinia fructicola* [19], while the cell-free supernatants of other isolates (12-09-11 and 12-09-4) were effective against wheat powdery mildew (*Blumeria graminis*) when applied as preventive treatments. Similarly, these strains suppressed the spore germination of *Botrytis cinerea* and *Fusarium oxysporum* f. sp. *cucumerinum* by 95.38–100% [5]. *Streptomyces hundertgensis* sp. nov. inhibited the mycelial growth of *Bipolaris oryzae*, *Curvularia oryzae*, *Fusarium oxysporum*, *Pyricularia oryzae*, *Rhizoctonia solani*, and *Rhizoctonia oryzae-sativae* by 50–66% [81]. Likewise, *Streptomyces fodineus* co-cultured with phytopathogenic fungi on potato dextrose agar effectively controlled the growth of *Alternaria panax*, *Botrytis cinerea*, *Colletotrichum acutatum*, *Rhizoctonia solani*, *Sclerotinia minor*, *Stemphylium lycopersici*, and *Pyricularia oryzae* [82].

Actinobacteria contribute to plant disease suppression through both direct and indirect mechanisms. Direct antagonism involves the secretion of antibiotics, hydrolytic enzymes, and volatile organic compounds (VOCs), or hyperparasitic activities (Table 2). The most promising candidates for biocontrol formulations are those exhibiting a multitude of these mechanisms simultaneously [83].

Table 2. Main direct mechanisms of actinobacteria involved in the suppression of phytopathogenic fungi and mycotoxin production.

Biocontrol Mechanism	Antifungal Effects	References
Production of antifungal compounds	Inhibition of cell wall biosynthesis; disruption of pyrimidine, purine, and nucleic acid biosynthesis; disruption of cell membranes; modulation of energy metabolism.	[84]
Production of volatile organic compounds	Suppression of fungal growth; attraction of various organisms.	[85,86]
Production of extracellular hydrolytic enzymes	Direct degradation of fungal cell wall components.	[85,87]
Hyperparasitism or mycoparasitism	Direct parasitism and destruction of fungal hyphae, oospores, and fungal sclerotia.	[83,88]
Modulation of mycotoxin production	Regulation of mycotoxin synthesis through bioactive metabolites or by downregulating gene expression; potential detoxification of fungal secondary metabolites.	[89]

4.1. Control of Phytopathogenic Fungi by the Production of Antibiotic Compounds

Actinobacteria are renowned for their ability to produce a wide array of bioactive secondary metabolites, many of which act as potent antifungal agents. A significant proportion of these natural products is synthesized via secondary metabolic pathways encoded by biosynthetic gene clusters. The transcription of these clustered genes is tightly regulated by a complex network of regulatory genes, accounting for up to 12% of the genome and encompassing approximately 50 superfamilies/families based on their protein sequences and biological functions. However, a major bottleneck in the discovery of novel biocontrol species is that, although some actinobacterial species harbor multiple biosynthetic gene clusters, many remain inactive or are weakly expressed under standard laboratory conditions [90,91].

Among biocontrol microbes, actinomycetes contribute to approximately 50% of all antibiotic production, with the filamentous *Streptomyces* genus alone accounting for two-thirds of the natural antibiotics used in agriculture and medicine [5,81]. More than 50 clinically important antibiotics, including chloramphenicol, neomycin, streptomycin, and tetracyclines, have been isolated from *Streptomyces* species [78]. In addition, species such as *Streptomyces lincolnensis*, *Streptomyces pacificus*, *Streptomyces nodosus*, and *Streptomyces* RAUACT-1 are recognized as reservoirs of valuable antimicrobial compounds, including 10-anthraquinone, aureomycin, lajollamycin, lincomycin, and mitomycin [92]. Beyond *Streptomyces*, rare actinomycetes have also been explored as untapped sources of unique antimicrobial metabolites [93]. Genera such as *Actinomadura*, *Micromonospora*, *Nocardiopsis*, *Nonomuraea*, *Saccharopolyspora*, and *Verrucosispora* are recognized as sources of a wide range of bioactive compounds, many of which possess notable antifungal potential [62,94]. Overall, a plethora of these structurally diverse compounds have been extensively studied and utilized to suppress disease development in agricultural settings, encompassing aminoglycosides, peptides, macrolides, nucleosides, polyenes, and terpenoids [93].

4.1.1. Polyketides and Polyketide-Derived Metabolites

Among other secondary metabolites, polyketides represent one of the most important classes of antifungal compounds, displaying broad-spectrum activity against various fungal pathogens [95]. Their agricultural relevance is underscored by the successful development of polyketide-derived biopesticides in crop protection [96].

Notable examples include spiroacetal polyketides such as reveromycins, first purified from *Streptomyces reveromyceticus* SN-593 [80], and ossamycin from *Streptomyces hygroscopicus* var. *ossamyceticus* [97]. However, from an agronomic perspective, the simultaneous antifungal and cytotoxic properties of compounds like ossamycin [97] require cautious evaluation. Extensive toxicological profiles for purified ossamycin reveal exceptionally narrow safety margins, with an acute LD₅₀ of 1.8 mg/kg in mice following both intraperitoneal and intravenous administration. Consequently, despite its favorable storage stability and resistance to degradation under proper storage conditions, environmental and handling concerns may limit its direct field application [98].

Pentacyclic aromatic polyketides also show significant potential for protective disease management; for instance, resistomycin, produced by the termite-associated *Streptomyces canus* BYB02, showed strong *in vitro* efficacy against *Valsa mali* and *Magnaporthe grisea*, with IC₅₀ values of 1.1 and 3.8 µg/mL, respectively. More importantly, resistomycin also provided substantial *in planta* protection against rice blast, achieving a disease control efficacy of 66.8%. However, its curative activity remained below 25% efficacy, suggesting that this compound is more effective as a preventive treatment than as a post-infection intervention [99,100]. One possible explanation for this limited curative efficacy of resistomycin may reflect poor systemic translocation within plant tissues. Restricted vascular mobility can reduce its ability to reach active infection sites and, consequently, diminish its curative efficacy. Once pathogens such as *Valsa mali* have extensively colonized the phloem and xylem, successful systemic control becomes considerably more challenging [101].

Macrolides are a diverse group of secondary metabolites characterized by a macrocyclic lactone ring, typically consisting of 12–16 atoms, frequently glycosylated with one or more sugar moieties. While the most biologically active macrolides generally feature 14-, 15-, and 16-membered rings [93], macrolides with larger rings have also been reported to possess notable antifungal properties [102], demonstrating the immense structural diversity of this metabolite class.

Actinomycetia inhabiting environments ranging from marine habitats to terrestrial soils synthesize a vast array of antifungal macrolides. For instance, marine-derived glycosylated macrolides, iseolides, demonstrated strong antagonistic effects against *Glomerella cingulata* (anamorph: *Colletotrichum gloeosporioides*), with minimum inhibitory concentration (MIC) values ranging from 0.19 to 0.78 µg/mL. This potency is comparable to the *in vitro* efficacy reported for the commercial synthetic fungicide pyraclostrobin against wild-type fungi (MIC < 4.5 µg/mL) [103,104]. On the other hand, kongjuemycin A, B1, B2, and B3 from *Pseudonocardia kongjuensis* SCSIO 11457 were less effective against *Colletotrichum gloeosporioides*, with MICs ranging from 32 to >64 µg/mL [105]. This contrast highlights that antifungal performance depends on specific structural characteristics, rather than on the presence of a macrocyclic lactone ring alone. Additionally, the efficacy of these metabolites is highly pathogen specific.

The importance of structure–activity relationships is further demonstrated by irumamycin, novonestmycins, and notonesomycins. The 20-membered irumamycin was effective against *Aspergillus niger* and *Fusarium oxysporum*. In parallel, the larger 32-membered macrolides, novonestmycin A and B, showed inhibitory activity against various pathogens, including *Corynespora cassiicola*, *Septoria nodorum*, and *Rhizoctonia solani*. Structurally, novonestmycin B shares the same backbone as notonesomycin A, differing only by substitutions

on the macrolide and benzene rings; despite this similarity, notonesomycin A is characterized by only moderate antifungal activity. This structural sensitivity is further illustrated by the fact that the non-sulfated notonesomycin B exhibited four times higher antifungal activity against *Aspergillus fumigatus* than notonesomycin A [102,106–108].

Similar trends were evident among oligomycins and bafilomycins produced by *Streptomyces* species. While oligomycin-producing strains were effective in inhibiting *Botrytis cinerea* [109], the efficacy of bafilomycins varied considerably depending on the examined derivative and target pathogen. For example, bafilomycin A₁ and K displayed only moderate antifungal activity against *Pyricularia oryzae* and remained less effective or entirely inactive against *Botrytis cinerea*, *Rhizoctonia solani*, *Colletotrichum orbiculare* (formerly *Colletotrichum lagenarium*), and *Bipolaris maydis* (formerly *Helminthosporium maydis*). Similarly, bafilomycin D demonstrated only weak inhibitory effects [110]. In contrast, another derivative had profound biocontrol efficacy. Bafilomycin C₁ was used in pot experiments to control cucumber anthracnose (*Colletotrichum orbiculare*): a concentration of only 0.2 µg/mL achieved 78.5% disease control. This compound also maintained favorable storage and thermal stability, characteristics that are highly desirable for future commercial development [111].

Beyond *Streptomyces*, the relatively understudied genus *Kitasatospora* also represents a valuable source of antifungal macrolides. Despite difficulties associated with its isolation, they thrive under harsh environmental conditions. Cultures of setamycin (bafilomycin B1)-producing *Kitasatospora* sp. showed distinct antagonistic activity [77].

Among macrolides, guanidine-containing polyhydroxyl derivatives have attracted considerable attention because of their antifungal activity and broad target spectrum. These compounds are predominantly produced by *Streptomyces* species [112]. Among these, the 36-membered macrolide guanidylfungin A, isolated from *Streptomyces* sp. A3265, had potent activity against several economically important phytopathogens, including *Botrytis cinerea*, *Fusarium oxysporum*, *Alternaria panax*, *Colletotrichum gloeosporioides*, *Rhizoctonia solani*, and *Magnaporthe grisea*. Notably, methyl guanidylfungin A was characterized by a stronger antifungal activity [95,113]. However, the practical agricultural application of guanidylfungin A may be tempered by mammalian toxicity concerns, given its low intraperitoneal LD₅₀ value of 12.5 mg/kg in mice [112].

In contrast, other guanidine-containing macrolides appear to offer a more favorable balance between efficacy and application potential. *Streptomyces yongxingensis*, isolated from marine soft coral, synthesizes niphimycin C, which showed strong activity against the causal agent of banana Fusarium wilt, *Fusarium oxysporum* f. sp. *cubense*, with an EC₅₀ value of 1.20 µg/mL [114]. Similarly to many membrane-active macrolides, niphimycins increase fungal membrane permeability, resulting in leakage of cellular components [112]. Furthermore, niphimycin C induced mitochondrial dysfunction, disrupted cellular metabolism, and reduced the activities of enzymes involved in the electron transport chain and the tricarboxylic acid cycle in *Fusarium oxysporum* f. sp. *cubense* [114]. Their agricultural relevance is further supported by a study involving crude methanolic extract of *Streptomyces hygroscopicus* containing both niphimycin and the polyether ionophore, nigericin. This extract demonstrated strong *in vitro* and *in planta* efficacy by inhibiting *Alternaria alternata* isolates (IZ: 44.33 and 47 mm) and successfully reducing wound colonization and subsequent necrotic lesion development on apple fruits [115,116]. When evaluated as a purified compound, niphimycin could inhibit the growth of several fungal pathogens, with MIC values ranging between 8 and 64 µg/mL, though it remained ineffective against *Alternaria brassicicola* and *Diaporthe citri*. Under greenhouse conditions, pure niphimycin proved as effective as commercial chemical fungicide chlorothalonil in the control of pepper anthracnose [117]. Overall, these findings suggest that certain guanidyl-

containing macrolides represent promising candidates for bio-based disease management, particularly when incorporated into multi-component biocontrol formulations.

Polyene macrolides represent a significant subgroup of polyketides renowned for their potent antifungal properties. To date, over 200 polyene antibiotics have been isolated. While the majority are secreted by *Streptomyces* species, polyene biosynthetic gene clusters have also been reported in other actinomycetes, including *Amycolatopsis*, *Actinokineospora*, *Sinosporangium*, *Salinispora*, and *Saccharopolyspora* [46,63]. Structurally, these macrolides typically consist of large macrolactone rings containing 20–40 carbon atoms and 3–8 conjugated double bonds. Most of them are glycosylated with a single aminodeoxysugar. These complex molecules are synthesized through the repeated enzymatic condensation of small carboxylic acids driven by polyketide synthases [118–120].

The promising antifungal efficacy of polyenes primarily derives from their ability to interact with ergosterol, a sterol component of fungal cell membranes. Binding to ergosterol lyses fungal membranes while showing low affinity for mammalian cholesterol and plant phytosterols, thereby conferring excellent agricultural selectivity. Because membrane ergosterol is an evolutionarily conserved target, polyenes trigger a remarkably low frequency of resistance development in contrast to synthetic fungicides with single-site modes of action. However, recent studies indicate that not all polyenes rely exclusively on classical ergosterol binding. For example, mandimycin A appears to interact directly with membrane phospholipids, particularly phosphatidylinositol, suggesting that alternative membrane-targeting strategies may contribute to the biological diversity of these compounds [121].

Despite their profound chemical diversity, only a limited number of polyenes have been thoroughly evaluated for agricultural applications against fungal pathogens. Well-known examples include nystatin and amphotericin B, produced by *Streptomyces noursei* and *Streptomyces nodosus*, respectively [81]. Interestingly, the disruption caused by polyene macrolides extends beyond membrane permeabilization, affecting critical cellular processes such as endocytosis, exocytosis, hyphal tip septation, and the movement of nutrient transporter proteins between intracellular compartments and cytoplasmic membranes, thereby exerting multifaceted antifungal effects [118]. Beyond direct growth inhibition, these metabolites can target multiple cellular sites within fungal pathogens, an important feature that may help reduce disease recurrence. Antifungalmycin, along with fungichromin, secreted by *Streptomyces padanus* 702, had strong toxicity against *Rhizoctonia solani*, *Penicillium notatum*, *Gibberella zeae*, *Mucor* sp., *Ustilagoidea virens*, *Helminthosporium sigmoideum*, *Fusicoccum* sp., and *Magnaporthe grisea*, with EC₅₀ values between 0.21 and 26.72 µg/mL [122]. In addition to mycelial suppression, antifungalmycin 702 effectively inhibited sclerotial formation in *Rhizoctonia solani* by concurrently altering cell membrane integrity, disrupting cytoskeletal organization, and interfering with intracellular organelles [123]. This multi-target mode of action translated into *in planta* success, as demonstrated by the analogue antifungalmycin N2, which markedly reduced the severity of rice sheath blight caused by *Rhizoctonia solani* through both preventive and curative applications [124]. However, the protective capacity of this polyene macrolide appears to depend on not only on its ability to disrupt membrane structure and function but also on its capacity to inhibit succinate dehydrogenase activity [125]. Furthermore, some polyenes appear capable of enhancing host defense responses [121]. Tetramycins, for example, are primarily registered for the management of fungal diseases affecting fruits and rice in China; nonetheless, beyond their direct fungicidal action, they can stimulate certain plant defense enzymes [96]. Similarly, natamycin affects polyphenol oxidase and peroxidase activity, thereby elevating disease resistance in treated plants [121].

The practical agricultural performance of polyene macrolides is strongly influenced by their structural subclass and the specific mechanism through which they interact with

fungal cells. For instance, the polyketide pentaene macrolide 32,33-didehydroroflamycin, produced by *Streptomyces durmitorensis* MS405, effectively inhibited numerous preharvest fungal pathogens, including *Alternaria alternata*, *Aspergillus flavus*, *Botrytis cinerea*, *Colletotrichum acutatum*, *Colletotrichum gloeosporioides*, *Fusarium avenaceum*, *Monilinia fructigena*, *Mucor piriformis*, and *Penicillium expansum*, with inhibition zones ranging from 13 to 51 mm [46]. Further evidence of the agricultural potential of pentaene macrolides is provided by strevertene A and B. Under *in vitro* conditions, these compounds inhibited the mycelial growth of *Aspergillus oryzae*, *Alternaria mali*, *Colletotrichum orbiculare*, *Cercospora canescens*, *Diaporthe citri*, *Colletotrichum coccodes*, *Colletotrichum gloeosporioides*, *Fusarium oxysporum* f. sp. *lycopersici*, *Fusarium oxysporum* f. sp. *cucumerinum*, *Cylindrocarpon destructans*, and *Sclerotinia sclerotiorum*. Furthermore, treatment of tomato plants with strevertenes effectively controlled the development of *Fusarium* wilt [126]. Such broad-spectrum activities may be valuable in agricultural settings, where multiple pathogens often coexist within the same cropping system.

Similarly promising, newly isolated actinospene demonstrated good inhibitory activity against a diverse selection of fungi and oomycetes, including *Fusarium oxysporum*, *Fusarium graminearum*, *Sclerotium rolfsii*, *Colletotrichum capsici*, *Alternaria alternata*, and *Phytophthora capsici*, with minimum inhibitory concentration (MIC) values between 2 and 50 µg/mL [63]. Another agent, faeriefungin, was proven effective for controlling infection caused by *Fusarium* species. This polyene exhibited inhibitory effects against *Fusarium oxysporum* f. sp. *asparagi*, the causal agent of stem wilt and root rot in asparagus [127].

Evaluating the structural potency for these antifungal interactions reveals that glycosylation is not an absolute prerequisite for high potency. Filipin III, produced by the *Trapa japonica* endophyte *Streptomyces miyashii*, is a non-glycosylated polyene that interacts with membrane sterols. Thus, it was highly active against *Aspergillus niger*, *Alternaria mali*, *Colletotrichum coccodes*, *Colletotrichum orbiculare*, *Colletotrichum gloeosporioides*, *Cylindrocarpon destructans*, *Diaporthe citri*, *Fusarium oxysporum* f. sp. *cucumerinum*, *Fusarium oxysporum* f. sp. *lycopersici*, and *Sclerotinia sclerotiorum* at lower concentrations from 1 to 25 µg/mL. Nonetheless, while highly effective against phytopathogens, its systemic use in human therapy remains constrained due to mammalian toxicity [128,129].

Taken together, these studies demonstrate that polyene macrolides offer a versatile solution to agricultural disease management, displaying distinct operational ranges; while certain metabolites provide highly effective protection against a wide array of fungal phytopathogens at lower doses, others may feature specialized, narrow-target activity. In terms of application strategy, these compounds have been applied as protective or preventive treatments to inhibit early colonization, rendering them less effective once an active infection has been fully established. To overcome the inherent limitations that hindered the field adoption of these compounds, such as poor water solubility, low tissue adhesion, and UV sensitivity, improved delivery systems are increasingly being utilized to maximize their field performance. For instance, formulating cell-free supernatants into nanoemulsions can drastically improve dispersion, stability, and bioavailability, thereby enhancing their localized antifungal efficacy compared to crude cell-free supernatants or raw suspensions. In parallel, increasing attention has been directed toward exploiting the natural metabolic diversity of actinobacteria rather than relying exclusively on purified compounds, as deploying complex multi-metabolite systems can yield broader ecological benefits. A representative example is *Streptomyces murinus* JS029, which simultaneously secretes filipin I, pentamycin, and a mixture of cell-wall-degrading enzymes, including chitinase, cellulase, and protease. When applied to Chinese cabbage, this multi-targeted approach exerts a powerful antifungal effect against *Sclerotinia minor*. Crucially, the efficacy of this strain extends beyond direct fungicidal action; it concurrently activates the host

plant's induced systemic resistance pathways while favorably modulating the surrounding soil microbiome [121,130,131].

Beyond macrolides, macrolactam polyketides represent a growing class of bioproducts featuring diverse biological activities [132]. Although their agricultural potential remains less explored than that of polyene macrolides, several members of this class have demonstrated promising antifungal activity against plant pathogens. For instance, naphthomycins may be utilized against *Fusarium moniliforme*, *Fusarium oxysporum*, *Verticillium cinnabarinum*, *Pyricularia oryzae*, and *Gaeumannomyces graminis*, albeit at relatively higher MIC values [133].

In addition to cyclic configurations, several linear polyketides have demonstrated antifungal activity. The linear polyene inha-neotetrafricin, isolated from *Streptomyces rubrisoli* Inha501, was utilized to restrain the growth of phytopathogenic fungi. The sugar moiety of this compound plays an important role in its antifungal activity [134]. Additionally, linear aminopolyol polyenes, including linearmycin or mediomycin, exert their antifungal effects through interactions with ergosterol-containing membranes. This binding promotes the formation of ion channels, causing the disruption of fungal cell membrane integrity and triggering the efflux of crucial intracellular ions [65].

This linear structure is not restricted strictly to primary metabolic pathways. Both dorrigin A and B are classified as shunt metabolites of iso-mygrastatin, formed via an H₂O-mediated rearrangement. In a biocontrol evaluation, soil-isolated *Streptomyces* sp. was found to produce metabolites annotated as dorrigin B, along with pepstatin A and oligomycin A. The extract obtained from the strain demonstrated comparable or stronger fungal growth inhibition against soybean phytopathogens (*Macrophomina phaseolina*, *Rhizoctonia solani*, and *Sclerotinia sclerotiorum*) than the control mixture of trifloxystrobin and prothioconazole [135].

4.1.2. Peptide Antibiotics

Unlike conventional chemical pesticides that generally act on specific molecular targets, peptide antibiotics produced by actinomycetes display distinct modes of action that target fungal structural integrity and interfere with essential intracellular mechanisms [136,137].

Cyclic lipopeptides, such as the mixture of lipopeptin A and B, disrupt fungal membrane integrity, thereby inhibit conidial sporulation and mycelial growth, while reduce fusaric acid production [138]. Cyclic depsipeptides represent another prevalent class of effective antimicrobials: for instance, kutznerides 1–4 demonstrated efficacy against root-rotting fungi, although their agronomic application at higher concentrations may be constrained by poor water solubility [139]. Valinomycin, another cyclic depsipeptide, facilitates potassium ions across otherwise impermeable cellular membranes, thereby disrupting mitochondrial oxidative phosphorylation [136].

Other peptide antibiotics, such as coronamycins, have also demonstrated antifungal activity [137]. In addition, actinomycins, a group of chromopeptide lactone antibiotics secreted by various *Streptomyces* species, showed broad-spectrum antifungal effects. Among these, actinomycin D exhibited bioactivity against economically important pathogens, including *Verticillium dahliae*, *Fusarium oxysporum*, *Fusarium graminearum*, *Rhizoctonia solani*, *Magnaporthe grisea*, *Dothiorella gregaria*, *Valsa mali*, *Penicillium italicum*, and *Botrytis cinerea* [140,141]. Pepstatin A, a hexapeptide and potent inhibitor of aspartic protease, represents another notable antifungal metabolite [135].

Collectively, these structurally diverse peptide antibiotics underscore the immense potential of actinomycetes as a sustainable source of biologically active crop protection agents. However, several critical limitations currently impede their widespread agricultural adaptation, including instability, sensitivity to harsh environmental conditions, susceptibility to enzymatic degradation by proteases, lack of target selectivity, and potential

toxicity toward non-target eukaryotic cells. Furthermore, scalable metabolic production using native strains is severely limited: the cultivation of *Streptomyces* species is highly time-consuming, typically requiring several days. Meanwhile, the genetic manipulation of these bacteria is still complex and laborious [136,142,143].

4.1.3. Nucleoside and Nucleotide Antibiotics

Among other bioactive compounds, nucleoside and nucleotide antibiotics that target vital intracellular processes such as protein biosynthesis have been assessed for their biocontrol potential. Based on their structural characteristics, nucleoside antibiotics are classified into pyrimidine and purine nucleoside families [144]. *Streptomyces violaceoniger* was utilized for tubercidin production, which inhibited the growth of several pathogens, such as *Magnaporthe grisea*, *Botryosphaeria dothidea*, *Rhizoctonia solani*, *Alternaria solani*, *Phytophthora capsici*, *Mycosphaerella melonis*, and *Colletotrichum gloeosporioides*. In greenhouse experiments, tubercidin applied at concentrations of 50–500 µg/mL reduced the severity of *Phytophthora* blight in pepper plants, with the preventive application being more effective than curative treatment [145]. Tunicamycins, nucleotide antibiotics synthesized by various *Streptomyces* species, may be active against filamentous fungi [146]. However, they also interfere with N-linked glycan formation in the mammalian glycoprotein precursors, resulting in toxicity concerns [147]. A bicyclic perhydrofuropyran C-nucleoside, malayamicin, isolated from *Streptomyces malaysiensis*, significantly decreased the growth rate of *Stagonospora nodorum* SN15 in a dose-dependent manner [148].

Peptidyl–nucleoside antibiotics constitute a unique class of antifungal metabolites characterized by their ability to interfere with distinct cellular processes to inhibit fungal proliferation. For instance, polyoxins and nikkomycins interfere with chitin biosynthesis, whereas mildiomycin primarily inhibits protein synthesis, providing effective control of diseases such as powdery mildew [72,144,149,150].

One of the earliest representatives of this class is blasticidin S, isolated from *Streptomyces griseochromogenes* [144,145]. It was among the first actinomycete-derived antibiotics to be commercialized as an agricultural fungicide and was successfully utilized as a foliar treatment for the control of rice blast disease caused by *Magnaporthe grisea* (syn. *Pyricularia oryzae*) [83,151]. This compound inhibits protein synthesis by binding to the peptidyl transferase center of the ribosome [152]. Despite its importance and strong antifungal activity, several limitations have restricted its broader application. Certain *Aspergillus* species possess intrinsic resistance mechanisms that enable the conversion of blasticidin S into the non-toxic derivative deaminohydroxy-blasticidin S [153]. Furthermore, because the compound lacks selectivity and can inhibit protein synthesis in both eukaryotes and prokaryotes, concerns regarding off-target toxicity have persisted [152]. These limitations stimulated the search for alternative antibiotics, leading to the development of and subsequent commercialization of several compounds, including polyoxin and mildiomycin [83].

4.1.4. Aminoglycoside and Aminocyclitol Antibiotics

Aminoglycoside antibiotics also contribute to agricultural disease management. Among them, kasugamycin, produced by *Streptomyces kasugaensis*, has been used to control rice blast disease. The antifungal activity of kasugamycin is primarily attributed to its ability to interfere with the interactions between mRNA and the 30S ribosomal subunit [78,154]. In addition to its broad-spectrum antimicrobial activity, kasugamycin is also valued for its favorable safety profile. However, its practical field performance is constrained by several limitations. Similarly to other antibiotic-based biopesticides, kasugamycin exhibits high hydrophilicity, poor adhesion to leaf surfaces, and susceptibility to photothermal

degradation. These properties reduce its persistence on plant tissues, resulting in reduced application efficiency and shortened residual activity period under field conditions [155].

Validamycin A is a C₇N aminocyclitol-containing antibiotic that has been widely recognized as an eco-friendly, harmless fungicide. Introduced over five decades ago, it is primarily utilized for the management of soil-borne diseases, particularly rice sheath blight caused by *Rhizoctonia solani*. Validamycin A acts primarily as a competitive inhibitor of trehalase. Its activity is believed to depend on intracellular uptake followed by hydrolysis by a cytosolic β -glucosidase, resulting in the release of validoxylamine A, a metabolite with a stronger inhibitory effect. Although its direct antifungal activity against some other phytopathogenic fungi may be limited, accumulating evidence suggests that this compound may contribute to disease suppression not only through direct effects on pathogens but also by enhancing host defense responses and inducing resistance-related mechanisms in plants [156–159].

4.1.5. Terpenes and Their Derivatives

Terpenes and their oxygenated derivatives constitute the largest and most structurally diverse class of secondary metabolites obtained from natural sources [160]. Although research on actinobacterial terpenes has historically lagged behind that on plant-derived ones, increasing evidence indicates that actinomycetes represent a valuable source of bioactive terpene metabolites with antifungal activity. For instance, Bi and Yu [161] reported that several diterpenoids, namely chloroxaloterpin A and B, viguiepinol, and oxaloterpins C–E, isolated from *Streptomyces* sp. SN194 had antagonistic activity. When evaluated against *Botrytis cinerea*, these compounds effectively suppressed disease development by inhibiting both mycelial growth and spore germination. However, the composition of their side chains influenced their antifungal efficacy [114].

4.1.6. Alkaloids

An endophytic actinomycete associated with *Artemisia annua* L. was identified as a source of indole and tyramine alkaloids, of which N-acetyltyramine was characterized by weak antifungal activity against *Aspergillus niger*, with an MIC value of 256 μ g/mL [162]. Two indole alkaloids, pimprinine and streptochlorin, have also been assessed for their antifungal properties; however, their efficacy was limited at lower concentrations [163]. Furthermore, a carbazole alkaloid, streptovercillin, and a novel 2-azetidinone, streptovercillinone, were isolated by Feng et al. [164] from the mycelial culture of *Streptomyces morookaensis*. Both metabolites demonstrated relatively weak activity against *Peronophythora litchii*, with MICs of 250 and 1000 μ g/mL, respectively.

4.2. Control of Phytopathogenic Fungi by the Production of Volatile Compounds

Actinobacteria can synthesize volatile compounds (VCs) that enhance plant quality and productivity. During co-culturing, interactions with other phylum-shared bacteria can influence the secondary metabolism of actinobacterial species through the production of VCs, leading to either the overproduction of specific compounds or the biosynthesis of novel metabolites [91].

One such inorganic volatile metabolite, hydrogen cyanide (HCN), is naturally produced by various soil microorganisms. HCN can impair cellular respiration in eukaryotic pathogens via inhibition of mitochondrial cytochrome c oxidase or inactivating other metalloproteins [165]. Similarly, other inorganic VCs, including hydrogen sulfide and ammonia, are considered to contribute to the inhibition of target microorganisms [166]. Volatile amines are also involved in biocontrol processes by exerting anti-oomycetal activity and enhancing the efficacy of antibiotic secondary metabolites [167].

Beyond these inorganic components, microbial volatile organic compounds (mVOCs) have attracted considerable attention as potential biocontrol agents [168]. These low-molecular-weight compounds can readily diffuse through soil environments and stored agricultural products [169]. While certain VOCs are commonly produced by phylogenetically unrelated microbes, others are specific for particular taxa. Ecologically, these bioactive compounds are highly versatile; they can suppress fungal growth, inhibit or stimulate plant development, enhance plant resistance, and attract various organisms [86]. However, both the composition and the quantity of VOCs are strongly influenced by environmental conditions and nutrient availability [170]. Due to their low molecular mass, low boiling points, and high vapor pressure, these compounds are highly volatile at ambient temperature. While some VOCs arise as by-products of primary metabolism, others are synthesized via specialized secondary metabolic pathways. Common mVOCs include alcohols, esters, ketones, aromatic hydrocarbons, alkanes, alkenes, terpenes, and sulfur- and nitrogen-containing compounds [171,172]. A majority of these molecules are characterized by low structural complexity and lipophilic properties [166]. Representative examples include dimethyl disulfide, dimethyl trisulfide, butan-1-ol, 2-methylpropan-1-ol, 3-methylbut-3-en-1-ol, 3-methylbutan-1-ol, 2-phenylethanol, methyl vinyl ketone, and geosmin [173].

Streptomyces species, in particular, produce numerous VOCs with antifungal activity, such as dimethyl sulfoxide, carvacrol, cyclohexanol, and naphthalene [174]. For instance, VOCs emitted by *Streptomyces* demonstrated antagonistic effects against *Rhizoctonia solani* under *in vitro* conditions. Among the five synthetic analogs of the identified VOCs, 1,3,5-trichloro-2-methoxybenzene completely suppressed fungal growth and induced hyphal melanization. Furthermore, after two days of exposure, methyl 2-methylpentanoate and a mixture containing all five VOCs reduced the radial growth of *Rhizoctonia solani* by 25% and 42%, respectively [86]. In another study, Gómez et al. [174] observed that VOCs emitted by *Streptomyces* sp. PNM-149 inhibited the growth and conidia production of *Colletotrichum gloeosporioides* by 48% and 67%, respectively. This broad-spectrum inhibition is further evidenced by *Streptomyces* sp. AN09126, a strain known for its potent antimicrobial activity. It produced a complex blend of aromatics, alcohols, sulfides, and esters, with dimethyl disulfide, 2-propylfuran, 2-methyl-1-butanol, and 3-methyl-1-butanol as the dominant constituents. These emitted VOCs effectively inhibited the mycelial growth of several phytopathogens, with *Fusarium graminearum* being the most sensitive, followed by *Colletotrichum coccodes*, *Cryphonectria parasitica*, *Botrytis cinerea*, and *Fusarium oxysporum* f. sp. *lycopersici* [175]. Similarly, Sudha et al. [176] investigated the effect of *Streptomyces rochei* on sorghum grain molds, specifically *Fusarium moniliforme* and *Curvularia lunata*. During interactions with these pathogens, a total of 45 VOCs was detected. The volatile profile included alcohols, alkanes, alkenes, esters, ketones, terpenoids, and sulfur compounds. Among the identified VOCs, several were differently regulated during co-cultivation with the pathogens.

The ability to inhibit pathogenic growth and spore germination represents a key indicator of the antifungal efficacy of biopesticides. The mechanisms underlying this inhibition are multifaceted. For example, VOCs producing *Nocardiopsis dassonvillei* not only inhibited spore germination of *Rhizopus stolonifer* but also impaired fungal cell membrane integrity, increased membrane permeability, and caused the leakage of nucleic acids and proteins. These critical cellular damages were accompanied by membrane lipid peroxidation and mitochondrial dysfunction, ultimately leading to fungal growth inhibition [177].

Given these potent mechanisms, the application of VOCs as biofumigants has also shown promise for postharvest disease management. For instance, VOCs produced by *Streptomyces salmonis* PSRDC-09 were utilized to control anthracnose in chili fruits. Fu-

migation with these VOCs for 24 h completely inhibited postharvest spoilage caused by *Colletotrichum gloeosporioides* PSU-03, resulting in 0% disease incidence and no measurable lesion development. The major volatile constituents were identified as L-linalool, decane, and disulfide [178].

It is important to note that the efficacy and composition of VOCs can be strain- and pathogen-dependent. Cuervo et al. [179] reported that the VOCs emitted by the tested *Streptomyces* strains showed no antifungal activity against *Sclerotinia* spp. or *Phytophthora cinnamomi*, which are not naturally associated pathogens of the isolation environment of these strains. In contrast, VOC-mediated antifungal activity was observed against *Escovopsis weberi*, a pathogen native to the same environment from which the *Streptomyces* strains were obtained. However, this antagonistic effect may have been driven, at least in part, by ammonia production. Collectively, these findings suggest that the ecological relationship between microbial antagonists and their natural competitors may influence VOC production, composition, and antifungal activity.

Despite these contrasting findings, VOCs generally appear to be effective against a broad range of fungal pathogens, including species belonging to the genera *Aspergillus*, *Botrytis*, *Ceratocystis*, *Colletotrichum*, and *Rhizopus*. Consequently, these VOCs have considerable potential as biofumigants for controlling important postharvest pathogens during seed and crop storage [177,178,180–183]. Table 3 provides a comparative overview of the efficacy and practical limitations of the direct mechanisms discussed.

Beyond their direct antimicrobial effects, VOCs play important roles in host–pathogen interactions, microbial signaling, and competition. Although laboratory studies commonly evaluate the biological activity of individual VOCs against a limited range of target organisms, the effects of VOCs under natural conditions are shaped by a complex interplay of environmental factors. This variability suggests that the concentration, relative abundance, and combined effects of volatile compounds ultimately determine their ecological functions within diverse microbial communities [184].

In agricultural applications, appropriately selected fumigants can do more than merely inhibit pathogens; they can actively help preserve crop quality by maintaining plant cell membrane integrity and functionality. VOCs have been shown to activate the phenylpropanoid pathway while simultaneously enhancing disease resistance, indicating a dual mode of action. Furthermore, microbial VOCs offer a significant production advantage: they can be continuously synthesized on simple culture media, whereas plant-derived volatiles require extraction from plant material or chemical synthesis. Therefore, the use of microbial VOCs for the fumigation of postharvest pathogens may offer a more cost-effective alternative [177].

Nevertheless, potential safety considerations should not be overlooked. Because microbial volatiles may persist on the surface of, or even within, stored crops, their toxicological profiles require rigorous evaluation. Although many microbial VOCs are naturally occurring compounds and are generally regarded as safe, their potential health effects associated with long-term or high-level exposure should be carefully evaluated before their widespread commercial application [177].

4.3. Control of Phytopathogenic Fungi by the Production of Hydrolytic Enzymes

Naturally, actinobacteria can degrade and biotransform organic substrates through the secretion of a wide array of lytic enzymes, including chitinase, protease, cellulase, and β -1,3-glucanase, effectively breaking down complex biopolymers. These bioactive enzymes can inhibit the spread of microbial pathogens either acting alone or working in synergistic combination with other cell wall-degrading enzymes [10,185,186].

Table 3. Comparative ranking and evaluation of direct antifungal mechanisms based on the reviewed scientific literature.

Rank	Direct Mechanism	Frequency of Occurrence	Relative Effectiveness	Primary Limitations
1	Production of diffusible antifungal compounds	Very high	Very high: exert broad-spectrum fungistatic and fungicidal activity at low minimum inhibitory concentrations. A diverse array of compounds is available that can affect various pathogens, cellular components, and metabolic activities.	– Several biosynthetic gene clusters remain silent under standard laboratory conditions. – Effectiveness remains highly compound-specific. – Hydrophobic properties of certain metabolites require advanced delivery formulations. – Potential toxicity requires additional toxicology screening and regulatory approval.
2	Production of cell-wall-degrading enzymes	High	High: directly degrade structural cell wall polymers, inducing structural deformities, hyphal damage, and lysis.	– Expression often requires additional substrate induction. – Enzyme stability and activity are highly dependent on environmental fluctuations. – Required effective concentrations are generally higher than those of diffusible antifungal compounds.
3	Production of volatile organic compounds	High–medium	Medium to high: provide excellent biofumigants capable of inhibiting spore germination and fungal growth.	– High volatility leads to rapid degradation under open-field conditions. – Their utilization requires an enclosed environment to maintain active levels. – Required effective concentrations are generally higher than those of diffusible antifungal compounds.
4.	Modulation and degradation of mycotoxins	Medium	High: from a toxicological perspective, actinobacteria and their metabolites can protect crop quality and increase food safety by downregulating fungal toxin biosynthetic pathways or directly degrading mycotoxins.	– Does not always directly eliminate or reduce the primary fungal biomass. – Carries the potential of generating biologically active secondary metabolites.
5	Hyperparasitic activity	Low–medium	High: localized effect is achieved via the destruction of host mycelia.	– The visible antifungal effect may be slower. – Living actinobacteria require specific environmental conditions to successfully initiate and sustain colonization, penetration, and inactivation. – The survival and effectiveness of the introduced bacterial inoculum may be suppressed by the indigenous microflora.

Chitin, an insoluble linear β -1,4-linked homopolymer of N-acetylglucosamine, is a common structural polysaccharide of fungal cell walls, comprising 10–30% of the cell wall dry weight depending on the fungal species and culture conditions. Among prokaryotes, actinobacteria are potent degraders of this polymer, utilizing chitinases to hydrolyze the bonds between N-acetylglucosamine residues [187–193]. Based on amino acid sequencing, these enzymes are classified into the GH18, GH19, and GH20 families of glycosyl hydrolases [194]. Chitinases have frequently been isolated from diverse acti-

nobacterial genera, including *Actinoplanes*, *Nocardia*, *Microbispora*, *Micromonospora*, and *Streptomyces* [195]. In *Streptomyces* species, chitinase production correlates with the inhibition of germ tube elongation, spore germination, and bursting of fungal spores [188]. The antifungal effect of chitinase can materialize through two mechanisms: first, chitinase degrades chitin in the fungal cell walls. Second, they may affect fungal growth and development by interfering with chitin biosynthesis [196]. For example, the crude enzymatic extracts from *Streptomyces rimosus*, *Streptomyces albus*, *Streptomyces riseoflavus*, and *Streptomyces flavogriseus* demonstrated inhibitory effects against various phytopathogens. The chitinase obtained from *Streptomyces albus* showed stronger antifungal activity against *Magnaporthe oryzae*, *Fusarium graminearum*, *Rhizoctonia solani*, *Puccinia* spp., and *Botrytis cinerea*, with inhibition zones ranging from 8.10 to 10.74 mm. Against *Puccinia* species and *Botrytis cinerea*, the enzyme displayed a level of effectiveness comparable to the positive control, mancozeb [188].

Beyond terrestrial strains, marine isolates also show significant biocontrol potential; the enzymatic extract of *Curtobacterium* sp. CBMAI 2942, an Antarctic marine isolate, had an antagonistic effect on *Aspergillus* sp. series *Nigri* CBMAI 1846, isolated from tomato. By interacting directly with chitin in the cell wall, the enzyme disrupts morphogenesis, cell division, and cell wall reconstruction, thereby hindering the nutrient uptake of the phytopathogen. Nonetheless, no activity was observed against *Fusarium* spp. and *Botrytis cinerea* [194]. On the other hand, the chitinase produced by *Streptomyces variabilis* Am1 showed a strong inhibitory effect against *Fusarium verticillioides* and *Fusarium oxysporum* [197]. Downstream products of this degradation process also demonstrate bioactivity: chitooligosaccharides produced by *Pseudonocardia antitumoralis* 18D36-A1 from shrimp shell waste effectively induced fungal death in a concentration-dependent manner. These oligomers inhibited hyphal branching, increased cellular permeability, altered cell metabolism, and caused the fungal mycelia to wrinkle [198]. Furthermore, the presence of chitin in the surrounding environment can modulate enzyme expression. For example, the antifungal effect of *Streptomyces avidinii* INA 01467 was reinforced when cultured on a medium containing chitin, whereas no such induction or additional effect was observed with *Micromonospora aurantiaca* INA 01468 under identical conditions. Although many actinobacterial strains produce chitinase, this strain-dependent response suggests that chitin differentially regulates the chitinase genes expression and the production of additional antifungal compounds [195]. Additionally, chitin content in fungal cell walls varies considerably. For instance, when exposed to adverse environmental conditions, *Aspergillus fumigatus* can alter its dynamic cell wall structure in various ways, allowing it to withstand environmental stress [191].

In addition to chitin, β -1,3-glucan is another major structural component of fungal cell walls, accounting for approximately 50–60% of the cell wall dry weight. Certain actinobacteria are characterized by the production of β -1,3-glucanases, which effectively degrade the cell walls of phytopathogenic fungi by hydrolyzing β -1,3-glycosidic bonds [199]. Mufida et al. [199] reported that both rhizospheric *Streptomyces* isolates and their purified glucanases inhibited the growth of *Fusarium oxysporum*. Microscopic observations revealed severe hyphal damage, characterized by holes and a wrinkled appearance resulting from the leakage of cellular content through the compromised cell wall. Cellulases and glucanases also play an important role in degrading the cell walls of oomycetes, whose cell wall composition differs from that of true fungi. The *in vitro* production of β -1,3-, β -1,4-, and β -1,6-glucanases by rhizospheric actinomycetes (*Streptomyces griseoalbus*, *Actinoplanes philippinensis*, *Micromonospora chalcea*, and *Microbispora rosea*) hydrolyzed the complex glucans in the target cell walls, inducing the lysis of *Pythium aphanidermatum* hyphae [200].

Although glucanases and chitinases are the primary mycolytic enzymes, certain proteases have been characterized by antifungal activity [201]. These enzymes hydrolyze the proteins embedded within the filamentous fungal cell wall, leading to structural destabilization and eventual cell wall lysis [202]. Furthermore, extracellular proteases produced by *Streptomyces phaeopurpureus*, a rhizosphere isolate from yam, suppressed *Colletotrichum coccodes* infection on tomato fruits by interfering with spore adhesion, spore germination, appressorium formation, and subsequent infection establishment [203]. The antifungal activity of a serin protease against *Fusarium udum* was confirmed by Singh and Chhatpar [201]. The purified enzyme inhibited spore germination in a dose-dependent manner, and its high stability suggested potential applicability as a biocontrol agent in agricultural systems. Similarly, the findings of Al-Askar et al. [204] indicated that protease activity contributes to antagonistic interactions; however, the pronounced antifungal activity of the *Streptomyces* strain indicates that its biocontrol effect may involve additional mechanisms.

The use of purified free enzymes offers several advantages over whole-cell microbial application, as it overcomes several limitations associated with living microbes, such as the comparatively slow rates of biodegradation processes, which may require weeks to months [205]. Despite the compelling *in vitro* antagonistic activity of actinobacterial enzymes, their widespread translation into commercial biocontrol agents remains hindered by several limitations. In addition to their poor stability and limited shelf life, free enzymes are highly susceptible to rapid abiotic degradation and biotic inactivation [206].

Nevertheless, enzymes derived from bacterial sources offer several advantages over other antimicrobial metabolites, such as lipopeptides and VOCs. In particular, they can often be produced at higher yields and generally require less complex purification processes [207].

To overcome the limitations associated with free enzymes, enzyme immobilization has been proposed as an effective strategy to improve enzyme performance [205] by enhancing stability, resistance to denaturation, and reusability. Some formulations included the immobilization of chitinase onto cobalt metal–organic frameworks [208], zinc oxide nanoparticles [209], and nanosilica particles [210].

4.4. Hyperparasitic Activity of Actinobacteria

Parasitism is an interaction in which one organism (the parasite) derives nutrients from another organism (the host). When the host is itself a parasite, the interaction is termed hyperparasitism. Plant-pathogenic fungi are common hosts in hyperparasitic interactions [211]. Although most actinobacteria antagonize fungal pathogens through the secretion of antifungal compounds and hydrolytic enzymes, certain strains can directly colonize and penetrate fungal hyphae, disrupt cellular integrity, and ultimately induce cell lysis [212].

Hyperparasitic interactions between various actinobacteria and phytopathogenic fungi has been extensively documented. For instance, Palaniyandi et al. [203] showed that *Streptomyces phaeopurpureus* ExPro138 colonized the mycelium of *Colletotrichum coccodes* within two days and completely parasitized it after 72 h. During this interaction, the actinobacterial filaments coiled around and penetrated the fungal mycelium, exhibiting intramycelial growth. As a result, the affected fungal mycelia lost structural integrity, underwent lysis, and displayed morphological distortion. Similarly, the parasitic activity of *Streptomyces rochei* against *Sclerotinia sclerotiorum* resulted in hyphal deformation, contraction, and collapse of the mycelial network, accompanied by active colonization, mycelial penetration, and intrahyphal growth. Actinobacteria can suppress the growth of the phytopathogenic fungi by lysing hyphal tips, leading to swelling, pore formation, irregular membrane borders, and overall shrinkage of the affected hyphae [213]. In another example, *Streptomyces alni* disrupted the normal development of *Fusarium oxysporum*, resulted in

altered hyphae, branching hyphae, conidiophores, and conidiospores by *Streptomyces alni* was reported by Ziedan et al. [214]. The targeted antagonistic effect of this actinobacteria on the fungal host was hypothesized to result from a chemotropic response to substances leaked or released from the fungal hyphae. In addition, researchers observed an extracellular matrix connecting the interacting spore and hyphae, suggesting an adhesive function that facilitated attachment and secured the subsequent parasitic interaction.

4.5. Affecting Mycotoxin Production

Biological treatments have emerged as promising approaches to mitigate mycotoxin accumulation in agro-ecosystems, offering a lower risk of residual toxicity or undesirable modification to food properties [215]. To date, several antimycotoxigenic effects driven by beneficial microbes have been characterized: the direct antagonism and inhibition of toxin-producing fungi, the transcriptional repression of biosynthetic gene clusters, and the adsorption, biodegradation, and detoxification of mycotoxins themselves. Biological detoxification typically relies on specific metabolic pathways that transform these hazardous secondary metabolites into less toxic compounds [89,216,217].

Actinobacteria frequently deploy concurrent mechanisms to restrict both the synthesis and stability of Ochratoxin A (OTA). El Khoury et al. [218] found that co-culturing *Aspergillus carbonarius* S402 with *Streptomyces* species isolated from Algerian soils affected fungal growth and repressed OTA production. At the molecular level, exposure to *Streptomyces* strains MS1, ML5, and G10 repressed the expression of *acpks*, *acOTApks*, and *acOTAnrps*, leading to reductions in OTA accumulation of 23.94%, 13.70%, and 13.50%, respectively. Interestingly, although another strain in the study, AT8, demonstrated greater overall OTA detoxification capacity, it did not significantly affect fungal gene involved in OTA biosynthesis.

Zearalenone (ZON) is highly susceptible to rapid enzymatic breakdown by specific actinobacterial lineages. For instance, *Streptomyces rimosus* subsp. *rimosus* LMG19352 fully degraded and detoxified 5 mg/L of ZON within 24 h during liquid cultivation in Luria–Bertani broth. This protective effect also translated successfully to a plant-based system by significantly reducing mycotoxin concentration in detached wheat ears [219]. Similarly, near-complete ZON degradation with no detectable estrogenicity was reported for two *Streptomyces rimosus* strains. In the same study, none of the examined strains showed significant ZON adsorption onto the cell surface. The comparable hormonal effects observed in untreated and inactivated cell systems suggest that cell wall binding may play a limited role in ZON mitigation, indicating the potential involvement of active enzymatic degradation mechanisms [217]. Beyond ZON, various *Streptomyces* species were effectively used as biocontrol agents to inhibit other destructive mycotoxins, including deoxynivalenol [220] and fumonisins [221].

Aflatoxins are toxic secondary metabolites produced *Aspergillus* species, posing a significant risk to human health [222]. Aflatoxin B₁ (AFB₁), one of the most potent naturally occurring mycotoxins, has been subject to biological control strategies by diverse actinobacteria using both extracellular enzymatic cleavage and multi-tiered transcriptional repression. Several *Streptomyces* isolates inhibited the mycelial growth of *Aspergillus flavus*, while degrading AFB₁. Assays using cell-free extracts demonstrated that this degradative capacity was driven by extracellular enzymes rather than cell-associated binding. Both heat-labile and heat-resistant compounds and/or enzymes contributed to this detoxification [223].

The primary mechanisms underlying AFB₁ degradation involve the enzymatic hydrolysis of the lactone ring and/or modifications of the coumarin structure and difuran ring. Key enzyme classes involved in these modifications include microbial laccases, oxidases,

peroxidases, and reductases [223]. In another study, mycobacterial enzymes catalyzed the reduction of the α,β -unsaturated ester moiety of aflatoxins. This reaction is mediated by specialized enzymes utilizing the deazaflavin cofactor $F_{420}H_2$, thereby triggering spontaneous hydrolysis and detoxification [222]. Furthermore, two distinct classes of F_{420} -dependent reductases, designated FDR-A and FDR-B, with aflatoxin-reducing activity were identified and characterized in *Mycobacterium smegmatis* [224].

Beyond direct chemical degradation, actinobacteria synthesize specialized secondary metabolites that can suppress aflatoxin biosynthesis without influencing the source fungus. An important example is aflastatin A, a complex metabolite obtained from *Streptomyces* sp. MRI142, which completely abolished aflatoxin production in *Aspergillus parasiticus* at a minimum effective concentration of 0.5 $\mu\text{g/mL}$ without restricting fungal growth [225]. Kondo et al. [226] revealed that introducing aflastatin A to *Aspergillus parasiticus* cultures reduced the accumulation of norsolorinic acid, an aflatoxin intermediate. This compound also decreased the mRNA levels of biosynthetic enzymes (*pksA*, *ver-1*, *omtA*) and the regulatory gene *aflR*.

Similarly, co-cultivation of *Aspergillus flavus* with *Streptomyces roseolus* triggered an extensive downregulation of almost the entire AFB₁ gene cluster, with the sole exception of *aflT*. This microbial interaction induced a reduction in the abundance of the AflR/AflS regulatory complex, thereby suppressing activation of the AFB₁ biosynthetic pathway. Transcriptional analysis under co-culture conditions revealed that early-stage genes of the enzymatic cascade (*aflA*, *aflB*, and *aflC*) were less affected compared to genes encoding enzymes required for intermediate and late-stage conversions, including *aflK*, *aflM*, *aflO*, and *aflP* [227].

Conversely, Maud et al. [228] reported that even *aflT* could be heavily repressed when *Aspergillus flavus* was exposed to a four-day-old cell-free supernatant derived from *Streptomyces roseolus*. The cell-free extract also induced morphological anomalies in the pathogen, resulting in a 77% reduction in fungal dry weight and a severe reduction in conidiation without altering the overall colony diameter. Providing a broader spectrum of control, de la Huerta-Bengoechea et al. [229] reported that *Arthrobacter* and *Rhodococcus* strains could influence the production of both OTA and AFB₁ in important molds, such as *Aspergillus carbonarius*, *Aspergillus niger*, or *Aspergillus flavus*.

The available evidence indicates that actinobacteria, particularly species within the genus *Streptomyces*, can protect crop products against mycotoxin contamination. Rather than relying on a single mode of action, these versatile bacteria exert their effects through a multicomponent defense system that targets both the source pathogen and the produced toxins.

5. Future Perspectives of the Use of Actinobacteria Against Fungal Pathogens

In line with the European Green Deal and the Farm to Fork Strategy, reducing reliance on chemical plant protection products has become a key objective. Microbial and microbe-based biocontrol agents, including actinobacteria and their derivatives, have been recognized as promising alternatives because of their lower environmental impact [57]. However, their widespread adoption has been constrained by regulatory, ecological, technological, and economic challenges.

Historically, the regulatory framework for microbial biocontrol agents has largely been adapted from that developed for synthetic pesticides. As a result, the EU registration process is relatively complex, involving both EU- and Member State-level procedures [57,230,231]. Recent legislative updates introduced in 2022 sought to address these limitations by streamlining the evaluation of microbial substances while maintaining

high standards for human, animal, and environmental safety. Under Regulation (EC) No. 1107/2009, active substances (i.e., microorganisms) are first approved at the EU level, followed by product authorization by individual Member States [57,232]. Additional initiatives, such as those led by the Single Market Enforcement Taskforce (SMET), aim to address delays in Member State-level authorization by promoting the exchange of good practices and improving procedural efficiency. However, these measures have not yet proven sufficient [233]. Further regulatory simplifications proposed in 2025 seek to facilitate commercialization and market access [233].

Actinobacteria, particularly members of the genus *Streptomyces*, have shown considerable promise as microbial biocontrol agents against phytopathogenic fungi. Commercial products such as Mycostop[®] (candididin-producing *Streptomyces griseoviridis* K61), Actinovate[®] (natamycin-producing *Streptomyces lydicus* WYEC108), and Rhizovit[®] (*Streptomyces rimosus*) have demonstrated effective control of numerous phytopathogens, such as *Fusarium*, *Botrytis*, *Rhizoctonia*, *Phytophthora*, *Alternaria*, *Phomopsis*, and *Pythium* species [35,65,78,234,235]. Additional *Streptomyces*-based products include Mycocide KIBC, Safegrow KIBC, Kasumin, Polyoxorim, and Validacin [10]. Furthermore, BioSpectra[™] 100SC is another commercially available fungicide that contains natamycin, obtained from *Streptomyces natalensis* to control postharvest gray mold [236]. Despite the successful commercialization of these products, the relatively small number of commercially available actinobacteria-based biocontrol agents compared with the extensive research efforts devoted to identifying promising isolates highlights the persistent gap between laboratory findings and practical agricultural application.

One of the major limitations affecting field application is the inconsistency of biocontrol performance under diverse environmental conditions. In many regions, climatic conditions can alter efficacy, often necessitating repeated applications or integration with complementary control measures [237] such as solarization [234]. Moreover, microbial biocontrol agents may show a narrower host range compared to synthetic chemical pesticides, further constraining their broader applicability [231].

At the ecological level, the success of introduced actinobacteria is strongly influenced by complex plant-associated environments, including the rhizosphere, endosphere, and phyllosphere. Nutrient availability regulates both microbial growth and secondary metabolite production. Although nutrient limitation can stimulate secondary metabolism [238], field conditions are generally more restrictive, limiting both metabolite synthesis and diffusion. Consequently, the strong antagonistic activity frequently observed under controlled *in vitro* conditions may not directly translate to field performance [239]. Nonetheless, conventional cultivation techniques are often unable to exploit the full biosynthetic potential of actinobacteria, as many biosynthetic gene clusters remain silent or cryptic under standard laboratory settings. Consequently, the efficient activation of these gene clusters is still a major challenge [240]. To better exploit the metabolic potential of actinobacteria, several complementary strategies have been developed to stimulate the production of otherwise inaccessible secondary metabolites. Among them, the “one strain many compounds” (OSMAC) strategy has been employed to activate silent biosynthetic gene clusters and enhance metabolite diversity [238]. Similarly, the addition of biological or chemical elicitors can induce the expression of cryptic biosynthetic gene clusters [241]. Furthermore, metabolomics-based studies during co-cultivation with phytopathogens have emerged with valuable insights into interaction dynamics and enable the characterization of metabolite profiles [242]. Recent studies also indicated that interactions between introduced actinobacteria and native soil microbiota may enhance disease suppression beyond the effects of a single strain alone, as demonstrated for *Streptomyces* species [243]. Additionally, several traditional and advanced genetic techniques have been created to acti-

vate these biosynthetic gene clusters, including PCR-targeted gene replacement, ribosome engineering, the transcription factor decoy strategy, the Cre-LoxP recombination system, and CRISPR/Cas-mediated genome editing [240].

Safety remains another important consideration during product development. Although actinobacteria produce a wide range of antifungal compounds, some secondary metabolites may also exert undesirable effects on non-target organisms or mammalian cells. Furthermore, these metabolites may alter the indigenous soil microbiota that contribute to plant health and ecosystem functioning [83]. Similarly, microbial biodegradation of mycotoxins represents both an opportunity and a potential risk. While microbial detoxification can reduce mycotoxin contamination, degradation products also require careful evaluation [217]. Regarding AFB₁, several by-products, including aflatoxin B_{2a}, aflatoxin D₁, and aflatoxicol, generally exhibit lower toxicity than the parent compound. However, other modified forms, such as AFM₁-8,9-epoxide and AFB₁-8,9-epoxide, can interact with DNA, resulting in the induction of mutagenic and carcinogenic effects [223,244,245]. Therefore, the development of new microbial agents must be accompanied by comprehensive toxicological evaluation. Furthermore, future studies should evaluate not only the efficiency of mycotoxin degradation of actinobacteria but also the toxicity of resulting metabolites to ensure that detoxification does not generate other harmful metabolites.

In addition to biological efficacy, formulation technology has been a critical determinant of successful commercialization. Commercial products typically consist of the viable beneficial microorganisms combined with carrier materials and additives. Solid forms, such as powders and granules, are typically considered more suitable than liquid formulations due to their greater stability [235]. Product performance is also influenced by inoculum concentration [246]. At the same time, large-scale production requires specialized expertise in organism-specific production and formulation strategies, and although registration costs are lower than those for chemical pesticides, they may still represent a significant barrier for small- and medium-sized enterprises, which are often the primary developers of such products [231]. To improve economic sustainability, agro-industrial waste streams such as potato waste [247], food waste digestate [248], and palm oil mill waste [249], have been explored as alternative substrates for microbial cultivation and secondary metabolite production, thereby reducing manufacturing costs while contributing to sustainable production.

Lastly, the successful implementation of biocontrol strategies also depends on practical considerations at the farm level. Limited access to technical knowledge, insufficient advisory services, potential bias in information sources, and concerns regarding yield losses associated with reduced pesticide use continue to hinder farmer adoption [237]. Thus, increasing farmer awareness, improving agricultural extension services, and demonstrating the consistent field efficacy of actinobacteria-based biocontrol products will be essential for wider adoption.

Overall, the successful implementation of actinobacteria-based biocontrol agents will depend on integrating advances in microbial ecology, genomics, metabolomics, and formulation technologies. Since *in vitro* assays alone are insufficient to accurately predict true field performance of certain strains or formulations, future research should incorporate experimental models that better mimic natural environmental conditions rather than relying on solely controlled laboratory environments. Moreover, the lack of standardized *in vitro* testing methods further complicates comparisons among studies and limits the reliable selection of promising biocontrol candidates. Establishing harmonized screening protocols, followed by systematic validation under greenhouse and field conditions, would facilitate the translation of research findings into practical agricultural applications.

In addition to evaluating direct antagonistic interactions between actinobacteria/secondary metabolites and phytopathogenic fungi, greater attention should be given to

the interactions between the introduced strain/compound and native microbial communities, as they may influence colonization, persistence, and biocontrol activity. The use of microbial consortia or combinations of beneficial actinobacteria and bioactive secondary metabolites may further enhance disease suppression compared with single-strain or compound applications. The selection of resilient strains capable of tolerating various abiotic stresses, together with the optimization of formulation and delivery systems, will improve the efficacy of the utilized bioactive agent under field conditions. Genetic advancements combined with metabolomics is expected to accelerate the identification of new metabolites and facilitate the development of more effective actinobacteria-based biocontrol products.

6. Conclusions

Actinobacteria (also referred to as *Actinomycetota*), particularly members of the genus *Streptomyces*, represent a versatile source of antifungal compounds and biocontrol mechanisms exploited by the agro-industry to manage preharvest and postharvest fungal diseases affecting fruits, vegetables, and cereals. Their effectiveness as biocontrol agents is attributed to a combination of direct antagonistic mechanisms, including the production of diverse diffusible antifungal metabolites, volatile organic compounds (VOCs), and hydrolytic enzymes, as well as hyperparasitic interactions and modulation of mycotoxin production. These direct antifungal activities are often complemented by indirect effects, such as plant growth promotion.

Among the direct antifungal mechanisms, the production of diffusible antifungal compounds, including polyketides and polyene macrolides, represents one of the most potent strategies for combating fungal infections. However, the effective agricultural application of purified compounds requires the development of advanced delivery systems that enable the curative treatment of established infections rather than being restricted to preventive use. Furthermore, the utilization of specific metabolites may be constrained by potential toxicity toward non-target organisms. Alternative formulation candidates, such as hydrolytic enzymes and VOCs, also show promise for the development of biocontrol products; however, their practical adoption may be limited by lower stability under fluctuating environmental conditions and, in some cases, less pronounced antifungal activity compared with polyketides. Overall, the use of purified compounds offers distinct advantages over biocontrol agents containing living actinobacteria, providing rapid antifungal action and reduced dependence on interactions and competition with indigenous microbial communities. Nonetheless, living microbial agents may offer additional benefits, such as combined production of secondary metabolites, modulation of mycotoxin production, and hyperparasitic activities, highlighting the need for application-specific formulation strategies.

Despite the profound antifungal potential of actinobacteria and their secondary metabolites, their commercialization remains constrained by regulatory complexity, ecological variability, technological limitations, and safety considerations. Furthermore, current research on actinobacteria relies heavily on *in vitro* assays, which are often time-consuming and difficult to compare due to the diversity of experimental approaches and evaluation criteria. Overcoming these technological, methodological, and safety boundaries through standardized testing protocols, genetic and omics-based approaches, and advanced formulations represents a critical step toward the successful implementation of more actinobacteria-based antifungal agents into agricultural practice.

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